Hormone Research
in Paediatrics



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Abstracts

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Abstracts

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Plenary Lectures

PL1

Copeptin in vasopressin-dependent fluid disorders

Mirjam Christ-Crain

University Hospital Basel, Basel, Switzerland

This talk will discuss general issues about Copeptin, (e.g. physiology, normal values in children and adults), and the value of Copeptin in vasopressin-dependent fluid disorders, i.e. in patients with diabetes insipidus on the one hand and in patients with the syndrome of inappropriate antidiuresis (SIAD) on the other side.

Arginine Vasopressin (AVP) is a peptide composed of 9 amino acids that is synthesized in the hypothalamus. The physiological function of AVP is homeostasis of fluid balance, vascular tonus and regulation of the endocrine stress response. AVP is difficult to measure due to complex pre-analytical requirements and due to technical reasons. Copeptin is the C-terminal part of the vasopressin precursor and has been shown to be a stable, sensitive and simple to measure surrogate marker of AVP release. Therefore, it has emerged as a new diagnostic marker in vasopressin-dependent fluid disorders.

The differential diagnosis of diabetes insipidus is challenging. For decades, the water deprivation test was the diagnostic gold standard, but its interpretation is often misleading and the test is cumbersome for patients, adults and children alike. In this presentation, new copeptin-based osmotic and non-osmotic stimulation tests will be discussed.

The differential diagnosis of hyponatremia is again challenging. Whether copeptin can be a marker improving differential diagnosis and guide treatment decisions will be debated.

PL2

Abstract Unavailable

PL3

Abstract Unavailable

PL4

Abstract Unavailable

PL5

Abstract Unavailable

PL6

Abstract Unavailable

PL7

Why science needs philosophy and vice-versa

Lucie Laplane

CNRS, University Paris 1 Pantheon-Sorbonne, Paris, France.
Gustave Roussy, Hematopoietic tissue aging, Villejuif, France

Science was formerly an integral part of philosophy, but these two broad disciplines have gradually grown apart and are now typically viewed as completely different endeavors. In this talk, I will argue in favor of a renaissance in the integration of science and philosophy.

I will argue first that philosophy can fruitfully contribute to science. I will take the example of stem cells in various contexts (homeostasis, regeneration and regenerative medicine, cancer) to illustrate how philosophy can contribute to science and medicine. Relying on this example, I will also show that for such positive contribution, philosophy needs a good understanding and knowledge of science.

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The current strong separation of science and philosophy is a barrier to wider thinking in science, and to scientifically well-informed philosophy. In the last part of the talk I will thus suggest more practical solutions to bridge the two disciplines.

Symposia

Novel insights into adrenal insufficiency

S1.1

Abstract Unavailable

S1.2

Abstract Unavailable

S1.3

Abstract Unavailable

HPG

S2.1

Abstract Unavailable

S2.2

Abstract Unavailable

S2.3

Abstract Unavailable

All around Beta cells - the problem and future solutions

S3.1

Abstract Unavailable

S3.2

Abstract Unavailable

S3.3

Abstract Unavailable

Regulation of growth

S4.1

Abstract Unavailable

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S4.2

Abstract Unavailable

S4.3

Abstract Unavailable

Pathophysiology of hypopituitarism and its clinical implications

S5.1

Abstract Unavailable

S5.2

Abstract Unavailable

S5.3

Abstract Unavailable

Clinical management of calcium and phosphate disorders

S6.1

The effects of vitamin D supplementation on infant bone mass and body composition

Hope A. Weiler

Nutrition Research Division, Bureau of Nutritional Sciences, Food Directorate, Health Products and Food Branch, Health Canada, Ottawa, Ontario, Canada

Vitamin D supplementation is recommended for breastfed infants as primary prevention of vitamin D deficiency and nutritional rickets. Globally, the most commonly recommended dosage of vitamin D is 400 IU/day for healthy breastfed infants. Whether there are benefits of higher dosages of vitamin D to infant bone mass and body composition has been investigated. The objective of this presentation is to review the evidence from randomized controlled trials conducted in healthy term born and breastfed infants with emphasis on two trials from Montreal, Canada. In a randomized dose-response parallel group trial (clinicaltrials.gov NCT 00381914) of 400 to 1600 IU/d of vitamin D supplementation in infants (n=76 males; n=56 females) from 1 to 12 months of age, all dosages supported the primary outcome of plasma 25-hydroxyvitamin D [25(OH)D] with >97% achieving 25(OH)D ≥50 nmol/L. No differences in whole body or lumbar spine bone mass were observed among trial groups. Subsequently, a second randomized controlled parallel group trial (clinicaltrials.gov NCT02563015) was conducted in infants (n = 58 males; n = 40 females) born with serum 25(OH)D <50 nmol/L and randomized to 400 or 1000 IU/d of supplemental vitamin D from 1 to 12 months of age. Mean serum 25(OH)D was higher (P<0.0001) with 1000 IU/d vitamin D supplementation from 3 to 12 months of age, with no differences observed in the proportions meeting ≥50 nmol/L (400 IU/d: 93.2 to 97.5% vs. 1000 IU/d: 92.9 to 100%) between the dosage groups over time. Modest increments (4.8%) were observed in lean body mass as the primary outcome at 12 months of age (400 IU/d: 6690 ± 1122 vs. 1000 IU/d: 7013 ± 905 g, P = 0.0428). The secondary outcomes of whole body and lumbar spine bone mass were not different across the trial. These trials reinforce that 400 IU/d of vitamin D supplementation is enough to build and maintain serum 25(OH)D ≥50 nmol/L and to support bone health from the neonatal period through to 1 year of age. The implications of the modest benefits of higher vitamin D status to lean body mass require further longitudinal studies. Population health and health care professionals should continue to recommend 400 IU/d of supplemental vitamin D for healthy breastfed infants in support of vitamin D status and bone health outcomes.

S6.2

Abstract Unavailable

S6.3

Abstract Unavailable

Insight into Metabolic disorders and new therapeutic targets

S7.1

Abstract Unavailable

S7.2

The circadian clock in insulin resistance and diabetes

Andries Kalsbeek[1,2], *Dirk Jan Stenvers*[1]

[1]Amsterdam University Medical Center, Amsterdam, Netherlands. [2]Netherlands Institute for Neuroscience (NIN), Amsterdam, Netherlands

In healthy humans, plasma glucose excursions depend on the time of day of glucose ingestion, with higher glucose tolerance in the morning compared to the evening. Recent studies using a circadian desynchrony protocol clearly demonstrated that the diurnal rhythm in glucose tolerance is robustly regulated by the circadian timing system, separate from behavioral and environmental changes. The mammalian circadian timing system consists of a central brain clock and peripheral clocks in tissues throughout the body, including muscle, adipose tissue, and liver. Environmental light synchronizes the approximately 24-hour (i.e. circadian) rhythm of the brain clock with the exact 24-hour rhythm of the environment. The entrained timing signal from the brain clock is forwarded via neural and hormonal signals to the peripheral tissue clocks. The molecular mechanism of the central and peripheral clocks is based on transcriptional translational feedback loops, which are present in virtually every cell of the human body. Molecular clocks in different tissues and organs are involved in the control of the daily rhythm in glucose tolerance, insulin sensitivity and insulin secretion.

The first clue that the circadian timing system may be involved in the pathophysiology of insulin resistance was the observation in the 1960s of an altered daily rhythm in glucose tolerance in patients with diabetes mellitus. Later, observations including the development of metabolic syndrome in the Clock mutant mouse, food intake at the wrong circadian phase causing obesity in mice and circadian misalignment resulting in decreased glucose tolerance in humans led to the circadian disruption hypothesis. Sophisticated tissue specific pancreatic, hepatic, muscle, and adipose transgenic and knockout models gave further support for this hypothesis.

Taken together, it is likely that disturbance of the central and/or tissue clock rhythms contributes to the pathophysiology of insulin resistance. Circadian disruption may also cause misalignment of nutrient fluxes, both between and within tissues. For instance, a mismatch between hepatic glucose production, muscle glucose uptake, and carbohydrate intake, may contribute to elevated glucose levels, and metabolic inflexibility in muscle tissue may result in insulin resistance. Randomized clinical trials investigating the effects of natural light/dark exposure, sleep improvement, time restricted feeding, and the daily timing of exercise to prevent these metabolic complications are needed.

S7.3

Polycystic Ovary Syndrome in Adolescent Girls: Towards a Treatment Focusing on Ectopic Fat

Lourdes Ibáñez[1,2], *Francis de Zegher*[3]

[1]Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain. [2]Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III, Madrid, Spain. [3]University of Leuven, Leuven, Belgium

Polycystic ovary syndrome is the most common cause of hirsutism and menstrual irregularity in adolescent girls and young women. It is often accompanied by obesity and insulin resistance and is associated to lifelong co-morbidities, including subfertility, type 2 diabetes, non-alcoholic fatty liver disease, pre-menopausal cancer, depression, low health-related QoL, and pregnancy and offspring complications.

PCOS in adolescent girls is commonly driven by fat excess in subcutaneous adipose tissue, leading to insulin resistance and ectopic (hepato-visceral) fat excess. There is still no approved pharmacological therapy for adolescent PCOS. The most common treatment is an intervention focusing on symptoms; oral estro-progestagens are used off-label as first-line treatment, even in young girls who don't need contraception. However, this approach does not address the core problem, so upon treatment discontinuation, the clinical symptoms may re-emerge.

Over the last years, the research in progress has been directed towards a reduction of body adiposity, and specifically, hepato-visceral fat excess. There are promising results with sustained lifestyle changes, albeit they are difficult to maintain. In PCOS girls with obesity, Glucagon-Like-Peptide-1 (GLP-1) agonists are under investigation. In PCOS girls without obesity, a low-dose combination of medications with additive effects, for example, a combination of spironolactone, pioglitazone and metformin, has proved to be effective and safe in pilot studies and is now under further

investigation within the scope of SPIOMET4HEALTH, a multicentric, double-blind, placebo-controlled clinical trial funded by the European Union's H2020 Research and Innovation Programme.

Key learning points:

§ Polycystic ovary syndrome is a prevalent disorder driven by ectopic fat
§ Most girls with PCOS receive only symptomatic treatment, so far
§ The new therapeutic approach in adolescent PCOS is to aim for a reduction of ectopic fat

Emerging problems in thyroid diseases

S8.1

Abstract Unavailable

S8.2

Diagnosis and Management of Central Congenital Hypothyroidism

Nitash Zwaveling-Soonawala

Emma Children's Hospital, Amsterdam University Medical Centre, Amsterdam, Netherlands

Central congenital hypothyroidism (central CH) refers to an inborn deficient thyroid hormone production due to insufficient pituitary TSH stimulation of an otherwise normal thyroid gland. Central CH may be part of combined pituitary hormone deficiencies (CPHD) (60%) or may occur in isolation. The most common cause of CPHD consists of a characteristic pituitary malformation referred to as pituitary stalk interruption syndrome. Up until 2012 most cases of isolated central CH remained unexplained and only *TSHB* and *TRHR* gene variants were described in very rare cases. In the last decade, the use of next generation DNA sequencing techniques, has led to the identification of three new genetic causes of central CH: *IGSF1* (2012), *TBL1X* (2016) and *IRS4* (2018).

Diagnosing central CH is often challenging since TSH concentrations are normal and diagnosis is based solely on a free T4 concentration below age-specific reference intervals. The lack of neonatal free T4 reference intervals makes diagnosing central CH at the newborn age especially difficult.

The Netherlands has a longstanding history of neonatal screening for central CH which enables early detection and treatment. In a recent study on cognitive outcome of early treated Dutch central CH patients, full-scale IQ scores of isolated central CH patients were similar to that of healthy siblings while patients with CPHD had significantly lower full-scale IQ scores (mean of -7.9 points). Unfortunately comparison with late detected patients isn't possible since systematically collected data on developmental outcomes in these patients is lacking. This leaves the question whether early detection and treatment of central CH improves prognosis unanswered.

In this symposium the Dutch experience of screening for central CH will be presented. Challenges in coming to a diagnosis will be highlighted and a practical approach to diagnosis and management of this intriguing condition will be provided.

S8.3

Abstract Unavailable

Individualised monitoring and treatment of type 1 diabetes

S9.1

Abstract Unavailable

S9.2

Abstract Unavailable

S9.3

Abstract Unavailable

Microbiome and Metabolic Disorders

S10.1

Abstract Unavailable

S10.2

TYPE 1 DIABETES AND THE MICROBIOME

Mikael Knip

Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland. Pediatric Research Center, New Children's Hospital, Helsinki University Hospital, Helsinki, Finland

The conspicuous increase in the incidence of type 1 diabetes (T1D) in the Western world after World War II cannot be explained solely by genetic factors but suggests that this rise must be due to crucial interactions between predisposing genes and environmental changes. Three parallel phenomena in early childhood – the dynamic development of the immune system, the maturation of the gut microbiome and the appearance of the first T1D-associated autoantibodies – imply that these phenomena might reflect causative relationships. A lot of novel data on the role of the microbiome in the development of T1D has accumulated recently but proving causality has remained challenging. The gut microbiota plays definitely an important role in the training and maturation of the immune system. A dysbiotic intestinal microbiota including decreased microbial diversity, increased abundance of potentially pathogenic bacteria and a reduced number of functional genes have been reported to be characteristic features of children, who progress to clinical T1D. In the INNODIA study the gut microbiome of 98 individuals affected by TID were analysed at the time of diagnosis and 3, 6, 12 and 24 months later. The gut microbiome composition – both individual taxa and functional modules – varied between the participating 12 clinical sites. Relative abundances of several bacterial species, increased after the diagnosis of T1D. Several statistically significant associations were seen between the microbiome and clinical parameters, including insulin dose, fasting C-peptide and HbA1c. Increasing insights into the role of the gut microbiota in T1D will improve the possibilities to manipulate the microbiota to reduce the risk of T1D in risk individuals and to improve the metabolic control in patients with established disease. Microbial metabolites may be stronger tools for the manipulation of the intestinal microbiota than specific microbes.

Fertility preservation in girls with ovarian insufficiency

S11.1

Abstract Unavailable

S11.2

Abstract Unavailable

S11.3

Abstract Unavailable

Bone fragility – from mechanisms to clinical management

S12.1

Abstract Unavailable

S12.2

Abstract Unavailable

S12.3

Abstract Unavailable

Meet the Expert

MTE1

Pediatric Cushing disease

Constantine Stratakis

IMBB, FORTH, Heraklion, Greece. ELPEN Research Institute, Athens, Greece. NICHD, NIH, Bethesda, USA

By far, the most common type of CS is due to exogenous causes, i.e. medication-induced CS. Endogenous causes are rare by they are all associated with one form of another of a tumor. We call Cushing Disease (CD) what is caused by pituitary adenomas only. It is common for children with CD to show an increase in rate of weight gain accompanied by a decrease in growth rate (linear height) due to decreased growth hormone secretion. This is often easily detected in growth charts of children with CS. Other symptoms include: rounded face, reddened cheeks, acne, headache, excess hair growth (fine downy hair on cheeks, arms, and legs), purplish-pink stretch marks (more common in older children), darkened skin around neck and armpit areas, easy bruising, development of pubic hair at a younger age than usual, irregular or absent menstrual periods, and high blood pressure. Compared to adults with CS, symptoms that are less commonly seen in children include: sleep disruption, mental changes, and muscle weakness. A review of the child's growth chart is essential: if the growth chart shows an increase in the rate of weight gain and decrease in the rate of linear growth (height velocity) during the same time period, then further evaluation and monitoring is needed to determine the cause. Other diagnostic testing in children with CD is similar to that in adults. Pituitary adenomas are usually treated by surgical removal (transsphenoidal surgery or TSS). In certain patients, treatment with medication(s) that control or block cortisol production, may be done on a short-term basis. In some patients, in those that surgery has failed (or if they were not good candidates for surgery, which is very rare in children but more frequent in adults), radiation therapy is indicated. Various studies report that one year after surgical cure of pediatric CS most children had lost weight and body mass and their height and growth velocity had increased; however final adult height is often impaired (by at least an inch or more). Many children and adolescents recovering from CD experience changes in cognitive performance that can be stressful for both the child and the parents. We have identified several hereditary diseases associated with genetic predisposition to the development of CD (MEN1 and MEN4, Carney complex, succinate-dehydrogenase mutations and others); more genes genetic factors are expected to be identified that may even lead to better medical treatments.

MTE2

Abstract Unavailable

MTE3

The key role of physical activity against the cardiometabolic risk in childhood obesity

Giuliana Valerio

University of Naples Parthenope, Naples, Italy

Children and adolescents with obesity and clustering of cardiometabolic risk factors, such as hypertension, dyslipidemia, and prediabetes are exposed to endothelial damage, vascular and myocardial remodeling, and atherosclerosis. If not adequately treated, these alterations may contribute to early morbility and mortality for adverse cardiovascular events in adulthood.

Physical activity (PA) plays an important role in the treatment of obesity and its cardiometabolic comorbidities. Youths with obesity are less active and are as much as sedentary than their healthy weight peers. Their poor motor skills reduce PA, sustaining a vicious circle of inactivity, low self esteem, poor quality of life and weight gain.

Both inactivity and body fat excess significantly impair several components of the health-related physical fitness, such as cardiorespiratory and muscular fitness, which have been associated to an unhealthy cardiometabolic profile.

PA and exercise increase energy expenditure, improve physical fitness and reduce cardiometabolic risk. During exercise, a variety of "exerkines" are secreted, activating a complex cross-talk between muscles, adipose tissue, liver, vasculature and pancreas. The resulting adaptations contribute to the systemic metabolic health effects of exercise.

Aerobic and/or resistance exercises may improve cardiorespiratory fitness and muscular strenght/endurance in youths with obesity with positive effects on insulin resistance, blood lipid and arterial pressure.

Children and adolescents should accumulate at least 60 min per day of moderate-vigorous PA, involving aerobic activities. Exercises that promote flexibility and muscle strenght should be performed at least 3 days per week. Aerobic and/or resistance training can be started at moderate intensity, gradually increasing in frequency, intensity and duration. Type and amount of PA should be developmentally specific, enjoiable and should limit the overload to the muscle skeletal system.

MTE4

Abstract Unavailable

MTE5

Initial evaluation of a suspected difference or disorder of sex development

S. Faisal Ahmed

University of Glasgow, Glasgow, United Kingdom

It is important that any child or adolescent with a suspected difference or disorder of sex development (DSD) is assessed by an experienced clinician with adequate knowledge about the range of conditions associated with DSD. In most cases, the paediatric endocrinologist within this service acts as the first point of contact but involvement of the regional multidisciplinary service is critical. The members of this service should be involved in education and training as well as quality care improvement. The underlying pathophysiology of DSD and the process of delineating this should be discussed with the parents and affected young person with all diagnostic tests undertaken in a timely fashion. Finally, for rare conditions such as these, it is imperative that clinical experience is shared through national and international clinical and research collaborations.

MTE6

Abstract Unavailable

MTE7

Diagnostics and management of hyperandrogenism during childhood and adolescence

Raimo Voutilainen

University of Eastern Finland, Kuopio, Finland. Kuopio University Hospital, Kuopio, Finland

Abstract: The source of hyperandrogenism can be adrenal, gonadal, mixed or exogenous. The reason of excessive androgen secretion for age can be primarily gonadal/adrenal or it could be secondary to trophic stimulation (LH, hCG, ACTH, insulin, IGFs). Clinical signs of hyperandrogenism in children include virilization (clitoral hyperplasia, labial fusion, even unclear sex in a newborn), premature pubarche, premature penile growth, accelerated linear growth, increased musculature, acne and/or comedones, adult type body odor, greasy skin and/or hair. Premature adrenarche and precocious puberty (clinical signs before 8 years in girls and 9 years in boys) are the most common hyperandrogenic disorders for age. Congenital virilizing adrenal hyperplasia (CVAH; 21-hydroxylase deficiency the most common form), adrenal and gonadal neoplasms, and exogenous androgen exposure have to be excluded when clinical and laboratory findings do not fit with usually benign marginally premature adrenarche or puberty. Careful clinical evaluation of the child with growth charts and pubertal staging can give clues to the origin of hyperandrogenism. Androgen effects with bilateral testicular enlargement in boys (Tanner G-stage 2 or higher) and breast development in girls (B2 or higher) suggest gonadal origin, androgen effects without testicular enlargement (G1) or breast development (B1) suggest adrenal or exogenous origin of androgens. Initial laboratory tests could include serum 17-OH-progesterone, DHEA(S), androstenedione and testosterone measurements; serum LH, FSH and free beta-hCG (in tumor suspicion) are needed if pubertal development (G2 or higher; B2 or higher) is present. Obesity predisposes to both adrenal and ovarian hyperandrogenism, including polycystic ovarian syndrome (PCOS); fasting plasma glucose, insulin, sex hormone-binding globulin, and lipid measurements are thus relevant. Imaging studies (ultrasonography and/or MRI) are needed when a neoplastic reason for hyperandrogenism is suspected. Management of hyperandrogenism depends on the discovered etiology. CVAH needs careful adjustment of hydrocortisone and possibly fludrocortisone treatment. Surgery is usually needed for neoplastic tumors. Premature adrenarche needs no specific treatment, but overweight should be tried to avoid, as in PCOS.

MTE8

Abstract Unavailable

How Do I…

How Do I…Session 1

HDI1.1

How Do I Diagnose and manage primary adrenal insufficiency

Donatella Capalbo

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Primary adrenal insufficiency (PAI) is a rare, potentially life-threatening, condition due to abnormalities of steroid biosynthesis or of adrenal gland development and responsiveness. PAI is characterized by impaired secretion of glucocorticoids and can be accompanied by mineralocorticoid and adrenal androgens deficiency or excess, depending on the underlying cause. In adults, the most common etiology is represented by autoimmunity. In contrast, the disease in children is more frequently associated with inherited monogenic disorders either isolated or in the context of syndromes. The most common cause of PAI in children is represented by Congenital Adrenal Hyperplasia due to 21 OH deficiency.

Prompt recognition is important since delayed treatment or more severe symptoms will increase mortality or morbidity. The diagnosis of PAI is challenging due to its insidious onset; clinical presentation in children is indeed related to the respective hormone deficiency and is highly variable, ranging from subtle and nonspecific symptomatology to acute onset with life-threatening adrenal crisis. The diagnostic process includes the demonstration of low cortisol concentrations along with high plasma ACTH. Plasma renin and aldosterone levels should be measured to determine the presence of mineralocorticoid deficiency.

Once PAI has been confirmed, the etiology should be investigated. Establishing a diagnosis has great importance to patient care for the correct management, treatment, and monitoring as well as for counseling about inheritance patterns. The diagnostic workup should take into account detailed clinical and biochemical characterization of the subject. Although many forms of PAI do not have diagnostic specific features, in recent years the emergence of NGS approaches has extended the knowledge on the genetic background of childhood-onset PAI.

The mainstay of treatment is glucocorticoid replacement. Oral hydrocortisone is the first choice treatment in children. In case of mineralocorticoid deficiency, replacement with fludrocortisone is needed. However, currently available glucocorticoid preparation fails to replicate the physiological cortisol circadian rythm and additional advances are needed to improve therapy and outcomes.

In this session, the diagnostic approach and management of children with PAI will be discussed.

HDI1.2

How do I manage severe obesity

Erica van den Akker

Erasmus MC, Rotterdam, Netherlands

Pediatric severe obesity is a major threat to health and longevity. Around 7% of children worldwide have early onset severe obesity before the age of 7. Pediatric obesity is caused by an interplay of multiple factors: lifestyle, environmental, sociocultural, psychological, biological and genetic factors. Endocrine, monogenetic or syndromal causes are rare, but currently underdiagnosed and important to identify for the need of specific treatment. Cardiovascular risk factors and other weight related comorbidities are common in children with obesity and early detection and treatment is necessary before long-term health complications result. The complexity of causes and complications of pediatric obesity warrant a structured diagnostic approach. When is endocrine or genetic screening indicated?

Treatment should be tailored to the need and situation of the child and its family. How to find which barriers play a role in behavioral change towards a healthy lifestyle? What other factors besides diet and exercise are important? What can you do as a healthcare provider? To tackle obesity in children, integrated care in a multidisciplinary setting is needed. Combined lifestyle interventions (CLI) aim at obtaining a healthier lifestyle and reducing BMI. But once severely obese, long-lasting weight loss with lifestyle modification is rare. How to define success? And what are the next steps if treatment fails? In recent years, several novel pharmacotherapeutic drugs have been approved and come to market for use in children and adolescents. Bariatric surgery has been shown to be effective in the most seriously affected, mature adolescents.

Pediatric obesity is a complex disease, needing care by a specialized multidisciplinary team of health care professionals. Children and adolescent with severe obesity undergoing lifestyle therapy, medication regimens, or bariatric surgery need a structured diagnostic and therapeutic approach with long term follow up and monitoring.

Weblinks and open access references

- Pediatric Obesity—Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline (https://academic.oup.com/jcem/article/102/3/709/2965084?login=true)
- The epidemiological burden of obesity in childhood: a worldwide epidemic requiring urgent action. BMC 2019. Di Cesare et al. (https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-019-1449-8)
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- https://easo.org/
- Erasmus MC Obesity center CGG (https://www.youtube.com/watch?v=uByJKC63apQ)

HDI1.3

Abstract Unavailable

How Do I…Session 2

HDI2.1

How do I …Manage communication with families after onset of T1D?

Karin Lange

Hannover Medical School, Hannover, Germany

Even today, the majority of families are caught completely unprepared by the diagnosis of diabetes in their child. The "bad news" hits them like a bolt from the blue and calls into question the future plans of parents and children. The first talk with the paediatric diabetologist, in which the diagnosis is communicated and the therapy is roughly outlined, sets the course for the acceptance of diabetes in the family and the long-term trusting cooperation with the diabetes team. Besides the verbal component of breaking bad news, other skills are also required. These include responding to the emotional reactions of the family, managing the stress of parents' expectations, engaging the child and parents, and

the dilemma of how to convey hope when talking about a chronic disease. Not only words, but also many non-verbal aspects influence whether a family feels accepted and understood. This workshop will discuss key aspects of communicating with affected children and their parents: 1) the cognitive receptivity of parents and children during diagnosis delivery; 2) preparing and setting up the conversation; 3) presenting the diagnosis age-appropriately; 4) assessing families' experiences and perceptions; 5) actively listening to children and parents; 6) delivering tailored information in small chunks; 7) checking the family's correct understanding; 8) addressing families' emotions with empathic responses, e.g. feelings of guilt and anxiety; 9) information about the support and diabetes education provided by the team; 10) giving an outlook on the first weeks with diabetes with a clear structure; 11) presenting appropriate sources of information; 12) outlook on further cooperation with the diabetes team and hopeful conclusion.

HDI2.2

How do I replace oestrogens in Turner syndrome?

Theo Sas

Erasmus Medical Center, Rotterdam, Netherlands

In Turner Syndrome (TS) the ovaries usually start to involute within 4 or 5 months of gestation. Consequently, the majority of patients have diminished ovarian estrogen production leading to the (partial) absence of puberty. These girls need estrogen therapy to induce pubertal maturation. For many parents of girls with TS, talking about ovaries, puberty and, particularly, infertility is a stressful thing. However, timely age-appropriate disclosure about these subjects, starting between the age of 8-10 years, is essential. Although ultra-low dose estrogens before the pubertal age could be beneficial for growth and psychological development, there is not enough evidence yet to support this. In addition, treatment with estrogens in the prepubertal phase has the risk of overtreatment with as a consequence premature breast development and early epiphyseal closure. From a psychosexual point of view, it is important that the pubertal induction starts at a similar age as their peers. Estrogens should be started when breast development does not occur and the serum gonadotrophins are high at the age of 11-12 years. The girls need information about the expected tempo of the breast development and the fact that the adult size of the breasts is not influenced by the estrogen dose. Although it is clear that a fast increase of the estrogen dose leads to earlier epiphyseal closure and consequently a lower adult height than desired, a slow increase in estrogen dose over 4 years is not associated with an impairment on growth. Dependent on the body weight of the girl, a starting dose of 1/10th – 1/16th of the adult dose is appropriate. Although dose transdermal 17 β-estradiol seems to be the most optimal treatment, studies comparing low dose transdermal vs. oral estrogens are lacking. The absence of availability of low dose estrogens in many countries can interfere with the most optimal choice for pubertal induction. Fortunately, most matrix estradiol patches can easily and safely be cut in small pieces and can be stored at room temperature up to temperatures of 35o C. Measuring estrogen levels during pubertal induction does not seems to be helpful in the decision to change the dose, but it can help in searching for the correct adult dose. Progestogens are recommended once breakthrough bleeding occurs or after 2 years of estrogen. In every step, the wish of the girl has to be taken into account, since at pubertal age some girls find height less important than breasts.

HDI2.3

Abstract Unavailable

Controversies

CON1.1

Abstract Unavailable

CON1.2

Abstract Unavailable

Novel Advances

NA1.1

Abstract Unavailable

NA1.2

Abstract Unavailable

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GPED Symposium

GPED1.1

Abstract Unavailable

GPED1.2

Abstract Unavailable

Young Investigators

YI1.1

Abstract Unavailable

YI1.2

Abstract Unavailable

YI1.3

Abstract Unavailable

Working Group Symposia

ESPE Working Group on Disorders of Sex Development (DSD) Symposium

WG1.1

Fertility Preservation in Experimental Models in DSD

Rod Mitchell

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The impact of DSD on future fertility is dependent on several factors. The key determinant of fertility potential is the status of gonadal development and function, and whether the individual has ovarian tissue with viable oocytes, or testicular tissue capable of producing functional sperm. Fertility risk will be primarily determined by the underlying diagnosis, modified by several additional factors. Whilst fertility preservation options are well established for many patient groups such as those receiving gonadotoxic treatment for cancer, there are a number of important additional considerations for those with DSD that must be evaluated on an individual patient basis. This includes potential for ongoing germ cell loss, risk of gonadal malignancy, genetic risk to offspring and factors related to feasibility of future use of gonadal tissues or gametes [1]. Developing appropriate fertility preservation options in individuals with DSD requires understanding of gonadal and germ cell development, which in turn requires a combination of clinical studies and experimental models, including a range of established in-vivo and in-vitro approaches [2,3]. We will discuss the clinical and experimental evidence for fertility potential and options for fertility preservation across a range of DSDs.

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2. Hurtado-Gonzalez P et al. Effects of Exposure to Acetaminophen and Ibuprofen on Fetal Germ Cell Development in Both Sexes in Rodent and Human Using Multiple Experimental Systems. *Environmental Health Perspectives*. 126(4):047006. 2018
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WG1.2

Abstract Unavailable

WG1.3

Abstract Unavailable

ESPE Working Group on Obesity (OWG) Symposium

WG2.1

Abstract Unavailable

WG2.2

Abstract Unavailable

WG2.3

Abstract Unavailable

WG2.4

Abstract Unavailable

WG2.5

Abstract Unavailable

ESPE Working Group on Bone and Growth Plate (BGP) Symposium

WG3.1

Abstract Unavailable

WG3.2

Abstract Unavailable

WG3.3

Abstract Unavailable

ESPE Working Group on Diabetes Technology (DT) Symposium

WG4.1

Use of Automated Insulin Delivery systems (AIDs) in preschool children

Carine de Beaufort

DECCP-Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg

Management of type 1 diabetes in preschool children is a huge challenge for their caregivers. Age-specific factors (e.g. unpredictable food intake and physical activity, small insulin doses, high insulin sensitivity, frequent intercurrent infections, high variability in insulin requirements) increase the complexity of daily

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diabetes management. Furthermore, the preschool child depends completely on his/her caregiver. To meet recommended treatment targets while avoiding hypoglycaemia is traveling between Scylla and Charybdis: accept an increase in risk for chronic complications or risk hypoglycaemia with a potential impact on brain function.

Continuous subcutaneous insulin infusion pumps (CSII), followed by continuous glucose monitoring (CGM) have facilitated treatment and improved quality of care and outcome in preschoolers (1). Hypoglycaemia fear though, especially at night, persists (2).

Over the last 5 years several Automated Insulin Delivery Systems (AIDs) have been approved for adults and older children. Only recently these tools have been tested in preschoolers, a population who may benefit most of this technology. In a randomized controlled crossover study (KIDSAP02), the use of CamAPS FX showed a significant better metabolic control, without increase in hypoglycemia (3). Caregivers reported less hypoglycemia fear and better perceived well being. When asked, parents report the CamAPS FX is a 'game changer' and helped them 'getting back their life'.

Use of AIDs in preschoolers improves metabolic control and reduces diabetes burden. These results suggest that AIDs in this population should be first line treatment to optimize short and long term outcome.

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WG4.2

Abstract Unavailable

WG4.3

Abstract Unavailable

WG4.4

Abstract Unavailable

ESPE Working Group on Paediatric and Adolescent Gynaecology (PAG) Symposium

WG5.1

Epigenetics of delayed puberty: recent advances

Alejandro Lomniczi

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To attain sexual competence, all mammalian species go through puberty, a maturational period during which body growth and development of secondary sexual characteristics occurs. Puberty begins with the reawakening of the gonadotropin-releasing hormone (GnRH) pulse generator. Reduction in inhibitory transsynaptic inputs combined with increased transsynaptic and glial excitatory inputs to the GnRH neuronal network are responsible for pubertal activation of GnRH neuro-secretion.

During the infantile to juvenile transition, increased Arcuate Nucleus (ARC) Kiss1 expression is needed for activation of GnRH pulsatile secretion, since humans and animal models with mutations in the Kiss1 signaling pathway show pubertal failure and infertility. Although the pubertal process is known to have a strong genetic component, during the last several years, evidence has emerged suggesting that these genes are regulated by an epigenetic mechanism. Using the Kiss1 gene as a molecular readout of reproductive maturation, we demonstrated that the Polycomb group (PcG) of transcriptional repressors is in charge of epigenetically repressing ARC Kiss1 expression during the infantile period. Moreover, as animals approach the juvenile period, the Trithorax group (TrxG) of epigenetic activators counteract the PcG by imposing activating histone marks in the Kiss1 5' regulatory regions, allowing for increased Kiss1 expression and thus puberty to progress. Furthermore, using a model of metabolic alteration of pubertal development we identified NAD-Dependent Protein Deacetylase Sirtuin-1 (SIRT1) as a relay of metabolic information in ARC Kiss1 neurons that controls Kiss1 expression by regulating the levels of histone acetylation and PcG binding in response of metabolic status.

Here, we will briefly review the function of these epigenetic modifying enzymes and discuss the overall role of epigenetic markers in neuroendocrine reproductive development.

WG5.2

Pubertal induction of female delayed puberty: when and how

Marco Bonomi[1,2], *Silvia Federici*[1,2], *Giovanni Goggi*[1,2]

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Delayed puberty (DP) is defined as a retardation of sexual maturation beyond the expected age, which conventionally is between 8 and 13 years in females. Since DP due to hypogonadism requires a specific treatment, it is crucial to promptly define the underlying pathogenesis and identify a tailored program of care. Hormonal therapy is essential to promote the development of secondary sexual characteristics, bone, muscle, and social, sexual, and psychologic skills. Despite the optimal age to start treatment has not been universally established yet, in order to recapitulate physiology pubertal induction should be considered at 11 years in girls with known hypogonadism or otherwise as soon as such diagnosis is established, avoiding to delay treatment too long beyond the age of 13 even when constitutional delay of puberty is suspected. In females, adequate pubertal development is achieved with progressively increasing doses of estrogens alone, while the main role of progesterone is to prevent endometrial hyperplasia. Several studies have proposed different therapeutic regimens for pubertal induction, which differ in formulation, duration, initial dose and subsequent augmentation, and timing of progestin introduction: however, the best approach has not been defined yet. Puberty should be induced over a period of 2–4 years until a satisfactory outcome is achieved, usually when an adult dose has been reached. Puberty induction in late-diagnosed patients must be individualized and a faster tempo in the increase of estrogen doses can be considered. Therapy should involve 17βestradiol and most Authors currently recommend transdermal estradiol as the first choice. Most of the recommendations regarding estrogen dosing are based on data extrapolated from girls with Turner Syndrome and Literature sources are scant regarding other etiologies of female hypogonadism. Hence, it is mandatory to encompass the heterogeneity of the population to treat and underline the key differences in therapeutic timing and goals.

WG5.3

Differential diagnosis of pubertal delay in girls - What's new?

Sasha Howard

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Pubertal delay in females is defined as the lack of development of Tanner breast stage 2 by 13 years of age. Recent cohort studies have recapitulated the findings of classic studies over the last few decades, that constitutional delay (also known as self-limited delayed puberty) is less common in girls than in boys. This diagnosis is found in 30% of girls presenting with delayed puberty, with a further 30% classified as functional hypogonadotropic hypogonadism due to chronic illness or undernutrition. Syndromic and isolated hypogonadotropic hypogonadism, as well as pituitary endocrine causes account for 20% and the final 20% is due to primary gonadal causes including Turner syndrome and primary ovarian insufficiency. Primary amenorrhoea may also be seen in adolescent females with hyperandrogenism as part of the spectrum of polycystic ovarian syndrome.

As in males, one of the diagnostic dilemmas in clinical practice is to distinguish between self-limited delay and permanent hypogonadotropic hypogonadism in girls presenting with delayed puberty onset. Genetic diagnosis may significantly aid this distinction, especially as in girls red flags such as low testes volume, micropenis and cryptorchidism are not relevant. At present, genetic testing usually involves panel exome sequencing for common genes known to cause hypogonadotropic hypogonadism. Increasing understanding of genes underlying both self-limited delayed puberty and hypogonadotropic hypogonadism will further assist this strategy and in the future whole exome or genome sequencing in such patients may be adopted. Biochemical biomarkers such as inhibin B and AMH may also be of diagnostic value in adolescent females, as well as prognostic indicators of future fertility potential with correlation with oocytes number.

Mini-puberty provides a window of opportunity for the diagnosis of both hyper and hypogonadotropic hypogonadism in female infants, with recent publication of high quality normative data. The understanding of the physiological role of mini-puberty in females, and the interpretation of pathology is still limited and requires further study.

WG5.4

Abstract Unavailable

ESPE Working Group on Gender Incongruence (GI) Symposium

WG6.1

Abstract Unavailable

WG6.2

Abstract Unavailable

WG6.3

Abstract Unavailable

WG6.4

Long-term outcomes in transgender adolescents

Chantal Wiepjes

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Since around twenty years ago, transgender adolescents can be treated with puberty suppression before the age of 18 years. This is usually achieved by using a gonadotropin releasing hormone agonist (GnRHa). The suppression of puberty can prevent stressful changes in unwanted physical characteristics, while it provides time for exploring their gender identity, or to bridge the time until one becomes eligible for gender-affirming hormones (GAH). When gender dysphoria persists during puberty suppression, testosterone or estradiol can be added in incremental dosages to induce puberty. This so-called Dutch protocol has become routine care for transgender adolescents in many gender identity clinics and is part of the treatment guidelines. However, more recently, puberty suppression for minors has become subject of public debate and even legal measures have been taken to ban its use. Although short-term studies have shown a beneficial effect of the Dutch approach, the treatment is regarded by some as experimental because long-term follow-up is lacking. During this session, the continuation rate of using GAH in adulthood of people who started GnRHa and GAH during adolescence are presented. In addition, the long-term effects of the treatment with puberty suppression followed by GAH with regard to bone health and cardiovascular risk are presented.

ESPE Working Group on Turner Syndrome Symposium

WG7.1

Abstract Unavailable

WG7.2

Abstract Unavailable

WG7.3

Abstract Unavailable

WG7.4

Abstract Unavailable

WG7.5

Abstract Unavailable

WG7.6

Abstract Unavailable

ESPE Nursing and Allied Health Working Group (PENS) Symposium

WG8.1

Benefits of multidisciplinary care in Prader-Willi syndrome

Nadia Amin

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Prader-Willi syndrome (PWS) is a complex genetic disorder which affects endocrine and neurological systems, metabolism and behaviour. In the neonatal period PWS is characterised by

hypotonia, and resultant failure to thrive, whilst in childhood hyperphagia and obesity typically predominate.

Patients can develop hypothalamic dysfunction and a range of endocrinopathies, including growth hormone deficiency, hypogonadism and hypothyroidism. Patients with PWS benefit from early and consistent endocrine care from infancy to adulthood. Early use of growth hormone, irrespective of baseline growth hormone secretion has been shown to have a range of benefits for patients including linear growth, increased lean muscle mass, motor development and increased energy expenditure.

Leeds Children's Hospital has developed a multi-disciplinary regional clinic to address the complex needs of patients with PWS. Patients with PWS have evolving nutritional, medical, social and psychosocial needs, and management requires collaboration with community and local services as well as other hospital based medical teams. Clear care pathways used within multidisciplinary clinics have been shown to have positive benefits for patients and families, improving standards of care and ensuring consistency of care for all patients in the region.

WG8.2

Abstract Unavailable

Endo-ERN Symposium

EE1.1

Endo-ERN – paving the way to life-long expert care for rare endocrine conditions

Olaf Hiort

Universität zu Lübeck, Lübeck, Germany

The European Reference Networks (ERNs) have been installed by the European Union to promote the patients' rights in cross-border health care in 2017. They are accredited networks of health care providers offering transparency and dissemination of expertise to make an individual choice for best care. The ERN for rare endocrine conditions (Endo-ERN) is the largest ERN and has the aim to bridge care from infancy to senescence. Therefore, it has an adult and a paediatric chair and, in its format, tackles each group of endocrine conditions from both angles, also including patient advocacy of childhood and adult care.

Within the last five years, Endo-ERN has put its efforts on five different aims: 1. Installing and usage of the clinical patient management system for virtual consultation, 2. monitoring performance and outcome through patient registries, 3. Promotion research and innovation through connection with EU research programmes, 4. Harmonizing disease management through guideline development, as well as 5. Training and disease information through webinars and learning modules. All these aims are promoted through interaction with the scientific societies ESE and ESPE.

In the future, Endo-ERN will strengthen its efforts with further linking with the societies to offer a gateway to clinical care and clinical/translational research in rare endocrine conditions. Endo-ERN will act in concert with ESE and ESPE to achieve maximal synergy for endocrine care across the life-span.

EE1.2

Abstract Unavailable

EE1.3

Abstract Unavailable

EE1.4

Abstract Unavailable

ESPE Yearbook Sessions

Yearbook of Paediatric Endocrinology 1

YI1.1

Abstract Unavailable

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YI1.2

Abstract Unavailable

YI1.3

Abstract Unavailable

YI1.4

Abstract Unavailable

YI1.5

Abstract Unavailable

Yearbook of Paediatric Endocrinology 2

YI2.1

Abstract Unavailable

YI2.2

Abstract Unavailable

YI2.3

Abstract Unavailable

YI2.4

Abstract Unavailable

YI2.5

Abstract Unavailable

Yearbook of Paediatric Endocrinology 3

YI3.1

Abstract Unavailable

YI3.2

Abstract Unavailable

YI3.3

Abstract Unavailable

YI3.4

Abstract Unavailable

YI3.5

Abstract Unavailable

Henning Andersen Award Winners

HA1

Development of Anorexigenic and Glucoregulatory Chimeric Peptides

Christian Roth[1], *Kylie S. Chichura*[2], *Ian Sweet*[3], *Clinton Elfers*[1], *Therese Salameh*[1], *Varun Kamat*[3], *Brandon Milliken*[2], *Robert Doyle*[2]

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Designing monomeric dual or triple agonists based on glucagon-like peptide (GLP)-1 with glucagon, and/or glucose-dependent insulinotropic polypeptide (GIP) are promising novel approaches for anti-obesity drugs tackling different weight-regulatory pathways, albeit such developments continue to suffer from significant gastrointestinal illnesses. Our own studies have focused instead on the combination of GLP-1 receptor agonists (GLP-1RAs) with neuropeptide Y1- and Y2-receptor (Y1-R/Y2-R) agonists based on peptide YY (PYY). Our current lead is the first triagonist of GLP-1R, Y1-R and Y2-R (GEP44), which is a chimeric peptide, comprised of amino acid residues from both the GLP-1RA exendin-4 (Ex-4) and peptide YY (PYY). GEP44 showed potent anorectic effects in lean and diet-induced obese (DIO) rats with up to 80 % reduction of food intake and stronger reductions of body weight than known GLP-1RAs, including Ex-4 and liraglutide (LIRA), and without triggering nausea as assessed by kaolin intake and behavioral scoring. Recent experiments in DIO male rats (n=4-6 rats/group) demonstrate a more robust reduction of body weight, food intake, and conjunct reduction in blood glucose in response to GEP44 vs. equimolar LIRA (10 nmol/kg for 9 days, followed by 25 nmol/kg for 7 days). At the 25 nmol/kg/d dose, food intake was reduced by 62% (GEP44) vs. 25% (LIRA). At the end of the 16-d treatment, body weight reduction was -12.1% (GEP44) vs. 3.2% (LIRA) and mean fasting glucose levels were 86 (GEP44) vs. 109 (LIRA) vs. 110 mg/dL (vehicle), $p<0.01$ GEP44 vs. LIRA. Body weight changes in GEP44 treated animals were similar to pair-fed vehicle treated animals, suggesting that the strong reduction of body weight in response to GEP44 is related to reduction in food intake and not to changes in energy expenditure. We have also evaluated glucose-stimulated insulin secretion rate (ISR) by rat and human pancreatic islets in response to GEP44 in vitro. ISR was significantly increased in response to GEP44 and Ex-4, but not to PYY1-36 or PYY3-36. We also tested glucose uptake in response to these peptides in skeletal muscle cells. GEP44 and PYY1-36, but not Ex-4, increased glucose uptake into muscle. In conclusion, GEP44 is a strong anorectic peptide which leads to strong reduction of body weight devoid of nausea. In addition, it has glucoregulatory properties as evidenced by increased islet ISR and muscle glucose uptake. GEP44 is a promising chimeric peptide which may become suitable for treatment of obesity and type 2 diabetes.

HA2

The genetic landscape of children born small for gestational age with persistent short stature

Ledjona Toni, *Lukas Plachy*, *Petra Dusatkova*, *Shenali Anne Amaratunga*, *Lenka Elblova*, *Zdenek Sumnik*, *Stanislava Kolouskova*, *Marta Snajderova*, *Barbora Obermannova*, *Stepanka Pruhova*, *Jan Lebl*

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Background: Approximately 10% of children born small for gestational age (SGA) fail to catch-up nd remain short (SGA-SS). Although several mechanisms causing SGA-SS have been elucidated, the primary cause remains speculative in most cases.

Aim: To decipher genetic causes of SGA-SS defined as birth length and/or birth weight <-2 SD for gestational age, and body height <-2.5 SD after the 3rd year of life within a large single-center cohort.

Methods and Patients: In 208/304 children with SGA-SS treated with GH at our center within years 2008 – 2018 triplet DNA samples (child and both parents) were available for genetic testing. Targeted genetic examination (karyotype/FISH/MLPA/Sanger sequencing) was performed in case of clinical suspicion of a specific genetic condition (42/208). The remaining patients were examined using next-generation sequencing methods (whole exome sequencing or targeted panel of 399 growth-related genes). Identified genetic variants were classified using American College of Genetics and Genomics (ACMG) guidelines.

Results: Genetic etiology of SGA-SS was elucidated in 79/208 children (38%). Of these, 18/79 (23%) carried (likely) pathogenic gene variants affecting components of cartilaginous matrix (ACAN [4], COL11A1 [2], COL1A1, COL1A2, COL2A1 [5], COL9A2, COL9A1, FLNB [2], MATN3), 8/79 (10%) had impaired paracrine chondrocyte regulation (FGFR3 [2], FGFR2, NPR2 [4], SOX9), 10/79 (13%) carried SHOX gene defects, in 13/79 (16%) gene variants affecting other components of intracellular regulation and signaling were revealed (CDC42, KMT2D, LMNA, NSD1, PTPN11 [2], PROKR2, SRCAP, SON, SOS1 [2], TLK2, THRA), 11/79 (14%) had variants affecting abnormal regulation of pituitary development and/or of GH-IGF-1 axis (GHSR, HGMA2, IGFALS, IGF1R [in three], LHX4, OTX2, STAT3, POU1F1, PTCH1), 13/79 (16%) had Silver-Russell syndrome (11p15 [in eight], UPD7) and 6/79 (7%) additional miscellaneous single-gene or chromosomal aberrations (THRA, TRHR, TRPS1, RAI1, chromosomal microdeletions and/or translocations).

Conclusions: High percentage of pathogenic variants found in our cohort sheds a new light on the etiology of short stature in children born SGA-SS. The spectrum of genes in which we have detected pathogenic variants reflects the complex regulation of growth, with the central role of the growth plate, and with substantial contributions from the GH-IGF-1 axis and from the fundamental processes of intracellular regulation and signaling.

Free Communications

Thyroid

FC1.1

Neonatal TSH screening for congenital hypothyroidism: before discharge or at home?

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In Belgium, neonatal TSH screening for congenital hypothyroidism has been performed between day 3 and 5 of life since the late seventies. In January 2015, a policy of early discharge of healthy neonates was implemented so that the neonatal screening strategy had to be adapted. Between January 2015 and September 2019, dried blood spot sampling was mostly collected at home AFTER discharge at 72 hours of life (Newborn Screening Strategy 1 (NBS1)). After October 2019, sampling was mostly collected in hospital BEFORE discharge at 48 hours of life (Newborn Screening Strategy 2 (NBS2)).

Our primary aim was to compare neonatal TSH screening results with sampling at 48 hours and at 72 hours of life. Our secondary aim was to compare home and hospital sampling in terms of screening efficiency.

This retrospective study includes live births ≥ 37 weeks of gestation, screened by the U.L.B. Newborn Screening Center between January 2019 and December 2021. We compared the characteristics of newborns screened < 72h to those screened ≥72 h. We also compared TSH screening results obtained with NBS1 and NBS2. The whole blood TSH cut-off value to request a second DBS sample is determined using the p99.5 calculated on the newborn population.

A total of 54,700 newborns were included. The median TSH at various time points is shown in the Table.

The false positive rate of NBS was similar: 0.12% in newborns screened <72h and 0.13% in newborns screened ≥72h. As expected, the age at receipt of NBS result was younger with NBS2 (7.0 versus 5.8 days, p<0.05). NBS2 resulted in a slightly higher screening coverage (calculated on 14911 Births) (99.9% versus 99.7%, p 0,2328).

Full term newborn TSH screening performed before discharge as soon as 48 h of life is a valid strategy as it does not increase the false positive and recall rates and allows for a better screening coverage. The same TSH cut-off can be used for screening at 48 and 72 h of life. Sampling at home entails increased costs that need to be factored in.

FC1.2

Comorbidity in congenital hypothyroidism – A nationwide population-based cohort study

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Aim of the Study: The aim of this nationwide population-based register study was to investigate the incidence of congenital malformations, neonatal and chronic comorbidities, and the use of prescribed drugs in patients with primary congenital hypothyroidism (CH).

Methods: The study cohort and matched controls were identified from national population-based registers in Finland (The Social Insurance Institution of Finland and The Finnish Institute for Health and Welfare).

All diagnoses from birth until the end of 2018 were collected from the Care Register for subjects born between 1996 and 2018 (cases = 484, controls = 966). Subject-specific prescription drug purchases were identified from The Prescription Register from birth until the end of 2017. The use of antipsychotics and antidepressants was assessed for subjects born between 1987 and 2017 (cases = 566, controls = 1 130).

Results: Newborns with CH were small for gestational age more often than their controls (5.2 %, and 2.2 %, respectively, p = 0.002). Neonatal jaundice (12.0 %, and 3.2 %, p < 0.001), hypoglycemia (8.9 %, and 3.7 %, p < 0.001), metabolic acidemia (3.7 %, and 1.1 %, p = 0.001), and respiratory distress (6.2 %, and 2.3 %, p < 0.001) were diagnosed significantly more often in newborns with CH than in their controls.

Congenital malformations or chromosomal abnormalities were diagnosed in 90/484 CH patients and in 78/966 controls (18.6 %, and 8.1 %, respectively, p < 0.001). The most affected extrathyroidal organs were the circulatory system (8.1 % in CH cases and 3.4 % in controls, p < 0.001) and the musculoskeletal system (5.0 % in CH cases, and 2.4 % in controls, p = 0.009).

Age in hours	0-24 h n = 155	24-48h n = 799	48-72 h n = 23663	72-120 h n = 29097	120-240 h n = 199	>240 h n = 184
TSH mu/L median (IQR)-p99,5	3.00 (5.80) - 43.72	1.80 (1.70) - 8.40	1.50 (1.50) - 7.50	1.20 (1.27) - 7.30	1.10 (1.10) - 7.68	1.20 (1.10) - 6.13

The cumulative incidences of epilepsy (2.3 % in CH patients and 0.3 % in controls, $p < 0.001$), hearing loss (4.3 %, and 0.6 %, respectively, $p < 0.001$), disorders in psychological development (14 %, and 4.8 %, $p < 0.001$), and mental retardation (3.3 %, and 0.4 %, $p < 0.001$) were significantly higher among CH patients as compared to their controls.

ADHD medication was used more frequently by CH patients than their controls ($p = 0.032$) but antidepressant and antipsychotic use was similar.

Conclusions: CH patients have more neonatal morbidity and congenital malformations than their matched controls. The cumulative incidence of neurological diseases, particularly disorders of psychological development, is higher in CH patients. However, our results do not support the existence of severe psychiatric comorbidity.

FC1.3

Meta-analysis of DNA methylation datasets identifies aberrant DNA methylation of thyroid function and development genes in Down syndrome

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Down syndrome (DS) is characterized by a higher incidence of congenital hypothyroidism (CH) and a high prevalence of subclinical hypothyroidism (SH) early in life. Children and adults with DS have an increased risk of developing autoimmune thyroid disease, however CH and early SH cannot be explained by thyroid autoimmunity. The etiology of CH and early SH in DS remains to be elucidated.

Considering the recently discovered genome-wide transcriptional and epigenetic alterations in DS, we hypothesized that CH and early SH might be caused by promoter region hypermethylation of genes involved in thyroid gland function or development, which in general is associated with transcriptional downregulation.

To investigate this, we performed linear regression on blood DNA methylation (DNAm) profiles of DS and non-DS subjects, focusing on thyroid-related genes. DNAm profiles were extracted from four independent Illumina array-based datasets, including 252 DS subjects and 519 non-DS subjects, spanning three age groups: newborns (n=650), toddlers (n=34) and adolescents/adults (n=87). We replicated the findings of the largest dataset in an aggregate validation dataset (composed of the remaining three datasets) and performed a meta-analysis.

In the largest (discovery) dataset we found significant associations for DS in 18 thyroid-related genes. 21 of 30 differentially methylated positions (DMPs) were replicated in the validation set. The meta-analysis identified 31 DMPs with concordant methylation patterns across the datasets, and two differentially methylated regions (DMRs). Of these DMPs, 27 were hypomethylated and promoter-associated. The difference in mean methylation between cases and controls of these hypomethylated thyroid-related DMPs decreased with age (ANOVA P value = < 0.0001).

Contrary to our hypothesis, we mainly found promoter region hypomethylation, suggesting transcriptional upregulation of thyroid-related genes. According to these data, we can infer that CH and early SH in DS are probably not caused by differential methylation/expression of thyroid function and development genes.

Since epigenetic regulation is dynamic by definition, we may speculate that the identified changes to DNAm of thyroid-related genes could be a rescue phenomenon to ameliorate the phenotype. This hypothesis aligns with the decreasing methylation difference of thyroid-related genes with age. The prevalence of early (non-autoimmune) SH declines with age, so hypothetically, the need for epigenetic upregulation of thyroid-related genes also diminishes. However, the etiology of CH and early SH in DS remains unknown. Focus of further research should be centered around obtaining and analyzing DS thyroid tissues and thyroid hormone target tissues, and age-matched controls, for (multi-)omics analyses.

FC1.4

Children at cardio-metabolic risk raise their circulating concentrations of TSH and free T3

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Introduction: Thyroid hormones regulate body composition and metabolism, and are among the key drivers of body growth and maturation. In children, associations of cardio-metabolic measures with the circulating prohormone thyroxine (T4) have been extensively studied, but not with active triiodothyronine (T3). In apparently healthy children, we studied whether circulating free T3 (fT3) [and its ratio with free T4 (fT3/fT4)] associates with cardio-metabolic measures at age 8 ± 2 years (baseline), and with the same measures approximately 4 years later (follow-up).

Methods: At baseline, the study cohort consisted of 600 apparently healthy school-age children (49% girls) and, at follow-up, of 271 children (52% girls). Circulating concentrations of TSH, fT3, and fT4 were measured, and cardio-metabolic risk was assessed by calculating BMI and by measuring waist circumference, visceral fat (by ultrasound), blood pressure and circulating HDL-cholesterol and triglyceride levels, and by deriving the HOMA-IR index.

Results: All children had TSH, fT3 and fT4 values within euthyroid range. Circulating fT3 – and also fT3/fT4 – associated positively with BMI, waist circumference, visceral fat, blood pressure, triglycerides and HOMA-IR index, not only at baseline but also at follow-up (all $p<0.05$). Multivariate regression analysis, adjusting for sex and for baseline age and BMI, showed independent longitudinal associations between baseline fT3 and follow-up BMI, systolic blood pressure, pulse pressure, HOMA-IR and HDL-to-HOMA-IR ratio (adjusted R2 model from 0.216 to 0.484). Further analysis by tertile of baseline TSH showed that the longitudinal associations between baseline fT3 and follow-up BMI, systolic blood pressure, pulse pressure, HOMA-IR and HDL-to-HOMA-IR ratio were more robust in children with a TSH level in the upper tertile, who were also characterized as being heavier, and having higher fT3 and higher fT3/fT4 than the rest of the children.

Conclusion: Apparently healthy children at higher cardio-metabolic risk were found to raise – still within normal range – their circulating TSH and free T3 concentrations, conceivably to accelerate their tempo of growth and maturation, in a homeostatic attempt to reduce such risk.

FC1.5

Subclinical Hypothyroidism and Incident Depression in Adolescents and Young Adults: Results from a Nationwide Representative Prospective Study

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Background: While the relationship between subclinical hypothyroidism and major depressive disorder (MDD) has been studied in adults in cross-sectional and prospective population-based studies, this has not yet been done in adolescents. However, since thyroid function and MDD risk are subjected to maturational processes and ramifications of illness duration over the life span, these findings may not readily transfer to adolescents.

Methods: The relationship between subclinical hypothyroidism and MDD was studied in a representative subsample of the nationwide KIGGS ('The German Health Interview and Examination Survey for Children and Adolescents) survey. A total of 4,118 adolescents were examined over a median period of 6 years, and data were analyzed by a logistic regression approach accounting for important covariates related to thyroid function and/or MDD risk. The same approach was chosen to investigate the relationship between quartiles of TSH and fT4 levels and incident MDD in euthyroid participants to broaden the focus on the relationship between thyroid hormone levels and MDD in a dose–response manner.

Results: During the observation period, 121 cases of MDD were reported. There was no association between subclinical hypothyroidism and MDD when comparing 111 adolescents with subclinical hypothyroidism to 4,007 euthyroid adolescents, representative of approximately 106,000 and 3,610,000 adolescents from the general pediatric population, respectively. This also applied when studying the relationship between quartiles of TSH and fT4 levels and MDD in euthyroid participants.

Conclusions: Consistent with findings in adults, there is no association between subclinical hypothyroidism orquartiles of TSH and fT4 levels in the normal range and MDD in adolescents, despite potential age-related differences regarding thyroid function and MDD risk.

FC1.6

Thyroid complications after haemopoietic stem cell transplantation in children and adolescents

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Background: Haemopoietic stem cell transplantation (HSCT) has become the treatment of choice for many inherited and acquired pediatric disorders. Cure is not without consequences, and HSCT survivors are at risk of early mortality and developing endocrine complications. Thyroid is highly susceptible to damage from the conditioning therapy for HSCT. The aim of this study is to evaluate the percentage and risk factors of thyroid dysfunction and risk factors of it in allografted children in a single center.

Patients and Methods: This is an observational, retrospective, monocentric cohort study. We included 194 patients (58.6% boys) who survived at least one year after allogenic bone marrow transplantation (BMT) between January 1, 1995, and December 31, 2020. Selected conditioning regimens depended upon diagnosis and protocols active at the time of transplantation. Some patients received irradiation, either CNS prophylaxis, or total body irradiation (TBI). For each patient, thyroid function was evaluated by thyroid-stimulating hormone (TSH), free thyroxine (fT4) and thyroid autoantibodies tests. Furthermore, we analyzed all ultrasound assessments performed during follow-up. Descriptive statistics were performed. Univariate and multivariate logistic models were used to examine the association of the above-mentioned factors with hypothyroidism. Class separation capacity was tested by AUROC (Area Under the Receiver Operating Characteristics).

Results: The mean age at diagnosis was 7.51 years ±0.46 while the mean age at BMT was 7.58 ±0.36. The median follow up was 4.83 years (Interquartile Range: 6.8). We report 33 cases of hypothyroidism (17,7%) for the whole group of patients, 4 after TBI. Factors associated with the onset of thyroid dysfunction were male sex [OR: 3.394, 95% CI(1.328-8.677)], the initial diagnosis of malignancy [OR: 3.450, 95% CI (1.647-7.225)], irradiation therapy [OR: 6.824, 95% CI (3.193-14.584)] and the years after HSCT [OR: 1.147, 95% CI (1.046-1.258)] in the univariate models. Male sex, [OR: 3.005, 95% CI (1.145-7.890)], irradiation, [OR: 2.876, 95% CI (1.120-7.386)], and years after HSCT [OR: 1.148,95% CI (1.042-1.266)], remained also significant in the multivariate model that presents a good class separation capacity [AUC=72%, 95% CI(61.4%-82.4%)]. 17 patients presented with ultrasound anomalies during follow-up. We found 2 cases of secondary thyroid cancer, both among children who had TBI.

Conclusion: Thyroid disorders are common after allogenic bone marrow transplantation in children. Patients who were treated for malignancy and those who have received radiotherapy are at higher risk. A careful follow-up is recommended, in order to detect, prevent, and treat thyroid dysfunction before overt symptoms occur.

Bone, Growth Plate and Mineral Metabolism

FC2.1

Derivation of local reference intervals for serum phosphate to improve diagnosis of Hypophosphataemic rickets

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Background: Hypophosphataemic rickets is a rare, and challenging condition to diagnose as the biochemical and radiological features are subtle compared with the more common calcipaenic rickets. Retrospective review of 4yr-old girl with PHEX mutation initially managed as Blount's disease with surgery showed low (0.93mmol/L), but within reference interval phosphate levels at initial presentation which caused some diagnostic uncertainty. Paediatric phosphate reference intervals in use at the time were from UK Pathology Harmony Group (PHG). The aim of the study was to generate indirect reference intervals using local phosphate data and compare these to both PHG and published direct reference intervals in order to determine more appropriate reference intervals and potentially improve the diagnosis of hypophosphatemic rickets.

Methods: Using open source software we applied two different indirect statistical methods – Hoffman (H) and Bhattacharya (B) to generate reference intervals on anonymised data collected during the clinical care of patients. A total of 7094 inpatient, outpatient and community phosphate results were used, all of which had been generated between Jan 2020 and April 2021 using Siemens ADVIA 2400 analysers. We used the same age groupings as published paediatric phosphate reference interval data from the Canadian Laboratory Initiative on Paediatric Reference Limits (CALIPER) group, which had been generated in equivalent laboratory instrumentation.

Results: The two different indirect methods generated very similar reference intervals at each age group. Direct comparison of these locally generated reference intervals with PHG and CALIPER

showed that of the 6 reference age groups (<1 month, 1 month-1yr, 1-5yr, 5-13yr, 13-16yr and 16-18 yr), PHG, CALIPER and locally generated reference intervals were very similar apart from 1-5yr and 5-13 yr. In these age groups, the lower limit from the PHG was significantly lower than the published CALIPER lower limit; 0.9 vs 1.42mmol/L for 1-5yrs and 0.9 vs 1.29mmol/L for 5-13yr. The indirect methods provided lower limits for these age groups that were intermediate between PHG and CALIPER ranges; 1.17 (H) and 1.21 (B) mmol/L for age 1-5yr and 1.08 (H) and 1.09 (B) mmol/L for age 5-13yr.

Conclusion: Indirect methods can be used to generate paediatric reference intervals from routinely collected local laboratory data. These reference intervals can be used to verify published direct reference intervals or to generate more appropriate intervals for the local population.

Keywords: Hypophosphataemic rickets, phosphate

FC2.2

Final heights in 398 patients with X-linked hypophosphatemia (XLH) over the last decades in France, a surrogate marker of improved disease management. Study of a large cohort of XLH patients born between 1950 and 2006

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Introduction: XLH is caused by mutations in *PHEX* leading to increased FGF23 levels, phosphate wasting, and impaired endogenous calcitriol synthesis. Affected patients present with rickets and diminished growth velocity during childhood, and osteomalacia and short stature in adulthood. Adult height is linked with health within and across generations suggesting that adult height may be a potential tool for monitoring health conditions, e.g., XLH.

Methods: Observational study based on medical records of final heights in men and women with XLH grouped according to their birth year, 1950-1975, 1976-2000, and 2001-2006. XLH was assessed by biochemistry and X-linked inheritance and/or a mutation in *PHEX*. Final height was defined by height reached after 18 years or 16 years and growth velocity <2cm/year. Pearson's correlation test (R software) was used to evaluate the evolution of final heights. Comparison with healthy peers was made using WHO references.

Results: Final heights from 398 XLH patients were recorded (278 females). Patients born between 1950 and 1975 (n=127, mean age 26.1 yrs at study) have a mean final height of -2.31 (SD 1.11); patients born between 1976 and 2000 (n=193, mean age 20.6 yrs) have a mean final height of -1.63 (SD 1.13) and patients born between 2001 and 2006 (n=78, mean age 17.3 yrs) have a mean final height of -1.34 (SD 0.87). There is a significant increase in mean final heights between birth year groups for men and women ($p=3.8 \times 10^{-14}$).

In addition, the mean final height in men [-2.08 (SD 1.18), i.e., 160.5 cm] is significantly smaller than that of women with XLH [-1.70 (SD 1.12), i.e., 151.7 cm], (p=0.002).

Conclusion: Our study shows that final height can be used to monitor global health in XLH. Similar to other studies, our results suggest that, for XLH, males may display more severe disease than females. More importantly, we show that the final height in patients with XLH has significantly improved over the last decades in France which very likely reflects better disease management. Final height increased the most for patients born before 1975 and between 1975 and 2006. In fact, vitamin D analogs were added to phosphate supplements for the treatment of XLH in the late 1970s; the organization of care including multidisciplinary clinics, and reference centers for rare diseases were developed in France in the early 2000s. Another 10-15 years will be necessary to evaluate the benefit of burosumab on final heights.

FC2.3

First interim analysis of the International X-Linked Hypophosphataemia (XLH) Registry: Baseline characteristics of children treated with conventional therapy and burosumab

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Objectives: X-linked hypophosphataemia (XLH) is a rare, hereditary phosphate-wasting disorder characterised by excessive activity of fibroblast growth factor 23. The International XLH Registry (NCT03193476) (initiated in August 2017, target 1,200 children and adults with XLH, running for 10 years) will provide information on the natural history of XLH and impact of treatment on patient outcomes. This report summarises baseline data from the first interim analysis from paediatric participants (age <18y), according to the treatments they were receiving at study entry.

Methods: At the time of analysis (Last Patient In: 30/11/2020; Database Lock: 29/03/2021), participants diagnosed with XLH were enrolled from 81 hospital sites in 16 countries. Baseline parameters included demographics, clinical presentation data, and medical and treatment history.

Results: Overall, 360 children were included in this interim analysis; 61.7% female. Treatment data at entry were available for the majority of participants (281/360; 78.1%): 58.7% were receiving burosumab (BUR) (165/281); 40.6% conventional therapy (CT) (oral phosphate and active vitamin D) (114/281); 0.7% reported no treatment (2/281). Age distribution of children according to treatment at entry: BUR (n=165) : n=0, <1y; n=31, 1–<5y; n=78, 5–<12y; n=56, 12–<18y; mean (SD) age 9.60y (4.20); CT (n=114) : n=5, <1y; n=23, 1–<5y; n=45, 5–<12y; n=41 12–<18y; mean (SD) age 9.34y (5.18). Mean (SD) time from first symptoms to diagnosis 1.01y (1.87) in BUR group and 0.95y (1.90) in CT group.

Retrospective XLH clinical data were available at entry for 115/165 children in BUR group and 81/114 in CT group. Craniosynostosis was reported in 27.0% (31/115) children in BUR group and 14.8% (12/81) children in CT group. In children with renal clinical conditions, nephrocalcinosis was reported in 100% (39/39) children in the BUR group and 100% (15/15) children in the CT group. In children with dental conditions, tooth abscess was reported in 80.4% (41/51) in the BUR group and 86.7% (26/30) in the CT group.

Conclusions: This is the largest data set of children with XLH collected to date. The mean time to diagnosis was 6–7 years; increased disease awareness of XLH may improve and shorten the diagnostic journey. Children receiving BUR at study entry tended to be slightly older than those receiving CT and reported more craniosynostosis. This may reflect triaging of children XLH with more severe symptoms to receive this new treatment modality.

Authors acknowledge the contribution of all the International XLH Registry Steering Committee members.

FC2.4

Patient-reported outcomes from a randomized open-label phase 3 trial comparing burosumab versus conventional therapy in children with X-linked hypophosphatemia: results from the 24-week treatment extension period

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In a randomized open-label phase 3 trial in 62 children (1–12 years) with X-linked hypophosphatemia (XLH) (NCT 02915705), switching from conventional therapy (oral phosphate plus active vitamin D) to burosumab, a monoclonal antibody targeting fibroblast growth factor 23, significantly improved serum phosphate concentration, rickets, lower-extremity deformities, growth, mobility, and patient-reported outcomes (PROs) at 64 weeks. Children in Europe, USA, Canada, and Australia who completed 64 weeks' treatment could continue to receive burosumab in the extension period (burosumab continuation group) or cross over from conventional therapy to burosumab (crossover group) to 124 weeks. A Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaire was used in children aged ≥5 years to measure Pain Interference, Physical Function Mobility, and Fatigue; health-related quality of life was measured using the SF-10 Health Survey for Children (n=35). Here, we describe changes in PROs from baseline to weeks 64 and 88, and report whether the 3-point minimal important difference (MID) was reached for PROMIS domains (Thissen et al., 2016; PMID 26118768). The mean change from baseline exceeded the MID for Pain Interference at weeks 64 and 88 and for Fatigue at week 64 in the burosumab continuation group, and for Pain Interference and Fatigue at week 88 in the crossover group. Similar improvements in SF-10 Physical Health were seen baseline to week 64 in the burosumab continuation group, and week 64 to 88 in the cross-over group. SF-10 Psychosocial Health changed little in either group at the two timepoints.

Treatment with burosumab improved Pain Interference and Fatigue beyond the MID in children with XLH who switched from conventional therapy to receive 24 weeks of burosumab. Improvements were also maintained in children who received an additional 24 weeks' burosumab treatment.

Change from baseline in PROMIS and SF-10 scores

Instrument	Domain	Week	Burosumab Continuation group (n=15)	Crossover group (n=20)
PROMIS	Pain Interference	64[a]	−3.8 (10.03)	−0.5 (7.14)
		88[b]	−8.2 (10.70)	−3.3 (9.61)
	Physical Function Mobility	64[a]	2.8 (6.96)	0.9 (4.41)
		88[b]	2.7 (7.21)	2.7 (5.13)
	Fatigue	64[a]	−3.6 (8.97)	−2.1 (8.36)
		88[b]	−2.7 (9.89)	−4.9 (8.80)
SF-10 Health Survey for Children	Physical Health	64[a]	6.1 (8.47)	0.3 (10.81)
		88[b]	4.8 (10.62)	7.0 (8.70)
	Psychosocial Health	64[a]	1.3 (8.18)	1.2 (6.24)
		88[b]	1.2 (9.50)	2.7 (7.92)

Values are mean (SD); bold indicates that PROMIS-specific MID was reached. Negative change scores indicate improved Pain Interference and Fatigue, positive change scores indicate improved Physical Function Mobility and SF-10 scores.
[a]n=35
[b]n=26

FC2.5

Effects of burosumab treatment on mineral homeostasis in children and adolescents with X-linked hypophosphatemia: lessons from the German XLH Registry

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Introduction: Burosumab was approved for treatment of pediatric patients with X-linked hypophosphatemia (XLH). However, data on its efficacy in adolescents (age > 12 years) and in real-world settings are lacking.

Material and Methods: Here we assess the effects of 12 months burosumab treatment on mineral homeostasis in 77 pediatric XLH patients (50 children, 27 adolescents) enrolled in the German XLH Registry. Age and sex related SD scores (SDS) were calculated for serum phosphate and alkaline phosphatase (ALP) levels, and renal tubular reabsorption of phosphate per glomerular filtration rate (TmP/GFR).

Results: At baseline, all patients presented with profound hypophosphatemia (-4.5 SDS), reduced TmP/GFR (-6.5 SDS), and elevated ALP (2.7 SDS, each p<0.001 versus healthy children) suggesting persisting rickets despite long-term therapy with oral phosphate and active vitamin D. Burosumab treatment resulted in rapid increases in mean serum phosphate and TmP/GFR by approx. 0.3 mmol/l amounting to -2.2 SDS and -2.5 SDS at 12 months, respectively (each p<0.001 versus baseline). This was paralleled by a continuous decrease in serum ALP (1.3 SDS, p<0.001 versus baseline). Serum phosphate, TmP/GFR, and ALP values were normalized in approximately 40%, 30% and 80% of patients, respectively. Two patients had transient hyperphosphatemia due to a dosing error. At 12 months, the median burosumab dosage amounted to 0.8 mg/kg (range 0.6-1.2). Serum phosphate levels at 12 months were comparable between children (-2.3 SDS) and adolescents (-2.1 SDS) and associated with parathyroid hormone (PTH) levels. Serum ALP z-scores were associated with PTH levels in adolescents but not in children.

Conclusions: In this real world setting 12 months burosumab treatment was effective to normalize serum ALP levels in children and adolescents with XLH suggesting healing of rickets despite persisting mild hypophosphatemia in about half of patients. Elevated PTH levels are a risk factor for failure to normalize mineral homeostasis.

FC2.6

Pseudohypoparathyroidism Type 1A (PHP1A): Growth patterns under growth hormone therapy for short stature

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Background: Pseudohypoparathyroidism 1A, newly classified as inactivating PTH/PTHrP signaling disorder type 2 (iPPSD2), is defined by resistance to parathyroid hormone, short stature and early-onset obesity. Short stature is caused by skeletal dysplasia and additionally, in some cases, also by the coexistence of growth hormone deficiency, as other hormonal resistances might be present (e.g. thyroid-stimulating hormone, growth hormone releasing hormone (GHRH), gonadotropins and calcitonin). Patients with iPPSD2 are often born with moderate intrauterine growth retardation. Hanna et al. (2018) showed that the average final height of patients lies <-2 SDS. Literature data on the effect of recombinant human growth hormone (rhGH) therapy for short stature in PHP1A children are sparse and there is no evidence regarding its influence on final height.

Objectives: Our multicentric, observational study describes growth patterns in PHP1A patients treated with rhGH compared to untreated controls.

Methods: We recruited 190 PHP1A patients from France, Italy and Spain. Twenty-six participants received rhGH for at least one year during the observed period, the rest did not. Birth history, height, weight and body mass index (BMI) at different time points, final height and pubertal stage the latter only during rhGH, were documented. We have analyzed the therapeutic effect of rhGH on final height on those patients, where pre-pubertal as well as final height measurements were available, by adjusting the comparison of rhGH-treated with untreated individuals for differences in mean pre-pubertal height standard deviation score (SDS) using a linear regression model.

Results: RhGH was started rather late (median age 9 years, range 2 to 14). In this group, 25% were born small for gestational age, comparable with the percentage seen in the control group (26%). Final height was available for 9/22 of rhGH-treated and for 45/164 of the participants that were not treated.

We could show a gain in height SDS (mean± SD) after 1 year of rhGH (0.63± 0.52), as well as after 3 years of treatment (1.34±0.97).

We could also show a clear beneficial impact of rhGH on final height: the difference in final height SDS between treated and untreated participants was of 1.36 (CI 0.59 - 2.14, p<0.002). BMI SDS did not vary between the two groups.

Conclusion: We show that rhGh treatment of iPPSD2 patients with short stature improves height and final height, but we recognize the need for more studies with data on final height.

Early Life and Multisystem Endocrinology

FC3.1

HYPO-CHEAT: Personalised Technology Reduces Real-World Hypoglycaemia by 25%

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Background and Aims: Hypoglycaemia is a life-threatening risk for many patients and prevention is individualised and complex. Continuous Glucose Monitoring (CGM) shows promise but current accuracy is insufficient for acute hypoglycaemia detection and data review services are complex and generic. Machine Learning is increasingly used but ignores weekly hypoglycaemia patterns and behaviour change and thus has demonstrated no real-world reduction in hypoglycaemia. Children with congenital hyperinsulinism (CHI) have recurrent hypoglycaemia and we developed **HYPO-CHEAT** (**HY**poglycaemia-**P**revention-thr**O**ugh-**C**gm-**HE**atmap-**A**ssisted-**T**echnology): a personalised technology to proactively prevent hypoglycaemia for this underserved group.

Methods: HYPO-CHEAT automatically undertakes iterative analysis of individual CGM data and generates personalised hypoglycaemia heatmaps to allow actionable visualisation of high-risk periods throughout the week. The simple to use output is accompanied by personalised targets for reflection and is specifically designed to change patient behaviours and proactively prevent hypoglycaemia (glucose <3.5mmol/L). Ten patients with CHI used a blinded CGM for four weeks to establish baseline time below range (TBR). Devices were then unblinded for four weeks, at the end of which patients and families used HYPO-CHEAT. CGM was subsequently re-blinded for four weeks.

Results: Six patients demonstrated baseline hypoglycaemia (all TBR >1.5%), while four showed negligible hypoglycaemia (mean TBR 0.2%). In those with baseline hypoglycaemia, TBR improved from a mean of 7.1% to 4.5% when devices were unblinded. Proprietary CGM software (Dexcom Clarity) failed to identify hypoglycaemia patterns in any patient. By contrast, HYPO-CHEAT identified weekly hypoglycaemia patterns in all patients. Furthermore, families all identified specific behaviours contributing to hypoglycaemia "hotspots".

After using HYPO-CHEAT, families did 70% more fingerpricks within suggested targets and reduced targeted TBR by 67%, despite the removal of real-time data through device re-blinding. By concentrating on personalised hypoglycaemia hotspots and associated behaviours, families reduced total TBR by 25% from baseline (5.4%). For those without initial hypoglycaemia and thus no use for HYPO-CHEAT, TBR increased from 0.2% at baseline to 3.2% when reblinded, strengthening the associated between HYPO-CHEAT and a reduction in TBR.

Patient feedback was positive and identified the utility of HYPO-CHEAT to change fingerprick behaviour and reduce hypoglycaemia.

Conclusions: HYPO-CHEAT's automated provision of personalised, hypoglycaemia heatmaps facilitated patient reflection and behaviour change to target fingerpricks and reduce total and targeted TBR even when CGM was blinded. HYPO-CHEAT offers a highly effective and immediately available personalised technology to proactively prevent hypoglycaemia and empower self-care. As CGM is not required after the initial four-week period, burden and costs are minimised.

FC3.2

Results from a Global, Multi-Center, Phase 2b Study (RIZE) in Congenital Hyperinsulinism: Characterization of a High Unmet Treatment Need and Glycemic Response to RZ358

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Background: Congenital Hyperinsulinism (CHI) is the most frequent cause of severe, persistent hypoglycemia in children. Persistent hypoglycemia places patients at risk for adverse clinical outcomes, and current guidelines recommend maintaining plasma glucose >3.9mmol/L. CHI patients often have substantial, residual hypoglycemia and fail to meet treatment goals with currently available standard of care (SOC) therapies. In this study, we aimed to characterize the demographics, disease history, and glycemic control by CGM and blood glucometer (BGM) before and after intervention with RZ358 (negative allosteric modulator of the insulin receptor) in CHI patients on SOC.

Methods: RZ358-606 (RIZE) was an open-label study (30-minute RZ358 IV infusion given biweekly for 8 weeks) conducted in CHI patients (4 sequential dose cohorts, 3-9mg/kg, 3-8 patients each) ages 2-45 years. Patients' history and extent of hypoglycemia on SOC by CGM [DexcomG6] and BGM were obtained.

Results: 23 patients (13M/10F; mean age 6.7y [2-22y]; 48% kATP mutations) were enrolled, of whom 16 (70%) had seizure

Table 1. Response Rates to RZ358 at Clinically Relevant Hypoglycemia Correction Thresholds

Hypoglycemia Correction Threshold	3mg/kg (n=4)	6mg/kg (n=8)	9mg/kg (n=7)	Titrate 3-9mg/kg (n=3)	RZ358 Pooled (n=22)
Responders N(%)					
≥25%					
Severe (<2.8mmol/L)	3(75%)	7(88%)	7(100%)	2(67%)	19(86%)
Overall (<3.9mmol/L)	3(75%)	7(88%)	7(100%)	3(100%)	20(91%)
≥50%					
Severe (<2.8mmol/L)	3(75%)	6(75%)	7(100%)	2(67%)	18(82%)
Overall (<3.9mmol/L)	1(25%)	7(88%)	7(100%)	1(33%)	16(73%)
≥75%					
Severe (<2.8mmol/L)	1(25%)	5(63%)	6(86%)	2(67%)	14(64%)
Overall (<3.9mmol/L)	1(25%)	3(38%)	5(71%)	1(33%)	10(45%)

history with five (22%) reporting seizures within past 12 months. Fourteen (61%) reported hospitalizations within past year due to CHI-related complications. At baseline, hypoglycemia (<3.9mmol/L) was present 23% [6-86%] of time by CGM with 16 [5-78] events/week by BGM on one or more SOC therapies (35% diazoxide, 56% somatostatin analogs,17% enteral feeds). RZ358 resulted in >50% improvement (p≤0.01) in hypoglycemia time and events across pooled doses, and up to ~75% improvement in hypoglycemia (p≤0.05) at the top doses. Patient response rates at clinically relevant hypoglycemia correction thresholds are shown in Table 1.

Conclusion: Additional therapeutic interventions demonstrating clinically-meaningful hypoglycemia correction beyond what is currently available could be expected to translate to better clinical outcomes. RZ358 was generally safe, well-tolerated and demonstrated clinically-relevant dose-response improvement in glycemic measures, particularly at planned phase 3 dose levels (6, 9mg/kg).

FC3.3

Targeting androgen production by post-translational regulation of CYP17A1 lyase activity

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Introduction: Over-production of androgens is linked to prostate cancer (PCa) in men and polycystic ovary syndrome (PCOS) in women. CYP17A1 produces dehydroepiandrosterone (DHEA), the precursor for androgens, via its 17,20 lyase activity. CYP17A1 lyase activity is regulated by the amount of P450 reductase for electron transfer; the presence of cytochrome b5; and protein phosphorylation. High androgen levels were linked to the phosphorylation of CYP17A1 protein through an unknown signaling pathway. Regulation of CYP17A1 activity via post-translational mechanisms can be used to specifically inhibit its lyase activity.

Aims: To study changes in CYP17A1 lyase activity via selective regulation of protein phosphorylation.

Methods: We analyzed transcriptomic databases to identify differentially expressed genes in PCa and PCOS. Then, a pathway analysis was performed to outline the links between genes differentially expressed in hyperandrogenic states. Human adenocarcinoma, NCI H295R cells were transfected with a selected number of cDNA for kinases and phosphatases. CYP17A1 lyase activity was determined using a tritiated water release assay. Functional assays were also performed in cells treated with kinase and phosphatase inhibitors to determine their impact on CYP17A1 activities.

Results: A significant decrease in DHEA production was observed in cells overexpressing protein phosphatase (PPP) 2CA, glycogen synthase kinase 3 (GSK3), and dual-specificity phosphatase 6 and 10 (DUSP6/10). However, there was no change in the activity with PPP1CB. An inhibitor of polo-like kinase 1 (PLK1) specifically altered the lyase activity of CYP17A1. Protein-protein interaction database (STRING) search revealed that PPP2CA indirectly interacts with ROCK1 and PLK1 which are predicted to be involved in the signaling pathway leading to phosphorylation of CYP17A1.

Discussion: The dynamics between phosphorylated and dephosphorylated states of proteins vary in the cell. The change in the lyase activity of CYP17A1 shows a dependence on the expression of different kinases and phosphatases. We showed that signaling events can regulate CYP17A1 lyase activity either directly or

indirectly through protein-protein interactions. Further analysis will establish whether PPP2CA, ROCK1, or PLK1 directly or indirectly interacts with CYP17A1.

Conclusion: Identification of missing links in the signaling pathways will help us understand mechanisms involved in the regulation of CYP17A1 activity during adrenarche as well as tumor progression in PCa. Selective inhibition of DHEA production by CYP17A1 via targeting phosphorylation mechanisms can be used for the development of drugs against PCa and PCOS with better efficacy and lesser side effects.

FC3.4

A common polymorphism in the human P450 reductase gene (POR) causes defective steroid and drug metabolism due to protein instability

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Cytochrome P450 oxidoreductase (POR) is the obligatory redox partner of steroid and drug-metabolizing cytochrome P450s located in the endoplasmic reticulum. Mutations in POR cause a broad range of disorders like congenital adrenal hyperplasia that may resemble bone malformations resembling Antley-Bixler syndrome. Genome sequencing studies have revealed the existence of a POR missense variant P228. We aimed to determine the detailed functional impact of POR variant P228L for its role in human metabolism.

We expressed human wild type and the P228L variant POR in bacteria and purified the proteins by Affinity Chromatography. We tested the stability of the proteins using fast proteolysis and performed kinetics assays of POR activities using small molecules substrates and cytochrome P450 proteins. POR (WT or P228L) were mixed with purified cytochrome P450 proteins and activities of cytochrome P450 proteins were assayed.

The single point mutation P228L had reduced thermal stability indicated by a lower melting point compared to the WT. In the kinetics studies, the rates of the reactions with P228L were considerably lower than the WT but the Km did not show substantial changes. We observed a decrease in the enzymatic activities of CYP3A5 and CYP2C9 of more than 40% with P228L form of POR compared to WT. Enzymes in liver matabolize many different steroids and drugs and their reduced function may affect several metabolic pathways. Metabolism of steroids by CYP17A1 was also affected, indicating disease-causing potential.

A single change in the amino acid sequence can affect protein stability and cause a severe reduction in POR activity. Molecular characterization of POR mutations is crucial to have a better understanding of the impact on the functionality of its redox Partners.

FC3.5

Evaluating the Utility of Bi-functional Degrader Molecules for Selective Inhibition of PDE4 In Acrodysostosis Type2

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Background: Acrodysostosis Type 2 (ACRDYS2) is a rare autosomal dominant skeletal dysplasia associated with intellectual disability and gain-of-function mutations in the phosphodiesterase type 4D gene (PDE4D) which, in turn, leads to a paucity of intracellular cAMP due to increased PDE4D activity. This increased PDE4 activity may be due to a greater existence of a mutant monomeric form of PDE4D. To date, the clinical use of PDE4 inhibitors in ACRDYS2 has been hampered by the possibility of off-target effects as there are 25 different PDE4 isoforms in humans.

Aim: To explore the utility of novel bi-functional PDE4 degrader compounds in ACRDYS2.

Methods: As PDE4 inhibitors act on all PDE4 isoforms as their catalytic sites are almost identical, a novel PDE4 bi-functional degrader was created by targeting the E3 ligase Cereblon to PDE4. To ensure selectivity, a PDE4 inhibitor was used to deliver the PROTAC complex and the ability of this complex to silence wild type and ACRDYS2 mutants of PDE4 isoforms was studied in over-expression studies using transiently transfected human embryonic kidney cells (HEK).

Results: The bi-functional degraders did not affect over-expressed, dimerised PDE4 longforms as they are sterically hindered from reaching their docking site within the PDE4 structure, however they degraded short-forms and mutated long-forms that cannot dimerise. The PDE4 degraders were effective at 10nM and worked well after 6 hours. Many of the ACRDYS2 mutations occur in the regions of the PDE4D enzyme that act as protein-protein interaction docking domains, which are vital for dimer formation. We have shown that our PDE4 degraders can target certain Acrodysostosis PDE4D mutants (e.g. T577A, PDE4D4), showing significant reductions in PDE4D protein expression via enhanced degradation. This degradation is channelled via the ubiquitin-proteosome system as it can be reversed using a proteosome inhibitor (Bortezomib). PDE4 proteolysis was induced by low nanomolar concentrations of the PDE4 degraders and was long lasting (no compensatory increases in PDE4 protein expression observed 96 hours after removal of degraders).

Conclusion: Our innovative approach represents an exciting novel therapeutic strategy for ACRDYS2 and possibly other cAMP-related developmental conditions.

FC3.6

The European Registries for Rare Endocrine Conditions (EuRRECa): the Use of a Core Registry for Collecting Common Data Elements and Clinician and Patient Reported Outcomes

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Introduction: The European Registries for Rare Endocrine Conditions (EuRRECa) was created in collaboration with the European Reference Network on Rare Endocrine Conditions (Endo-ERN), the European Society for Paediatric Endocrinology and the European Society of Endocrinology to support the needs of the endocrine community.

Aim: To describe the patient population and data entered in the EuRRECa Core Registry between June 2019 and December 2021.

Methods: Core Registry clinical contributors are invited to register new and existing cases of endocrine conditions seen in their centres. Diseases are organized in eight main condition groups. A core data set and a condition-specific data set collect information regarding demographics and diagnosis. Generic Patient-Reported Outcome Measures (PROMs) are available for clinicians and patients to complete. Patients can access the platform, view their data and complete outcomes.

Results: Nineteen centres from 12 countries, of which 17 are based in Europe, have registered cases. Of 19, 9 are Endo-ERN members. To date, a total of 644 cases have been added to the registry, 238 (36%) in the sex development and maturation condition group, 160 (24%) in the pituitary group, 153 (23%) in the calcium and phosphate group, 51 (8%) in the adrenal group, 24 (4%) in the thyroid group, 23 (3%) in the genetic endocrine tumour syndrome group, 10 (1%) in the growth and obesity group and 5 (0.7%) in the disorders of glucose and insulin metabolism. Of 664 cases, 183 (28%) were within the age range 0-9 years, 140 (22%) within 10-17 years and 321 (51%) over 18 years. The median age was 19 (0, 88) with 341(52%) cases over the age of 18 yrs. Of 664 cases, 442 (67%) were under active follow-up. One-hundred and thirteen (17%) had expressed an interest in using the patient platform; 76 (67%) had been sent an invitation to join the platform and of these, 18 (24%) activated their account. Thirty-two EQ-5D outcomes have been completed, 28 (87%) in cases of mineral conditions and 2 (6%) in pituitary. Of these, 26 (94%) have been completed by clinicians and 2 by patients.

Conclusion: The EuRRECa Core Registry has shown its ability to collect information on a very wide range of endocrine conditions in patients of all ages. The additional functionality for collecting patient reported as well as clinician reported outcomes has now been tested and can be used for studying the natural history and long-term clinical outcomes of rare endocrine conditions.

Fat, Metabolism and Obesity

FC4.1

Natural History of LEP, LEPR and MC4R Deficiencies – A Population-Based Study

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Background: Proteins encoded by *LEP*, *LEPR* and *MC4R* genes are principally involved in driving the leptin-melanocortin

pathway. Mutations in these genes induce a rare and severe form of monogenic obesity but the long-term evolution of these afflictions is unknown. Here, we carried out a clinical investigation on 132 children with LEP, LEPR and MC4R deficiency from Pakistan to evaluate progression of the disease and its impact on co-morbidities and mortality.

Methods: Severely obese children (BMI SDS ≥3.5) from 454 families were clinically examined and screened for mutations in three genes using Sanger and WES. Serum hormones, leptin, insulin, cortisol, TSH, and DNA damage marker, 8-OHdG, were determined using ELISA.

Results: We identified 132 probands and 13 family members with homozygous loss-of-function variants in LEP (n=83), LEPR (n=31) or MC4R (n=18). In majority of leptin and LEPR deficient children, obesity and hyperphagia manifested at an early infancy (<1-2 year) compared to MC4R deficiency (4-6 year). Our data demonstrate no remarkable remission of longitudinal growth in LEP or LEPR deficient subjects compared to controls. However, a discernible increase in growth was evident in MC4R deficient subjects during 10-15 years of life. Insulin levels were significantly higher in the mutant groups as compared to control that increased progressively with advancing age. Hyperinsulinemia was more pronounced in LEPR deficiency at the age of 10-15 years. Serum leptin concentrations tended to be higher in LEPR deficiency compared to subjects with MC4R mutations in the first 5 years of life but not at a more advanced age. Cortisol levels that were higher in leptin deficiency during early childhood compared to other groups, declined with age. Mean TSH concentrations were normal in the three mutant groups. DNA damage as evidenced by serum 8-OHdG was more pronounced in LEP deficient children than those in other two groups and was minimal in MC4R deficiency. Mortality due to severe respiratory, gastric problems or pneumonia was reported to be higher in LEP deficient (26%) compared with LEPR deficient children (9%). No deaths were reported in MC4R deficiency.

Conclusions: This large study revealed a distinctly higher incidence of morbidity and mortality at an earlier age in leptin and leptin receptor deficiency compared with MC4R deficient subjects. Remarkably, longitudinal growth was normal in LEP and LEPR deficient but noticeably increased in MC4R deficient subjects. A predisposition to diabetes increased with age in the mutant groups and oxidative stress was maximal in leptin deficiency.

FC4.2

Positive effects of a structured pre- and post-bariatric surgery program on follow-up rate and supplement intake in adolescents and youths- Results from the German YES cohort

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Introduction: Until recently, bariatric surgery (BS) has been the only option for clinically meaningful weight reduction for adolescents and youth with extreme obesity. Low participation rate in follow-up examinations and low supplement intake after BS in adolescents has been described in literature (PMID: 24048144, 25078533). We developed a structured pre- and post-bariatric surgery program in order to improve follow-up rate and supplement intake in adolescents and youth after BS. The aim of the structured preparation program was also to enable patients with interest in BS to make an active decision for BS or to rethink interest in BS.

Methods: The Youth with Extreme Obesity Study (YES) is a multicenter cohort study, including adolescents and young adults (14–24 years) with obesity (BMI≥30.0 kg/m^2). The effect of weight loss surgery (sleeve gastrectomy) within a structured pre- and 12-month post-surgery program (clinicaltrials.gov NCT02062164) was studied (subproject of YES). A multidisciplinary team provided training on medical aspects of BS and on nutrition and physical activity after BS.

Results: After participation in the structured pre-surgery program, 17/26 (f:67%) decided to undergo BS. Nine patients did not undergo surgery. Reasons were: patients lost weight in pre-surgery preparation due to participation in an inpatient program that favors lifestyle modification and decided against surgery, active decision against surgery since they felt too young for such a life threating operation, patients changed their mind several times. Follow-up rate 12 months (T1) after BS was high (94%). All patients achieved a significant weight reduction with a relevant weight loss (ΔBMI: -16.1±5.6 kg/m^2). Six patients achieved BMI values ≤35kg/m^2 at T1. 71% of the patients reported that they took the prescribed dietary supplements in the first year after BS, 42% of them daily. 11/17 patients achieved BMI values that fall within the range of parental BMI values. In contrast to the high follow-up rates at T1, majority of the patients stopped active presentation at the specialized centers in the long-term course (24-month FUp:43%, 36-month FUp:27%).

Conclusion: The participation in a structured pre bariatric surgery program resulted for some patients in a change of their previously made decision. Adolescents and youth with extreme obesity with BS may benefit from a structured pre- and post-treatment program in a specialized obesity center in the first year after surgery. We also realize that new long-term treatment concepts after BS in adolescents and youth are necessary in order to assure long-term safety and efficiency.

FC4.3

Impaired Brain Satiety Responses by Functional Neuroimaging After Weight Loss Therapy in Children with Obesity

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Background: Obesity interventions often result in increased motivation to eat after weight loss.

Objective: We investigated relationships between obesity outcomes and changes in brain activation by visual food cues and hormone levels in response to obesity intervention by family-based behavioral treatment (FBT).

Design, Methods, and Participants: Functional neuroimaging and plasma hormone assessments before and after 24-week FBT intervention in children with obesity (OB, n=28), or children of healthy weight without intervention (HW, n=17), all 9-11-year-old males and females.

Main Outcome Measure(s): Evaluation of meal-induced changes in neural activation in response to viewing high- vs. low-calorie food cues across appetite-processing brain regions and gut hormones.

Results: Among children with OB who underwent FBT, greater declines of BMI z-score were associated with less reductions after the FBT intervention in meal-induced changes in neural activation to high- vs. low-calorie food cues across appetite-processing brain regions ($p<0.05$), and the slope of relationship was significantly different compared to children of HW. In children with OB, less reduction in brain responses to a meal from before to after FBT was associated with greater meal-induced reduction in ghrelin and increased meal-induced stimulation in peptide YY and glucagon-like peptide-1 (all $p<0.05$). Furthermore, a greater reduction of BMI z-score was associated with a greater reduction of free leptin index and increase of the adiponectin to leptin ratio (all $p<0.01$), indicating an increase in leptin sensitivity. After FBT, an increased buffet meal intake was associated with higher leptin levels ($p<0.05$).

Conclusions: In response to FBT, adaptations of central satiety responses and peripheral satiety-regulating hormones were noted. After weight loss, changes of peripheral hormone secretion support weight loss, but there was a weaker central satiety response. The findings suggest that even when peripheral satiety responses by gut hormones are intact, the central regulation of satiety is disturbed in children with OB who significantly improve their weight status during FBT, which could favor future weight regain.

FC4.4

Inhibition of Neuritin 1 induces browning in human white adipocytes and protects from obesity in vivo

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Recently, we identified Neuritin 1 (NRN1) as preferentially expressed in human white compared to brown adipocyte progenitor cells. In mice, Nrn1 deficiency leads to a reduction in body weight, indicating that it might regulate body weight. In this study, we aim to address the function of NRN1 regarding adipocyte metabolism in vitro and in vivo.

We used human SGBS preadipocytes as an in vitro model system. NRN1-deficient cells were generated using lentiviral miRNA constructs. In vivo effects were studied in Nrn1-deficient mice.

In human preadipocytes, NRN1 deficiency did not interfere with adipogenic differentiation, but resulted in an increase of basal glucose uptake by 60%, accompanied by increased GLUT1 mRNA levels. Further, NRN1 knockdown significantly induced mRNA and protein levels of UCP1, and resulted in increased basal and cAMP-mediated uncoupling, suggesting that NRN1 might be involved in the regulation of adipocyte browning. In Nrn1 deficient mice, lower body weight was accompanied by reduced relative inguinal and gonadal fat pad weights (both -28% vs wt). Although we could not detect alterations in browning markers in white adipose tissue (WAT) between wildtype and Nrn1-deficient mice, we found that treatment with the ß3-adrenergic agonist CL316243 lead to a significant increase of glucose uptake in WAT of Nrn1-deficient mice by 2.2-fold (iWAT) and 4.3-fold (gWAT). To further investigate if Nrn1 has an impact on body weight regulation, mice were challenged with a high-fat diet for 12 weeks. Of note, Nrn1-deficient mice gained 30% less weight compared to wt controls, accompanied by reduced white fat pad mass. Additionally, Nrn1-deficient mice were protected from liver steatosis.

Our data suggest that inhibition of neuritin 1 affects fat cell metabolism. We are currently investigating species differences between human and mouse.

FC4.5

Pten knockout in osteoprogenitor cells leads to loss of adipose tissue

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Background and Aim: Pediatric patients with germline mutations in the phosphatase and tensin homolog (Pten) gene frequently develop aberrant adipose tissue growth called lipomas. In severe cases, recurrent lipoma formation can have adverse effects on organ function and quality of life. Due to the lack of understanding the basis of lipoma development, no systemic treatment options are available. We therefore aimed to characterize an already described lipoma bearing mouse model with conditional knockout of Pten in osteoprogenitor cells. Surprisingly, these mice did not develop lipomas, but showed an age-dependent decrease in adipose tissue weight.

Methods: We compared metabolic characteristics and adipose tissue histology of mice with inducible knockout of Pten (Pten cKO) in osteoprogenitor cells expressing the transcription factor Osterix/Sp7 and respective control mice. We analyzed lipolysis induction in isolated adipocytes from Pten cKO mice and controls as well as corresponding signaling pathway activation on protein level.

Results: We found an age-dependent loss of fat mass in Pten cKO mice affecting specifically the inguinal as well as gonadal white adipose tissue (WAT) depots, with no observable effect on brown adipose tissue. Other metabolically active organs were not affected by atrophic changes and no change in body weight was observed. When analyzing Pten expression we found an expected decrease of Pten protein in the bone marrow. Surprisingly, we also observed a higher expression of Pten specifically in WAT with concomitant downregulation of AKT phosphorylation, a downstream target of Pten action. Phosphorylation of hormone sensitive lipase (Hsl/Lipe) was increased in Pten cKO WAT. In line with this, we saw a higher release of glycerol from adipocytes isolated from Pten cKO mice compared to control adipocytes. Adipose tissue histology revealed distinct morphological differences between Pten cKO mice and controls. White adipocytes of Pten cKO mice were significantly smaller compared to those from control mice. Interestingly, Pten cKO WAT depots also contained regions of normal up to giant (> 200 μm diameter) adipocytes next to smaller adipocytes (approx. 20 μm).

Conclusion: Knockout of Pten in osteoprogenitor cells leads to alterations in adipose tissue composition and loss of adipose tissue, which is potentially due to increased lipolysis. A downregulation of Pten in osteoprogenitor cells leads to a selective upregulation in WAT indicating a Pten regulation loop between different body compartments.

FC4.6

Influence of growth hormone status and glucose metabolism on hs-Troponin T and NT-proBNP levels in a cohort of healthy children (The LIFE child study)

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Background and Objectives: N-terminal-pro hormone Brain Natriuretic Peptide (NT-proBNP) and hs-Troponin T (hs-TnT) are commonly used cardiac biomarkers despite lacking a deeper understanding about influencing parameters especially in the healthy pediatric population. We previously found associations between NT-proBNP and hs-TnT and a child´s age, sex, pubertal status, Body Mass Index (BMI) and serum lipid levels. Subsequently, we explored associations with growth hormone status represented by Insuline-like Growth Factor-1 (IGF1) and IGF1-Binding Proetin-3 (IGF-BP3), glucose metabolism (HbA1c) and Cystatin C (CysC).

Material and Methods: Serum values, medical history and anthropometric data provided by 2522 children aged 0.25-18 years, who participated in the prospective longitudinal population-based cohort study, "LIFE child" in Leipzig, Germany, were collected and analyzed as per study protocol.

Results: NT-proBNP values decreased throughout childhood and dropped rapidly with advancing pubertal stage. Furthermore, the negative associations seen between lower NT-proBNP values and higher BMI and higher values for serum lipids, IGF1 and IGF-BP3, was also found for HbA1c with a greater effect in children above 11 years of age and no difference between the sexes. For IGF-BP3 levels, this interaction was found to be modulated by both, sex and age. There was no general correlation between NT-proBNP and CysC, we could only demonstrate a negative association between these values for children 5 to 11 years.

HsTnT levels showed positive associations with higher BMI and IGF-BP3 levels, as well as with higher CysC levels. The latter effect was stronger in girls, an interaction with age was only seen in boys. The association between hsTnT and HbA1c levels was significantly negative and did not show an interaction with sex but with age, resulting in a substantially stronger effect in children older than 11 years. We could not find any significant interaction between hsTnT and IGF1.

Conclusion: We have identified important associations between cardiac markers and certain metabolic parameters to increase the understanding of their influence in the development of healthy children.

Adrenals and HPA Axis

FC5.1

Transcriptome profiling of adrenocortical tumors from children with unfavorable disease presentation

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Children diagnosed with adrenocortical tumors (ACT) have variable prognosis depending on disease presentation at diagnosis. Available therapeutic options render excellent outcome for a subset of patients, but limited improvement in the survival of those diagnosed with non-localized/advanced disease. ACT DNA methylation was recently demonstrated to be a robust and independent prognostic biomarker. Aiming to identify potential therapeutic targets for these children, we compared the transcriptomes of ACT presenting with favorable and unfavorable-disease features. Total RNA was extracted from 53 fresh-frozen, microdissected samples. RNA-Seq was performed according to Illumina's protocol. FASTQ files were merged and aligned to GRCh37 (*STAR*). Read counts were normalized by each library's size using the Counts Per Million method, processed and analyzed (*HTSeq*). Genes with adjusted p-value <0.05 and log2 fold change >1 or <-1 were considered differentially expressed (*DESeq2*). Pathway enrichment analysis was preformed using *Enrichr* and *Panther 2016*. The study included 37 girls (70%, female-to-male ratio 2.3:1), with median age of 1.7 years (range: 0.2-16.6). Five-year overall survival (5y-OS) was 91%. OS was reduced in patients diagnosed after 4 years [n=8 (15%): 7 (13%) between 4-12 and 1 (2%) >13 years, 5y-OS=50%, p<0.0001), with advanced/non-localized disease (IPACTR stages III and IV; n=12 (27%), 5y-OS=80%, p=0.03) or carcinomas (Wieneke score ≥4; n=13 (24%), 5y-OS=72%, p=0.019), and in those whose tumors had pACT-1 methylation signature (n=5 (9%), 5y-OS=20%, p<0.0001). Compared with younger patients, ACT from older patients exhibited underexpression of genes (n=15) associated with immune response and tumorigenesis, and overexpression of genes (n=79) involved in calcium reabsorption and CYPP450 metabolism. ACT from advanced/non-localized disease had underexpression of genes (n=48) associated with carbohydrate metabolism, interleukin signaling, cadherin and Wnt pathway, and overexpression of genes (n=7) associated with immune response, tumorigenesis and B cell activation. Compared with adenomas, carcinomas exhibited underexpression of genes (n=210) involved with immune response, B cell activation, metabolism and the Hedgehog pathway, whereas among overexpressed genes (n=228), metabolic, integrin and cell cycle signaling pathways stood-out. Compared with pACT-2 methylation signature, pACT-1 tumors were underexpressed for genes (n=210) associated with TGF-B, PI3K and insulin/IGF signaling, and overexpressed for genes (n=210) involved in carbohydrate metabolism, integrin, P53 and Wnt signaling pathways. Our data strengthens the importance of pathways known to be deregulated in ACT and reveals novel targets to be investigated in order to develop precision therapeutic options for children diagnosed with unfavorable disease.

FC5.2

Thioredoxin Reductase 2 (*TXNRD2*) Variant As A Cause Of Micropenis, Undescended Testis And Selective Glucocorticoid Deficiency

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Introduction: The molecular aetiology of familial glucocorticoid deficiency (FGD) is very heterogeneous. A recent report of a genetic variant in *TXNRD2*, the gene encoding thioredoxin reductase Type 2, in a South Asian kindred with FGD suggests that the maintenance of redox balance may be critical for adrenocortical function. We present the second report of an individual from another south Asian family harbouring a different pathological variant in *TXNRD2*.

Case Description: The index case presented with a right undescended testis and micropenis at birth. The family were of South Asian origin and parents were first cousins. His two sisters were healthy and one older brother had been diagnosed with mild dysplastic pulmonary valve without any obstructive symptoms. Endocrine investigations at 1.9 yrs showed serum AMH of 872 pmol/l (ref 300-1700), post-hCG serum testosterone and dihydrotestosterone of 9.9 nmol/l and 1.31 nmol/l, respectively and a post-LHRH LH and FSH of 12.0 U/L and 5.2 IU/l, respectively. Urinary steroid analysis by GCMS did not reveal any abnormalities. At the age of 10.3 years, he re-presented with a history of fatigue and hyperpigmentation and investigations revealed a plasma ACTH of 1070 mU/l, undetectable cortisol post ACTH stimulation and a plasma renin concentration of 26.5 mIU/l (ref <125). Adrenal autoantibodies were negative. Following 5 months of replacement, his plasma ACTH had reduced to 265 mU/L. Targeted genetic analysis using XY DSD panel and congenital

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adrenal hypoplasia panel revealed a variant of uncertain significance in *CYP11B1*. Exome analysis revealed an autosomal recessive homozygous missense variant (c.1081G>A; p.(Val361Met)) in *TXNRD2* which was absent from gnomAD. In silico analysis provided equivocal evidence of the variant's pathogenicity. However, functional studies on peripheral blood mononuclear cells showed decreased mRNA expression on quantitative RT-PCR of *TXNRD2* (1.6 fold, p=0.0007), decreased TNXRD2 protein (1.3 fold, p<0.0001) on immunoblotting studies and decreased glutathione: oxidized glutathione ratio (6.7 fold, p<0.0001) in the index case compared to the heterozygote parents and controls. Other than atypical genitalia and adrenal insufficiency, he had no other health issues and his echocardiogram was normal.

Discussion: This second report of isolated glucocorticoid deficiency with a homozygous missense variant in *TXNRD2* strengthens the role of this protein in adrenocortical redox homeostasis. In addition to isolated glucocorticoid deficiency, our case had micropenis and undescended testis, which have not been reported in the previous kindred with *TXNRD2* variants, thus extending the associated phenotype.

FC5.3

The liver as a site for rAAV-induced ectopic adrenocortical enzyme expression

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Background: The adrenal cortex undergoes constant cellular renewal and any effect from recombinant adeno-associated vectors (rAAV) targeting differentiated cells will be transient as extrachromosomal DNA will be lost by dividing cells. A novel option is to use rAAV to express ectopic adrenocortical enzymes in a stable organ outside the adrenal gland. Our aim was to correct the biochemical phenotype in a mouse model for congenital adrenal hyperplasia (CAH) with 21-hydroxylase expression in the liver.

Method: A 21-hydroxylase deficient (-/-) mouse model was used. An AAV8-CYP21A2 vector was produced using established protocols and administered at 5e11 vector genomes/mouse (n=10). After 4 weeks steroid profiles were measured using liquid chromatography tandem mass spectrometry. Hepatic vector copy number (vgc/diploid cell) was determined using digital droplet PCR and transgene expression was determined as a ratio of CYP21A2: albumin transcripts using quantitative PCR. Statistical analysis used the Mann-Whitney U test.

Results: The total and relative adrenal mass improved in the treated -/- mice, suggesting reduced chronic ACTH stimulation (table 1). Serum aldosterone normalised and serum corticosterone improved in the treated. Serum progesterone improved in the females but not in the males. The median vgc/diploid cell was 12.34 (males) and 13.06 (females). Despite more pronounced effect on progesterone in females, males had higher transgene expression: median 0.79 vs 0.20.

Conclusion: In a mouse model of CAH, rAAV-induced expression of 21-hydroxylase in hepatocytes completely recovered aldosterone, improved corticosterone, improved progesterone in females and reduced adrenal mass. This validates the potential of the liver as a site for ectopic adrenal enzyme expression, serving as a pre-clinical model for a potential treatment for CAH. This also demonstrates that some effect on phenotype seen by adrenal-targeting gene therapy may be due to ectopic 21-hydroxylation. Experiments are ongoing to extend this study using simultaneous dual AAV8-CYP21A2 and AAV8-CYP11B1 vectors to boost corticosterone production.

Table 1. Data are listed as medians. +/+ wild-type, -/- 21-hydroxylase deficient

	Sex	+/+	Untreated -/-	Treated -/-	p value
Total adrenal mass (mg)	Male	3.2	10.2	6.8	0.009
	Female	5.2	13.4	9.2	0.034
Adrenal mass as percentage of body weight (%)	Male	0.0114	0.0360	0.0287	0.014
	Female	0.0228	0.0599	0.0425	0.034
Serum aldosterone (pmol/L)	Male	794.0	321.8	1205.8	0.004
	Female	1217.0	301.4	1360.4	0.009
Serum corticosterone (nmol/L)	Male	408.5	38.6	175.3	0.004
	Female	1003.0	42.2	219.6	0.009
Serum progesterone (nmol/L)	Male	10.9	470.0	432.0	0.372
	Female	22.8	770.6	517.4	0.028

FC5.4

Reference Growth Charts in Children with Congenital Adrenal Hyperplasia

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Introduction: Adult height in individuals with Congenital Adrenal Hyperplasia (CAH) is reduced compared to the general population as their growth during childhood can be negatively impacted by both the disease and its treatment. Excess production of androgens through aromatization to estrogens can accelerate height velocity and skeletal maturity, and lead to short stature if not adequately suppressed. Over suppression of adrenal steroids through excess glucocorticoid therapy can impede linear growth. Since the growth pattern of children with CAH differs from the general population, normative data for growing CAH children can help guide treatment decisions and evaluate the effectiveness of new treatments in clinical trials.

Objective: To develop CAH specific reference growth charts for children ages 6 month through 20 years.

Methods: Data for this study came from a single institution between 1970 and 2021. Height and weight data were obtained from clinical records of 210 (124 female) children with CAH from birth through 20 years. Growth data from 5289 clinic visits (3115 females) were used. The Lambda-Mu-Sigma growth modeling technique was used to estimate Height-for-age, weight-for-age, and BMI-for-age reference percentile ranges for CAH children. Derived percentiles were then compared to the WHO growth standard for patients <2 years and the CDC 2000 reference chart for US children for those ages 2-20 years.

Results: Relative to the WHO and CDC charts, height-for-age and BMI-for-age percentiles of CAH patients varied dramatically over the entire growth period. Weight-for-age tracked closely with the normative growth only for the first 2years of life in both males and female but were higher after 4 years. Median height-for-age percentiles in CAH males and females were higher than the normative reference beginning at 3 years, lack a pubertal growth spurt and fall below the reference population at an age when children without CAH typically have achieved most of their pubertal growth. Median BMI-for-age percentiles in CAH children were higher than the normative reference beginning at 10 (female) and 14 months (male).

Conclusion: Growth patterns of CAH patients follow vastly different trajectories relative to available normative charts. CAH growth charts are needed by parents and clinicians to monitor the growth of CAH children in response to currently available treatment and provide historical reference data to guide the interpretation of new treatment paradigms.

FC5.5

Influence of prenatal environment and genetic background on glucocorticoid steroid metabolism in monozygotic twins with intra-twin birthweight-differences

Sandra Schulte[1], *Felix Schreiner*[1], *Michaela Plamper*[1], *Charlotte Kasner*[1], *Mathias Gruenewald*[1], *Peter Bartmann Bartmann*[2], *Rolf Fimmers*[3], *Michaela F. Hartmann*[4], *Stefan A. Wudy*[4], *Joachim Woelfle*[5], *Bettina Gohlke*[1]

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Preliminary Results

Objective: Although low birthweight (bw) and unfavourable intrauterine conditions have been associated with metabolic sequelae in later life, little is known about their impact on steroid metabolism. We studied genetically identical twins with intra-twin bw-differences from birth to adolescence to analyse the long-term impact of bw on steroid metabolism.

Methods: 68 monozygotic twin-pairs with bw-difference of <1SDS (concordant; n=41, 18 female) and ≥1SDS (discordant; n=27, 15 female, 6 female and male pairs with catch-up) were recruited. At mean age of 14.9 yrs morning urine samples were collected and analysed by gas chromatography–mass spectrometry.

Results: In the concordant group no significant differences in urinary steroid metabolites were detected in females or males. In contrast, in the discordant female group with catch-up growth, we found significantly higher concentrations in the smaller twins for α-Cl, a cortisone metabolite (p=0.028, 1941 vs 1169 µg/l). Ratio of 11β-hydroxy-steroiddehydrogenase activity (cortols/cortolones) was significantly lower in smaller discordant females (p=0.032, 0.23 vs 0.27). Overall cortisol metabolite secretion was higher in female smaller twins with catch-up (11783 vs 7256 µg/l), although not significantly. Smaller female twins without catch-up showed slightly lower concentrations than their larger co-twins (11842 vs 13713 µg/l), again without significant difference. In the male pairs, the smaller discordant twins without catch-up showed significantly lower metabolite concentrations in 9/13 (69.2%) metabolites analysed and significantly lower cumulative major cortisol metabolites (p=0.046, 8053 vs 10060 µg/l) and overall cortisol metabolite secretion (p=0.028, 11879 vs 14867 µg/l). Male smaller twins with catch-up showed concentrations not significantly different than their larger co-twins (13483 vs 14284 µg/l). Within all twin pairs, we found significant intra-twin correlations in all steroid metabolites, cumulative metabolites, and enzyme activities analysed. Multiple regression analyses of the smaller twins showed that individual steroid concentrations of the larger co-twin were the strongest influencing factor among nearly all parameters analysed.

Conclusion: In monozygotic twins with intra-twin bw-differences, we could show that bw has a long-lasting impact on steroid metabolism with significant differences regarding cortisol metabolites and enzyme activities in pairs with greater bw-differences. Pronounced in the male group, we could see that lower overall cortisol metabolite secretion was represented in smaller twins without catch-up. Whether this might be source or result of a missing catch-up growth in childhood remains unclear. However, most parameters showed highly significant intra-twin correlations, suggesting also a major importance of the genetic background.

FC5.6

ACTH Stimulation Decreases Ischemia-Modified Albumin Levels In Vivo

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Introduction: The production of ischemia-modified albumin (IMA) is associated with the production of reactive oxygen species modifying the metal-binding sites of albumin. IMA is considered a non-specific early biomarker in the evaluation of oxidative stress status. Cortisol is known to trigger anti-inflammatory actions through genomic and non-genomic pathways that eventually lead to decreased production of cytokines, chemokines, and inducible nitric oxide synthase, as well as increased anti-inflammatory mediators. However, the effect of ACTH stimulation on IMA levels is unknown. In this study, we aimed to evaluate the effect of ACTH stimulation on IMA levels.

Methods: A total of 99 subjects were enrolled in this study. A standard dose ACTH test was performed to 80 subjects while the remaining 19 subjects were performed low dose ACTH test. To determine cortisol and IMA levels, blood samples were collected at 0, 30, and 60 minutes following the standard dose ACTH test, and at 0 and 30 minutes following the low dose ACTH test.

Results: Peak cortisol levels were lower in subjects given low dose ACTH compared to those given standard dose ACTH with a median value of 22.5mcg/dl (min-max:15.1-27.7) and 31.8mcg/dl (min-max:19.2–41.9), respectively (p:0.0001). No significant changes were detected in IMA levels after low dose ACTH stimulation (p:0.161). However, after standard dose ACTH stimulation, a significant decrease was observed in IMA levels within 30 minutes, and this decrease continued to 60 minutes (p:0.002 and p:0.002). The median value of basal, 30 and 60 minutes IMA levels were 1.22 ABSU (min-max:0.36–1.34), 1.20 ABSU (min-max:0.4–1.30), and 1.20 ABSU (min-max:0.19–1.33), respectively. The difference in IMA levels at 30 minutes and 60 minutes were not significant (p:0.773). A positive correlation was detected between basal and 30 minutes IMA levels (r:0.675, p:0.0001). Furthermore, a weak negative correlation was observed between peak cortisol and IMA levels at 30 minutes (r:-0.233, p:0.02).

Conclusions: To our knowledge this is the first study to show that ACTH stimulation which is known to trigger endogenous cortisol production reduces levels of IMA, an oxidative stress marker, rapidly, in vivo. These results might suggest that the rapid decline in levels of IMA after ACTH stimulation might be mediated by non-genomic pathways of cortisol. On the other hand, the observation of the weak negative correlation between cortisol and IMA levels suggests that ACTH may exert its anti-inflammatory effects directly through the activation of certain melanocortin receptors expressed in peripheral immune cells.

Sex Development and Gonads

FC6.1

AMH levels in infancy and mid-childhood predict ovarian activity in adolescence: a longitudinal study of healthy girls

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Background: Anti-Müllerian hormone (AMH) is produced by granulosa cells in small follicles prior to gonadotropin dependent growth and serum levels reflect the number of small antral follicles. There are currently no longitudinal data of individual AMH levels from infancy to adolescence.

Aim: To evaluate whether AMH in infancy and childhood is associated with AMH levels and ovarian morphology peripubertal and in adolescence, and whether high AMH in childhood is associated with a PCOS-like profile of reproductive hormones and ovarian morphology in adolescence.

Methods: A total of 695/1210 girls from the longitudinal Copenhagen Mother-Child Cohort were included in this nested cohort. Inclusion criteria: available AMH assessment; n=1483 AMH samples (mean samples pr. girl, n=3). Age at infancy: median (IQR) 0.26 (0.24-0.28), childhood: 7.4 (6.6-8.1), peripubertal: 11.4 (10.8-11.9) and adolescence: 16.1 (15.7-16.6) yrs.

We assessed the individual dispersion of the AMH standard deviation score (SDS) from infancy to adolescence. Number of ovarian follicles was assessed by transabdominal ultrasound (TAUS) (peripubertal and adolescence) and Magnetic Resonance Imaging (MRI) (peripubertal).

Results: Each girl maintained her relative AMH SDS from infancy to adolescence (individual AMH SDS, mean 0.56±0.31 SD).

Serum levels of AMH in infancy, childhood and peripubertal correlated with AMH in adolescence (infancy: n=115, Spearman r=0.347, p<0.001; childhood: n=145, r=0.637, p<0.001; peripubertal: n=204, r=0.675, p<0.001).

Serum levels of AMH in infancy and childhood correlated with the number of small antral follicles (<7 mm) peripubertal and in adolescence; AMH infancy vs. TAUS peripubertal: n= 77, r=0.253, p=0.026 and vs. MRI peripubertal: n=74, r=0.229, p=0.05; AMH childhood vs. TAUS peripubertal: n=78,r=0.461,p<0.001 and vs. MRI peripubertal: n=137,r=0.368,p<0.001; AMH childhood vs. TAUS adolescence: n=127, r=0.344, p<0.001.

Girls with high AMH in childhood (AMH>30 pmol/L = highest 16% vs. other girls) had elevated levels of LH (median 4.53 vs. 3.29 IU/L, p=0.041) (Mann Whitney U-test), LH/FSH ratio (1.0 vs. 0.67, p=0.019), AMH (38.7 vs. 22.4 pmol/L, p<0.001), inhibin B (87 vs. 71 pg/ml, p=0.030), testosterone (1.05 vs. 0.81 nmol/L, p=0.005), and number of small follicles (2-7mm) (22 vs. 18, p=0.013) in adolescence.

Conclusions: Relatively stable individual levels of AMH from infancy to adolescence cause remarkable correlations of AMH in infancy and childhood with AMH levels as well as the number of AMH producing follicles peripubertal and in adolescence. These findings suggest an individual setpoint of ovarian activity of small antral follicles independently of gonadotropin stimulation throughout childhood. Furthermore, high AMH in childhood is associated with a PCOS-like profile in adolescence.

FC6.2

Predictive value of ovarian reserve parameters for follicle detection in ovarian tissue cryopreservation

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Introduction: In youth, primary ovarian insufficiency (POI) is due to genetic, autoimmune, iatrogenic, and idiopathic etiologies. When POI is diagnosed early with evidence of an ovarian reserve, fertility preservation can be offered. When the girl is premenarchal, the preferred fertility preservation method is ovarian tissue cryopreservation (OTC) containing primordial follicles. In the past, when OTC was performed in an unselected group of children and adolescents with Turner syndrome, only 25% had follicles in ovarian tissue.

Aims: To evaluate the yield of ovarian reserve parameters as predictors of OTC outcomes in girls suffering from non-iatrogenic POI, to avoid unnecessary invasive procedures.

Methods: We retrospectively assessed the ovarian reserve parameters of girls ≤ 18 years with non-iatrogenic POI who were referred for fertility preservation counseling in one tertiary center during the years 2010-2020. OTC was recommended if at least one positive parameter suggesting ovarian activity was present. A positive parameter was defined as anti-Mullerian hormone (AMH) > 0.16ng/ml, follicle-stimulating hormone (FSH) ≤ 20mIU/ml, or detection of ≥1 antral follicle by transabdominal sonography. Patients with 46XY gonadal dysgenesis were excluded.

Results: The cohort included 37 patients (27 Turner syndrome, 6 idiopathic POI, 3 Galactosemia, and one Blepharophimosis, Ptosis, and Epicanthus Inversus syndrome). Sixteen patients underwent OTC, at a mean age of 14.2±3.1 years. Among the group who underwent OTC, compared to the group who did not have OTC, FSH was lower (29.0±31.7 vs. 53.4±52.6 mIU/ml, p=0.05), and the proportion of measurable AMH was higher (50% vs. 15%, p=0.03). The proportion of Turner patients was 1.5-fold lower among the patients who underwent OTC compared to those who did not have OTC (56% vs. 88%, p=0.02). Among the group who underwent OTC, follicles were detected among 79% of the patients, and in all patients (100%) who had 2 or 3 positive parameters. The median number of follicles was 2.5 (range 0-75) in patients who had ≥1 positive parameter, and 22.5 (range 13-64) in patients with 2-3 positive parameters.

Conclusion: This study shows that if OTC is performed in patients with ≥1 positive parameter of ovarian activity, a 79% positive predictive value is achieved for the detection of follicles. The incorporation of these criteria will improve the success rate of OTC as a fertility preservation procedure in these patients and minimize the risk of harvesting ovarian tissue with a low number of follicles.

FC6.3

Gonadal morphology in 46,XY gonadal dysgenesis: I-DSD Registry-based study

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Background/Aims: 46,XY gonadal dysgenesis (GD) is classified as complete (CGD) or partial (PGD) depending on gonadal morphology and function. In contrast to the typical female external genitalia in CGD, the phenotype of PGD is variable depending on androgen production. A diagnosis of PGD is based on clinical/biochemical features, gonadal histology and genetic findings. The aim of this study is to characterise these features, particularly histological, in a large cohort of PGD using CGD as a comparator, and to determine germ cell cancer (GCC) risk in each group.

Methods: Patients with 46,XY GD were identified from the I-DSD Registry. Histology data were submitted as local written reports (n=70), digital images (n=16) or using a proforma (n=197). CGD inclusion criteria: (1) 46,XY (2) typical female genitalia (3) presence of Mullerian duct derivatives and/or undetectable

Table 1.

	CGD n=108	PGDf n=83	PGDm n=109
Median age of presentation (interquartile range) Yr	14.9 (10.5)	0.79 (13.8)	0.5 (2.9)
Median age of gonadectomy (Interquartile range) Yr	15.8 (8.5)	5.2 (13.6)	4.5 (8.6)
Gonadectomy			
Bilateral	90/108 (83.3%)	54/83 (65.1%)	23/109 (21.1%)
Unilateral	0/108 (0%)	2/83 (2.4%)	17/109 (15.6%)
Not done	6/108 (5.6%)	20/83 (24.1%)	55/109 (50.5%)
Gonadal regression (Uni/bilateral)	6/108 (5.6%)	7/83 (8.4%)	7/109 (6.4%)
Gonadal GCC (in situ lesion or invasive)	30/95 (32%)	12/60 (20%)	5/40 (13%)*
Type of GCC (per gonad)			
Gonadoblastoma	19/44 (43.2%)	9/22 (40.1%)	3/8 (37.5%)
Seminoma/Dysgerminoma	12/44 (27.3%)	4/22 (18.2%)	0/8 (0%)
Germ cell neoplasia in situ	4/44 (9.1%)	3/22 (13.6%)	2/8 (25%)
Other GCC	7/44 (15.9%)	4/22 (18.2%)	3/8 (37.5%)
Non germ cell gonadal tumors	0/44 (0%)	2/22 (9.1%)	0/8 (0%)

*$p<0.05$ vs CGD

AMH (4) if pubertal, elevated LH/FSH. PGD: (1) 46,XY (2) atypical genitalia (3) at least one of the following: (A) evidence of GD (AMH in-between male and female references, low inhibin B or Mullerian derivatives), (B) histology consistent with PGD, or (C) pathogenic gene variants associated with GD. Group categories: CGD, PGD assigned female at birth (PGDf), PGD assigned male at birth (PGDm).

Results: For results please refer to Table 1.

Conclusion: The higher frequency of GCC in CGD (32%) compared to PGDf (20%) and PGDm (13%) can be partly explained by the timing of gonadectomy. A centralised expert pathology review of the reports is now underway to correlate gonadal GCC risk with gonadal morphology and patient characteristics (e.g. virilisation), and to better characterise PGD from a histological perspective. Such studies are needed to predict GCC risk, particularly in PGDm.

FC6.4

FATE-1 expression during human fetal testis development, in prepubertal boys and in infertile men

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Recently, knowledge about the molecular genetic of male infertility has increased. However, in many cases, the etiology of infertility remains unknown. The Cancer/testis antigen: Fetal and Adult Testis Expressed (FATE-1), mainly expressed in human testis has been described two decades ago for his potential role in male infertility. FATE-1 is located on the X chromosome, contains a putative SF1 binding site and is co-expressed with SRY in human fetal testis. To date, only few data are available about FATE-1 expression in developing human testis and in infertile men.

In order to improve the understanding of FATE-1's role in testicular development and infertility, we made immunohistochemistry experiments on testicular tissue from abortions from 8 to 41 gestational weeks and on infertile men who had testicular biopsy for fertility preservation or for infertility issue who consulted in the Lyon university hospital.

The preliminary results from 50 fetuses and 25 biopsies of infertile men and one a pre pubertal boy showed that FATE-1 is present in the cytoplasm of the Sertoli cells expect for the pre pubertal boy. Its expression increases during fetal development. It was expressed at various degrees in infertile men. Two of the 5 patients with a non mosaic Klinefelter syndrome had an intense expression of FATE-1. They could not preserve sperm. Patients without spermatogenesis disorders had moderate expression.

We describe here for the first time the expression of FATE-1 in human testis from fetal life to adulthood. We show that FATE-1 is expressed in Sertoli cells cytoplasm. The preliminary results on pre pubertal boy and infertile men seem to show various levels of FATE1 expression. These first results need additional studies to improve mechanisms understanding of expression variations.

FC6.5

Phenotypes in a large international cohort of individuals with SF-1/NR5A1 variants

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Background: Loss of function variants in Steroidogenic Factor 1 (NR5A1/SF-1) lead to a broad spectrum of phenotypes, but data on the whole picture of phenotypes are currently lacking. We aimed to investigate the phenotype of individuals with SF-1 variants in a large international cohort.

Methods: We identified the individuals through the international I-DSD network and through contacting researchers from previous publications on SF-1 variation. Collaborators from 27 centres retrospectively entered phenotypic data on 107 individuals, according to the I-DSD registry and the Human Phenotype Ontology project in a REDCap database. Collaborators of SF1next study group are listed here: https://www.dropbox.com/s/wza2bud5naw2ftd/SF1next%20study%20group.pdf?dl=0.

Results: Of 107 individuals, 96 (89.7%) were 46,XY, nine were 46,XX (8.4%), and two were 47,XYY and 47,XXY respectively (0.9% each). Median age at follow-up was 12 years (range 0-54 years). Sex assignment at last follow-up was male in 62/107 (57.9%) and female in 45/107 (42%) individuals. Ten individuals had sex reassignment during the follow-up period (eight from female to male, one from male to female, one from other to male). Most (101/107, 94.3%) had differences of sex development (DSD), including 84/101 (83.1%) with disorders of gonadal development, 12/101 (11.8%) with non-specific XY DSD, and 1/101 (0.9%) with disorders of androgen action or other types of DSD (4/101, 3.9%). In 95 individuals, we had sufficient data on overall health problems. Thirty-six of 95 individuals (38%) had health problems which were not DSD-related in the following organ systems: urinary (10/95, 11%), blood and spleen (each 9/95, 9.4%), skeletal and central nervous system (each 7/95, 7.3%), head/neck (3/95, 3.1%), adrenal, metabolism/homeostasis and psychosocial (each 4/95, 4%), integument and muscle (each 3/95, 3.1%), immune and endocrine (each 2/95, 2.1%), cardiovascular, connective tissue and peripheral nervous system (each 1/95, 1%). There were no abnormalities in abdomen, breast, vasculature or respiratory system.

Conclusion: More than one third of individuals with SF-1 variants had multiple organ abnormalities, with a broad spectrum of phenotypes. Blood and spleen abnormalities were as frequent as urinary tract problems. Comprehensive gene profiling will allow to assess genotype-phenotype correlation and identify likely disease-causing variants in additional genes that might impact the phenotype. Genotype-phenotype patterns may help to identify individuals at risk for additional health problems.

FC6.6

Breast ultrasonography: How useful in the diagnosis of precocious puberty?

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Context: Assessment of breast development by physical examination (PE) can be difficult especially in overweight girls and in early stages. We aimed to study ultrasonography (USG) on evaluation of breast tissue in girls with breast development <8 years of age.

Patients and Methods: In this prospective study, 125 girls (age 7.1±1.5 years) with early breast development were evaluated by breast USG for ultrasonographic breast staging (Garcia), breast volume and shear wave elastography, in addition to routine clinical and hormonal evaluation.

Results: PE revealed, glandular breast enlargement in 100 and lipomastia in 25. Breast USG in the former group confirmed the presence of glandular breast development in 92:(USG+), but in 8:(USG-). All Tanner stage III and above breasts on PE were also reported to have glandular breast tissue on USG, whereas all (USG-) subjects had Tanner stage II breasts on PE.

Comparison of the 8 USG(-) with 92 USG(+) patients demonstrated lower Tanner (2±0 vs 2,5±0,5, p:0.014) and Garcia staging (1 vs 3 p<0.01), BA/CA (0.9±02 vs 1,1±0,1, p<0.05), basal LH (0,28±0,12vs0,69±1,2, p:0.09), breast volume (0,45±0,28 vs 8,3±8cc, p<0.001), uterine length (26,5±6,1 vs 33,1±5,9mm, p<0.05), uterine volume (1,0±0,4vs2,6±1,6cc, p<0.01) and ovarian volume (2,1±0,72vs4,2±2,4cc, p:0.02).

Breast USG in 25 lipomastia patients demonstrated no breast tissue in 19:(USG-), but Garcia stage >II in 6:(USG+). There were no differences in the features of CPP between two groups except slightly elevated breast volume in USG(+)(2,04±1,9 vs 0,39±0,2cc, p:0.02).

After clinical evaluation and follow-up (19.8±4.2 month), 46/125 subjects were diagnosed with progressive CPP and started on treatment. Garcia stage (3,2±0,7 vs 2,3±0,9), total breast volume (11,6±10,9 vs 3,9±4,1), and elastography (17,8±3,4 vs 14,9±4,2) were significantly higher in the progressive group compared to nonprogressive group ($p<0.01$ for all). Receiver operative characteristics and sensitivity and specifity of significant variables for diagnosis of CPP were calculated. Total breast volume> 6.2cc had sensitivity of 78% and specifity of 71%, $p<0.0001$. Elastography>16kPa had sensitivity of 68% and specifity of 65%, $p<0.001$. These were 73% and 88% for peak LH>5.4 mIU/L and 73% and 71% for uterine volume>2.1cc, respectively.

Conclusion: Breast USG is a useful predictive tool for diagnosis of PP in girls<8yr with Tanner stage II breasts. Higher USG Garcia scores, breast volume and elastography increases the likelihood of eventual diagnosis of PP.

Growth and Syndromes

FC7.1

How to detect children with monogenic etiology of familial short stature?

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Introduction: Familial short stature (FSS) describes vertically transmitted growth disorders. Traditionally, polygenic inheritance is presumed, but monogenic inheritance seems to occur more frequently than expected. Clinical predictors of monogenic FSS have not been elucidated thus far. The aim of the study was to identify the monogenic etiology and its clinical predictors in FSS children.

Patients and Methods: Of 747 patients treated with growth hormone (GH) in our centre, 95 met the inclusion criteria of FSS (pre-treatment height ≤-2 SD in both child and his/her shorter parent, excluded secondary short stature, excluded Turner/Prader-Willi syndrome). Their median age was 12 years (IQR 9-15 years), their life-minimum height was -3.0 SD (-3.5 to -2.7 SD), and the height of their shorter parent was -2.7 SD (-2.9 to -2.2 SD). Of them, 64 were classified as having growth hormone deficiency (GHD), 51 children were born small for gestational age (SGA), 20 children therefore had combined GHD and SGA. Genetic etiology was known in 11/95 children before the study, the remaining 84 were examined by targeted next-generation sequencing panel containing 398 genes known to influence growth. All the variants with a potential clinical significance were evaluated by the American College of Medical Genetics (ACMG) standards. Nonparametric tests evaluated differences between monogenic and non-monogenic FSS, an ROC curve estimated quantitative cut-offs for the predictors.

Results: Monogenic FSS was confirmed in 36/95 (38%) children. Of these, 29 children (81%) carried causative genetic variants affecting the growth plate (SHOX [6], COL2A1 [5], NPR2 [4], COL11A1 [2], ACAN [2], FGFR3 [2], PTPN11 [2], COL11A2, COL1A2, COMP, MATN3, EXT2, and NF1 genes), and 4 children (11%) carried variants affecting the GH-IGF1 axis (GHSR, HMGA2, IGFALS, and OTX2 genes), the remaining 3 children carried variants in miscellaneous genes (TRHR, SALL4, and MBTPS2 genes). Lower shorter parent's height ($p=0.015$) and less delayed bone age (BA) before GH treatment ($p=0.026$) predicted monogenic FSS. In children with BA delayed less than by 0.4 years and with shorter parent heights <-2.4 SD, monogenic FSS was revealed in 13/16 (81%) cases.

Conclusion: In FSS children treated with GH, a monogenic etiology is frequent, gene variants affecting the growth plate are the most common. Shorter parent's height and a less delayed bone age predict monogenic form of FSS.

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FC7.2

Post-hoc subgroup analysis of the pivotal phase 3 study of once-weekly somatrogon vs once-daily Genotropin: results from subjects with peak stimulated growth hormone value <6.7 ng/ml

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Objectives: Somatrogon is a long-acting recombinant human growth hormone (GH) approved by the EMA as a once weekly treatment for children with GH deficiency (GHD). The peak stimulated GH cut-off value for diagnostic criteria for GHD varies according to country-specific guidelines. The objective of this

subgroup analysis of the pivotal phase 3 somatrogon study was to evaluate the primary and secondary efficacy endpoints for subjects with a peak GH value <6.7 ng/ml.

Methods: This phase 3 study enrolled 224 subjects, randomized 1:1 to receive either once-weekly somatrogon (0.66mg/kg/week) or once-daily Genotropin (0.24mg/kg/week) for 12 months. Randomization was stratified by geographic region, peak GH level, and age. The study's primary endpoint was height velocity (HV) at month 12; secondary endpoints included HV at month 6, change in height SDS at month 6 and 12, IGF-1, IGF-1 SDS, and bone maturation. This subgroup analysis focused on 135 subjects with a peak GH value <6.7 ng/mL (67 subjects received somatrogon and 68 received Genotropin).

Results: In this subgroup, the least squares (LS) mean HV at month 12 was 10.11 cm/year and 9.77 cm/year in somatrogon- and Genotropin-treated subjects, respectively, with the treatment difference of 0.34 cm/year favoring somatrogon. This was similar to the overall study population (peak GH value <10 ng/ml), whose LS mean HV at month 12 was 10.10 cm/year and 9.78 cm/year for somatrogon- and Genotropin-treated subjects, respectively, with a treatment difference of 0.33 favoring somatrogon. The efficacy of once-weekly somatrogon was statistically demonstrated to be non-inferior to once-daily Genotropin in the overall study population. In this subgroup, mean changes in height SDS at months 6 (0.57 vs 0.50) and 12 (0.96 vs 0.91) were numerically higher in somatrogon-treated subjects. Stratification by age (3 to 7 years, >7 years), gender, and region showed most values for HV and change in height SDS at months 6 and 12 were higher for the somatrogon group compared with the Genotropin group. The increase in IGF-1 SDS from baseline to month 12 was higher in the somatrogon group (+2.84) versus the Genotropin group (+1.06). Mean bone maturation observed at 12 months was similar between both groups (both 0.69).

Conclusions: The findings from this analysis of subjects with a peak GH value <6.7 ng/mL are consistent with those from the overall study population, in which non-inferiority of once-weekly somatrogon to once-daily Genotropin was statistically demonstrated.

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FC7.3

Italian long-term data on efficacy and safety of rhGH therapy in children with SHOX deficiency: the final report of a national survey performed into ISPED Growth Study Group

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Background: Among children with idiopathic short stature, Italian data reported a prevalence of short stature homeobox-containing gene (SHOX) deficiency disorders (SHOX-D) near to 1/1.000-2.000 (1.1-15%) with a wide phenotypic spectrum. Current guidelines support recombinant human growth hormone (rhGH) therapy in SHOX-D children, but long-term data are still lacking. This national survey aims to evaluate long-term efficacy and safety of rhGH therapy in Italian children with SHOX-D and to identify potential predictive factors influencing response to rhGH therapy.

Methods: This is an Italian multicentric, observational study collecting anamnestic, anthropometric, clinical (Rappold score), instrumental (bone age) and therapeutic data (rhGH dose, side effects) in children and adolescents with a genetic confirmation of SHOX-D treated on rhGH. Data were collected at the beginning of rhGH therapy (T0), yearly during the first 4 years of rhGH therapy (T1, T2, T3, T4) and at final height (T5), when available. Statistical analysis was carried out on STATISTICA (StatSoft Inc, Tulsa, OK, USA).

Results: 106 SHOX-D children started rhGH therapy (initial dose of 0.24±0.05 mg/kg/week) at a mean age of 8.67±3.28 years

(81% prepubertal). During rhGH therapy (mean follow-up 5.94±2.04 years), height (H) SDS and growth velocity (GV) SDS improved significantly (H SDS: T0 -2.36±0.68, T1 -1.91±0.65, T2 -1.66±0.71, T3 -1.49±0.54, T4 -1.45±0.58, T5 -1.57±0.93, p <0.05 and GV SDS: T0 -1.40±1.66, T1 +1.77±2.02, T2 +1.24±2.31, T3 +0.86±2.05, T4 +0.40±2.40, p <0.05) together with sitting height/H ratio (T0 0.56±0.02 vs.T5 0.55±0.01, p <0.05). Mean H SDS gain from T0 was +1.14±0.58 at T4 and +0.83±0.99 at T5. Multiple regression analysis identified the initial dose of rhGH and GV SDS during the first year of treatment as independent positive predictive factors of H SDS gain at T4 (R2 0.40, SE 0.62). No adverse effects were reported apart from: transient impaired glucose metabolism (4/106 cases), elevated IGF-1 levels (1 case) and transient headache (1 case).

Conclusions: Italian data confirm the efficacy and safety of rhGH therapy in SHOX-D children. Moreover, rhGH therapy seems to blunt SHOX-D phenotype improving body proportions as sitting height/height ratio. The response to rhGH in the first year of treatment significantly impacts the final height gain.

FC7.4

Novel puberty aligned references for height, weight and BMI-making personalized medicine in paediatric endocrinology possible

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Background and Aim: Despite the broad individual variation of pubertal maturation, references traditionally describe growth in relation to just chronological age and not biological age. Hence, growth references for the adolescent period have been of limited usefulness for monitoring individual growth in clinic and for research. Especially for children and adolescents with chronic diseases is there a need to better evaluate if changes in SD-scores just before and during the adolescent years are due to sub-optimal care or just a reflexion of early or late maturation. To fill this gap, we aimed to develop novel pubertal height, weight and BMI references for the adolescent years, adjusting for the broad variation in onset of pubertal growth.

Methods: To model QEPS-weight, 3595 subjects (1779 girls) from GrowUp1974Gothenburg and GrowUp1990Gothenburg were used. The QEPS-height-model was transformed to a corresponding QEPS-weight-model; thereafter, QEPS-weight was modified by an individual weight-height-factor (WHF). The QEPS-height and weight models were used to define a corresponding QEPS-BMI model. QEPS-BMI was modified by the same WHF. Longitudinal measurements from GrowUp1990Gothenburg were used to create weight references aligned for height at pubertal onset, defined as 5% of the specific pubertal growth (AgeP5). GrowUp1974Gothenburg subgroups based on pubertal timing, stature at pubertal onset, and childhood body composition were assessed using the novel references. We then have the opportunity to look at individual growth patterns aligned for the individual timing for both height, weight and BMI. 4 individuals (2 girls) were used to show the usefulness of the puberty aligned references in comparison with traditional references based on just chronological age.

Results: The new knowledge concerning individual variations due to the variation of pubertal timing and the impact of BMI and stature to these variations makes it possible to show individual growth patterns. Growth patterns aligned for the individual timing for both height, weight, and BMI as shown for 4 different individuals of both sexes with variations from the mean pubertal maturation as well as variations in mean stature and BMI. The results are compared with the traditional way of just relating height, weight, and BMI to chronological age.

Conclusions: Novel pubertal height, weight, and BMI references consider individual variations in pubertal timing. These references will improve growth monitoring, especially for children with chronical diseases and overweight, obesity or underweight. Puberty aligned growth references may be a practical tool for making personalized medicine in paediatric endocrinology possible as demonstrated at ESPE 2022 meeting.

FC7.5

Population-based assessment of cardiometabolic-related diagnoses in youth with Turner Syndrome: A PEDSnet Study

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Background: Cardiovascular diseases are the leading cause of premature death among women with Turner syndrome (TS). Studies in youth with TS suggest that cardiometabolic-related dysfunction is present in childhood, however these small convenience samples may not be generalizable to the whole TS population. PEDSnet, the largest pediatric Health Learning System in the United States (US) representing >6 million children, offers a unique opportunity to examine cardiometabolic-related outcomes among a large, nationally representative cohort of youth with TS.

Methods: Electronic medical record data for all females with a diagnosis of TS (n=2,019) were obtained from PEDSnet and each matched to four controls on site, race, ethnicity, payor type, age at most recent visit (mean 14.9 yrs), and duration in PEDSnet (mean 7.6 yrs). The prevalence of a diagnosis of overweight/obesity, hypertension, dyslipidemia, dysglycemia, and liver dysfunction were compared between TS and controls with alpha set at 0.01 (Bonferroni correction). Odds ratios (OR) and 95% confidence intervals (CI) were computed using generalized estimating equations in both an unadjusted model then adjusted for risk factors that were all associated with cardiometabolic risk including age, obesity and prescriptions for somatropin, estrogens, and/or antipsychotic medications.

Results: TS was associated with a higher odds of all five cardiometabolic-related outcomes in unadjusted analyses: hypertension (OR 4.5 [95% CI 3.9-5.2]), liver dysfunction (4.3 [3.8-5]), dyslipidemia (3.5 [3.0-4.2]), overweight/obesity (2.1 [1.9-2.3]), and dysglycemia (1.8 [1.3-2.5]). In the adjusted model, higher odds of hypertension (3.0 [2.4-3.7]), liver dysfunction (2.4 [1.9-2.9]), and dyslipidemia (1.7 [1.3-2.3]) persisted, while dysglycemia was no longer significant (1.0 [0.7-1.6]).

Conclusions: In this large, clinical population-based cohort of US youth, individuals with TS had higher odds of all cardiometabolic-related diagnoses compared to matched controls. Accounting for obesity and treatments commonly used in TS only partially explained this increase, underscoring the appropriateness for universal, rather than targeted, screening for cardiometabolic-related conditions in youth with TS.

FC7.6

The Multifaceted Burden Experienced by Caregivers of Individuals With Bardet-Biedl Syndrome: Findings from the CARE-BBS Study

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Background: Caregivers of patients with Bardet Biedl syndrome (BBS) face substantial burden from highly prevalent features of the disease, namely hyperphagia, or uncontrollable hunger, and obesity. However, the burden experienced by caregivers of individuals with BBS is not well characterized.

Methods: A multicountry cross-sectional survey of caregivers of individuals with BBS was conducted to quantify the burden experienced by these caregivers. Eligible respondents were adult caregivers who had cared for ≥6 months individuals with BBS who had obesity or were in the ≥95th weight percentile and hyperphagia ("uncontrollable hunger"). The survey included several observer- and caregiver-reported instruments, such as the Revised Impact on Family Scale (RIOFS; score range, 6-24 and 9-36 for personal strain and familial/social impact domains, respectively, with higher scores indicating greater impact), the Impacts of Hyperphagia (IOH) scale, PROMIS® Global Health 1.2, and Work Productivity and Activity Impairment (WPAI).

Results: In total, 242 caregivers from Canada, Germany, the United Kingdom, and the United States met the inclusion criteria and completed the survey. The mean (standard deviation [SD]) age of the caregivers was 41.9 (6.7) years, and the mean (SD) age of individuals with BBS in their care was 12 (3.7) years. On average, caregivers used 8 different weight management approaches for those in their care and expressed a strong desire for more effective weight management methods. From the IOH, caregivers reported hyperphagia experienced by persons with BBS had a moderate-to-severe impact on their own mood (56.6%), sleep (46.6%), and relationships (47.9%). The physical health of caregivers also was affected (mean [SD], 38.4 [3.5]), as reported through PROMIS®. On the basis of RIOFS, caregivers experienced a high level of personal strain (mean [SD], 17.1 [2.9]) and family impact (mean [SD] score, 26.0 [3.8]) due to BBS. From the WPAI, caregivers also reported an impairment in total work productivity (mean [SD], 60.9% [21.4%]) due to BBS. BBS led 48% of employed caregivers to experience an employment event after the BBS diagnosis, such as temporarily or permanently stopping work (34.1%) and switching jobs (7%). Reported out-of-pocket medical costs for this population (median, $1882.80) were 5-10 times greater than average per capita medical estimates.

Conclusions: This novel multicountry study demonstrated that the burden on caregivers in BBS is considerable and multifaceted. This deeper understanding of caregiver health–related burden highlights the need for new strategies to sustain caregivers in their vital roles in caring for patients with BBS.

Diabetes and Insulin

FC8.1

Clinical effectiveness of Liraglutide 3.0 mg for weight management as an adjuvant therapy in obese adolescents with type 1 diabetes: A single-center pilot study

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Background: Recent data from multiple international registries showed higher rates of overweight and obesity in adolescents with type 1 diabetes (T1DM) compared with their non-diabetic peers. Management of weight gain should be emphasized as obesity is a modifiable cardiovascular risk factor. Liraglutide is a glucagon like peptide-1 receptor agonist approved for chronic weight management in adolescents with body weight above 60 kg and body mass index (BMI) corresponding to ≥30 kg/m^2 for adults by international cut-offs.

Aim of the Study: To assess the effectiveness and safety of daily 3 mg subcutaneous (sc) Liraglutide amongst obese adolescents with T1DM.

Methods: The 26-week trial involved 28 T1DM obese adolescents (12 to 17 years) and a poor response to lifestyle therapy and exercise. They received liraglutide 3 mg sc daily with their usual insulin dose. Dose was titrated up on a weekly basis starting from 0.6 mg per day in weekly intervals of 0.6 mg, taking 5 weeks to achieve the maintenance dose of 3.0 mg daily. BMI, mean BG levels, HbA1c %, insulin dose, systolic and diastolic blood pressure were obtained at baseline and after the intervention.

Results: Of the 28 patients (females 85.7%), 20(71.4%) continued therapy for 26 weeks reached daily dose of Liraglutide 3.0 mg. Reduction in BMI of at least 5% was observed in 15 of 28 participants and a reduction in BMI of at least 10% was observed in

9 participants. The change from baseline in the BMI SD score at week 26, with an estimated treatment difference from baseline was (−0.28, [CI] −0.35 to −0.09; P=0.003).

There was significant reduction of HbA1c from 8.3 to 7.7% (P=0.02). Mean fasting glucose concentrations significantly decreased from 142±12 to 115±8mg/dl. Mean post-prandial glucose increment decreased from 193±10 to 144±6mg/dl. There was a concomitant fall in basal insulin from 28.5±6 to 21.3±9 units (P<0.001 for all) and total bolus insulin from 22.5±4 to 15.5±3 units (P=0.02) with moderate decrease in blood pressure but not significant. While adverse events were mainly gastrointestinal including nausea, dyspepsia, vomiting and constipation; no serious adverse events were reported.

Conclusion: Daily Liraglutide as an adjuvant therapy is effective in producing significant body weight reduction in obese adolescents with T1DM with tolerable minimal side effects. This was associated with improvement of glycemic control despite lower doses of insulin and without increase in hypoglycemic events.

FC8.2

Detection of anti-islet antibodies in capillary blood by the antibody detection by agglutination-PCR (ADAP) technology is sensitive and suitable for general population screening programs

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Background: Detection of type 1 diabetes (T1D) at the preclinical stage is possible by detecting islet autoantibodies (IA) years before the appearance of symptomatic diabetes. An efficient screening program based on these antibodies will identify children at risk of developing diabetes during childhood. The antibody detection Israeli research (ADIR) is a general population screening program in Israel searching for children with multiple IA who are at risk of developing T1D. IA are measured in capillary blood samples using the novel ultrasensitive antibody detection by agglutination-PCR (ADAP) technology by Enable Biosciences. The ADAP assay reliably detects the three cardinal IA namely, GAD (GADA), IA-2 (IA-2A), and insulin (IAA) in 1mL of serum with higher sensitivity than the currently used radio-binding assays (RBA). Nevertheless, the reliability and accuracy of the assay were not tested in venous or capillary whole blood (WB), which are a more desirable sample matrix for general population screening programs.

Objective: To assess the accuracy and reliability of the ADAP assay in venous and capillary WB.

Methods: Fifty children with T1D and fifty healthy controls participated in the study. Venous and capillary blood samples were drawn from participants with T1D, while only venous blood was drawn from the controls. The ADAP assay was performed in 4mL of WB (capillary or venous), while RBA was performed in serum as customary. The assays were compared in their ability to detect GADA, IA-2A, and IAA.

Results: The area under the curve using the receiver operating characteristic (ROC) curvs was comparable between the ADAP assay in WB and standard RBA for all 3 IA indicating similar clinical sensitivity and specificity [GADA 0.946 (95%CI: 0.900-0.991) vs 0.949 (95%CI: 0.906-0.992), P=0.873; IA-2A 0.747 (95%CI: 0.649-0.844) vs. 0.666 (95% CI: 0.587-0.744), P=0.106; IAA 1.000 (95%CI: 1.000-1.000) vs. 1.000 (95%CI: 1.000-1.000),P=1.000]. IA levels in venous and capillary WB using ADAP were comparable for GADA (difference=0.3±0.6, P=0.565), IA2-A (difference=0.04±0.6, P=0.401), and IAA (difference=0.14±0.8, P=0.901). The correlation between the levels of IA in venous and capillary WB using ADAP was R2= 0.958 (P<0.01), R2= 0.943 (P<0.01), and R2= 0.711 (P<0.01) for GADA, IA-2A and IAA, respectively.

Conclusions: The ADAP assay is reliable in detecting IA in venous and capillary WB samples with comparable performance to standard RBA. These findings open avenues for widespread use of the ADAP assay in future general population screening programs to detect children at risk of developing T1D.

FC8.3

Increased zinc alpha2-glycoprotein in patients with type 1 diabetes

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Introduction: Zinc α2-glycoprotein (ZAG) is a single-chain polypeptide with molecular weight of 40-kDa, and is secreted from various tissues. It plays several imperative functions in the human body, such as lipid mobilization and immunoregulation. ZAG enhances lipolysis and is involved in reduction of fatty acids in adipose tissues. ZAG has High sequence similarity to MHC-I molecules and is suggested to be a truncated secretory MHC-I–like protein. Thus, ZAG is considered to be a member of immunoglobulin superfamily and therefore seems to have a role in the immunomodulation. The aim of this study was to investigate the levels of ZAG in the patients with type 1 diabetes (T1DM) and its association with metabolic parameters.

Methods: A total of 77 subjects (39 patients with T1DM and 38 normal subjects) with the mean age of 10.4 were enrolled in this study after careful clinical examination. Routine biochemical tests including fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured by colorimetric methods and HbA1c levels were assessed by immunoturbidometry. ZAG levels were measured using enzyme-linked immunosorbent assay (ELISA).

Results: The level of ZAG was significantly higher in patients with T1DM than that in control subjects (2.65 (1.26-3.78), vs. 0.74 (0.47-1.22), respectively). It showed a significant positive correlation with BMI and FBG, while it was negatively correlated with TC and HDL-C. No significant correlation was observed between ZAG and HbA1c. The levels of ZAG did not differ between male and female subjects.

Conclusion: ZAG might contribute to the pathogenesis of T1DM and might also be considered an interesting target for the management of immune responses in T1DM. Long-term studies are recommended to establish the relationship between ZAG and the pathogenesis and progression of T1DM.

FC8.4

Unravelling environmental and genetic determinants of glycaemic control in children and young adults with Type 1 Diabetes

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Achieving adequate glycaemic control in children with type 1 diabetes (T1D) is essential to reduce incidence and progression of microvascular and macrovascular complications. However, factors that influence glycaemic control remain to be understood. The present study aimed to evaluate clinical, personal, genetic and eating behaviour characteristics underlying glycaemic control in T1D. 325 T1D individuals aged 6 and 20 years and with at least 1 year of disease duration have been recruited in several paediatric diabetes centres. Personal, clinical and genetic data were collected. Standardized questionnaires on eating behaviour measures (food neophobia, food preferences, parental attitudes on child feeding) were administered. Glycaemic control was defined grouping participants based on HbA1c values as follow: Optimal Control (OC), HbA1c <7.5% (<58 mmol/mol); Intermediate Control (IC) HbA1c 7.5–8.5% (58–70 mmol/mol); Poor Control (PC), HbA1c > 8.5% (>70 mmol/mol). PC was significantly associated with higher duration of the disease (p-value=0.003), ketoacidosis at onset (p-value=0.008), greater value of standardized BMI (p-value=0.01) and total cholesterol level (p-value=0.01), pubertal status (p-value=0.04), lower parent education (p-value<0.001). Analysis of eating behaviour measures showed an increased level of food neophobia ("tendency to avoid eating new or unfamiliar foods") in individuals with PC (p-value=0.01). Moreover, an association between parental practices, assessed by the Child Feeding Questionnaire, and glycaemic control emerged. Specifically, higher scores of "Restriction" (p-value<0.001), "Pressure to eat" (p-value<0.001) and "Concern about weight" (p-value=0.01) were observed in T1D individuals with poor control. Finally, preliminary genetic analysis on 176 individuals revealed that rs1800497 polymorphism in DRD2 gene is associated with HbA1c values (p-value=0.009); particularly, TT homozygous individuals showed higher values of HbA1c compared to heterozygous and homozygous for the alternative allele. This polymorphism has been related to several disorders in which neurotransmitter dopamine signaling is affected. Associations of rs1800497 with eating behaviour, glucose metabolism, body mass index and type 2 diabetes have been previously reported. This study, exploiting a comprehensive database of genetic, phenotypic and very deep clinical data, identified several factors, including eating behaviour characteristics, associated with glycaemic control in children and young adults withT1D. Identifying environmental and genetic factors predicting T1D glycaemic control could help to early recognize patients most at risk and establish specific controls or personalized therapeutic interventions.

FC8.5

Pancreas Unfolded Protein Response is activated in Intrauterine Growth Restriction

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Background: Intrauterine growth restriction (IUGR) is associated with higher risk of cardiometabolic disease. Perturbation of endoplasmic reticulum (ER) homeostasis activates a set of ER-to-nucleus signaling pathways known as unfolded protein response (UPR). We previously showed that IUGR is associated with the activation of hepatic UPR and abnormal glucose profile in male Sprague-Dawley rats. Herein, we report the impact of IUGR on pancreas UPR in the same experimental model.

Objective and Hypotheses: To longitudinally evaluate UPR in islets of Langerhans of male IUGR rats.

Methods: On day 19 of gestation, Sprague-Dawley pregnant rats were anesthetized and suture placed around both the uterine arteries and then either tied or withdrawn before closing the abdomen. Dams recovered quickly from uterine artery ligation and sham procedures, and resumed feeding the same day. After recovery, rats had ad libitum access to food and water. The pregnant rats were allowed to deliver spontaneously. The offspring was either

weighed and killed at 8 hrs after delivery or followed up to 105 d. Results from 6 IUGR animals were compared with those from 6 SHAM offspring and analysed separately according to the gender. Densitometric analysis of immunofluorescence was performed on pancreatic islets.

Results: IUGR animals had significantly lower birth weight than controls (p<0.001). At PND 20, IUGR male rats showed reduced islet area (p= 0.05), downregulation of PDX1 gene (p=0.02), increased expression of XBP1s (p=0.02) and reduced proinsulin expression (p=0.05). No difference in mass islets, activation of cleaved caspase 3 and insulin expression was observed. At PND 105, IUGR rats showed increased pancreatic islet area (p =0.01), downregulation of PDX1 expression (p=0.02), increased activation of cleaved caspase 3 (p=0.02), decreased expression of Xbp1s (p=0.01) and reduced proinsulin expression (p=0.03). No significant difference in insulin expression was observed.

Conclusion: The offspring of mothers exposed to uteroplacental insufficiency shows intense pancreatic UPR activation which changes over time. These findings suggest that pancreas ER stress/UPR signaling may play a role in the metabolic risk associated with IUGR.

FC8.6

Radio-guided surgery using 68Ga-labelled Exendin in patient with congenital hyperinsulinism

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Congenital hyperinsulinism (CHI) is a life-threatening disease and manifests in the majority of cases in the first days after birth. Based on the distribution of affected cells, focal CHI forms are distinguished from diffuse CHI forms. Focal forms occur in most cases due to a paternally inherited heterozygous mutation in a subunit of an ATP sensitive potassium channel (ABCC8, KCNJ11). Within the diagnostic setting, focal forms can be visualized by 18F DOPA PET scan, as a marker for beta-cell secretion activity. However, appropriate intra-operative detection of CHI focus is still pretentious. For this reason, we evaluated whether radio-guided surgery – a procedure which is well established for tumor resection of other entities - may facilitate the surgical approach. For this proof-of-concept study, we used 68Ga-Exendin-4 as a tracer, which binds to GLP1 receptors and is thereby supposed to visualize beta-cell mass. This tracer has already been evaluated for the CHI diagnostic set-up (Boss et al, J Nucl Med. 2022).

In 12 CHI patients, 18F-DOPA CT and 68Ga-Exendin-4 PET MRI scan has been performed. Then, during surgery approx. 25 mBq Exendin was injected intravenously. Approximately 30-60 minutes after the injection of the radiotracer, a hand-held cable free positron probe with a spatial resolution of 7 mm for positron radiation was placed over the pancreas and surrounding organs to intraoperatively localize the lesion by radiation signal detection.

Radio-guidance led to a convenient and facilitated identification of the affected pancreatic region and removal of the lesion. We analyzed the frequency of complications due to surgery, duration of the operation and clinical outcome and compared the data with 12 operations, performed without radio-guidance.

In conclusion, we demonstrate data about specificity and accuracy of 68Ga-Exendin-4 as a diagnostic and therapeutic tool to improve the surgical procedure in patients with focal forms of congenital hyperinsulinism.

Pituitary, Neuroendocrinology and Puberty

FC9.1

COVID-19 and increased prevalence of female precocious puberty in Germany

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Background: Several studies observed a positive secular trend for the occurrence of earlier puberty. Genetic background, weight gain, and environmental factors are assumed as contributors.

In March 2020, WHO declared a worldwide pandemic of COVID-19. To reduce transmission, Germany and many other countries imposed regulations of social distancing and lockdowns leading to significant changes in daily life for children followed by an increase in obesity but also in the incidence of psychological disturbances. As reported from Italy, we noticed an unusual high number of girls diagnosed with central precocious puberty (CPP).

Aims of the Study: Retrospective single center evaluation of newly diagnosed CPP incidence during the pandemic (group A), comparing data with previous five years (2015-2019; group B). In addition, a German-wide survey of all pediatric-endocrinological centers on the frequency of CPP was conducted.

Patients and Methods: Auxological, clinical, endocrinological and radiological data from patients who presented with CPP 2015-2021.

Results: Number of patients with CPP remained stable (n<10/year) for 2015-2019. In 2020 numbers more than doubled (n=23) with a further increase (n=30) in 2021[WJ3]. This was confirmed by the survey: 28/43 (65%) reported an increase, confirmed by those who could quantify their patient number (2019: n=608; 2020: n=845; 2021: n=1140).

Differences were observed between the two groups. Although mean BMI-SDS was not different between the two groups at time of diagnosis, it was already in the upper normal range in group B at the age of five years (0.74; SD 0.9) with no significant change thereafter (0.87; SD 0.8) whereas a significant increase was observed in group A (BMI-SDS at 5yrs: 0.002 (SD 1.1); at diagnosis: 0.55; SD 1.1; p=0.04). Patients diagnosed during the pandemic were

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significantly younger than those diagnosed previously (6.86 yrs SD 1.9 vs 7.6 SD 1.3; p<0.05). Tanner stages at diagnosis in girls out of group B were significantly more advanced than those diagnosed during the pandemic. No significant differences were found for endocrine or sonographic parameters. In both groups mean time of menarche of mothers was comparably early (11.7 yrs SD 1.4 vs 11.9 yrs SD 1.4).

Conclusion: Our data confirms Italian data showing an increased incidence of newly diagnosed CPP during and after lockdown compared to previous years. The known positive secular trend for thelarche might be aggravated by psychosocial and environmental factors e.g. disproportional weight gain. Additionally greater awareness of the family for physical changes of their children could be assumed.

FC9.2

Can pre-treatment BMI influence long-term anthropometric and metabolic outcomes in girls with idiopathic central precocious puberty treated with GnRHa?

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Background: Gonadotropin releasing hormone analogs (GnRHa) are effective in improving adult height in children with precocious onset of puberty, rapid progression, and good growth potential. In last years, however, some transient metabolic complications have been described during the treatment without the reassurance of long-term data yet. The aim of our study is to clarify if body mass index (BMI) at diagnosis of idiopathic central precocious puberty (iCPP) could influence long-term anthropometric and metabolic outcomes.

Methods: This is an observational study recruiting a monocentric cohort of girls with iCPP. Anthropometric measures, bone age (BA), fasting lipid profile and glucose metabolism data (HOMA-index, fasting glucose to insulin ratio) were collected at baseline (when GnRHa started) [T0], at the end of the treatment [T1], and at near final height (nFH) [T2]. Predicted adult height (PAH) was calculated at T0 according to Bayley and Pinneau's method. Analysis was performed according to BMI SDS categories at T0 (Group A: normal-weighted vs. Group B: over-weighted and obese girls – WHO 2007).

Results: Fifty-seven girls with iCPP treated with GnRHa were enrolled [Group A vs. B: 33 vs. 24 patients, aged at T0 7.86±0.81 vs. 7.06±1.61 years (p<0.05), BA discrepancy at T0 +1.73±1.04 vs +2.26±1.20 years (p 0.10)]. In the study population, the achieved nFH was in line with target height (TH) (-0.20±1.11 vs. -0.40±0.81 SDS, p 0.54) with a mean absolute height gain of 11.82±5.35 cm in comparison to PAH evaluated at T0. Even if in group B, the length of therapy was shorter (1.42±1.11 vs. 2.10±0.81 years, p<0.05) and their age at menarche was earlier than in group A (10.56±1.01 vs. 11.44±0.85, p<0.05), the near final height gain was comparable in the two groups (p 0.82). BMI SDS was still greater in group B than in A at nFH (0.96±1.33 vs. 0.18±0.99, p 0.012), even if BMI SDS significantly increased from T0 to T2 only in group A (p < 0.05). ANOVA analysis did not document a worsening of lipid profile and insulin resistance status in both groups from T0 to T2.

Conclusions: Our results do not support the concern that overweight and obesity could impair the long-term anthropometric outcomes of GnRHa therapy. Moreover, this treatment does not seem to deteriorate the long-term metabolic profile of patients already overweighted and obese at iCCP diagnosis.

FC9.3

Therapeutic outcomes in gonadotropin-replaced males with congenital hypogonadotropic hypogonadism (CHH) with identified genetic variants

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Background: To delineate testicular responses to gonadotropin replacement in young males with genetically proven CHH.

Patients and Methods: In n=72 young males with CHH and at least one variant detected within twenty-four investigated known CHH genes, gonadotropin replacement with hCG and rFSH s.c. was performed over a mean of 2±1 years. Bi-testicular volumes and serum Inhibin B served as baseline parameters, maximal bi-testicular volumes and maximal sperm concentrations in semen achieved on treatment were used as outcome parameters.

Setting and Study Design: Single centre retrospective cohort study.

Results: 74 genetic variants were detected within 22/24 investigated CHH genes. The most commonly affected genes were FGFR1 (17%), ANOS1 (9%) GnRHR (8%), PROKR2 (8%), TACR3 (6%), SPRY (5%), CHD7 (4%) and NSMF (4%).

Mean bi-testicular volumes at baseline in males with PROKR2 variants were 11±12 ml, vs. 10±9 ml in those with GnRHR variants, 9±9 ml in FGFR1, 4±2 ml in ANOS1, and 4±1 ml in those with TAC3R variants.

Inhibin B at baseline was 69±48 pg/ml in males with GnRHR variants; 61±54 pg/ml in those with PROKR2, 53±52 pg/ml in FGFR1, 27±9 pg/ml inTAC3R, and 20±12 pg/ml in those with ANOS1 variants.

Mean maximal bi-testicular volumes (by ultrasound) achieved on treatment were 26±6 ml (GnRHR), 22±10 ml (TAC3R); 20±6 ml (PROKR2), 18±9 ml (FGFR1) and 14±8 ml (ANOS1).

Median sperm concentrations in semen were 16.4 mill/ml (0-247) in males with GnRHR variants, 15.5 mill/ml (4.7-184) in those with PROKR2 variants, vs. 4.0 (0-66) in FGFR1, 1.2 (0-21) in ANOS1 and 1.1(0-50) in those with TACR3 variants, respectively.

Two males with GnRHR mutations had full reversal of their central HPG axis function: One had persisting spermatogenesis on hCG alone and one persisting spermatogenesis on subsequent testosterone gel replacement.

Conclusion: Testicular baseline parameters and responses to gonadotropin replacement are most favourable in males with variants in GnRHR and PROKR2; they are worst in those with variants in ANOS1 and TAC3R.

Males with GnRHR variants have a chance for reversal of their central HPG axis dysfunction after therapeutic induction of testicular maturation by gonadotropin replacement.

FC9.4

Delayed puberty: unraveling the different trajectories and contributions of AI

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Introduction: Differentiation between constitutional delay of growth and puberty (CDGP) and congenital hypogonadotropic hypogonadism (CHH) during early adolescence is challenging, as patients exhibit a similar clinical picture and there are no definite clinical or biochemical markers that distinguish these 2 pathologies. A delay in diagnosis, especially for CHH, may have short and long-term health consequences.

The aims of this study were: 1) To evaluate the utility of clinical and biochemical markers alone or in combination to discriminate between CDGP and CHH; 2) To chart trajectories of patients with delayed puberty (DP) up to final diagnosis; 3) To investigate the added value of machine learning and genetic score for the early diagnosis.

Methods: This prospective observational study included 41 male patients who sought medical attention between 14-16.5 yrs for DP. Patients were followed yearly up to final diagnosis and their clinical trajectories were charted. CDGP was defined by a testicular volume (TV) ≥12 ml, associated with testosterone (T) ≥10 nmol/l, and full virilization by age 18. Complete CHH was defined by a TV < 4 ml, and partial CHH by a TV ≥ 4ml by age 18 both in the setting of T <4mmol/l and low/normal LH and FSH values. Parametric and non-parametric tests, receiver operating characteristic (ROC) analyses, whole exome sequencing and machine learning models were employed to distinguish between CDGP, complete and partial CHH.

Results: Out of 41 DP patients, 27 had CDGP; 6 complete and 8 partial CHH. At presentation, Inhibin B<62 pg/ml, as well as the association of a history of cryptorchidism with either testicular volume <3ml or LH <0.8U/L exhibited a 100% sensitivity and specificity for complete CHH. However, none of the clinical and hormonal markers allowed to differentiate CDGP from partial CHH. Machine learning algorithms improved identification of partial CHH from CDGP with an accuracy of 77%. Further, adding a genetic score increased the prediction by 4%. Longitudinal analyses showed that CDGP differ from partial CHH by age 15.5- 16. Finally, 20% of patients with DP had a final diagnosis of partial CHH. and exhibited 3 distinct clinical trajectories.

Conclusions: Partial CHH is more common than previously thought among DP. Distinction between CDGP and partial CHH is difficult at early adolescence but feasible by age 15.5-16. Machine learning associated with genetic score improves diagnostic accuracy and may be a useful tool in the management of DP patients.

FC9.5

Gonadal Function, Pubertal Development, and Fertility Outcomes in Male and Female Survivors of Medulloblastoma - a Single Tertiary Centre Experience

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Background: Endocrine deficiencies, including impairment of the hypothalamic-pituitary-gonadal axis (HPGA), are found in the majority of survivors of medulloblastoma, due to high-dose craniospinal irradiation and gonadotoxic chemotherapy. Data

regarding HPGA function in survivors of medulloblastoma is limited to small groups of patients and focusses mainly on female survivors. Furthermore, few studies investigated specific risk factors such as treatment protocol, age at diagnosis, and time elapsed from treatment.

Methods: A retrospective study comprising all patients diagnosed with medulloblastoma between 1987-2021 and followed at The Late Effects Endocrine Clinic at Sheba Medical Centre. Clinical markers of HPGA function included onset and progression of puberty, regularity of menstrual cycles, and fertility outcomes in both male and females. Biochemical parameters included levels of LH, FSH, estradiol, testosterone, and anti-Mullerian hormone. Patients still undergoing treatment, and those that had died within 2 years of diagnosis or had not completed 2 years of follow-up after completion of treatment were excluded.

Results: Sixty-two patients were included in the analysis (41 male). There was a significant ($p<0.01$) difference in prevalence of HPGA dysfunction between males and females. Among female patients, 16/21 (76%) showed clinical or biochemical evidence of HPGA dysfunction. Furthermore, biochemical evidence of diminished ovarian reserve was seen in all prepubertal girls (n=4). Among the male cohort, 14/41 (34%) showed clinical or biochemical evidence of HPGA dysfunction: eleven had high FSH levels suggesting primary testicular failure, and 3 had hypogonadotrophic hypogonadism (HH); twelve patients were prepubertal with age-appropriate LH and FSH levels. Two female patients achieved successful pregnancies following fertility treatment, and two male patients achieved spontaneous conception, resulting in 7 live births. Treatment by "High risk" protocol was associated with HPGA dysfunction in males ($p=0.02$) but not in females. There was no association between HPGA dysfunction and other endocrine deficiencies, age at diagnosis or length of follow up.

Conclusions: Damage to the pituitary-gonadal axis is common after treatment for childhood medulloblastoma. This is seen more in females, likely due to damage to the ovaries from spinal radiotherapy. In males, both primary testicular failure and HH were observed. The association between HPGA dysfunction and "High risk" treatment protocol is likely due to the higher dose of irradiation to the posterior fossa, resulting in HH. These data may assist in counselling patients and their families with regards to risk to future fertility and need for fertility preservation.

FC9.6

Cerebral infarction in childhood-onset craniopharyngioma patients: results of KRANIOPHARYNGEOM 2007

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Background: Cerebral infarction (CI) is a known vascular complication following treatment of suprasellar tumors. The purpose of our study was to determine the incidence of cerebral infarction (CI) in a cohort of 244 German childhood-onset craniopharyngioma (CP) patients recruited between 2007 and 2019 with a high degree of completeness in the prospective, randomized trial KRANIOPHARYNGEOM 2007 (Clinical Trial No. NCT01272622). Up to now, risk factors for CI, incidence rate, and long-term prognosis are unknown for patients with childhood-onset CP.

Methods: The MRI of 244 CP patients, recruited between 2007 and 2019 in KRANIOPHARYNGEOM 2007, were reviewed for CI by neuroradiologists blinded for clinical information. Risk factors for CI and outcome after CI were analyzed. The Pediatric Quality of Life (PEDQOL) and the German daily life ability scale Fertigkeitenskala Münster-Heidelberg (FMH) questionnaires were used to assess health-related QOL and functional capacity, respectively.

Results: Twenty-eight of 244 patients (11%) presented with CI based on reference assessment of MRI. One CI occurred before initial surgery and one case of CI occurred after release of intracystic pressure by a cyst catheter. 26 of 28 CI were detected after surgical tumor resection at a median postoperative interval of one day (range: 0.5-53 days). Vascular lesions during surgical procedures were documented in 7 cases with CI. No relevant differences with regard to surgical approaches were found. In all 12 irradiated patients, CI occurred before irradiation. Multivariable analyses showed that hydrocephalus and gross-total resection at the time of primary diagnosis/surgery both were risk factors for CI. After CI, quality of life (PEDQOL) and functional capacity (FMH) were impaired.

Conclusions: CI occurs in 11% of surgically-treated CP cases. Degree of resection and increased intracranial pressure are risk factors, which should be considered in the planning of surgical procedures for prevention of CI. We conclude that especially initial hydrocephalus and radical surgical procedures such as gross-total resection leading to complete resection in complicated tumor locations such as hypothalamic involvement and adhesion of vessels, increase the risk of CI. CI leads to severe impairment of QOL and functional capacity during long-term follow-up after childhood-onset CP.

GH and IGFs

FC10.1

Growth hormone and childhood-onset craniopharyngioma: When to initiate growth hormone replacement therapy?

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Objective: Craniopharyngioma is a benign brain tumour with frequent local recurrence after treatment. Growth hormone replacement therapy (GHRT) is prescribed in children with growth hormone deficiency due to childhood-onset craniopharyngioma.

The objective was to evaluate whether shorter time delay of GHRT initiation after childhood-onset craniopharyngioma completion therapy increased the risk of recurrence.

Design: Our retrospective, observational study compared a cohort of childhood-onset craniopharyngiomas diagnosed between February 2003 and November 2019 all treated with recombinant human growth hormone (rhGH) in the paediatric Necker-Enfants Malades University hospital in Paris, France.

Results: We studied 71 childhood-onset craniopharyngiomas (median age 7,4 years). Twenty-seven patients were treated with rhGH at least 12 months after craniopharyngioma treatment (38%, ">12 months group") and forty-four patients before 12 months (62%, "<12 months group") among which twenty-nine patients were treated between 6 and 12 months (40%, "6-12 months group"). The main outcome was the risk of tumour recurrence in the ">12 months" group and in the "<12 months" or in the "6-12 months" group patients.

In the ">12 months group", the 2- and 5- years recurrence-free survivals were respectively 81,5% (95% CI 61,1-91,9) and 69,4% (95% CI 47,9-83,4), as compared with 72,2% (95 IC 56,3-83,1) and 69,8% (95% CI 53,8-81,2) in the "<12 months" group. The 2- and 5- years recurrence-free survivals were the same in the "6-12 months group" (72,4%, 95% CI 52,4-85,1). By Log-rank test, the recurrence-free survival was not different between the ">12 months group" versus the "<12 months group" (p=0,98) or versus the "6-12 months group" (p=0,91).

The median time for recurrence was not statistically different between the ">12 months group" (13 months, IQR 3,9-34,9) versus the "<12 months group" (10,4 months, IQR 6,8-18,0, p=0,51) or versus the "6-12 months group" (10,9 months, IQR 8,7-16,2, p=0,66).

In univariate and multivariate analysis, the risk of craniopharyngioma recurrence was not associated with the GHRT time delay after craniopharyngioma treatment (>12 months versus <12 months or versus 6-12 months).

Conclusion: No association was found between GHRT time delay after childhood-onset craniopharyngioma treatment and an increased risk of recurrence, suggesting GH replacement therapy can be initiated 6 months after last treatment for craniopharyngiomas.

FC10.2

The first-year growth response to once-weekly growth hormone (GH) treatment can be predicted from the pre-treatment blood transcriptome in children with GH deficiency (GHD)

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Growth response to daily GH treatment can be predicted using pre-treatment gene expression profiles.[1] Once-weekly GH treatment potentially reduces the burden of daily injections[2] and thus may be a major advancement in care for patients with GHD, versus standard, daily GH treatment. Here we investigate the prediction of first-year growth response based on pre-treatment blood transcriptome in children with GHD undergoing treatment with daily or once-weekly GH.

Two hundred GH-treatment-naïve prepubertal children with a confirmed diagnosis of GHD and no prior exposure to GH therapy were enrolled into a randomised, multinational, multicentre, open-labelled, and active-controlled parallel-group phase 3 trial, REAL 4. One-hundred-and-twenty-eight of these consented to participate in a baseline blood transcriptome profile. These children with GHD were treated with daily GH (n=47) or once-weekly somapacitan (n=81) over 52 weeks. Participants were categorised based on their response to GH treatment. The participants within the upper quartile of annualised HV (cm/year) were identified as good responders; the lower quartile as poor responders.

Differential expression was assessed between the target quartile and the remaining three quartiles to identify the top 100 differentially expressed genes (DEGs) by adjusted p-value. Classes were balanced using a synthetic minority oversampling technique (SMOTE) and Boruta, a feature selection algorithm that models background noise, was used to refine gene lists. Random forest was performed using these genes and "out of box" (OOB), area under the curve (AUC), and OOB error rate (ER), measures of predictive accuracy and robustness respectively, were calculated. All analyses were performed in R 4.4.1.

There was no difference in baseline clinical phenotype or annualised height velocity between daily GH and once-weekly somapacitan. Prediction of growth response using the baseline (pre-treatment) blood transcriptome was excellent for both treatments (AUC range: 0.91–0.98) but prediction was consistently more robust in the identification of the good (ER: 7.0–11.5%) than the poor responders (ER:13.2–15.8%). Gene transcripts previously identified as predictive of growth response in daily GH treatment[1] were demonstrated to have predictive value in both daily and once-weekly GH treatment (AUC range: 0.84–0.97, ER <22%).

This is the first demonstration of the use of pre-treatment blood transcriptome to predict first-year growth response to a novel once-weekly GH treatment. This study presents an independent validation of previous observations of the prediction of first-year response to daily GH treatment.

References

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FC10.3

Near final height in 62 twin pairs with twin-to-twin transfusion syndrome is not associated with the GHRd3 genotype

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Background: Alterations of pre- and early postnatal growth can have long lasting impact on adult height, body composition and metabolic health throughout life. In monozygotic twins discordant for prenatal growth due to twin-to-twin transfusion syndrome (TTTS), we previously demonstrated lower cord blood IGF-I concentrations and earlier pubertal maturation, indicative of prenatal programming of endocrine systems, to be linked to reduced final height of the former growth restricted twin. The individual capacity of postnatal catch-up growth may also depend on genetic factors, as shown for the growth hormone receptor exon 3 deletion (GHRd3) gene variant in very low birth weight preterm infants or children with GH deficiency.

Methods: We longitudinally analyzed growth patterns from birth to near final height (mean age at last visit 15.0 yrs) in relation to the GRHd3 genotype in a cohort of 62 monozygotic TTTS twin pairs. TTTS had been treated by laser coagulation of communicating vessels before 25 weeks of gestation. At birth, 28 of 62 pairs still showed an intra-twin difference of >1.0 SDS for length and/or weight. GHRd3 genotype (exon 3 deletion vs. full length) was analyzed by multiplex PCR.

Results: Birth parameters including mean intra-twin differences were not different between the GHRd3 genotype groups. Transiently and irrespective of their TTTS status, children carrying at least one GHRd3 allele (fl/d3, d3/d3) had lower height-SDS compared with noncarrier (fl/fl) at ages 12 months (donors: d3-carrier -1.42±1.06 SDS vs. noncarrier -0.50±1.25 SDS, p=0.007; recipients: d3-carrier -0.59 ±1.13 SDS vs. noncarrier 0.00±1.19 SDS, p=0.085) and 2 yrs (donors: d3-carrier -0.96±0.80 SDS vs. noncarrier -0.12±0.96 SDS, p=0.008; recipients: d3-carrier 0.39±0.86 SDS vs. noncarrier 0.43±1.29 SDS, p=0.030). Intra-twin differences, however, were not different between genotypes. Up to the last visit during adolescence, most children (116/124) reached a near final height within normal ranges, while height-SDS (d3-carrier 0.15±1.15 SDS vs. noncarrier 0.37±1.10 SDS, p>0.1) as well as mean intra-twin height-SDS differences (d3-carrier 0.32±0.55 SDS vs. noncarrier 0.31±0.49 SDS, p>0.1) again were not different between genotype groups.

Conclusions: During early postnatal catch-up growth at ages 1 and 2 yrs, GHRd3 carrier were significantly shorter than noncarrier, which is in contrast to previous observations regarding GHRd3 and catch-up growth. However, the GHRd3 genotype does not seem to affect near final height or the degree of long-term height approximation within twin pairs in monozygotic twins discordant for prenatal growth.

FC10.4

Cerebral white matter hyperintensities in young adults born small for gestational age treated with growth hormone during childhood in comparison with untreated controls

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Background: The French population of the SAGhE study showed an increased morbidity and mortality due to cerebrovascular disease in growth hormone (GH) treated subjects compared to the general population. Cerebrovascular health can be assessed using neuroimaging markers on MRI. One of the markers is white matter hyperintensity (WMH).

Objective: To assess cerebrovascular health by scoring WMH on MRI in young adults born small for gestational age (SGA) who were treated with GH during childhood compared to age-matched untreated controls.

Methods: The study cohort consisted of 4 different groups; adults born SGA treated with GH during childhood (SGA-GH), adults born SGA with persistent short stature (SGA-S), adults born SGA with spontaneous catch-up growth to a normal adult height (SGA-CU) and adults born with normal birthweight and birthweight (AGA). We performed 3T-MRI of the brain which included a FLAIR sequence to assess WMH. WMH was scored by two independent medical doctors using the Fazekas scale and divided in deep WMH (DWMH) and periventricular WMH (PWMH).

Results: We included 306 subjects: 98 SGA-GH, 45 SGA-S, 64 SGA-CU, and 99 AGA. Mean age at MRI was 28.6 (SGA-GH), 31.6 (SGA-S), 32.3 (SGA-CU) and 32.3 years (AGA). Mean adult height SDS was -1.6 (SGA-GH), -2.3 (SGA-S), -0.2 (SGA-CU) and 0.4 (AGA).

Percentage of total WMH was 52.2 (SGA-GH), 42.9 (SGA-S), 75.0 (SGA-CU) and 41.6 (AGA), resp. Percentage of DWMH was 45.7 (SGA-GH), 35.7 (SGA-S), 67.2 (SGA-CU) and 36.7 (AGA), resp. No differences between SGA-GH, SGA-S and AGA were shown concerning total WMH and DWMH. SGA-GH showed significantly less WMH and DWMH compared to SGA-CU (p=0.004, p=0.008). No differences between subgroups were seen in percentages of PWMH.

Participants with DWMH had a lower birthweight (p=0.005), birth length (p=0.017) and gestational age (p=0.004) compared to those without DWMH. No difference in age at MRI, SES (income and education) and lifestyle (smoking, alcohol, drugs, physical activity) was found in participants with DWMH compared to those without DWMH.

Conclusion: No differences were found in WMH and DWMH between SGA-GH, SGA-S and AGA. However, SGA-CU had the highest percentage of WMH and DWMH. Prenatal characteristics might play a role in the development of WMH.

FC10.5

Features and outcomes of syndromic vs non-syndromic children born small for gestational age (SGA) under growth hormone therapy in a Belgian cohort

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Background and Aim: A substantial proportion of SGA patients have a syndrome underlying their growth restriction. Most SGA cohorts comprise both syndromic (S-SGA) and non-syndromic patients (nonS-SGA) impeding delineation of the recombinant human growth hormone (rhGH) response. We present a detailed characterization of the Belgian SGA cohort and analyze rhGH response based on adult height (AH).

Patients and Methods: Clinical and auxological data of SGA patients treated with rhGH that reached AH were retrieved from BELGROW, a national database of all rhGH treated patients held by BESPEED (Belgian Society for Pediatric Endocrinology and Diabetology). Z-score calculation: Niklasson 1991 / Intergrowth (< 28.5 weeks) for birth parameters; Roelants 2004 for follow-up data. AH SDS was calculated using SDS for 21 years. Patients were classified as S-SGA if they had: genetically confirmed syndrome, fetal alcohol syndrome (FAS), or minimum 2 additional symptoms suggesting a syndromic origin (congenital heart defects, mental retardation, dysmorphic features). Subjects with an underlying chronic disease known to impair growth were excluded.

Results: 276 patients were included, 42 were classified as syndromic (most frequent diagnosis: 10 FAS, 8 Silver-Russel syndrome, 3 3M syndrome). Compared with nonS-SGA, S-SGA were more frequently male (74% vs 54%), had lower birth weight (values expressed as median, (P10/P90): -2.79 SDS, (-4.26/-1.34) vs -2.26 (-3.46/-1.41), p=0.0018), lower birth length (-3.09 SDS, (-4.72/-1.2) vs -2.47 (-3.72/-1.63), p=0.0308),were younger (7.58 years (4.3/12.71) vs 10.24 (5.42/13.95), p=0.0022), shorter (-3.37 SDS (-5.42/-2.62) vs -3.07 (-3.74/-2.62), p=0.0438) and thinner (BMI SDS -1.61 (-3.65/0.25) vs -1.13 (-2.47/0.28), p=0.0198) at start of rhGH. Midparental height was lower in nonS-SGA (-1.38 SDS (-2.25/-0.49) vs -1.23 (-2.18/-0.02), p=0.0416). First year rhGH response was comparable (delta height SDS +0.5 (0.24/0.94) vs

+0.56 (0.26/0.91), p=0.92). Mean dose rhGH was higher in S-SGA (0.047 mg/kg/day (0.039/0.064) vs 0.043 (0.035/0.056), p=0.0052). AH was lower in S-SGA (-2.59 SDS (-4.95/-1.57) vs -2.32 (-3.3/-1.2), p=0.0136; (mean±SD) male 162.1±8.2 / female 147.6±11.2 cm vs male 165.9±6.4 / female 152.6±5.1 cm). The majority in both groups remained short (syndromic 71%, non-syndromic 63%). Total height gain was comparable in both groups (delta height SDS +0.73 (-0.95/1.48) vs +0.85 (-0.11/1.84), NS p=0.25).

Conclusions: Compared to non-syndromic SGA patients, syndromic patients have lower birth weight and length and shorter stature when starting rhGH therapy, started rhGH therapy earlier, and received a higher rhGH doses. At AH, syndromic patients were shorter than non-syndromic patients, but their height gain under rhGH therapy was comparable.

FC10.6

Defects in *QSOX2*, a novel regulator of STAT5B nuclear import and transcriptional activity, lead to severe post-natal growth restriction

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Background: Growth Hormone Insensitivity (GHI) is characterised by short stature and functional IGF-I deficiency associated with normal/elevated GH levels. Marked genetic and phenotypic heterogeneity exist, and heritable defects in GH-IGF-I axis genes/associated pathways account for mild-moderate to severe GHI cases. We report twin brothers from a non-consanguineous kindred who present with short stature and bi-allelic mutations in QSOX2 encoding the nuclear membrane protein, quiescin sulfhydryl oxidase 2. Genome-wide association studies have identified the LHX3-QSOX2 locus as a significant adult height quantitative trait locus. We hypothesise QSOX2 is a novel regulator of STAT5B nuclear translocation, a key step in GH-induced IGF-I production.

Methods: Variant constructs generated by mutagenesis of an N-terminal FLAG tagged-QSOX2 cDNA were expressed in HEK 293-hGHR cells. QSOX2 and STAT5B cellular localisation were assessed by immunoblotting and immunofluorescence. Nano-luciferase complementation and dual luciferase reporter assays evaluated QSOX2-STAT5B interactions and GH-induced transcriptional activity, respectively. Mitochondrial morphology and membrane potential of patient fibroblasts were examined by confocal microscopy and TMRE assays.

Results: Monozygotic twin brothers presented with severe postnatal growth restriction, immunodeficiency, relative macrocephaly, mild dysmorphism, recurrent respiratory tract infections, oral feeding aversion and reduced gastrointestinal motility. Peripheral blood immune profiling revealed low IgM levels and elevated basal levels of tyrosine phosphorylated STAT5 compared to controls. Next generation sequencing revealed compound heterozygous variants in QSOX2; a novel paternally inherited single base deletion, predicted to result in a frameshift truncation and a maternally inherited missense variant, predicted deleterious in silico. We demonstrated a direct interaction between QSOX2 and STAT5B. Nano-luciferase complementation assays revealed attenuation of the interaction of both mutants with STAT5B when compared to wild type. Both mutations led to robust tyrosine phosphorylation of STAT5 following GH agonist stimulation with concomitant cytosolic accumulation and attenuation of nuclear translocation of STAT5B. This effect was phenocopied in patient-derived dermal fibroblasts and similar to the dominant negative STAT5B p.Gln177Pro mutant which disrupts the CCD, suggesting that this domain is integral for interaction with QSOX2. Furthermore, both mutants exhibit reduced STAT5B downstream transcriptional activity. A distinct mitochondrial phenotype was also observed in patient fibroblasts, with reorganisation of oxidative phosphorylation complexes and diminished mitochondrial membrane potential compared to WT.

Conclusion: We describe a definitive role of QSOX2 in modulating human growth, broadening the GHI spectrum. Deficiency of QSOX2 impairs STAT5B downstream activity and mitochondrial dynamics leading to a unique syndrome of postnatal growth failure and mild immunodeficiency similar to germline dominant-negative STAT5B deficiency.

Late Breaking

FC11.1

Deep subcutaneous adipose tissue is associated with hyperinsulinemia in adolescents

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Introduction: Abdominal subcutaneous adipose tissue (SAT) is subdivided into two depots by the fascia of Scarpa. The deep SAT (dSAT) and superficial SAT (sSAT) are morphologically and metabolically distinct, with dSAT reportedly being more similar to visceral adipose tissue (VAT) in terms of elevating the risk for obesity-related complications. Conversely, sSAT appears to be more similar to lower-body SAT. The relationship between dSAT and metabolic disease has been studied in adults, but to our knowledge, no such studies have investigated children and adolescents.

Methods: 203 subjects were included (males n=107, obesity n=182, age 14.1±2.1 years) from childhood obesity clinics in Uppsala, Sweden and Salzburg, Austria. Each participant underwent an oral glucose tolerance test (OGTT) after an overnight fast and magnetic resonance imaging (MRI) in close chronological proximity to the OGTT. Clinical MRI systems (1.5-T, Philips Medical System, Amsterdam, Netherlands) were used. Volumes of

VAT and SAT were determined using a fully automated segmentation method, from slices centered on L2-L3. dSAT and sSAT were assessed through manual segmentation of T1-weighted images by tracking the fascial plane using the software ImageJ. One single operator performed all manual measurements. Statistical analyses were carried out in RStudio. dSAT and sSAT were both normalized against total SAT for all calculations. To assess the relationship between SAT depots and insulin secretion, standardized major axis regressions were calculated through males and females.

Results: There was a positive correlation between total SAT volume and fasting insulin in both males (R^2=0.18, P=8.41x10^{-6}) and females (R^2=0.06, P=0.02). The correlation between dSAT and fasting insulin was also positive in males (R^2=0.16, P=1.94x10^{-5}) and non-significantly so in females (R^2=0.01, P=0.28), while the correlation between sSAT and fasting insulin was negative in both sexes (males R^2=0.20, P=1.37x10^{-6}; females R^2=0.09, P=0.003). The same pattern was seen in 120 min insulin (significant only in males). No significant relationships were found between SAT depots and glucose at fasting or 120 min.

Conclusion: SAT is associated with hyperinsulinemia in adolescents, and the relationship appears to be driven by the deep, rather than the superficial, depot. Although seen in both sexes, the association is more pronounced in males than in females. Accumulation of deep subcutaneous adipose tissue seems to be related to metabolic risk

FC11.2

The influence of Non-Alcoholic Fatty Liver Disease and of its genetics on thyroid function in children with obesity

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Background: The patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) I148M and the transmembrane 6 superfamily member 2 (*TM6SF2*) E167K polymorphisms have been recognized as the major risk polymorphisms for Non-Alcoholic Fatty Liver Disease (NAFLD). Data supported a close relationship of NAFLD with thyroid function both in adults and children. To investigate the influence of NAFLD and of its genetics on thyroid function.

Methods: We examined 2275 children and adolescents with obesity. Both clinical and biochemical evaluations were conducted. Subclinical hypothyroidism (SH) was defined by thyroid stimulating hormone (TSH)>4.2μUI/ml with normal fT3 and fT4. NAFLD was defined by ultrasound detected liver steatosis and/or ALT levels >40IU/L.

Results: Patients with NAFLD had higher TSH levels than those without NAFLD (3.04±1.57 vs. 2.80±1.34 μUI/ml, p<0.0001). Significant differences in SH prevalence were also found in these subjects compared to peers without NAFLD (15.4% vs. 7.4%, p=0.001). They also showed an odds ratio (OR) to have SH of 1.68 (95% CI 1.01-2.80, p=0.04) adjusted for age, BMI-SDS, and sex. Subjects with NAFLD carrying the *TM6SF2* 167K allele showed lower TSH levels than noncarriers (p=0.03), while no differences were found for TSH levels in patients with NAFLD carrying the *PNPLA3* 148M allele (2.97±1.43 vs 3.01±1.36, p=0.73). Carriers of the *TM6SF2* 167K allele with NAFLD presented with an OR to have SH of 0.10 (95% CI 0.01-0.79, p=0.02). Patients carrying the *TM6SF2* 167K allele in the Study Population also had lower TSH levels than noncarriers (2.60±1.41 vs 3.04±1.39, p=0.04). A general linear model for TSH variance (including gender, duration of obesity, NAFLD, *PNPLA3*, and *TM6SF2* genotypes, BMI-SDS, HOMA, LDL, and triglycerides) was run in the study population and TSH levels were found to be inversely associated with *TM6SF2* genotypes (r^2=0.09, adjusted r^2=0.05, p=0.03). The same analysis (including gender, duration of obesity, *PNPLA3*, and *TM6SF2* genotypes, BMI-SDS, HOMA, LDL, and triglycerides) was conducted both in patients with and without NAFLD. It confirmed an inverse and significant association of TSH with *TM6SF2* genotypes only in the NAFLD group (p=0.001).

Conclusion: NAFLD negatively affects thyroid function determining an increase in TSH levels and in SH prevalence. While the *PNPLA3* I148M polymorphism does not have any influence on thyroid function, the *TM6SF2* E167K exerts a protective role against the increase of TSH levels and SH in children with obesity and NAFLD, by expanding its influence on cardiometabolic health of these patients.

FC11.3

Dasiglucagon Significantly Reduces Requirement for Intravenous Glucose in Children with Congenital Hyperinsulinism ages 7 Days to 12 Months

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Background: Congenital hyperinsulinism (CHI) is a rare disease affecting neonates, infants, and children. CHI is characterized by dysregulated insulin secretion resulting in severe recurrent hypoglycemia. Early treatment is necessary to limit the risk of neurologic and developmental sequelae. Current treatment options are limited and inadequate. Dasiglucagon (DASI) is a glucagon analog suitable for continuous subcutaneous infusion which has been shown to raise blood glucose in a dose dependent manner.

Study Design and Objectives: This phase 2/3 trial evaluated the efficacy and safety of DASI in children with CHI ages ≥7 days and <12 months of age with intravenous glucose requirements ≥ 10 mg/kg/min. The study was a 2-period crossover (treatment periods 48 hours each), double-blind, placebo-controlled trial (Part 1) followed by open-label, single-arm DASI treatment (Part 2). Participants were treated with DASI or placebo (by continuous subcutaneous infusion) in random order. Study drug and glucose infusion rate (GIR) were adjusted per protocol to maintain plasma glucose in the normal range. Primary endpoint in Part 1 was GIR

during the last 12 hours of treatment during each 48-hour treatment period. Additional endpoints included total carbohydrate (IV and gastric).

Study Results: A total of 12 children (age 0.5-10.7 months, mean 2.4) were enrolled. Mean GIR for the 12 hours prior to initiation of treatment was 15.7 ± 4.5 mg/kg/min (mean ± SD). The results for the primary endpoint in Part 1 are shown in the table below.

	Mean GIR (SD) last 12 hours (mg/kg/min)
Placebo	9.5 (5.6)
DASI	4.3 (4.9)
DASI vs. Placebo	Treatment difference -5.2 [-8.3; -2.1] p= 0.0037

DASI significantly reduced GIR in the last 12 hours of treatment with a relative reduction in IV GIR of -55% as compared to placebo. DASI also reduced GIR over the entire 48-hour treatment period (treatment difference vs placebo -3.5 mg/kg/min, p=0.0107). Total carbohydrate intake (enteral + parenteral) was lower with DASI treatment (treatment difference vs placebo -31 g/day, p = 0.024), ~22% reduction in carbohydrate calories. No serious adverse events were reported and DASI was safe and well tolerated in study Part 1.

Conclusions: Dasiglucagon significantly reduces the requirement for intravenous glucose to maintain glycemia in neonates and infants with CHI and reduces glucose requirements to levels that potentially allow for discontinuation of IV glucose support. Dasiglucagon has the potential to be an effective, safe, and well tolerated novel treatment for newborns with CHI.

FC11.4

CRN04777, an oral, nonpeptide selective SST5 receptor agonist, dose-dependently suppresses both fasting and stimulated insulin secretion: results from a first in human study

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Congenital hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in neonates, infants, and children, and is caused by genetic mutations in pancreatic beta-cells. Current therapies are burdensome, have limited efficacy, and are associated with significant morbidity. CRN04777 is a potent, orally-bioavailable, selective SST5 agonist that suppresses insulin secretion in the terminal steps of the insulin secretion pathway and could be useful for patients with congenital HI.

We report results from a first in human randomized, double-blind, placebo-controlled study evaluating the safety, pharmacokinetics, and pharmacodynamics of CRN04777 in healthy volunteers. In multiple ascending dose cohorts, 30, 60 and 120 mg of CRN04777 or placebo was orally administered once daily for 10 days (6:3 active:placebo/cohort). Endogenous insulin secretion was stimulated on separate days with a mixed meal tolerance test (MMTT) and a sulfonylurea (SU) challenge, the latter simulating the most common form of congenital HI. In the MMTT (Day -1 [baseline] and Day 6), 400 mL Resource Energy® was consumed 4 hours after study drug dosing. For the SU challenge (Day -2 [baseline] and Day 10), CRN04777 was administered one hour after SU dosing (10 mg glibenclamide/glyburide), followed by continuous IV glucose infusion rate (GIR) measurement under automated euglycemic clamp conditions.

CRN04777 was well tolerated with mild/moderate GI side effects being the most common adverse effects and no serious adverse events. CRN04777 was rapidly orally absorbed (T_{max} 1-3 hours), demonstrating dose-dependent increases in systemic exposures and apparent terminal elimination $t_{1/2}$ of ~40-60 hours. Daily doses of CRN04777 suppressed fasting insulin and C-peptide and increased fasting plasma glucose starting after a single dose at all doses tested. CRN04777 at 60 and 120 mg reduced MMTT stimulated insulin by 33-38% and C-peptide by 20-24% compared to baseline, with increased MMTT-stimulated plasma glucose in all dosing groups. Daily oral doses of 30, 60, and 120 mg CRN04777 also dose-dependently reduced SU-induced insulin and C-peptide concentrations, and dose-dependently decreased the GIR required to maintain euglycemia (-73, -81, -97% with 30, 60, 120 mg respectively; Day 10 vs baseline).

These data demonstrate that once daily dosing with CRN04777 suppresses insulin secretion under both basal and stimulated conditions, including a pharmacologic model of congenital HI and presents an acceptable safety profile. The results from this study support the potential for CRN04777 as a novel oral therapy for patients with congenital HI. Planning for patient studies is currently underway.

FC11.5

Serum kisspeptin, neurokinin B and inhibin B levels can be used as an auxiliary parameter to distinguish idiopathic CPP from premature thelarche in the early stages of puberty

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Background: There are controversial results among the results of various studies evaluating diagnostic utility of kisspeptin, NKB, AMH, and INHB for demonstrating activation of hypothalamic-pituitary-gonadal axis in girls with CPP.

Aim: To evaluate these 4 neuropeptides in the same individuals who presented with early pubertal signs and their validity in the diagnosis and differential diagnosis of CPP.

Patients: Study included 99 girls (51CPP, 48PT) whose breast development started before 8 years and 42 age-matched healthy prepubertal girls. Clinical and anthropometric findings, pubertal

Table1. Serum kisspeptin, NKB, INHB and AMH levels in patients with CPP, PT and control group

	Group I CPP (n=51)	Group II PT (n=48)	Group III Control (n=42)	P values
Age (years)	7.1±1.2	7.2±1.3	7.0±1.0	0.344
Kisspeptin (ng/ml)	0.43±0.16[a,b]	0.26±0.10[a,c]	0.18±0.07[b,c]	<0.001
Neurokinin B (pg/ml)	945.48±315.95[a,b]	567.36±88.38[a,c]	388.60±117.84[b,c]	<0.001
Inhibin B (pg/ml)	412.00±86.77[a,b]	356.25±59.99[a,c]	308.37±56.44[b,c]	<0.001
Anti-Müllerian hormone (ng/ml)	0.60±0.32[a,b]	0.90±0.66[a]	0.80±0.57[b]	0.020

[a]IvsII <0.001, [b]IvsIII <0.001, [c]IIvsIII <0.001, PostHoc Tukey a,b,c p<0.016

stage at diagnosis, growth velocity, bone age (BA), and pelvic ultrasonography findings, basal/stimulated gonadotropin and basal E2 levels were recorded. GnRH stimulation test was performed in all cases with early breast development. Kisspeptin, NKB, INHB and AMH levels were measured in fasting serum samples.

Results: There was no statistically significant difference between mean age of girls with CPP (n=51), PT (n=48), and prepubertal controls (n=42). Girls with CPP had more advanced BA, lower height-adjusted for BA, higher growth velocity-SDS, higher ovarian volume and uterine longitudinal diameter, higher basal gonadotropin, peak LH and E2 levels (p<0.001 for all parameters). Serum kisspeptin, NKB and INHB levels were higher in CPP group compared to PT and control group, while serum AMH level was lower in CPP group (Table 1). Serum kisspeptin, NKB, and INHB were positively correlated with BA advancement, and peak LH in GnRH test. Multiple stepwise regression analysis revealed that the most important factors used to differentiate CPP from PT were advanced BA, serum kisspeptin, NKB and INHB levels (standardized β coefficients were 1.809, 1.528, 1.321 and 0.725, respectively) (r2:0.889; P<0.001).

Conclusion: We, to the best of our knowledge, firstly showed in the same patients group that serum kisspeptin, NKB and INH levels were higher in CPP patients and can be used as an auxiliary parameter to distinguish CPP from PT in early stages of puberty.

FC11.6

The follicle-stimulating hormone receptor is expressed in human pancreatic islet beta-cells and its activation increases glucose stimulated insulin secretion

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Background: Follicle-stimulating hormone (FSH) plays a key role in reproduction. The G-protein coupled FSH receptor (FSHR), is expressed primarily in gonads, and specifically binds FSH. FSHR is also expressed in vascular endothelium, osteoclasts, adipose tissue, monocytes and rodent pancreatic islets. Elevated FSH levels are associated with development of obesity, insulin resistance, osteoporosis, and cardiovascular disease. In a recent study, we showed that high FSH levels in prepubertal children with obesity are associated with increased risk of metabolic syndrome development during puberty. FSH levels correlated positively with plasma insulin levels, in this study. It is not known if the FSHR is expressed in human pancreatic islets and if so, whether binding of FSH to the receptor directly affects insulin secretion.

Hypotheses: FSHR is expressed in human islets and FSH acts via islet FSHR to potentiate glucose-stimulated insulin secretion.

Objective: To investigate FSHR expression in human pancreatic islets and effects of FSH on insulin secretion.

Methods: Human pancreatic islets were obtained from brain-dead donors without known metabolic disease from the Uppsala University Islet Transplantation Unit and from Prodo Lab Inc (CA). FSHR gene expression was assessed by quantitative polymerase chain reaction (qPCR). FSHR protein expression was evaluated by confocal immunofluorescence microscopy. Intracellular cAMP concentration changes were recorded from intact human islets transduced with an adenoviral vector encoding the FRET-based sensor Epac-S^{H187}. Islets were perfused and insulin secretion was measured dynamically at 5.5 and 11 mM glucose and in the presence (10 IU/L, pubertal level) or absence of human FSH (Sigma-Aldrich, St. Louis, MO). Insulin was measured by ELISA (Mercodia AB, Uppsala, Sweden) and normalized to total protein content (DC protein assay, Bio-Rad Laboratories, Hercules, CA, USA).

Results: FSHR gene and protein expression were detected in human pancreatic islets primarily localized to insulin-producing pancreatic beta-cells. Insulin secretion at 5.5 mM glucose from isolated human islets was not affected by FSH. In contrast, when the glucose concentration was increased to 11 mM in the continued presence of 10 IU/L FSH, approximately 2-fold accentuated insulin secretion was observed. The addition of FSH (10 IU/L) in the presence of 11 mM glucose was also associated with increased intracellular cAMP concentration.

Conclusion: The follicle-stimulating hormone receptor is expressed in human pancreatic islet beta-cells and its activation increases glucose stimulated insulin secretion, likely via increased cAMP production.

Rapid Free Communications

Thyroid

RFC1.1

European Thyroid Association Guideline on the Management of Pediatric Thyroid Nodules and Thyroid Carcinoma

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At present no European recommendations for the management of pediatric thyroid nodules and differentiated thyroid carcinoma (DTC) exist. Differences in clinical, molecular, and pathological characteristics between pediatric and adult DTC emphasize the need for specific recommendations for the pediatric population.

An expert panel was instituted by the executive committee of the European Thyroid Association (ETA) including an international community of experts from a variety of disciplines including pediatric and adult endocrinology, pathology, endocrine surgery, nuclear medicine, clinical genetics, and oncology.

The American Thyroid Association (ATA) pediatric guideline 2015 was used as framework for the present guideline. Areas of discordance were identified, clinical questions were formulated and literature searches were performed. The expert panel members discussed the evidence and formulated recommendations based upon the latest evidence and expert opinion.

Children with a thyroid nodule or DTC require expert care in an experienced center. The present guideline provides guidance for healthcare professionals to make well-considered decisions together with patients and parents regarding diagnostics, treatment and follow-up of pediatric thyroid nodules and DTC.

RFC1.2

Secondary thyroid carcinoma in survivors of childhood cancer: a need to revise current screening recommendations

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Thyroid cancer is the most common secondary malignancy for survivors of childhood cancer, with radiation exposure before age 18 being the most significant risk factor. Current guidelines from the Children's Oncology Group recommend yearly physical examination to palpate for thyroid nodules. Whilst other societies recommend periodic thyroid ultrasound, further evaluation with fine needle aspirate is typically not considered for nodules less than 10mm in diameter. We describe a case series of five patients with papillary thyroid carcinoma following radiation exposure, all with nodules <10mm (and some <5mm) and three with metastatic disease.

There is debate in the literature regarding both necessity of routine surveillance and the optimal modality for screening, citing surveillance as potentially exposing patients to unnecessary harms and avoidable distress. Over the past 20 years, we have undertaken surveillance of 339 patients post-radiation exposure, utilising 2-yearly ultrasound, with an abnormality detected in 129/339 (38%). We will highlight the impalpable nature of smaller thyroid nodules, recommend utilisation of screening ultrasound and indicate a need to revise clinical guidelines for surveillance of paediatric and adolescent thyroid cancer post-radiation exposure.

RFC1.3

The importance of extra-endocrine features at infancy in multiple endocrine neoplasia type 2B for early diagnosis

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Background: Multiple endocrine neoplasia type 2B is a rare genetic syndrome caused by germline mutations in the RET proto-oncogene. Approximately 75% of MEN2B cases are sporadic and caused by de novo RET mutations, whereas 25% of cases occurs in families with an autosomal dominant inheritance. The most common RET mutation found in 95% of MEN2B patients is the substitution of the amino-acid threonine for methionine at codon 918. In infants with de novo mutation of the RET codon M918T, the diagnosis of MEN2B is usually delayed than the appearance of medullary thyroid carcinoma; in fact the majority of these patients show extra endocrine features during childhood.

Case Reports: We report three cases of MEN 2B syndrome referred at our Endocrinology Unit for extra endocrine features.

Patient 1: a 17 months old male referred for episodes of central apnoea associated with cyanosis since 4 months of age. He also showed prominent lips and chronic constipation. To rule out congenital hypoventilation syndromes, we excluded by array-CGH genetic conditions of hypoventilation. Then we assessed whole exome sequencing that revealed the de novo heterozygous missense variant c. 2753T>C (p.Met918Thr) in RET gene.

Patient 2: a 17 months old male child evaluated for generalized hypotonia and delayed psychomotor development with full lips, macroglossia and relative macrocrania. Moreover, he showed chronic constipation since weaning and monocular alacrimia. Based on clinical features overgrowth syndrome was excluded through genetic test that showed de novo missense heterozygous variant, c.2753T>C (p.Met918Thr), in RET gene.

Patient 3: a 6-year-old male child referred for growth retardation. During first months of life he showed keratoconjunctivitis and alacrimia associated with constipation and intellectual disability. Based on clinical features and history, we assessed calcitonin level (872 pg/ml; nr < 9.5 pg/ml), thyroid function (normal FT4 and TSH). We confirmed our hypothesis by genetic test that showed de novo missense mutation c.2753T>C (p.Met918Thr) in RET gene.

Conclusion: MEN2B is an extremely rare condition associated with variability of clinical signs and symptoms. Our cases confirm the importance related to identify extra endocrine signs in these patients. This approach can contribute to detecting early potential neoplastic endocrine lesions (medullary thyroid cancer) and improve the average survival.

RFC1.4

Usefulness of thyroid function assessment in infants born to mothers with thyroid dysfunction in pregnancy

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Introduction: Maternal thyroid disease is considered as a risk factor for abnormal thyroid function at birth as well as for long-term morbidity in offspring. The potential harmful effects on the neonate had led to the clinical practice of thyroid function assessment in infants born to mothers with thyroid disease during pregnancy, despite well-established newborn screening programs with include congenital hypothyroidism screening. We evaluated the usefulness of routine thyroid function tests, in addition to newborn screening programs for congenital hypothyroidism, for every newborn of a mother with thyroid dysfunction.

Methods: Data were collected retrospectively from the medical files of mothers diagnosed with thyroid disease and their infants (701 mother–neonate pairs). all mothers with diagnosis of thyroid disease that gave birth between the years 2016-2019 in our medical center were included.

Results: Hypothyroidism was the most common maternal diagnosis (91.4%). Among which 48.7% had Hashimoto's thyroiditis. Hyperthyroidism was diagnosed in 8.6% of the cohort, —of whom 71.6% had a diagnosis of Graves' disease. None of the newborns was diagnosed with congenital hypothyroidism in the screening program. Thyroid-stimulating hormone was >10 mIU/l in 14.6% and >20 mUI/l in 2.2%, all had free thyroxine within normal range. Four infants were diagnosed with thyroid disease: hypothyroidism (3) and neonatal Graves' disease (1). Two neonates had congenital hypothyroidism not related to maternal thyroid disease, and one had transient familial congenital hypothyroidism.

Conclusions: Thyroid function testing for all newborns of mothers with thyroid dysfunction seems redundant. However, in cases of congenital hypothyroidism in siblings, a stricter approach is indicated and in maternal Graves' disease, thyroid function testing on day 2–3 of life is recommended.

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RFC1.5

"Screening for congenital hypothyroidism in preterm newborns: Thyroid Stimulating Hormone (TSH) percentiles for weight and gestational age and congenital hypothyroidism features"

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Background: Preterm newborns (PN) are at risk of developing congenital hypothyroidism (CH) with a high reported incidence (1:300 vs 1:2000 for at term newborns). The study's objective was to determine the TSH percentiles at neonatal screening (NS) in PN and to analyze the incidence of permanent and transient CH in this population.

Materials and Methods: PN born in the Piedmont Region of Italy in the period 2019-2021 were included.

Results: NS was performed by TSH detection on Guthrie cards in 5930 PN. The first TSH analysis was made at 3.3 ±1.48, the second at 15±1.4 and the third at 26.8±15.4 days of life. TSH mean levels and percentiles are represented in Table 1.

TSH levels considering weight and gestational age (GA) are shown in Table 2 and 3, respectively.

NS results for each TSH detection are depicted in Table 4. CH incidence was 1:156; in those born in 2019-20 the percentage of transient CH was 65%.

Conclusion: The incidence of CH in PN is much higher than in at term infants. In PN, targeted NS strategies are needed which should consider both neonatal weight and GA.

Table 1. Mean TSH levels and percentiles during NS in PN.

	Mean	1°	3°	25°	50°	75°	97°	99°
1st detection (n=5930)	2.3±0.02	0.2	0.4	1.17	1.9	3	6.4	8.5
2nd detection (n=5130)	1.77±0.02	0.3	0.4	1	1.5	2.2	4.5	5.7
3rd detection (540)	1.56±0.02	0.2	0.36	1.1	1.6	2.55	4.7	5.17

Table 2. TSH percentiles for weight at NS in PN.

	Neonatal weight					
	<1000 g	1000-1499 g	1500-2500 g	>2500 g	p	p
1st detection	2.08±0.15	2.01±0.08	2.28±0.03	2.41±0.03	p < 0.005	P < 0.005
2nd detection	2.13±0.11	2.32±0.23	1.93±0.04	1.62±0.02	p < 0.005	P < 0.005
3rd detection	2.07±0.16	3.87±1.43	2.29±0.2	1.62±0.09	p = 0.16	P = 0.16

Table 3. TSH percentiles for GA at NS in PN.

	Gestational age				
	22-<28 w	28-<32 w	32-<34 w	34-<37 w	p
1st detection	1.71±0.09	1.87±0.06	1.94±0.05	2.42±0.02	p < 0.005
2nd detection	1.89±0.11	2.15±0.21	2.2±0.16	1.75±0.02	p < 0.005
3rd detection	1.75±0.14	2.11±0.13	2.62±0.24	1.94±0.14	p = 0.01

Table 4. NS results for each TSH detection.

	Normal	TSH re-evaluation by screening	Serum TSH evaluation	CH
1st detection	5850	73	-	7
2nd detection	5232	10	39	29
3rd detection	521	-	17	2

RFC1.6

Frequency and risk factors of hypothyroidism following cardiac catheter in infants with congenital heart diseases: A prospective study

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Background: This study aims to determine the incidence, clinical course and risk factors of hypothyroidism following cardiac catheter (CC) in infants with congenital heart diseases (CHD).

Subjects and Methods: This prospective study included 102 patients with CHD, aged ≤ 3 years who underwent CC. Thyroid function tests were evaluated before CC, one day, one week, two weeks and four weeks after the procedure.

Results: 12% of the studied group showed hypothyroidism four weeks after CC. Univariate analysis revealed that the significant predictors of hypothyroidism following CC are aortic stenosis (RR=10.0 (1.49-66.99), P=0.018), duration of fluoroscopy (RR=1.12 (0.99-1.26), P=0.05), and total cumulative dose of iodinated contrast media (iCM) (RR=1.01 (1.003 -1.01), P=0.019). Multivariate analysis revealed that iCM dose was the only significant predictor of developing hypothyroidism (RR=1.00 (1.00-1.01), P=0.04). ROC curve analysis showed that the cut-off point of iCM dose for prediction of hypothyroidism evolution is 8.7 gm/kg (26.1 ml/kg), (sensitivity: 83.3%, specificity: 65.1%), while the cut-off point of fluoroscopy duration which predicts development of hypothyroidism is 24 minutes, (sensitivity: 83.3%, specificity: 65.9%). Acquired hypothyroidism after CC persists in 5% of this cohort for a median duration of 20 months.

Conclusion: Exposure to higher dose of iCM and longer duration of fluoroscope during CC are risk factors for evolution of thyroid hypofunction. We recommend assessment of thyroid profile 4 weeks after CC particularly in patients who received a dose of iCM higher than 8.7 gm/kg and/or exposed to fluoroscopy for more than 24 min.

Bone, Growth Plate and Mineral Metabolism

RFC2.1

Muscle function in XLH - Two year prospective observation of paediatric patients before and after treatment initiation with burosumab

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X-linked hypophosphatemia (XLH, MIM 307800) is a rare hereditary disorder of bone metabolism characterized by growth impairment, leading to bone deformities and short stature and beside others to muscle function deficits. XLH is caused by defect of endopeptidase PHEX leading to high levels of FGF-23 and thereby renal phosphate wasting. While conventional treatment includes substitution of phosphate and 1-25 OH-Vitamin D, now a treatment with a FGF-23 antibody (burosumab) is available, normalizing serum phosphate. We present prospective observational data of patients, with a detailed assessment of muscle function during conventional therapy and after changing to burosumab.

In eleven paediatric patients treatment with burosumab was initiated after approval by the European Medical Agency. We monitored this patients at five specific timepoints related to treatment (during conventional therapy (t1); wash out/no treatment (t2); three months (t3), 12 months (t4), 24 months (t5) after initiation of burosumab treatment). Monitoring included clinical/radiological follow up (auxiology, clinical chemistry, x-ray of the palm) and a defined set of muscle function tests (grip force, two-legged-jump (2LJ), chair rising test (CRT)).

In eleven patients (age: 9.6 ± 3.4 years) treatment with burosumab was initiated. During conventional therapy most clinical and functional parameters were outside of the age and gender specific reference range. Height standard deviation score (SDS) improved from -2.71 (t1) to -2.24 (t5) while BMI-SDS did not change. Although serum anorganic phosphate only increased slightly, from 0.53 (± 0.12) times lower fold of age/gender specific reference values to 0.69 (± 0.14), alkaline phosphatase normalized from 1.45 (± 0.37) times upper fold of age related reference values to 0.94 (±0.24). Regarding muscle function, there was a trend, but no significant improvement of grip strength SDS (neither age (-0.18 (t1) to 0.21 (t5)) or height corrected (1.68 (t1) to 1.84 (t5))), nor in force, power or the Esslinger Fitness Index (E.F.I) in 2LJ or CRT. Nevertheless, there is a strong trend to an improved average time per test SDS for CRT (2.86 SDS (t1) to 0.34 SDS (t5). Signs of rickets, radiologically assessed by Thatcher-Score improved over time.

Real-life observations support recent findings of improvement of clinical parameters in patients with XLH treated with burosumab. We could confirm and extend knowledge about muscle function deficits during conventional therapy. Additionally, we could show moderate improvements in muscle function after initiation of burosumab treatment. Further studies are needed to investigate the influence of phosphate homoeostasis on muscle function in XLH.

RFC2.2

Single-center analysis of quality of life in patients with X-linked hypophosphatemia (XLH)

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Background: X-linked hypophosphatemia (XLH) is a rare metabolic bone disease which is caused by inactivating mutations in Phosphate-regulating neutral endopeptidase, X-linked (PHEX). Due to dysregulation of Fibroblast growth factor 23 (FGF-23), increased systemic levels of FGF-23 lead to chronic renal

phosphate wasting and to impaired activation of 25OH-Vitamin D (25OHD). As a result, patients suffer from multiple musculoskeletal symptoms such as long bone deformities, short stature, bone pain, muscle weakness, dental abscesses, and fatigue. Conventional treatment with phosphate supplements and active vitamin D derivatives as well as FGF23-blocking antibody treatment are used to ameliorate symptoms in patients with XLH. To date, detailed data on QoL in well-defined XLH cohorts including treatment associated changes are sparse.

Methods: The German version of PedsQL^{TM} was performed by 16 pediatric patients with confirmed XLH (f: m = 10:6, conventional treatment n=15, Burosumab m=1). Comparison with an osteogenesis imperfecta (OI) cohort, historic data on healthy children and patients with achondroplasia were used for comparison. Patients switching from conventional to Burosumab treatment (n=5) were investigaed regarding changes of treatment-relevant parameters including QoL domains.

Results: Physical QoL was substantially reduced in the investigated XLH patients (-17.8% vs. historic healthy cohort), comparable to patients with achondroplasia (-19.1 vs. historic healthy cohort) and exceeded QoL impairment of patients with non-deforming Osteogenesis imperfecta (-11.8% vs. historic healthy cohort). BMI SDS and the number of osteotomies was negatively associated with physical QoL (BMI SDS: p=0.033; osteotomies: p=0.049). Disease specific factors such as age, alkaline phosphatase (ALP) or the rickets severity score (RSS) did not predict QoL. After a mean Burosumab treatment duration of 15 +/-3 months patients revealed an increase of +14% (+/-13) in physical QoL, as well as improvement of biochemical and radiographic parameters for rickets severity.

Conclusions: Impairment of QoL in patients with XLH is found in the range of patients with severe skeletal dysplasias such as achondroplasia. Lower physical wellbeing scores as compared to patients with osteogenesis imperfecta point to an often underestimated disease burden. Associations of BMI and the numbers of osteotomies with physical QoL suggest an impact of metabolic factors and burden of surgical interventions in this cohort. While data are limited, improvement of physical QoL under >1 year of Burosumab treatment raises the prospect of sustained amelioration of disease burden in this vulnerable cohort.

RFC2.3

The European Registries for Rare Bone and Mineral Conditions: Registering New Cases of Paediatric Rare Bone and Mineral Conditions Using an Electronic Reporting Tool

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Introduction: The European Registries for Rare Bone and Mineral Conditions (EuRR-Bone) are closely linked to the European Reference Networks on Rare Bone Diseases (ERN BOND) and Rare Endocrine Conditions (Endo-ERN) and with its registry EuRRECa. It is open to all professionals involved in the care of individuals with rare bone and mineral conditions. EuRR-Bone offers an electronic reporting tool (e-REC) for capturing newly encountered cases without collecting personal data.

Purpose: To describe the generated data on Bone and Mineral conditions via e-REC in the <18 years group from April 2020 to December 2021.

Methods: e-REC users received invitations to complete a monthly online return which collects the number of new paediatric (<18y) and adult (≥18y) cases of conditions that are included in the registry. Conditions are mapped according to ORPHANET codes.

Results: 43 centres from 18 countries are active reporters, of which 28 register paediatric cases. Of 43 centres, 18 are ERN BOND members, 26 are Endo-ERN members and 14 have no ERN affiliation. A total of 361 adult and 435 paediatric new cases of Bone or Mineral conditions were registered. Amongst children, 161 and 274 new cases of bone mineral and bone dysplasia conditions respectively were reported. Within the bone mineral group,

the most frequently reported were X-linked hypophosphataemia (52/161 cases,32%), pseudohypoparathyroidism (39/161 cases,24%) and hypoparathyroidism (25/161,16%). Within the bone dysplasia group, osteogenesis imperfecta (70/274,26%), achondroplasia (63/274,23%) and fibrous dysplasia/McCune-Albright Syndrome (39/274,14%) were the most frequently reported. An increase in the number of reporting centres from 12 to 43 and in the total number of cases from 23 to 800 cases, was documented in e-REC during the second year of activity.

Conclusion: e-REC is an easy-to-use online tool that objectively maps the occurrence of rare bone and mineral conditions among centres and countries. The growing e-REC user community and number of reported cases have facilitated the development of related projects such as secondary surveys that aim to collect relevant data for understanding specific aspects of the reported conditions.

RFC2.4

Dysosteosclerosis is also caused by null mutations of TNFRSF11A

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Dysosteosclerosis (DOS) is a rare form of dense bone disease and, short stature, recurrent fractures, optic atrophy, cranial nerve palsy, developmental delay, flattened fingernails, skin related complications, and failure of tooth eruption are the characteristic features of the disease (MIM %224300). Irregular osteosclerosis, flattened diffusely dense vertebral bodies, sclerotic skull, radiolucent sub-metaphyseal portions of the long tubular bones with sclerotic diaphysis are radiological features of DOS [1]. Moreover, metaphyseal osteosclerosis and platyspondyly are the characteristic and important guiding findings in differentiating DOS from other types of sclerosing bone dysplasia [2].

DOS is inherited in an autosomal recessive manner and is genetically and clinically heterogeneous. Various genetic causes associated with DOS disease have been described to date (1-3). SLC29A3 (solute carrier family 29 member 3) was the first identified causative gene for DOS, followed by TNSFR11A (tumor necrosis factor receptor superfamily member 11a), TCIRG1 (T cell immune regulator 1) and CSF1R (Colony stimulating factor 1 receptor), respectively [1-6].

It is well known that RANK (receptor activator of nuclear factor kappa B, also known as TNSFR11A), RANK ligand (RANKL, also known as TNFSF11) and osteoproteogerin, members of the TNF and TNF-receptor superfamily, play a crucial role in stimulating osteoclastic formation and differentiation [7]. To date, four individuals with DOS have been reported with five different mutations in TNFRSF11A (2 missense/nonsense, 2 splice-site, 1 deletion) [1,4-6]. According to the previous hypothesis, aberrant mutant RANK proteins (missense or truncated) cause DOS, while null mutations lead to osteopetrosis, autosomal recessive 7 (OPTB7) (1,4-6). Herein, we present the fifth case of TNFRSF11A-associated DOS in a 19-month-old boy, in whom we identified a novel homozygous variation in TNFRSF11A (c.19_31del; p.[Arg7CysfsTer172]). Unlike previously reported variants [1,4-6], the variant is predicted to cause nonsense mutation-mediated mRNA decay (NMD) in all RANK isoform transcripts, which enabled us to re-consider the phenotype and genotype characteristics of the TNFRSF11A-associated DOS.

RFC2.5

Bone biopsy histomorphometric features of vertebral changes in sickle cell disease

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Background: Vertebral changes such as biconcave end plate depressions are well described in children with sickle cell disease (SCD). However, as vertebral height reductions are a marker of osteoporosis in children, we aimed to determine whether these could present underlying osteoporosis, by performing transiliac bone biopsies in two patients.

Case 1: A 13-year-old female with SCD, presented with back pain. She had delayed puberty, history of subacute avascular necrosis of shoulder and periostitis of hip. Baseline DXA showed, Whole body less head (WBLH) bone mineral density (BMD) z-score: -1.6, Lumbar spine (LS) BMD z-score: -2. Baseline vertebral fracture assessment (VFA) showed multilevel end plate depressions. DXA after 12 months was stable (WBLH: -0.9, LS:-2.1, no further vertebral changes on VFA). MRI spine confirmed central end plate depressions, with no bone marrow oedema.

A bone biopsy was performed due to the persistence of back pain, low BMD and abnormal vertebral imaging.

Structural histomorphometric parameters on bone biopsy revealed slightly reduced cortical width (Ct.Wi) and bone volume per tissue volume (BV/TV), normal trabecular indices and osteocyte density. Bone formation rate (BFR/BV) was increased, whereas bone resorption parameters were normal. No mineralisation defect was identified.

Case 2: A 15-year-old female with SCD, with poor adherence to hydroxycarbamide treatment presented with back pain.

Baseline DXA z-scores: WBLH-BMD -0.2 and LS-BMD -0.5; VFA showed multiple endplate depressions with >25% height reductions in the thoracolumbar vertebrae.

Repeat DXA at 12 months showed stable BMD, however there was further T12 height reduction on VFA, with improvement in T11. MRI spine showed abnormal STIR signals in L4/L5 and S1.

Structural histomorphometric parameters on bone biopsy showed normal Ct.Wi, increased BV/TV, increased BFR/BV and hyperosteocytosis.

Discussion: Both biopsies demonstrated cortical and trabecular indices within the normal range, ruling out osteoporosis. There was, however, increased bone formation, but no evidence of mineralisation defect. Vertebral changes on VFA and abnormal signal on MRI are likely infarcts. This is in line with DEXA BMD reports. Therefore, treatment should focus on optimising SCD treatment and pain management. In equivocal cases diagnosis of osteoporosis should be made on basis of bone histomorphometry via bone biopsy.

RFC2.6

Genetic liability and late adverse musculoskeletal, metabolic and mental health effects in a cohort of survivors of childhood acute lymphoblastic leukemia – a PETALE study

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Objectives: Survivors of childhood acute lymphoblastic leukemia (cALL) present elevated fracture rates compared to the general population. A polygenic risk score for estimated bone mineral density (BMD), named gSOS, validated to predict the risk of adult osteoporotic fracture, has been previously associated with significant fracture risk in childhood. We hypothesized that gSOS could be associated with long-term, bone health-related mobidities in survivors of cALL.

Methods / Results: We recruited 245 (50.6% female) long-term cALL survivors, treated from 1987 to 2005 (PETALE cohort). Median age at recruitment was 21.7y (range 8.5 – 41y) and median time since diagnosis was 15.1y (range 5.4 – 28.2y). For all participants, BMD measures (Z-scores) were obtained using Dual-energy X-ray absorptiometry (DEXA) at the lumbar spine (LS-BMD), femoral neck (FN-BMD) and total body (TB-BMD), and vertebral fractures since cALL diagnosis were documented (Ntotal with vertebral fracture (yes/no)=57).

We computed gSOS measures in 220 PETALE participants (107 males, 113 females) with available imputed genotype data. gSOS was standardized (mean=0, SD=1) and tested for association with the three BMD Z-score measurements and vertebral fracture risk. Multivariate analyses adjusted for age at the time of BMD evaluation, sex, cumulative corticosteroid dose, cranial irradiation, fitness, and age at diagnosis. We also performed sex- and relapse risk group-stratified analyses.

gSOS was significantly associated with LS-BMD (β=0.15, 95% CI= 0.13-0.18 p=0.04) in both sexes. In sex-stratified analyses, this association was only present in females (β=0.27, 95% CI=0.22-0.32, p=0.008). We did not observe significant effects of gSOS on FN-BMD, TB-BMD, and vertebral fracture risk, but we had limited power to study the latter associations. Notably, risk group stratification did not unravel differences in the association of gSOS with the studied outcomes between standard and high-risk groups.

Conclusion: Our findings are a step towards using polygenic risk scores to predict bone health outcomes in survivors of childhood cancer. This could allow for targeted screening of cALL survivors who are at the highest risk of treatment-related musculoskeletal late effects, and for optimized allocation of health resources. We are applying a similar approach to assess effects of polygenic predictors on long-term cardiometabolic and mental health oucomes in PETALE.

Early Life and Multisystem Endocrinology

RFC3.1

Brain Magnetic Resonance Imaging Changes in Childhood and its possible correlation with Unrecognised Early Life Hypoglycaemia

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Introduction: The neonatal threshold for hypoglycaemia is debatable and makes its treatment challenging. Neonatal hypoglycaemia can be transient and yet pose a significant risk of neuroglycopaenia, especially with severe and recurrent hypoglycaemia in Congenital Hyperinsulinism. Untreated hypoglycaemia induced cerebral injury can be identified by magnetic resonance (MR) brain scan changes affecting cerebral white matter, occipital lobes and posterior parietotemporal regions. It is recognized that a proportion of MR scan changes of hypoglycaemia may be due to missed and untreated early life hypoglycaemia, but the frequency is not known.

Methods: We present retrospective MR scan data in children in a single centre, collected over a ten year period (2010-2020) to identify potential cases of missed and untreated early life hypoglycaemia. Specific criteria were used to identify hypoglycaemic brain changes. Scan search from an electronic radiology repository involved the term "hypoglycaemia" in the scan report. Early life hypoglycaemia was confirmed or rejected by review of electronic hospital records.

Results: A total of 107 MR scan and hospital records of patients with potential hypoglycaemia were reviewed, of whom 52 (48.5%) showed evidence of hypoglycaemic brain changes. We categorized them age group wise in relation to their initial presentation warranting admission, evidence of hypoglycaemia, MR findings, and further evaluation. Among these 52 patients with MR evidence of hypoglycemia, representation in different age groups were as follows: newborn 11, infants 12, 1-5 yrs 19 and >5 yrs 10.

Evidence of hypoglycaemia was documented in 26 patients (50%), with 8 experiencing hypoglycaemia in the neonatal period and the rest beyond the neonatal period. The remaining 26 patients (50%) did not have documented hypoglycemia in their medical records despite the MR Brain changes. This absence of hypoglycemia prior to scan was definite in 17(33%), probable in another 5

(9.5%), and unavailable in 4 (7.5%) patients based on the details obtained from medical records

Conclusion: Nearly half the children with hypoglycaemia specific brain MR scan changes may have unrecognized and untreated hypoglycaemia, implying the need for heightened awareness of early life hypoglycemia. Our study suggests the need to investigate similar scan changes in other cohorts to understand the true extent of hypoglycaemic brain injury in children.

RFC3.2

The Hypoglycaemia Error Grid: a UK-wide Consensus on CGM Accuracy Assessment in Hypoglycaemia due to Congenital Hyperinsulinism

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Background and Objective: Continuous Glucose Monitoring (CGM) is gaining in popularity for patients with paediatric hypoglycaemia disorders such as Congenital Hyperinsulinism (CHI), but no standard measures of accuracy or associated clinical risk are available. A small number of studies have shown suboptimal accuracy of CGM in CHI but assessments have been inconsistent, incomplete and offer no measure of clinical application. Error grids that categorise clinical risk from use of CGM were designed for use in diabetes and have no applicability to patients with hypoglycaemia disorders.

We aimed to develop a novel Hypoglycaemia Error Grid (HEG) for CGM assessment for those with CHI based on expert consensus opinion and apply this to a large paired (CGM/blood glucose) dataset to derive expert-informed clinical risk.

Design and Methods: Paediatric endocrinologists managing CHI in the two UK centres of excellence were asked to complete a questionnaire regarding glucose cutoffs and associated anticipated risks of CGM errors in a hypothetical model. Collated information was processed to calculate risk for 10,000 theoretical CGM vs glucometer combinations and, from these, the HEG was computationally generated before final expert confirmation of risk boundaries.

Ten patients with CHI underwent 12 weeks of monitoring with a Dexcom G6 CGM and self-monitored blood glucose (SMBG) with a Contour Next One glucometer to test application of the HEG and provide data for accuracy calculations.

Results: Based on 1441 paired values of CGM and SMBG (mean absolute time difference 1.3 minutes), device accuracy was suboptimal: Mean Absolute Relative Difference (MARD) of 19.3%, mean absolute difference of 0.93mmol/L and hypoglycaemia (glucose <3.5mmol/L) sensitivity of only 45%. Mean difference between CGM and SMBG was 0.43mmol/L demonstrating a mean over-reading of CGM devices. The HEG provided clinical context to CGM errors and contrasting risk profiles with existing diabetes error grids, reinforcing its utility in hypoglycaemia.

Conclusions: The HEG, based on UK expert consensus opinion, offers a standardised method for CGM accuracy analysis in patients with hypoglycaemia disorders and can be applied to historic and future datasets. Application in the largest ever paired CGM and SMBG dataset in patients with CHI has demonstrated inadequate accuracy of CGM to recommend as a standalone tool for routine clinical use. However, suboptimal accuracy of CGM relative to SMBG does not detract from the use as a digital phenotyping tool.

RFC3.3

Analysis of a series of italian APECED patients with autoimmune liver disease and enteropathies

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Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED, OMIM240300) is a rare monogenic disease due to biallelic mutations in the Autoimmune Regulator (AIRE) gene. This encodes for a thymus-enriched transcription factor responsible for central immune tolerance. Classic diagnostic criteria are the presence of two of main symptoms of chronic mucocutaneous candidiasis (CMC), hypoparathyroidism (HP) and Addison's disease (AD). Non-endocrine autoimmunity involving the liver, intestine, eye and kidney is generally reported in a minority of patients.

In Finnish, Sardinian and Iranian Jew populations APECED develops at the highest prevalence with homozygous AIRE mutations c.769C>T, c.425C>T and c.254A>G having a founder effect respectively. American APECED patients showed enrichment of organ-specific non-endocrine manifestations starting early in life as compared to European cohorts. This observation led to revise diagnostic clinical criteria that would permit earlier diagnosis

based on the appearance of one classic triad and one non-classical manifestation at young age in presence of IFNAbs or AIRE mutations (PMID29562162).

We analysed the clinical, genetic and autoAbs profile in a series of 10 Italian APECED pediatric patients with gastrointestinal manifestations (5 males, 5 females). Seven patients presented APECED-associated hepatitis (APAH). In 3 patients this occurred as first disease manifestation; 2 patients developed APAH following HP; one following MC and one following the dyad CMC, HP. The mean age of APAH diagnosis was 7.9 years (range 1.5-13).

APAH-related specificities LKMAbs tested positive in one patient, TPH in 3/7; AADC were enriched in 6/7 and cP450c21 in 5/7. Most frequent AIRE mutation was c.967_979del13.

Six patients were affected by signs of constipation/diarrhea/malabsorption. One patient was also affected by iron-deficiency anemia and two by atrophic gastritis, of these one with pernicious anemia. The mean age of intestinal dysfunction diagnosis was 6.8 years (range 5.6-9). The sera of 4 patients tested positive for TPH Abs and of 4 for AADCAbs known to be associated with autoimmune enteropathy (AIE) in APECED. AIE-75 and villin Abs tested negative. All patients' sera tested positive for IFNα4 and 9/10 for IFNωAbs. cP450c21Abs tested positive in 5/7 APAH patients and in 3/6 with gastrointestinal dysfunction. No specific AIRE genotype was prevalent.

Based on the age of appearance of non-endocrine manifestations (29562162), Ferre-Lionakis criteria (27588307), similar to the American cohort, would have allowed an expedited clinical diagnosis in 8/10 patients. This emphasize the importance to evaluate non-endocrine manifestations such as APAH and gastrointestinal dysfunction for an earlier diagnosis of APECED even in European cohorts.

RFC3.4

Immunophenotype and proinflammatory cytokines in ROHHAD(NET) patients compared to age- and sex-matched obese patients

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Background: ROHHAD(NET) syndrome has been proposed as an acquired neuroimmunological dysfunction. Aim of the study is to compare the phenotype of lymphocyte subpopulations in patients versus controls and to evaluate the plasma levels of proinflammatory cytokines/chemokines in ROHHADNET syndrome.

Patients and Methods: We included 14 patients (9F;5M), selected by clinical criteria, matched with 11 controls with simple obesity (7F;4M). Median BMI at sample day was respectively +3.8 SDS and +3.1 SDS. Lymphocyte subpopulations and proinflammatory cytokines/chemo kines were analyzed by Flow Cytometry performed on peripheral blood (PB) in the two groups.

Furthermore, soluble HLA-G (sHLA-G) and soluble HLA-E (sHLA-E) were assessed through Enzyme-Linked Immunosorbent Assay (ELISA) both in patients and in controls.

Results: Phenotypical analysis of PB samples revealed that T lymphocytes are significantly increased in ROHHADNET patients, compared to obese controls (cells/µl, mean±SD:1859±450,5 vs 1544±441,8, p=0.04) with a prevalence of CD4-T cells (1129±394,4 vs 749,3±316,2, p=0.03) and a lower number of activated CD8-T cells (90,90±47,15 vs 204,1±113,1, p=0.02).

Considering regulatory cell subsets, patients displayed an increase of regulatory B cells (Breg) (30,61±11,75 vs 19,07±14,44, p=0.05) and a significantly increased Type-1 regulatory T cell subset (Tr1) (4,880±2,740 vs 2,205±1,735, p=0.03).

Among CD8-T cells, we observed a lower number of T effector memory (TEM) (20,56±15,15 vs 57,66±35,47, p=0.02) in patients than in controls. In contrast, among CD4-T cells, we observed higher number of T naïve (826,1±413,9 vs 383,1±304,1 p=0.04) and T effector (TEFF) (34,32±26,53 vs7,59±3,82, p=0.0008) in ROHHAD(NET) patients.

Furthermore, in ROHHAD(NET) patients, we found a significantly increased serum level of IL-8 (pg/ml, mean±SDS:58,35±120,7 vs 30,03±72,43, p=0.008) and MCP-1(86,91±68,74 vs 28,15±16,59, p=0.01). No differences were shown in other chemokines tested (IP-10, MIG and RANTES).

Finally, sHLA-G was significantly lower in ROHHAD(NET) versus controls (ng/ml:1,31±3,09 vs 9,56±14,83, p=0.03), whereas sHLA-E concentration was similar between the two groups.

Conclusions: In agreement with published data, our findings seem to support the immune-dysregulation hypothesis in ROHHAD(NET) syndrome in comparison to simple obesity. If these assumptions are confirmed by larger and multicentric studies, there might be a rationale for therapeutic trials with immunosuppressors or immunomodulators in this syndrome.

RFC3.5

Chronotropic Insufficiency impairs Cardiorespiratory Fitness in Boys and Adolescents with Klinefelter Syndrome

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Background: Klinefelter syndrome (KS) is associated with an increased metabolic and cardiovascular risk profile[1,2] and a metabolic syndrome is evident at a prepubertal age in 10% of the affected boys. Boys with KS tend to avoid competitive sports and describe themselves as 'not good at sports'. Cardiopulmonary fitness in adults with KS has been found to be compromised by chronotropic insufficiency (CI) and a reduced maximal oxygen uptake (V'O2max; ml/min) as a parameter of aerobic cardiorespiratory fitness.[2]

We aimed to investigate cardiopulmonary fitness in boys and adolescents with KS as part of the KliBone study.

Methods: Boys and adolescents (6 – 25 years) with KS were included in the KliBone study (DRKS 00024870). Body composition was measured using a Tanita impedance scale. Hand grip strength (HGS) was measured using a Jamar handgrip dynamometer. Participants underwent an incremental symptom-limited cardiopulmonary exercise test (CPET) on a bicycle ergometer according to the recommended protocol. Individual z-scores for participants were calculated based on the age-appropriate normative data. Age-predicted maximal heart rate was calculated, and CI was defined according to Pasquali et al.[2]

Results: Nineteen participants with KS (five on testosterone replacement therapy) aged 15.90 ± 4.12 (range 9 – 25) years with a BMI z-score of 0.47 ± 1.22, (range -2.00 – 1.90) participated in the study. Mean adipose mass (%) was 23.36 ± 9.00. 17 participants underwent CPET. Mean z-scores were -2.48 ± 2.13 (range -7.97 – 0.41) for HRmax; -1.29 ± 1.37 (range -3.04 – 1.77) for Wattmax and -2.28 ± 2.48 (range -6.88 – 0.57) for V'O2max. Seven participants (41.2%) met the criteria for CI. These participants reached significantly reduced Wattmax (134.14 ± 29.70 vs. 182.20 ± 52.42; p = 0.04) and tended to a reduced V'O2max(1789.29 ± 568.32 vs. 2280.30 ± 652.84; p = 0.08) when compared to KS participants without CI. Mean HGS z-score was 0.97 ± 1.37 without differences between participants with or without CI.

Conclusion: Cardiopulmonary impairment has been reported in adult men with KS. Here we show that impaired cardiopulmonary fitness can be detected already in boys and adolescents with KS and in 40% of the participants CI was detected. The presence of CI is associated with further reduction of cardiopulmonary performance. Further research needs to focus on this important aspect of KS, that may explain the avoidance of competitive sports in KS and may contribute to the unfavorable metabolic phenotype.

References

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RFC3.6

Continuous growth reference from 24th week of gestation to 24 months by sex for length, weight, and head circumferences, based on the healthiest of Swedish Birth Registry 1990-99 and the GrowUp 1990 Gothenburg cohort

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Background: Since growth patterns change with time due to secular changes, there is a need to regularly update growth references[1]. We developed the first continuous birth size reference, from gestational age 24weeks with infancy growth references[2], computerized 2006 and used in Swedish health care settings and neonatal units. We now aimed to update this reference by exchanging GrowUp1974Gothenburg cohort to a selected population of healthy children of the GrowUp1990Gothenburg cohort, representing how infants optimally ought to growth.

Methods: To the present birth reference[2] of healthy infants born 1990-99, from 24weeks of gestation (around 800.000, 76%, of all 1.053 425 born and documented in Swedish Medical Birth Registry), we mathematically merged with growth data from GrowUp1990Gothenburg cohort in exchange of growth data from previous GrowUp1974Gothenburg cohort[3]. Growth data from healthy children with longitudinal measurements for length: 1572(763 girls)[4], weight: 1418(698 girls)[5], and head circumference (HC): 1325(642 girls) were used. Individuals from GrowUp1990Gothenburg cohort used were born at term to non-smoking mothers, Nordic parents. New infancy references for HC (LMS-method. QE-method), length (QE-method), and weight (LMS-method) were constructed. From QEPS-height-model[6], a QE-head-model was developed to construct QE-HC-references, first developed in the 1974-cohort with HC-measurements up to 4yrs, thereafter applied to the 1990-cohort 0-4yrs, resulting in a reference equal to the HC-reference constructed by LMS.

Results: Compared to the present birth-infancy 1974-reference 0-2yrs, the new birth-infancy 1990-references show the 1990-cohort for mean/median, +2SDS; -2SDS for: Length: to be 1cm longer around 1yr of age with similar lengths at birth and around 2yrs of age for both sexes. Weight: median to be similar, with age somewhat lighter mostly at +2SDS. Head circumference: (LMS to 2yrs) to be 0.5cm bigger at mean, 0.25cm at +2SDS, +0.75cm at -2SDS;

(QE to 4yrs) to be 0.5-1cm bigger with most fluctuations at -2SDS. A growth model-based HC-reference up to 4yrs was constructed.

Conclusion: A continuous reference bridging birth size with infancy growth of healthy infants born in the 90ies for head circumference, length, and weight was constructed. The references take gestational age into account for postnatal growth allowing for optimal identification of abnormal growth during the turbulent infancy period, important for present and future health.

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Fat, Metabolism and Obesity

RFC4.1

Molecular profiling between obese and non-obese PWS patients

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Objectives: Prader–Willi syndrome (PWS) is the most common genetic obesity disorder and results from lack of gene expression on paternally inherited chromosome 15q11.2-q13. However, the factors regulating obesity in PWS are poorly understood. We aimed to characterize genetic alterations in PWS using whole genome microarrays to analyze gene expression, and to understand the molecular mechanisms of obesity in PWS patients.

Methods: We performed microarray using RNA isolated from whole blood from 25 PWS subjects and 25 age matched control. Gene expression data was obtained by Affymetrix Whole Transcript Expression array (GeneChip Whole Transcript PLUS reagent Kit). After preprocessing of data to reduce heterogeneity, differentially expressed genes (DEGs) between groups were identified using a linear regression model package. Gene ontology and of genes and genome pathway enrichment analyses were conducted using R package 'limma'. The heat map for the gene expression data was generated using a pheatmap in R package. Separate KEGG pathway analysis using EnrichR for up-regulated and down-regulated genes was performed.

Results: Of 21,488 probes examined in the microarray, 4,156 were detectable. Twenty-five genes had significantly different expression in the obese relative to non-obese PWS patients (12 genes upregulated and 13 downregulated). All of these genes were not located in chromosome 15q11.2. S100A12, KCNJ15, and HCAR2 were most significantly upregulated in obese PWS patients. Most significantly downregulated genes were ARL17B, PRKY, and USP9Y. The upregulated genes were associated with sulfur metabolism, nitrogen metabolism, and fatty acid biosynthesis.

Conclusions: This study reveals 25 genes associated with obesity in PWS patients. These genes could suggest new therapeutic targets or potential biomarkers for obesity in PWS.

RFC4.2

Effect of Setmelanotide Treatment in Children and Adolescents With Proopiomelanocortin (POMC) Deficiency, Leptin Receptor (LEPR) Deficiency, and Bardet-Biedl Syndrome (BBS)

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Background: The melanocortin-4 receptor (MC4R) pathway is a key regulator of energy balance and satiety. Variants in genes upstream of MC4R encoding leptin receptor (LEPR),

proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1(PCSK1) and those involved in Bardet-Biedl syndrome (BBS) can impair MC4R pathway signaling. Clinically, these variants are characterized by hyperphagia (pathologic insatiable hunger) and early-onset, severe obesity. Early intervention, particularly in younger patients, is critical in reducing the development of long-term obesity-related morbidities and quality-of-life burden. Despite this unmet need with limited treatment options, there is no consensus on optimally assessing the effects of interventions targeting excess weight and hunger. We assessed the effects of setmelanotide, an MC4R agonist, in a cohort of pediatric patients in separate Phase 3 trials of patients with POMC deficiency (NCT02896192), LEPR deficiency (NCT03287960), and BBS (NCT03746522) using multiple age-appropriate weight-related measures, which are relevant to clinical practice and regulatory authorities, to understand the effectiveness of setmelanotide in this unique population.

Methods: Patients included were aged 6-17 years. Patients with POMC and LEPR deficiency received ~1 year of setmelanotide, inclusive of 4 weeks of placebo during a withdrawal period. Patients with BBS received 1 year of setmelanotide.

Results: Pediatric-relevant weight-related measures are reported in the Table.

Conclusions: Early, targeted intervention with setmelanotide resulted in improvements across all weight-related measures in pediatric patients with POMC deficiency, LEPR deficiency, and BBS. These results highlight the variability observed across pediatric measures and the need to identify an optimal measure.

RFC4.3

Phospholipid scramblase 4 regulates adipocyte differentiation via PIP_3-mediated AKT activation

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Background and Aim: PTEN hamartoma tumor syndrome (PHTS) is caused by germline mutation in the phosphatase and tensin homolog (PTEN) gene. PTEN is a tumor suppressor gene and antagonist of the growth and survival signalling Phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of Rapamycin (mTOR)- cascade. Patients with PHTS, amongst other symptoms, develop lipomas, for which the underlying mechanism is not completely understood. To investigate the role of PTEN in lipoma formation, we previously performed a PTEN knockdown (KD) in adipose progenitor cells (APCs) and observed enhanced proliferation and adipocyte differentiation. RNA sequencing showed downregulation of phospholipid scramblase 4 (PLSCR4) in PTEN KD APCs. While mice with knockout of the closely related PLSCR3 exhibit an adipose tissue expansion, the role of PLSCR4 in adipose tissue is unknown. We asked whether PLSCR4 downregulation is involved in adipose tissue expansion by modulating PI3K/AKT signalling.

Table. Weight-Related Measures in Pediatric Patients

	Proopiomelanocortin deficiency (n=9)[a]	Leptin receptor deficiency (n=4)	Bardet-Biedl syndrome (n=16)[b]
BMI, mean (SD), kg/m^2			
Baseline	36.3 (8.1)	40.7 (3.3)	37.4 (9.4)
~1 year of setmelanotide	27.2 (5.5)	34.4 (1.3)	34.2 (10.1)
Percent change	−26.5 (10.2)	−14.9 (10.3)	−9.5 (6.4)
BMI Z score, mean (SD)			
Baseline	3.5 (0.6)	3.5 (0.3)	3.7 (1.3)
~1 year of setmelanotide	1.9 (0.9)	3.0 (0.0)	3.0 (1.5)
Change	−1.5 (0.8)	−0.6 (0.3)	−0.8 (0.5)
Proportion of patients with ≥ −0.2-point change, n/N (%)	9/9 (100)	3/4 (75)	14/15 (93)
Proportion of patients with ≥ −0.3-point change, n/N (%)	9/9 (100)	3/4 (75)	11/15 (73)
Percent of BMI 95th percentile, mean (SD)			
Baseline	142.1 (19.5)	155.5 (19.9)	144.5 (35.8)
~1 year of setmelanotide	100.1 (16.1)	126.3 (2.2)	126.8 (37.0)
Change	−42.4 (15.3)	−29.2 (18.4)	−17.3 (7.7)

BMI, body mass index; SD, standard deviation. [a]n=9 at baseline; n=8 at ~1 year. [b]n=16 at baseline; n=14 at ~1 year.

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Methods: We compared PLSCR4 expression in lipoma tissue from lipoma Pten/Retinoblastoma (Rb) double knockout (DKO) mice in comparison to epididymal WAT (epiWAT) and inguinal WAT (ingWAT) from control mice. PLSCR4 expression during adipogenesis was analysed in human LipPD1 cells.

Further we established siRNA mediated knockdown and plasmid mediated overexpression of PLSCR4 in APCs. After transfection we analysed proliferation and adipocyte differentiation. For influence of PLSCR4 on PI3K/AKT/m-TOR signalling we analysed phosphatidylinositol-(3,4,5)-trisphosphate (PIP_3) levels and activation of AKT.

Results: We could observe that PLSCR4 expression in lipoma tissue from Pten/ Rb DKO mice was diminished in comparison to epiWAT by 67.7% ± 15.4% ($n = 7$, $p < 0.05$) and ingWAT by 58.4% ± 23.5% ($n = 7$, $p < 0.05$). During adipogenesis PLSCR4 was significantly downregulated in LipPD1 cells $p < 0.001$ ($n = 4$).

We saw an influence of PLSCR4 on adipogenesis but not on proliferation. The differentiated cell fraction in PLSCR4 knockdown cells was increased by 44.1% ± 10.5% ($n = 7$, $p < 0.05$). These results could be verified by PLSCR4 overexpression, which led to a decrease of differentiated adipocytes by 25.3% ± 7.3% ($n = 3$, $p < 0.05$). PLSCR4 KD APCs showed increased PIP_3 levels by 94.4% ± 24.5% in PLSCR4 KD compared to control APCs ($n = 3$, $p = 0.0611$). In line with this, AKT phosphorylation was increased in PLSCR4 KD ($n = 5$, $p< 0.05$).

Conclusion: PLSCR4 downregulation enhances adipogenesis in APCs via activation of AKT. This might contribute to adipose tissue overgrowth as observed in PHTS patients.

RFC4.4

New insights of monogenic hypercholesterolemia in pediatric patients: basing on a Chinese cohort

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Background and Objectives: Dyslipidemia especially hypercholesterolemia attracts much more attention recently. Given different management and treatment of multiple categories, precise diagnosis becomes increasingly important. However, studies in pediatric patients lacks around the world, especially in China. Consequently, this study was designed to confirm the molecular defect of persistent hypercholesterolemia with next-generation sequencing basing on a single-center cohort of pediatric patients.

Method: Patients were collected according to including and excluded criteria. Clinical information was collected, and then, physical and laboratory examination was performed. Genetic sequencing was performed on these patients.

Results: 35 patients were included and 32 patients of them (aged 1.0-13.8 years) were finally performed with genetic sequencing. Positive results were obtained in 65% of the patients including variants of LDLR, LIPC, JAG1, ABCG5, ABCG8, LPL, et.al. Of them, eight were novel. Furthermore, LDLR was the most common gene identified in these patients and ABCG5/8 ranks second. Also, 10% of the patients were identified variants from two different genes. Through analyzing patients with positive genetic results, we found that the average age was elder, and the levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apoB) were higher in patients with positive genetic results. Also, comparing with the patients with tendon xanthomas, the patients without tendon xanthomas were elder and the levels of apolipoprotein were higher. Interestingly, the levels of TC and LDL-C showed no difference in these two groups.

Conclusion: We identified 28 variants in 32 pediatric patients with persistent hypercholesterolemia, enriching genetic and phenotypic spectrum. Levels of apoB is probably a biomarker or potential therapeutic target of monogenic hypercholesterolemia. Heterozygotes ABCG5/8 variants could be underestimated in pediatric patients with hypercholesterolemia.

RFC4.5

Cerebral perfusion following childhood-onset craniopharyngioma and the relationship with metabolic rate

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Background: Craniopharyngioma is a non-malignant embryonic tumour in the pituitary-hypothalamic area, associated with hypothalamic obesity. Dysfunctional parasympathetic nervous system activity has been proposed as one mechanism underlying alterations in energy metabolism. Arterial spin labelling (ASL) is a non-invasive MRI technique that quantifies brain tissue perfusion as a proxy for functional activity. Here, we measure cerebral perfusion in patients with craniopharyngioma to investigate the impact

of the tumour and associated treatment on appetitive brain function, and the potential relationship with resting metabolic rate (RMR). This research forms part of a feasibility study exploring neuroimaging, eating behaviours, energy homeostasis and obesity in patients with childhood-onset craniopharyngioma.

Methods: Following an overnight fast, RMR was measured using indirect calorimetry (COSMED K4b2) and participants subsequently underwent a pseudo-Continuous ASL scan at 3T (pCASL) with multiple post-labelling delays. ASL data was processed and analysed using FSL tools in seven a priori regions of interest (ROIs). Data are reported as mean ± standard deviation. Kendall's Tau is reported for correlations due to the small sample size of this feasibility study.

Results: Nine patients with childhood-onset craniopharyngioma (age=14.6±3.8y; BMI SDS=0.97±1.93, 3 female) and nine sex-matched historical controls (age=22.4±2.7y; BMI SDS=-0.60±0.88, 3 female) were included in the pCASL analysis. Post-operatively all patients had endocrine dysfunction; eight in thyroid axis, four with diabetes insipidus and all had adrenocorticotropic hormone and growth hormone deficiencies. Rates of perfusion were in line with the diagnostic cut-off for low-grade paediatric brain tumours (50mL/min/100g). Lower perfusion was found in the craniopharyngioma patients compared to the controls in six of the seven ROIs ($p<0.01$), namely hypothalamus, insula, amygdala, nucleus accumbens, putamen and ventrofrontal cortex (VFC), but not the temporal occipital fusiform cortex (TOFC) which is a visual attention region. Negative correlations between perfusion and RMR in craniopharyngioma patients were found in all ROIs (insula $\tau=-0.556$; amygdala $\tau=-0.667$; nucleus accumbens $\tau=-0.444$; putamen $\tau=-0.500$; TOFC $\tau=-0.667$; VFC $\tau=-0.389$), except the hypothalamus ($\tau=0.056$).

Conclusions: Preliminary evidence suggests that brain perfusion, a proxy for neural activity at rest, is lower in craniopharyngioma patients in the appetitive brain network. Novel analyses suggest a relationship between cerebral perfusion and RMR, which may help to understand the impact of brain changes on altered energy metabolism in craniopharyngioma. The impact of these brain changes on the development of obesity should be investigated in future research.

RFC4.6

European Consortium of Lipodystrophies Registry, 2022

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Background: Lipodystrophy syndromes comprise a large group of extremely rare diseases characterized by loss or dysfunction of adipose tissue. Due to their extreme rarity and variability, research in the field of lipodystrophy is difficult for single centres warranting larger co-operations.

Methods: Therefore, the European Consortium of Lipodystrophies decided to found an international registry in 2016. This registry is based on an open-source software "OSSE" specifically designed for multicentre international registries for rare diseases, covering all aspects of General Data Protection Regulation (EU) of May 25, 2018. The registry has been registered at clinical trials (ClinicalTrials.gov ID: NCT03553420) and EURECA.

Results: Since the end of 2017, the registry is actively recruiting patients. Currently, 23 centres in Europe and neighbouring country are participating in the registry, 17 of which are recruiting patients. Until March 22, 517 patients with lipodystrophy have been included in the registry, of which 80% are female and 83% adults with a mean age of 38.7 years (36.8-40.6). However, 17.2% are younger than 18 years of age; 12.4% even younger than 14 years of age.

The predominant diagnosis is familial partial lipodystrophy (FPLD) 2 (39%), followed by FPLD1 (11%), congenital generalized lipodystrophy (CGL) 1 (8%), Barraquer Simons Syndrome (7%). 30 different diagnosis are documented in the registry all together.

Nearly 80% of the patients suffer from dyslipidaemia; diabetes mellitus and fatty liver are each diagnosed in 55% of all patients, hypertension in 35% of all patients. 23.5% of all patients have a polycystic ovary syndrome. Steatohepatitis and albuminuria are documented each in 15% of the patients. Muscular and cardiac comorbidities are rarer, however, 16% of all patients reported muscular pain/myalgia; and hypertrophic cardiomyopathy, ischemic cardiomyopathy and hypertrophic cardiomyopathy are each found in 8-11% of the patients.

Conclusion: Our results highlight the high burden of comorbidities especially metabolic problems in this patient group. As we have assembled the word-wide largest collection of patients with lipodystrophy, we will have the unique possibility in the future to analyse the natural course and also treatment outcomes in this vulnerable group of patients.

Adrenals and HPA Axis

RFC5.1

Single centre use of Hydrocortisone granules (Alkindi) in children with Adrenal Insufficiency: the patient experience

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Standard management of Adrenal Insufficiency (AI) in children is with hydrocortisone (HC). Under or over-treating impacts on growth and quality of life. Until recently, treatment involved dissolving 10mg HC tablets in water; this is time consuming and may give inaccurate doses. We have offered HC granules (Alkindi) to all new patients ≤6-years since January 2019 and 22 patients who were currently dissolving HC tablets. We have reviewed our patients' experience with Alkindi and monitored growth and safety data over this period.

Questionnaires were sent to families of children with AI who started HC ≤6-years, asking about treatment satisfaction, stress-dosing and hospital admissions. We also collected growth data from hospital e-records, including parental heights.

Thirty-six patients (≤6 years; 26M, 10F) with AI started/switched to Alkindi between January 2019 and March 2022. 21 were diagnosed with congenital adrenal hyperplasia, 13 combined pituitary hormone deficiency and 2 neonatal adrenal haemorrhage. Questionnaires were received from 26/34 patients (1 moved away; 1 had a recent bereavement) - 76% response rate. Alkindi has also been used in 3 older patients (aged 10-13 years) requiring smaller doses (not included in growth data).

All 11 patients who started on Alkindi at diagnosis continue. 16/20 (80%) patients who switched from dissolved HC to Alkindi remain on this, 4/20 (20%) did not tolerate the granules. A further 5 patients, with unsafe swallow, were not offered Alkindi. Patient satisfaction with their current treatment was high (96%). Families on Alkindi commented on accuracy of dosing and ease of use. In the last 6-months, stress dosing varied from 0-7 occasions (average 4 episodes/patient/year), with no significant difference between Alkindi and HC. Only 1 patient was admitted with an adrenal crisis (used Alkindi routinely, but stress-dosed with HC). For patients on Alkindi from diagnosis, height SDS remained stable (-0.68 baseline; +0.01 at 1-year; -0.36 at 2-years; parental +0.81). In those that switched to Alkindi, their height SDS moved closer to parental SDS (-0.62 baseline; -0.20 at 1-year; +0.17 at 2-years; parental +0.15).

This is the largest single-centre report of Alkindi administration over the longest time-period, demonstrating high acceptability for most AI patients. All patients on Alkindi from diagnosis tolerate it well; 20% of those switching to Alkindi returned to dissolved HC. Growth data, based on height SDS scores, is encouraging. No safety issues with increased stress dosing or adrenal crisis have been identified. On-going follow up will continue to monitor long-term growth.

RFC5.2

Case Series: Anastrozole Monotherapy for Non-Classic Congenital Adrenal Hyperplasia

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Background: Non-classic congenital adrenal hyperplasia (NC-CAH) is caused by pathogenic variants of the CYP21A2 gene, and in most cases is not associated with cortisol deficiency as is the classic (severe) form. The majority of children with NC-CAH are asymptomatic and do not require cortisol replacement therapy with hydrocortisone unless they develop symptoms of hyperandrogenemia such as early pubarche, growth acceleration, advanced bone age, and ultimately short stature. Elevated estrogen levels through aromatization of excess levels of adrenal androgen causes rapid bone maturation and early epiphyseal closure.

Third-generation aromatase inhibitors (AI), such as anastrozole and letrozole, which block the conversion of androgens to estrogens, have been used off-label in males with short stature to delay bone maturation and as an adjunct therapy in children with classic CAH. The use of AI as monotherapy for children with NC-CAH has never been reported.

Case Series: We present three female children with a diagnosis of NC-CAH who were treated with anastrozole monotherapy as

Figure 1. Patient Characteristics

	Start of Anastrozole therapy				End of Anastrozole therapy				
		Bone age				Bone age			
	Age (years)	Years	Z-score	Corrected height Z-score*	Age (years)	Years	Z-score	FAH height Z-score	Target height Z-score
A	3.7	6.8	6.4	-4.06	14.5	14	-0.75	-0.68	0.2
B	3.9	5.0	1.9	-0.95	12.6	14	0.52	0.7	0.2
C	6.7	8.8	2.9	-0.13	10.8	11	-0.07	2.65	2.0

*Corrected height Z-score for bone age = Height Z-score using bone age as chronological age.
FAH: Final adult height

they presented with advanced bone age and early pubarche, but no signs of genital virilization. Hydrocortisone was not used as all four children had normal peak cortisol in response to ACTH stimulation testing. Age of children at initiation of anastrozole therapy were 3.7, 3.9, and 6.7 years with bone age z-scores of 6.4, 1.9 and 2.9, respectively. Bone age Z-scores at the end of Anastrozole therapy were -0.75, 0.52 and -0.07.

Height z-scores were corrected for bone age at initiation of Anastrozole. While on therapy, bone age z-scores decreased (see Figure 1); all three patients reached or exceeded their target height.

Discussion: Monotherapy with AI can be an effective alternative in slowing down bone maturation and improving height outcomes in children with NC-CAH and normal adrenal cortisol production. All three patients had appropriate pubertal progression, normal ovarian ultrasounds, and normal bone mineral density accrual.

RFC5.3

Towards understanding the metabolic phenotype of glucocorticoid deficiency in 21-hydroxylase deficiency

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Background: Steroid 21-hydroxylase deficiency (21OHD) is the most common form of congenital adrenal hyperplasia. Patients present with cortisol and aldosterone deficiency as well as with hyperandrogenism, leading to virilisation in females and early adrenarche in both sexes. Requiring life-long glucocorticoid (GC) replacement, patients frequently experience daily fluctuations between GC overexposure and deficiency. Increased prevalence of metabolic disease contributes to raised morbidity and mortality in 21OHD. However, there is limited knowledge regarding the mechanisms leading to increased risk of metabolic disease. We previously established a zebrafish model of 21OHD deficiency in which we demonstrated interrenal hyperplasia in larvae. We aimed to explore the metabolic phenotype of *cyp21a2*-deficient zebrafish, in order to gain insight into the pathophysiology of metabolic problems in 21OHD.

Methods: We assessed the adult phenotype of *cyp21a2-/-* zebrafish and studied differential gene expression between mutant and wild-type fish in both 5-day-old larvae and 18 months-old adult fish livers by transcriptomic analysis following RNA-sequencing.

Results: Although steroid hormone analysis by LC/MSMS confirmed severe cortisol deficiency, *cyp21a2-/-* mutant zebrafish reached adulthood, had normal secondary sexual characteristics and were able to reproduce in the absence of hormonal replacement. Body measurements showed that adult *cyp21a2-/-* mutants were significantly larger than wild-type fish ($p < 0.001$, n=8-10), with greater weight and length. Macroscopic analysis following dissections revealed increased visceral and subcutaneous fat in mutants compared to wild-type siblings. Blood sugar levels varied widely with no significant difference between mutants and wild-type fish. Differential gene expression and statistical overrepresentation analysis of gene ontology terms showed significant ($p<10^{-5}$) dysregulation of several metabolic processes (small molecule, alpha-amino acid, organic acid, carboxylic acid, lipid metabolism) in both mutant larvae and adult livers. In mutant larvae the most prominent findings were downregulation of gluconeogenesis, glycolysis, insulin signalling, triglyceride and fatty acid biosynthesis. Transcriptomic analysis of adult livers indicated downregulation of fatty acid oxidation and upregulation of fatty acid biosynthesis, deranged lipid transport and adipocyte differentiation with increased lipid accumulation.

Conclusion: Our findings suggest a dynamic dysregulation of several metabolic pathways in the cortisol-deficient *cyp21a2* zebrafish model in keeping with their adult phenotype characterised by increased fat mass. Overall, our results suggest that GC deficiency contributes to the metabolic co-morbidities presented by patients with 21OHD, further highlighting the need for further research into the molecular and cellular mechanisms underlying this condition, and the importance of establishing optimised replacement regimes for patients that minimise lack and overexposure to GCs.

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RFC5.4

Increased resting-state functional connectivity in the medial orbitofrontal cortex of patients with autoimmune Addison's disease

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Background: Patients with autoimmune Addison's disease (AAD) lack production of glucocorticoids (GCs), mineralocorticoids (MCs) and androgens from the adrenal gland, due to autoimmune destruction of its cortex. Patients require replacement of GCs and MCs for the rest of their lives. In some cases, testosterone is supplemented in females. Brain function is sensitive to fluctuations in cortisol and may therefore be affected in AAD due to long-term disturbances in cortisol levels and rhythmicity. Such alterations in brain function may contribute to mood disturbances and reduced quality of life in this patient group. Currently, no brain research exists in AAD. The current study therefore sought to investigate resting-state functional connectivity in patients with AAD compared to controls.

Methods: Resting-state fMRI data was collected from 57 (33 females) patients with AAD and 69 (39 females) control participants, aged 19-43 years. Independent component analysis was used to identify resting-state brain networks in the entire cohort, using FSL MELODIC software. Next, dual-regression analysis was applied to test for group differences in resting-state functional connectivity (rs-fc) in the identified networks, using sex and age as covariates. We also tested the interaction between group and sex on rs-fc in the networks. Significant clusters were identified with threshold free cluster enhancement (TFCE), and clusters were considered to be significant at $p<0.001$.

Results: Patients with AAD had increased functional connectivity in the bilateral medial orbitofrontal cortex. There were no interactions with sex.

Conclusion: AAD seems to be associated with stronger functional connectivity at rest in the medial orbitofrontal cortex. This area is known to contain a high density of GC receptors. It has previously been implicated in reward-related processing, decision making and has often been linked with mood disorders, in particular depression. Further research is needed to investigate if this increased activity is part of an adaptive mechanism to having long-term cortisol disturbances, or if it contributes to disturbances in mood and/or executive functioning.

RFC5.5

Mosaic *PRKACA* duplication causing a novel and distinct phenotype of early-onset Cushing syndrome and acral cutaneous mucinosis

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Introduction: Genetic alterations within the cAMP/PKA pathway, including the genes *GNAS, PDE11A, PDE8, PRKAR1A/B,* and *PRKACA*, result in a spectrum of adrenocortical disorders. To date, somatic *PRKACA* variants and germline *PRKACA* copy number gain have been associated with the development of cortisol-secreting adrenocortical adenomas and bilateral adrenal hyperplasia, respectively. While variants within the *PRKAR1A* gene are known to cause Carney complex, *PKRACA* variants are rarely associated with an extra-adrenal phenotype.

Methods: Clinical, biochemical, and radiological data were collected from hospital patient records. Histopathological examination of relevant patient tissue was performed. Genetic testing including trio exome sequencing and comparative genomic hybridisation (aCGH) analysis was conducted.

Case: We describe a mosaic *PRKACA* duplication in an infant who presented with a Carney-like complex at the age of three months. He developed severe early-onset Cushing syndrome requiring bilateral adrenalectomy. Histopathology of the resected adrenal tissue showed bilateral non-pigmented micronodular cortical hyperplasia. He also had multiple non-tender, non-pigmented, firm lumps on his hands and feet at presentation. This distinct acral soft tissue overgrowth was demonstrated to be cutaneous mucinosis on histopathological examination. aCGH analysis of DNA extracted from the skin biopsy demonstrated a duplication on the short arm of chromosome 19, spanning a 900kB region inclusive of the *PRKACA* gene, which was absent from blood. This confirmed that the clinical features were due to a post-zygotic mosaic duplication of *PRKACA*. Post-adrenalectomy, the Cushing

syndrome features resolved and there was an improvement in the appearance of his skin lesions, suggesting that circulating cortisol may have contributed to the underlying dermatopathological process.

Discussion: We elucidate a novel manifestation of *PRKACA* disruption and broaden its extra-adrenal phenotype. To date, only germline *PRKACA* duplication has been associated with Cushing syndrome secondary to adrenal hyperplasia. This case suggests that the Cushing syndrome phenotypes arising from somatic and germline *PRKACA* abnormalities likely exist on a spectrum. Furthermore, the skin features described have not been associated previously with either germline or somatic *PRKACA* mutations. A confirmed mosaic *PRKACA* duplication linked the patient's adrenal disease to his extra-adrenal features. We emphasise the importance of ascertaining a genetic diagnosis for *PRKACA*-mediated disease.

RFC5.6

The unique methylation pattern of a rare Bilateral para-overian Adrenal Rest Tumor in a girl with severe virilization and Nicotinamide Nucleotide Transhydrogenase mutation

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Background: Patients with NNT (Nicotinamide Nucleotide Transhydrogenase) gene mutations, a rare cause of glucocorticoid and mineralocorticoid deficiency. Adrenal Rest Tumor (ART) in females, reported so far only in noncompliant patients with congenital adrenal hyperplasia and elevated ACTH levels, is very rare (<20 cases world-wide). This study characterizes the pathophysiology, the molecular ontogeny and methylation analysis of a unique ART in a female with adrenal failure due to the G200S mutation in NNT.

Clinical Presentation: A 15-year-old girl, with homozygous G200S NNT-mutation followed for adrenal insufficiency reappeared to follow-up with severe virilization and elevated serum testosterone (28.3 nmol/l) and ACTH (> 1500 pmol/l). Pelvic MRI and Ultrasound demonstrated one sided paraovarian round tumor with pathological vascularization. Laparoscopic exploration revealed bilateral para ovarian mesosalpinx masses involving the serosa of the Fallopian tube, (3 and 1 cm in diameter). The testosterone level normalized within one day after surgical removal of those masses (0.2 nmol/l).

Results: Histopathology demonstrated a pattern of adrenal rest tissue with strong intracellular positive staining for adrenal markers such as SF-1, calretinin, MART1, inhibin and the pituitary marker ACTH. The staining for ovarian marker PAX 8 was negative. Studying mRNA extracted from the tissue by RT-PCR revealed the positive Gene expression of Cyp17a1, Cyp21a2 and Mc2r cDNA but not Pomc suggesting adrenal but not pituitary origin of the tissue. We further profiled the epigenomic profile using the Infinium MethylationEPIC array. Surprisingly, the tumor methylome age was estimated as 40-year-old. The methylation pattern resembled mostly adrenal tissue but was not identical. In part, it expressed unique ovarian methylation pattern.

Conclusion: This study exemplifies severe virilization that resulted from a unique and rare type of ART in ovarian related tissue in a girl with NNT mutation. The laparoscopic surgicalfindings indicate that imaging techniques may be insufficient and call for laparoscopy when clinical findings are suggestive to save fertility. Using histopathology markers cDNA studies and methylation studies, our study shows for the first time that female ART albeit expressing mostly adrenal methylation pattern, is not identical and expresses specific ovarian methylation pattern as well. The growth of a functional androgen producing "tumor" indicates that functional NNT protein is NOT required for androgen synthesis in contrast to glucocorticoids. Identifying the specific methylation pattern, the hypomethylated genes in ART compared to ovarian and adrenal tissue and the reason for its older age as was demonstrated in our research calls for further research.

Sex Development and Gonads

RFC6.1

Sex-specific ranges and ratios for anogenital distance among Thai full-term newborns

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Introduction: Anogenital distance (AGD) is a useful marker of prenatal androgen exposure and a tool for assessment of differences of sex development. Normative data on AGD ranges for local references should be established as standards for comparison in clinical practice, but there is a paucity of data among newborns in Thailand.

Aim: To provide the sex-specific ranges for AGD in Thai full-term newborns.

Methods: A cross-sectional study was conducted in full-term newborns in Thailand, during 2016–2018. Newborns with ambiguous genitalia, dysmorphic features, and known maternal ingestion of androgenic medications or substances were excluded. During the AGD measurement, newborns were placed in a supine position. An assistant held both hips in flexion and pulled the knees back towards the shoulders. The caliper was positioned adjacent to the surface of the genitalia, with the digital screen turned away from the researcher. The AGD was measured to the nearest 0.1 mm, from anus to anterior base of penis (AGD_{AP}) and to perineoscrotal junction (AGD_{AS}) in males, and from anus to clitoris (AGD_{AC}) and to posterior fourchette (AGD_{AF}) in females. AGD ratio is defined as AGD_{AS} divided by AGD_{AP} in males and AGD_{AF} divided by AGD_{AC} in females.

Results: A total of 364 neonates aged zero to 72 hours were investigated, including 187 males (51.4%) and 177 females (48.1%). The mean ± SD gestational age was 38.69 ± 1.09 weeks. Anthropometrics data including birth weight, length, and head circumference were not significantly different between males and females by Student's t-test. The mean AGD_{AS}, AGD_{AP} and AGD ratio in males were 25.20 ± 4.80, 52.60 ± 6.90 and 0.48 ± 0.08 mm, respectively. The mean AGD_{AF}, AGD_{AC}, and AGD ratio in females were 16.50 ± 3.90, 42.60 ± 6.20 and 0.39 ± 0.08 mm, respectively. There were significant differences between AGD_{AS} and AGD_{AF}, AGD_{AP} and AGD_{AC}, and AGD ratio between males and females ($p < 0.001$). The AGD_{AS}, AGD_{AP}, AGD_{AF}, and AGD_{AC} had a statistically significant but weak positive correlation with birth weight and length by Pearson's correlation analysis, but no correlation between the AGD ratio and birth weight or length was found in both sexes.

Conclusion: The sex-specific ranges for AGD in Thai full-term newborns were determined. The AGD ratio is a more reliable indicator of prenatal androgen exposure than other AGD parameters since it is significantly different between sexes and unrelated to anthropometrics.

RFC6.2

Dynamic changes of reproductive hormones in male minipuberty: Temporal dissociation of Leydig- and Sertoli-cell activity

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Background: The male Hypothalamic-Pituitary-Gonadal (HPG) axis is transiently active during the first months of life with surging serum concentrations of reproductive hormones. This period, termed minipuberty, promotes masculinization, including testicular, and penile growth, as well as further testicular descent in males. It appears to be essential for priming specific cell types, i.e. Sertoli-, Leydig-, and germ cells, including subsequent growth and maturation. Despite the potential pivotal role of minipuberty on male reproductive function, comprehensive, longitudinal data on HPG axis activation with quantification of serum reproductive hormones dynamics as well as effects on target tissue are sparse.

Objective: We aimed to 1) explore the dynamics of HPG hormone activity in healthy male infants, 2) assess the association of HPG axis activity and testicular volume and 3) establish reference curves for serum levels of reproductive hormones.

Participants and Methods: In a prospective, longitudinal birth cohort (The COPENHAGEN Minipuberty Study, 2016-2018) we followed healthy, term, singleton newborns from birth onwards with repeated clinical examinations including blood sampling during a one-year follow-up. For this study, we included a total of 128 boys of which 119 participated in the postnatal follow-up. Serum reproductive hormone concentrations and testicular volume were measured.

Results: We provide reference curves for follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, insulin-like factor 3 (INSL3), Inhibin B, anti-Müllerian hormone (AMH), and sex hormone-binding globulin (SHBG) in healthy boys during the first year of life. Reproductive hormone concentrations showed marked dynamics during the first six months of age. FSH, LH, testosterone and INSL3 peaked at around one month of age. This represents a distinct difference to Inhibin B, AMH and testicular volume that peaked at around 4-5 months.

Conclusions: We provide reference curves for reproductive hormones in boys during the first year of life and demonstrate a temporal dissociation of Leydig- and Sertoli cell activity during male minipuberty. Our study provides a valuable resource for clinicians evaluating infants with suspected reproductive disorders.

RFC6.3

Reference intervals of serum estradiol during childhood: comparing and reviewing five studies, effects of gender and age

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Background: Specific measurement of low serum/plasma concentrations of 17β-estradiol (E2) is important in pre-pubertal and pubertal children in routine paediatric endocrinology. However, there is still a gap in available reference intervals (RIs) for E2 in paediatrics. The study was partially funded by the German Ministry of Health, grant number 2519FSB503.

Objective: First, we technically developed a highly sensitive LC-MS/MS method for E2. We then measured left-over control samples of 454 boys and 963 girls for calculation of RIs. Secondly, we performed a systematic review of published E2 RIs in children and adolescents. This was conducted by PubMed and Google scholar. Selection criteria were: a cohort size >700 and an age range covering the complete pediatric age range in both sexes.

Results: 157 initial literature hits were documented and screened. Only four publications fulfilled our selection criteria. We then compared the RIs of the four selected studies and of our own study. Two publication used an immunoassay-based method (Elmlinger et al.[1] and Konforte et al.[2]) and three used an

LC/MS-MS based method (Frederiksen et al.[3], Bae et al.[4], and our own study). The LODs ranged from 3 to 37 pmol/L and age groups were separated under different conditions, e.g. statistical reasons or fixed age groups. Although measurement and statistical methods were different, we found a similar trend in all studies. Minipuberty with an increase of E2 was clearly visible in four of the five studies in both sexes. Until start of puberty, there was no significant sex difference. In girls, E2 then increased markedly up to 1000 pmol/L at the age of 16 years. Interestingly, in boys, we also found considerable increase of E2 up to 300 pmol/L at the age of 14 years. Therefore, pubertal E2 levels in boys overlapped considerably with levels found in girls in both, the literature studies and our own study.

Conclusion: Our study provides a comprehensive analysis of RIs of E2 in children and adolescents of both sexes covering the complete pediatric age range. Interestingly, boys may show pubertal E2 levels comparable with girls even though boys usually do not show breast development. Therefore, regional differences in the pubertal regulation and cellular action of estrogens and androgens must exist in breast tissue. Our data will help to get more insights into the role and the variability of E2 during development from infancy to early adulthood in both sexes.

RFC6.4

Sertoli cell dysfunction at diagnosis in children with haematological malignancies

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Introduction: Haematological malignancies represent the most frequent cancer in children. Little is known about the function of testicular Sertoli cells in the context of haematological malignancies and their behaviour during chemotherapy.

Aim: To determine Sertoli cell function at diagnosis and after 3 months of chemotherapy.

Methods: A prospective cohort study was performed including children with acute lymphoblastic leukaemia, acute myeloid leukaemia, or non-Hodgkin lymphoma. Serum levels of AMH were evaluated at diagnosis and after 3 months during chemotherapy. Results were analysed as standard deviation scores according to pubertal stage and expressed as median (range).

Results: 93 boys, aged 6.09 yr (0.04-17.53) were included in the study, 75.3% were prepubertal at diagnosis, 73.1% with acute lymphoblastic leukaemia, 7.5% with acute myeloid leukaemia and 19.4% with non-Hodgkin lymphoma.

Median AMH was -0.50 SDS (-2.07 to +6.27 SD) at diagnosis. Mean AMH was significantly different from a theoretical value of 0 SDS (p value <0.0001). 9.7% of the children had serum AMH below the 3rd percentile and 41.9% below the 25th percentile.

After 3 months of chemotherapy, AMH was -0.30 SD (-1.74 to +5.00 SD), significantly higher than AMH at diagnosis (Wilcoxon matched pairs signed rank test, two tailed p value 0.0002), and not significantly different from a theoretical value of 0 SDS (p value 0.23). 3.2% of the children had serum AMH below the 3rd percentile and 30.1% below the 25th percentile.

Conclusion: Children with haematological malignancies have lower AMH concentrations compared to the reference population, reflecting a Sertoli cell dysfunction, at diagnosis. After 3 months of chemotherapy, AMH concentration increased significantly. The causes of the decreased function of Sertoli cells at diagnosis have yet to be determined.

RFC6.5

The effect of GnRHa and testosterone treatment on growth in trans boys

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Background: Pubertal growth and adult height are important to many transgender adolescents undergoing medical transition. However, few studies are available on the impact of puberty suppression (PS) with GnRH analogues (GnRHa) and hormonal therapy (HT) with testosterone on growth. In this longitudinal cohort study, we investigated the effect of PS and HT on growth and adult height in transgender boys.

Methods: A total of 147 trans boys who were treated with GnRHa and testosterone, and had reached adult height were included. Data on height, bone age (BA) and parental height were collected. Height SDS was calculated based on female references. Mid-parental height was calculated and predicted adult height (PAH) was determined according to Bailey & Pinneau. The cohort was divided in those with growth potential (BA <14 years at start PS or, if BA was not available, menarche <1 year before start of PS, n=62) and those with little/no growth potential (n=85).

Results: In subjects with growth potential, PS resulted in a decrease of female height SDS from 0.1 ± 1.5 at baseline to -0.2 ± 1.0 at start HT, and a significant decrease in bone maturation. During HT, height SDS significantly increased by 0.4 SDS (95% CI 0.2 to 0.5). The difference between height SDS at start PS and adult height was 0.1 (95% CI -0.2 to 0.5). Mean adult height was 172.0 ± 6.8 cm (0.2 ± 1.1 SDS), which was 4.0 ± 6.0 cm above mid-parental height and 3.0 ± 3.6 cm above PAH at start of PS. A younger BA at start PS resulted in an adult height significantly further above PAH (1.2 cm/year; 95% CI 0.4 to 2.1). Individuals with little or no growth potential (n=85) reached a mean adult height of 169.0 ± 6.8 cm (height SDS -0.3 ± 1.1) and were significantly smaller than the group with growth potential at start PS.

Conclusion: Growth decelerated during GnRHa therapy and accelerated during HT. Although adult height SDS was similar to baseline, adult height was larger than predicted by BA at baseline. This effect was greater in those who started treatment at a younger

BA. It is reassuring that PS and HT do not have a negative impact on adult height in trans boys and might even lead to a slightly taller adult height, especially in those who start at a younger age.

RFC6.6

Differently Normal: Making sense of Adolescent Perspectives of Early Childhood Experiences associated with Congenital Adrenal Hyperplasia (CAH)

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Background: There is limited reporting of the impact of genital difference on early childhood experience, although the young person's viewpoint should be at the core of patient centred clinical decision making. The experience of girls living with Congenital Adrenal Hyperplasia (CAH) may differ according to context, being influenced by interactions within the family, with specialist teams as well as prevailing social values. Clearly there is a need to investigate this topic sensitively. Our aim was to facilitate exploration of childhood experiences related to genital difference in CAH.

Methods: This was a qualitative study involving a series of four semi-structured interviews, representing various clitoromegaly treatment and management pathways (including feminising genitoplasty, concealment techniques, and non-intervention), as part of a wider two-centre study of 25 families of children diagnosed with CAH. Ethical approval was gained only for an indirect enquiry around experience of typical recreational activities: swimming, playground games and sleepovers, to avoid eliciting distress. Interviews were recorded and transcribed, with thematic analysis performed independently by two clinicians with different backgrounds (clinical psychologist and paediatrician). Descriptive themes were analysed through the lens of developmental theory.

Results: Four themes were identified including (1) Adolescent Awareness: participants demonstrated an emerging recognition of genital differences only as they reached puberty; (2) Differently Normal: participants accepted emerging awareness of difference as part of a normal anatomical spectrum; (3) Concealing Difference: where participants reflected on their own behaviours (and those of parents) that may conceal genital differences to others around them; (4) "I'm not all about CAH", denoting a sense of self only partially related to CAH.

Conclusion: From this process we reflected upon interpretive approaches of different professionals towards how genital difference is framed, and how girls can best be supported by the multidisciplinary team. We note how some participants might struggle to understand the purpose behind our indirect enquiry, arguably leading to tangential discussions unrelated to genital difference. We concluded that an indirect approach is based on unwarranted fears around acceptability and fear of triggering distress to participants, which may inhibit meaningful discussion. Two of the participants demonstrated eagerness to discuss issues frankly, which was not considered ethically permissible for this study. Future studies of this kind would benefit from a more open approach that includes direct enquiry, provided it is done with sensitivity by a skilled and informed researcher.

Growth and Syndromes

RFC7.1

The grandma X-rays-independent height prediction

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Background/Aim: Parents wanting to predict adult height (AH) often resort to the old practice of doubling a boy's height at age 2 years or a girl's height at 18 months. We coined this the 'Grandma prediction' (GMP1). It provides predictions with mean absolute error (MAE) 5.9 and 5.2, standard deviations of residuals (sdRES) 4.1 and 3.6, and Pearson correlation r=0.68 and 0.67 for boys and girls, respectively. The recent sophisticated machine learning methods are only modestly superior. Here, we aimed to optimize 'Grandma prediction', while keeping its simplicity.

Material and Methods: GrowUp1974 (2339 subjects, 1174 boys) and GrowUp1990 (1890 subjects, 964 boys) Gothenburg cohorts were used. Heights were imputed on a regular age grid (0-17.5 years, with 2 months step) using the Schumaker shape-preserving spline interpolation. We defined a new variable HAHA calculated as Half-Adult-Height Age per each subject. Given country-specific growth charts (Sweden, Germany, Belgium, Netherlands), we call "mean HAHA" (mHAHA) the age when a "zero-SDS" girl(boy) reaches her(his) Half-Adult-Height. We modify 'Grandma prediction' by optimizing the relevant parameters using GrowUp1974 and validate the predictions using GrowUp1990. Optimized GMP2 provides AH predictions by doubling the height at mHAHA of the relevant country, while GMP3 doubles the height at the age of 24 (18) months for boys(girls) as in GMP1, however corrects the prediction for target height.

Results: On average Swedish boys (girls) of either Gothenburg cohort reached their HAHA at age 27.3 ± 3.1 (20.6 ± 2.5) months. The mHAHA estimated from the Swedish growth charts were close to these values. Compared to 'Grandma prediction' GMP2 improves to MAE = 3.9 (3.9), sdRES = 3.0 (2.9), and r = 0.71 (0.68) for boys (girls). GMP2 is deemed appropriate for parents' use after adjustment by mHAHA, estimated from the available

country-specific growth charts. For example, we estimate the mHAHA to be 2.1 (1.6) years in Germany, 2.15 (1.65) years in Belgium, and 2.2 (1.8) years for Dutch boys (girls) in the Netherlands. The optimized GMP3 provides MAE = 3.9 (3.9), sdRES = 3.0 (3.0), and r = 0.70 (0.68) for boys (girls).

Conclusion: HAHA might become a new milestone in childhood at around 2 years of age, when adult height can be predicted by the GMP method. GMP2 proves useful for parents, while GMP3, corrected for target height, might be useful for pediatricians. Thus, the X-Rays-independent GMP2 and GMP3 are easy and practical methods for AH prediction.

RFC7.2

Efficacy, Observer-Reported Outcomes, and Safety of Once-Weekly Somapacitan in Children with Growth Hormone Deficiency (GHD): 4-Year Results from the REAL 3 Trial

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Children with GHD are currently treated with daily subcutaneous growth hormone (GH) injections, which can be burdensome. Somapacitan is a long-acting GH derivative in development for once-weekly use in children with GHD.

REAL 3 (NCT02616562) is a phase 2, multinational, randomised, open-label, controlled trial assessing efficacy and safety of somapacitan versus daily GH (Norditropin®). Prepubertal, GH-naïve children with GHD received 0.04 (n=16), 0.08 (n=15) or 0.16 (n=14) mg/kg/week somapacitan, or 0.034 mg/kg/day daily GH for 1 year. In a 2-year safety extension, all patients on somapacitan (n=45) received 0.16 mg/kg/week; patients receiving daily GH remained on daily GH. In a 4-year safety extension, treatment switched to somapacitan 0.16 mg/kg/week in the daily GH group (daily GH/somapacitan, n=11) and remained unchanged in the somapacitan group (somapacitan/somapacitan, n=39). We present results from year 4, the first year of the 4-year safety extension.

Data are mean (SD). Height velocity (HV) was 7.4 (1.6) cm/year for somapacitan/somapacitan and 6.6 (1.6) cm/year for daily GH/somapacitan, versus 8.3 (1.7) and 7.6 (2.0) cm/year for somapacitan/somapacitan and daily GH, respectively, at year 3. HV SD score (SDS) was 1.55 (1.70) and 0.88 (1.61) for daily GH/somapacitan; change in height SDS from baseline was 2.85 (1.25) and 2.28 (0.97); insulin-like growth factor-I SDS was 1.29 (1.23) and 0.94 (1.60) for somapacitan/somapacitan and daily GH/somapacitan, respectively. The Table shows overall scores of GHD-child treatment burden (CTB) and GHD-parent treatment burden (PTB), reported by parents/guardians.

During year 4, 20 patients (51.3%) receiving somapacitan/somapacitan experienced 84 adverse events (AEs), and eight patients (72.7%) receiving GH/somapacitan experienced 12 AEs. Most AEs were mild/moderate and unrelated to treatment.

Height-related outcomes were similar between and as expected for both treatment arms. Somapacitan may lead to improvement in treatment burden versus daily GH. Somapacitan safety profile was consistent with previous reports.

RFC7.3

Genetic analysis of children with clinically non-syndromic tall stature

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Introduction: The genetic investigation of tall stature (TS) is routinely indicated only in children with clinical suspicion of a specific syndrome associated with TS. After ruling out an endocrine disorder, the remaining tall children mostly receive a clinical

Table. GHD-treatment burden measures from years 2–4; mean (SD) scores (lower indicates improvement)

	Daily GH/somapacitan			Somapacitan/somapacitan		
	N=11			N=39/40	N=39	N=37/38
Year	2	3	4*	2	3	4
GHD-CTB†	6.4 (8.2)	15.1 (16.3)	7.1 (9.4)	7.6 (9.4)	7.4 (6.8)	5.8 (7.5)
GHD-PTB‡	8.7 (10.9)	11.3 (16.4)	6.3 (12.2)	9.5 (11.2)	9.6 (12.2)	8.7 (12.1)

*Patients switched after year 3.
†Across physical, emotional wellbeing and interference domains.
‡Across emotional wellbeing and interference domains.

diagnosis of „idiopathic" (ITS) or „familial" tall stature (FTS). The aetiology of their TS remains unknown.

Aims: To elucidate genetic cause of excessive growth of children with non-syndromic TS using next-generation sequencing (NGS) methods.

Methods: There was a total of 39 children (25 girls) with TS (height >2 SD) participating in our study, who were examined in our endocrine outpatient clinic in the last year or were already being followed up in our endocrine outpatient clinic for tall stature. In these children we ruled out endocrine cause of TS and there was no clinical suspicion on specific genetic syndrome. The median age was 12 years (IQR 5-20 years) and the median height was 2.86 SD (IQR 2.10- 4.83 SD). Seventeen of the children were clinically classified as FTS (height of taller parent >2 SD), and the remaining 22 as ITS. All the children underwent karyotype and FISH (SHOX region) investigation. Furthermore, the DNA samples were analyzed by NGS using targeted panel of 788 growth-related genes. Detected variants were evaluated by the American College of Medical Genetics (ACMG) standards.

Results: Altogether we identified a monogenic cause of TS in 8/39 (20%) of the children. Two children had sex-chromosome trisomy (karyotype 47, XYY and 47, XXX), 2 had Sotos syndrome (variants c.7939C>T and c.5374_5375insGA in *NSD1* gene), 1 had Simpson-Golabi-Behmel syndrome (variant c.81delinsTTC in *GPC3* gene), 1 had Loyes-Dietz syndrome (variant c.777T>A in *TGFRB2* gene), one had a pathogenic variant c.1959C>A in *FGFR3* gene typically associated with CATSHL syndrome and 1 had SHOX gene duplication. Moreover, in additional 6/39 (15%) children we found variants of uncertain significance in genes *FBN2, COL6A2, MATN3, COL1A2, COL6A3, TET3* which are currently being investigated in more detail.

Conclusion: Genetic findings typically associated with syndromic tall stature could also be found in tall children with no clinical suspicion of a specific syndrome. Further studies are needed to evaluate if these children are likewise at increased risk of life-threatening oncologic or cardiovascular complications typically associated with several TS syndromes.

RFC7.4

Efficacy and safety of bilateral epiphysiodesis in extremely tall adolescents

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Background: Treatment options in extremely tall adolescents are limited. Bilateral epiphysiodesis has been reported to be a safe and effective method to reduce predicted final height. However, there is still limited data on final height and long-term safety.

Objective: The aim was to assess the safety and efficacy of bilateral epiphysiodesis to reduce adult height in adolescent girls and boys with extreme tall stature.

Methods: The study includes 72 patients who presented to the Pediatric Endocrine Clinic at the Karolinska University Hospital, Stockholm (Sweden) and subsequently were subjected to bilateral epiphysiodesis (girls n=45, boys n=27). Final height predictions (PFH) were based on hand x-rays before the surgery.

Results: When compared to PFH, final height (FH) was significantly reduced in both girls and boys treated with epiphysiodesis surgery (Table). The calculated height reductions correspond to 26 ± 2.9% (girls) and 40.5 ± 3% (boys) of the predicted remaining growth at the time of surgery. A negative correlation was observed between bone age at the time of surgery and absolute height reduction. This correlation was higher in boys (r=-0.63, p<0.001) than in girls (r=-0.44, p<0.001). Postoperative pain with a duration of less than 2 weeks was present in 38% (n=25) of the patients. Other complications were rarely seen.

Conclusion: Bilateral epiphysiodesis is an efficient and safe method to reduce final height in extremely tall adolescents. The surgery was more efficient in boys than in girls and when performed at an earlier bone age.

	CA at op (yrs)	BA at op (yrs)	Height at op (cm)	PFH at op (cm)	FH (cm)	PFH-FH (cm)
Females (n=45)	12.3 ± 0.2	12.1 ± 0.1	175.7 ± 0.6	188.9 ± 0.5	185.3 ± 0.5*	3.6 ± 0.4
Males (n=27)	13.7 ± 0.2	13.6 ± 0.1	188.4 ± 1.1	208.4 ± 0.9	199.9 ± 0.9*	8.6 ± 0.9

Chronological age (CA), bone age (BA), predicted final height (PFH) at operation and final height (FH). Data is presented as mean ± SEM. Statistics: t-test was applied in males (normal distribution) and Wilcoxon rank test in females (non-normally distributed).
*p<0.001 vs PFH at op

RFC7.5

A relevant cellular model to study imprinting disorders: dental pulp stem cells

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Parental imprinting is an epigenetic process leading to monoallelic expression of certain genes depending on their parental origin. Imprinting disorders are a set of rare diseases that mainly affect growth and metabolism from birth to adulthood. These disorders are mainly due to methylation defects in imprinting control region that drive the abnormal expression of imprinted genes. Moreover, patients with imprinting disorders may present overlapping clinical features that can be explained by the co-regulation of imprinted genes that belong to a dynamic imprinted gene network. We currently lack relevant animal or cellular models to understand the pathophysiology of growth failure in imprinting disorders. Multipotent stem cells could be a promising alternative. In this context, we aimed to assess the relevance of mesenchymal stem cells derived from the dental pulp and osteogenic cells derived to their differentiation in modelling imprinting disorders. We collected dental pulp stem cells from five controls and seven patients (five with Silver-Russell syndrome, one with Temple syndrome and one with Beckwith-Wiedemann syndrome) and we cultured them under osteogenic conditions. We reported that methylation of imprinting control regions involved in these syndromes showed a normal profile in controls and the imprinting defect in patients. Besides, in three patients with Silver-Russell syndrome and one patient with Beckwith-Wiedemann syndrome we showed that these results were maintained in dental pulp stem cells derivation in osteogenic cells. An extensive analysis of methylation allowed us to confirmed the same pattern in six other loci involved in imprinting disorders in humans. Aside from methylation profile, we also confirmed monoallelic expression of H19 (an imprinted gene at the 11p15.5 region) in controls and its biallelic expression in one patient using a newly developed method based on SNP-genotyping RTQPCR. These data were concordant with the methylation profiles in both controls and patients and validate the imprint maintenance in these cells. In conclusion, this extensive imprinting control regions methylation analysis shows the potential of dental pulp stem cells in modelling imprinting diseases, in which imprinting regions are preserved in culture and during osteogenic differentiation. The availability of such a cellular model will allow to perform in vitro functional and therapeutic tests in cells derived from dental pulp stem cells. Further work has to be done to generate other cell-types responsible for phenotype in patients with imprinting disorders, such as chondrocytes or adipocytes.

RFC7.6

Hormone Replacement Therapy After Pubertal Induction in Adolescents and Young Adults with Turner Syndrome: A Survey Study

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Objective: The majority of individuals with Turner syndrome (TS) experience Primary Ovarian Insufficiency requiring hormone replacement therapy (HRT). As the international consensus guidelines are unclear on the optimal formulation and dosing for HRT after pubertal induction in adolescents and young adults (AYA) with TS, our aim was to assess the current HRT practice patterns of endocrinologists and gynecologists.

Methods: An IRB approved survey was disseminated via REDCap to the email listserv members of the North American Society for Pediatric and Adolescent Gynecology and the Pediatric Endocrine Society in 2021.

Results: The 155 respondents who completed the entire survey included 76% (118) pediatric endocrinologists, 16% (24) pediatric gynecologists, 2% (3) obstetrician/gynecologists, and 3% (4) adolescent medicine specialists. More than half (91, 59%) reported being in practice for more than 10 years and practicing in an academic center (99, 64%). The majority (81%, 126) saw an average of 5 or less patients with TS every 3 months. Of the 60% (93) who preferred transdermal estradiol (TDE), only 54% (50) favored a 100μg/day formulation. The remainder preferred lower doses citing "whatever is effective" and "depends on clinical response and blood levels" as determining factors. The majority (81%, 78) preferred oral progesterone. None of the 7% (11) who favored a levonorgestrel-releasing IUD were endocrinologists. Of the 35% (54) who preferred combination oral contraceptive pills (OCP), 46% (25) favored a dose of 30 or 35μg ethinyl estradiol with the remainder preferring lower doses. Factors significantly associated with preferred HRT included specialty (p=0.02) and number of patients per 3 months (p=0.02). Gynecologists were 4 times less likely than endocrinologists to prefer OCP (OR 0.25; 95%CI 0.08, 0.78) and 4 times more likely to favor TDE dose of 100μg/day as compared to lower doses (OR 3.9; 95%CI 1.2,13.3). Attending physicians with 5 or less patients per 3 months were 4.5 times more likely than those with more patients to favor OCPs (OR 4.5; 95%CI 1.2,16.6). Although 87% (135) reported confidence in prescribing HRT to AYA after pubertal induction, only half (51%, 79) were aware of published guidelines and most (88%, 136) would prefer additional guidelines.

Conclusions: Although most endocrinologists and gynecologists report confidence in prescribing HRT to AYA with TS after pubertal induction, there are clear differences in provider preference based on specialty and number of patients. Additional studies on comparative effectiveness of the HRT regimens and evidence-based guidelines are necessary for AYA with TS.

Diabetes and Insulin

RFC8.1

Clinical spectrum of HNF4A-MODY (MODY1): From neonatal hyperinsulinism to diabetes in adults

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Background and Aims: HNF4A-MODY clinical expression is broad, ranging from hypoglycemic hyperinsulinism in the neonatal period and early childhood to hyperglycemia and diabetes, as insulin secretion progressively decreases in adult patients. The main objective was to clinically and molecularly characterize patients with glycemic alterations, negative autoimmunity and confirmed molecular diagnosis of HNF4A-MODY.

Materials and Methods: Cross-sectional study of 121 patients with suspected monogenic diabetes analyzed by targeted NGS with a custom panel including up to 482 genes implicated in or associated with dysglycemia. Variants were classified according to ACMG criteria and prioritized using criteria of confidence and quality, coverage (20x/pb >95%), allele frequency (AF) in control population <1% (gnomAD controls), impact ("missense", "nonsense", "frameshift", "splicing effect") and in silico prediction of pathogenicity (CADD V1.4, score >20).

Results: Predicted deleterious HNF4A variants were detected in 9/121 (7.4%). They presented 9 different variants (1xfs + 8 missense; 4 previously described and 5 novel), all in functional domains of HNF4A, classified as pathogenic/probably pathogenic in 3 cases, or as VUS in the remaining 6. 4/10 presented hypoglycemia at diagnosis, two were 1-month-old infants with neonatal hyperinsulinism and hypoketotic hypoglycemias who responded adequately to diazoxide. The other two were 6 and 18 years old, respectively, the last one with an atypical presentation with recurrent hypoglycemia. Her 72h fasting test was normal with no endogenous hyperinsulinism, no response to the glucagon test, and a basal C-peptide of 1.1 ng/ml with normal OGTT.

Among those who presented hyperglycemia as a reason for consultation (6/10), 3 were between 14 and 15 years old and the remaining 3 were > 30 years old at molecular diagnosis. 3/6 were treated with sc insulin (0.7-1IU/kg/day), 2 patients with metformin (one of them associated with Glimepiride), and one patient (15 years old) was only on dietary treatment and exercise. The median HbA1C among patients with hyperglycemia was: 6.2% RIC (5.7-7.2%).

Conclusions: HNF4A-MODY has different clinical expressions, depending among other factors on age of diagnosis, being in general more frequent as hypoglycemia in younger patients.

The molecular diagnosis will allow to optimize/personalize treatment, given the known good response to treatment with sulfonylureas in patients with HNF4A-MODY (only 1/10 was treated with metformin and sulfonylurea before molecular diagnostics).

Neonates with hypoglycemic hyperinsulinism had a good response to treatment with diazoxide; the molecular diagnosis of these patients confirms the need for a continuous follow-up to early detection of diabetes in adulthood.

RFC8.2

The impact of age, body mass index, and pubertal stage on C-peptide at type 1 diabetes diagnosis

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Background: Assessment of beta-cell function in type 1 diabetes (T1D) has important implications in both clinical and research settings. Studies are limited by the lack of adjustments demonstrating the extent to which puberty influences C-peptide levels. The aim of this study was to evaluate the influence of pubertal stage as well as age and body mass index (BMI) on multiple C-peptide measures at T1D diagnosis.

Methods: This study included 275 consecutive children aged 1-18 years with newly recognized T1D. Fasting, prandial, and area under the curve (AUC) C-peptide, estimated using fasting and prandial C-peptide levels, were analyzed. In addition, C-peptide increment was also evaluated. Univariate and multivariable linear regression models were utilized.

Results: Median age at diagnosis was 8.4 (1.1-17.3) years, and mean BMI standard deviation score (SDS) was -0.4±1.5. Of the patients, 66% were prepubertal. Median fasting and prandial C-peptide levels at diagnosis were 0.26 (0.05-1.4) ng/mL and 0.43 (0.05-3) ng/mL, respectively. Fasting C-peptide was almost perfectly correlated with prandial C-peptide (r_s=0.80, p<0.001). Fasting, prandial, and AUC C-peptide were positively related with BMI SDS, age, and pubertal stage at diagnosis (p<0.001 for all). All the associations persisted when the variables were included as independent variables in regression models (p=0.022 to <0.001). BMI SDS, age, and pubertal stage together explained 19-25% of the variance of C-peptide measures. There was also a positive correlation between C-peptide increment and both age and pubertal stage (r_s=0.28, p<0.001 and r_s=0.35, p<0.001, respectively).

Conclusions: The findings presented here have implications for the clinical assessment of young individuals with diabetes and clinical trials evaluating interventions for preserving beta-cell function in patients with new-onset T1D. While age and BMI at diagnosis are key variables associated with beta-cell function, our data set sets the stage for a greater understanding of the disease process with additional findings regarding puberty.

RFC8.3

Peripheral nerve conduction velocity in children and young adults with type 1 diabetes mellitus as a marker of metabolic control

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Background: Nerve conduction velocity (NCV) abnormalities are considered as early signs of peripheral neuropathy in patients with diabetes mellitus (DM). We investigated which determinants NCV is subject to and how it is related to markers of metabolic control.

Methods: We included 51 patients treated at the outpatient clinic of paediatric diabetology because of their type 1 DM and randomly assigned them for a nerve conduction study (NCS) at the occasion of their annual check-up. During this check-up a whole clinical examination, measurement of HbA1c and analysis of the last 90 days glucose profile with the characteristics time in range, incidence of hyperglycaemia (>10 mmol/l) and serious hypoglycaemia (<3 mmol/l), variation of the average blood glucose was done. Besides, we checked for drug abuse, associated autoimmune diseases (thyroiditis, coeliac disease), complications of DM (nephropathy, retinopathy) and comorbidities (dyslipidaemia, vitamin D insufficiency). To characterize the study group well we registered the age, duration of DM with its type depending on diabetes antibodies or MODY. An impression about the long term metabolic control was obtained by the mean HbA1c values of the last five annual check-ups, the incidence of severe hypoglycaemia and ketoacidosis since onset of DM, the kind of therapy (conventional or functional basal-bolus regimen, continuous subcutaneous insulin infusion (CSII)) and monitoring (blood glucose meter, sensor). The associations of NCV with physical findings, markers for diabetes control and known risk factors for neuropathy were tested by the analysis of Kendal-Tau with a significance level of 5 %, which has to be expected lower because of multiple comparisons.

Results: The following table shows selected study group characteristics and the significance of their correlation to the NCV of the peroneus nerve, which was the most sensitive. Pathologic results occurred in 73 %.

Conclusion: The NCV of the peroneal nerve closely correlates with the control of diabetes and other risk factors of diabetic neuropathy, which can be present already in young patients.

	%	Median (range)	p Value
Age at onset (y)		8.4 (1.7-15.1)	0.205
Male sex	57		
Antibodies found	90		
MODY	4		
Age at NCS (y)		14.5 (6.0-23.8)	0.002**
Duration of diabetes (y)		6.2 (0.6-18.4)	0.032*
Height at NCS (cm)		160.8 (120.4-186.5)	6.5x10-7**
CSII	51		
Sensor	71		
HbA1c at time of NCS (%)		8.0 (6.2-12.7)	0.040*
TIR at time of NCS (%)		54 (21-97)	0.240
SD of average glucose (mmol/l)		4.4 (1.3-6.8)	0.006*
Mean HbA1c last five years (%)		7.9 (6.1-14.2)	0.008*

RFC8.4

Developing a regional Southeast Asia diabetes healthcare professional network and webinars programme initiative during the pandemic

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Background: In 2020, the average glycaemic index of Type 1 diabetes (T1D) in Southeast Asia (SEA) countries were reported to be at around 83mmol/mol. In many low-middle-income countries (LMICs) in SEA, insufficient infrastructure, lack of universal health coverage and professional knowledge are factors that affect T1D outcomes that adversely affect mortality and morbidity. Action4diabetes (A4D) currently provides comprehensive partnership programmes with defined local hospitals through a Memorandum of Understanding (MOU) signed with the governments in SEA that guarantees ongoing supplies of free insulin, blood glucose testing, HbA1c tests and hospital emergency funds.

Internet access in SEA has boomed in the last decade and is now affordable with cheaper phones and data access. Because of this, digital access is now the most efficient solution to reach out, foster collaborations and educate healthcare professionals.

Objectives: During the pandemic, 2020-2021, A4D facilitated the establishment of a SEA diabetes healthcare professionals (HCP) regional network to facilitate cross-country collaborations, knowledge exchange and best practice sharing through 3 different initiatives:

- HCP advisory group
- SEA Regional Network Meetings
- Free-to-access A4D webinars programme

Results: The HCP advisory group comprise 26 multi-disciplinary HCPs from 8 different countries and professions. Number of registrants attending the quarterly diabetes HCP regional network meeting in November 2021 showed that 80% of the HCPs who participated in the meetings were doctors and the average number attending was 60 with representation from Laos, Vietnam, Malaysia, Cambodia, Myanmar and the United Kingdom. The analytics from the webinar's attendance is demonstrated that the top 3 countries engaged with the A4D Webinars from Cambodia, Malaysia and Vietnam, and an average registration per webinar was approximately 150.

Conclusion: These initiatives are crucial in building up sustainable health capacity that advocates for improved medical and psychosocial support, closing the diabetes healthcare gaps in SEA that continue to exist between developed countries and resource limited countries. Medical knowledge of diabetes care in SEA will continue to fall short without continued investments, upskilling and continuous medical education provisions. Strengthening health systems, education and developing sustainable and locally owned solutions are vital to improve health and quality of life for people with T1D in SEA and are the first steps to closing the T1D gaps in this part of the globe.

RFC8.5

Impact of type 1 diabetes on the epicardial fat thickness in children and adolescents

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Introduction: Diabetes mellitus has been shown to be a major risk factor for development of early adult onset cardiovascular disease (CVD). Therefore, early detection and management of CVD became a major concern for health care providers. Epicardial fat thickness (EFT) is considered a new marker of visceral adiposity. The increased epicardial adiposity does not only increase the cardiovascular risk but also is considered an established risk factor for appearance of insulin resistance.

Objectives: The aim of this study is to determine the correlation between epicardial fat thickness (EFT) and glycemic control, duration of diabetes in children and adolescents with type 1 diabetes mellitus attending Diabetology clinic of Alexandria University Children's Hospital.

Methods: Forty children with T1DM, divided into 2 groups according to the duration of diabetes with 20 patients in each (group 1 with duration of diabetes less than 5 years and group 2 with more than 5 years duration), and 20 age- and gender-matched healthy children (group 3) were included in the study. Demographical characteristics of all patients were examined. In addition to conventional echocardiographic measurements, end-systolic EFT was measured from right ventricular free wall. Furthermore, HbA1c was assessed in all diabetic patients. Besides, Lipids profile was assessed in all groups.

Results: Mean age of the patient groups was determined to be 9.77 ± 3.33, 12.20 ± 2.22 and 9.39 ± 2.90 years in the three groups respectively. There was no significant difference between the groups in regard to body weight, height, body mass index and blood pressure. In the patient groups; EFT was determined to be significantly higher compared to the control group. There was statistically significant correlation between the EFT and the duration of diabetes. Although, there was no significant correlation between EFT and glycemic control.

Conclusion: There is an increased risk of cardiovascular diseases in the patients with type 1 diabetes starting early during the childhood which makes a concern about its impact on this cohort of patients.

RFC8.6

Short-term effects of elexacaftor/tezacaftor/ivacaftor modulator therapy on glucose tolerance in young people with cystic fibrosis

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Background: CFRD is a unique subtype of diabetes mellitus, distinct from type 1 and type 2, harbouring β-cell dysfunction and β-cell loss and insulin resistance. Modulator therapies directly target the underlying defect of CF, modulating or correcting the function of the CFTR gene (mutation-specific). Few studies investigated the effect of modulators on CFRD and glucose metabolism. We performed an observational study on the short-term effects of the triple-modulator-therapy elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) on glucose tolerance in people with CF.

Methods: 16 adolescents with CF (homozygous or heterozygous F508-CFTR variant) underwent oral glucose tolerance tests (OGTT) before and four- six weeks after initiating ELX/TEZ/IVA therapy. A continuous glucose monitoring (CGM) system was used three days before until seven days after starting ELX/TEZ/IVA. OGTT results were categorised into normal glucose tolerance (NGT), indeterminate glucose tolerance (INDET), a combined group of impaired fasting glucose/impaired glucose tolerance (IGT) and CFRD. In terms of CGM measurements, we calculated the percentage of time of glucose levels within the following categories: Very low (≤ 2.7 mmol/L), low (≥ 2.8 and ≤ 3.3 mmol/L), normal (≥ 3.4 and ≤ 7.7 mmol/L), high (≥ 7.8 and ≤ 11.1 mmol/L), and very high (≥ 11.2 mmol/L). People with known CFRD were excluded.

Results: OGTT results were available from 15 adolescents. Before ELX/TEZ/IVA treatment, OGTTs resulted in two new diagnoses of CFRD; six participants were categorised as having IGT, two as INDET and five as NGT. OGTT categories improved after initiating ELX/TEZ/IVA ($p = 0.02$): no participant fell into the category CFRD, two into the category IGT, four into INDET

and nine into NGT. Glucose levels of OGTT improved at 60, 90 and 120 min ($p < 0.05$), whereas fasting glucose did not change.

Eleven participants successfully performed CGM measurements. We did not find a difference in the percentage of the respective glucose level time before and after ELX/TEZ/IVA initiation. No episodes of hypoglycaemia (very low and low category) were observed after starting ELX/TEZ/IVA. Episodes of hyperglycaemia were similar before and after starting ELX/TEZ/IVA treatment (3.0% [IQR 0.6 - 4.46] vs 1.2% [IQR 0.84- 2.08].

Conclusions: Shortly after initiating ELX/TEZ/IVA therapy, glucose tolerance measured by OGTT improved in people with CF. This pilot study indicates that ELX/TEZ/IVA treatment has beneficial effects on the endocrine pancreatic function and might prevent or at least postpone future CFRD.

Pituitary, Neuroendocrinology and Puberty

RFC9.1

The Incidence of Congenital Combined Pituitary Hormone Deficiency in Denmark - a national observational study

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Background: Congenital combined pituitary hormone deficiency (cCPHD) is the loss of ≥2 pituitary hormones caused by genetic or prenatal factors.

Methods: For the period 1996–2020, patients with cCPHD were identified from the Danish National Patient Registry and the registries at the four Danish hospitals approved for the management of cCPHD. Retrospective hospital file reviews were performed to validate the diagnosis by uniform criteria. Incidence estimations were performed using background population data.

Findings: We identified a national cCPHD cohort of 127 cCPHD patients, whereof 115 patients were born in Denmark and diagnosed before age 18 years. Eighty-eight (69·3%) were males. The median (range) age at cCPHD diagnosis was 5·9 (0·01–19·04) years. The national incidence (95% CI) of cCPHD diagnosed before age 18 years was 10·12 (7·60–13·47) per 100,000 births from 1996–2002, corresponding to an annual incidence rate of 5·62 (4·22–7·48) per million. The incidence was highest in the group of patients diagnosed aged 1–17 years; 7·75 (5·59–10·75) per 100,000 births, whereas the annual incidence rate was highest in patients diagnosed <1 year; 19·8 (13·9–28·4) per million births. The median (p25, p75) number of hormone deficiencies at cCPHD diagnosis was 3 (2·5; 4) in patients diagnosed aged <1 year vs. 2 (2; 2) in patients diagnosed aged 1–17 years; p<0·0001. Abnormal brain MRI findings were seen in 96·7% (29/30) diagnosed aged <1 year, decreasing to 85·2% (69/81) in the 1–17 years group.

Interpretation: cCPHD had the highest annual incidence rate and the most hormonal deficiencies in patients diagnosed before age 1 year. As late-onset cCPHD had the highest incidence, our study underscores the need for investigations for cCPHD throughout childhood and adolescence in children with isolated PHD.

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RFC9.2

Investigation of Genes Associated with Multiple Pituitary Hormone Deficiencies *via* Next Generation Sequencing Technology

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Background: Deficiency of one or more pituitary hormones, often with growth hormone (GH) deficiency, is defined as multiple pituitary hormone deficiencies (MPHD) or congenital hypopituitarism (CH). CH cases are mostly sporadic and have a prevalence of 1/3000-4000 live births. There are many known and yet unknown molecular pathways explaining the complex structure and functions of the pituitary gland. Many different gross and small sequence variants in the genes encoding the transcription factors that play a role in the embryological development of the pituitary gland are found in association with CH.

Aim: To investigate the molecular etiology of MPHD in our cohort and to determine the genotype-phenotype correlation.

Patients and Methods: In our cohort, 102 patients (38 girls, 64 boys) with the clinical diagnosis of MPHD were investigated. Clinical and laboratory findings were retrospectively collected from medical files, and inheritance patterns were determined from pedigrees. A targeted next-generation sequencing (NGS) panel for MPHD (including 25 genes) was performed. Multiplex ligation-dependent probe amplification (MLPA P-216; *GHRHR, LHX3, POU1F1, PROP1, LHX4, GH1, HESX1*) was used to determine gene/exon deletions in patients with normal panel results.

Results: The median age at admission to endocrinology was seven years (range: 0.01-17), and the median age of the patients during the molecular studies was 19 years (2-35). The median duration of follow-up was 11 years (1-25). The rate of consanguineous marriage was 35.6%. Dysmorphic features were seen in 25% of patients. Pituitary anomaly in magnetic resonance imaging was detected in 60%. There were two hormone deficiencies in 40.8% of the patients, three in 26.5%, four in 26.5%, and five in 6.1%. Frequency of pituitary hormone deficiencies were as follows; GH 90.4%, thyroid-stimulating hormone (TSH) 77.9%, gonadotropins 42.3%, adrenocorticotropic hormone (ACTH) 37.5%, prolactin 28.8%, anti-diuretic hormone (ADH) 2.0 %. We identified 21 (20.5%) pathogenic/likely pathogenic gross and small variants in genes associated with MPHD: *PROP1*; n=4, *WDR11*; n=3, *IGSF1*; n=2, *GH1*; n=2, *HESX1*; n=2, *LHX3*; n=2, *POU1F1*; n=2, *PROKR2*; n=2, *GHSR* and *HHIP* (n=1 each).

Conclusion: Advances in molecular genetic technologies allow investigators to determine the etiology of MPHD. Implementing genetic diagnosis in clinical practice and genotype-phenotype correlation may enable a personalized medicine approach.

Keywords: Multiple pituitary hormone deficiencies, Next-generation sequencing, Congenital hypopituitarism

RFC9.3

Peak Serum Luteinizing Hormone Levels during Gonadotropin-Releasing Hormone Analog Test among Lean, Overweight and Obese Girls with Central Precocious Puberty

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Background: Elevated serum luteinizing hormone (LH) during gonadotropin-releasing hormone (GnRH) test is documented in girls with central precocious puberty (CPP). Lower LH secretion has been reported in obese girls as compared with lean girls. Few studies have addressed the effect of obesity on peak serum LH levels during GnRH test. This study aimed to determine peak serum LH levels during GnRH analog (GnRHa) test in CPP girls of different body mass index (BMI).

Methods: Medical records of 847 girls with premature breast development of Tanner stages II (TII) and III (TIII) who underwent subcutaneous GnRHa test were reviewed. Girls with premature breast development concomitant with accelerated height velocity and advanced bone age were defined as CPP, whereas girls without above findings were defined as premature thelarche (PT). All of them were classified into 3 groups according to their BMI Z-scores as lean, overweight and obese groups. Clinical data and GnRHa test results were analyzed.

Results: There were 553, 188 and 106 girls in lean, overweight and obese groups, respectively. Four hundred and thirty-nine and 408 girls had TII and TIII breasts, respectively. CPP was diagnosed in 520 girls (216, TII and 304, TIII). Medians (IQRs) peak serum LH levels did not differ among 3 BMI groups (lean, overweight and obese, respectively, CPP, TII: 6.3 (4.7, 9.9), 8.8 (6.0, 16.1) and 6.7 (5.3, 10.1) IU/L, $p = 0.114$; TIII: 8.6 (5.9, 16.7), 10.8 (6.6, 15.4) and 8.2 (5.2, 21.6) IU/L, $p = 0.300$; PT, TII: 2.7 (2.0, 4.1), 2.6 (1.9, 3.3) and 1.8 (1.3, 2.6) IU/L, $p = 0.065$; TIII: 2.7 (2.1, 3.8), 2.4 (1.6, 3.1) and 1.9 (1.6, 2.8) IU/L, $p = 0.093$). Peak serum LH cut-off for CPP diagnosis at the comparable sensitivity and specificity seemed to be lower in the overweight (TII: 4 IU/L, sensitivity 88%, specificity 93%; TIII: 4 IU/L, sensitivity 85%, specificity 86%) and obese groups (TII: 4 IU/L, sensitivity 83%, specificity 90%; TIII: 4 IU/L, sensitivity 86%, specificity 98%) as compared with those of the lean group (TII: 4.5 IU/L, sensitivity 85%, specificity 83%; TIII: 4.5 IU/L, sensitivity 85%, specificity 87%).

Conclusions: Peak serum LH level during GnRHa test were not different among girls with CPP of different BMIs. However, lower peak serum LH cut-off for CPP diagnosis in overweight and obese girls might be considered.

RFC9.4

Association of Birth Size, Dehydroepiandrosterone Sulfate and Cardiometabolic Risk Factors in Idiopathic Central Precocious Puberty Girls

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Background: Early timing of puberty is associated with worse cardiometabolic health in adulthood. Furthermore, birth weight (BW) is recognized to have implications for pubertal development and cardiometabolic risk factors. The study aimed to examine the independent association between birth size, dehydroepiandrosterone sulfate (DHEAS) and cardiometabolic risk factors in idiopathic central precocious puberty (ICPP) girls.

Methods: A total of 445 patients with newly diagnosed ICPP were selected and categorized into 80 small (SGA), 311 appropriate (AGA), and 54 large (LGA) for gestational age, according to the BW percentile. Anthropometric measures, sex hormonal levels, DHEAS, insulin-like growth factor 1 (IGF-1), blood pressure, laboratory cardiometabolic profile and a total cardiometabolic risk z-score were recorded. General linear models and logistic regression models were respectively used to evaluate the associations of birth size, DHEAS and cardiometabolic health, by primarily adjustment for age, body mass index standard deviation score (BMI SDS), Tanner stage, preterm delivery, delivery mode as well as feeding patterns in infancy.

Results: SGA showed increased risk of hypo-high density lipoprotein-cholesterolemia (hypo-HDL-C) than AGA (25.0% vs 13.9%, adjusted OR: 2.45, 95%CI: 1.26-4.73). Interestingly, compared with AGA, LGA was associated with a higher cardiometabolic risk z-score (adjusted OR: 2.03, 95% CI: 1.08-4.23), however, no significant difference in terms of non-obesity cardiometabolic risk z-score. Furthermore, LGA was lower in serum triglyceride and triglyceride/high-density lipoprotein cholesterol than AGA (adjusted mean difference standard deviation: -0.39, -0.30). Serum DHEAS was higher in SGA than AGA, which may partly explain

the advanced pubic hair growth of SGA (*P*=0.004). In multiple linear regression, lower BW SDS and higher BMI SDS predicted higher DHEAS. Remarkably, IGF-1 SDS included reduced the magnitude of the BMI SDS effect by 47.6%. In addition, a negative correlation was observed between serum triglyceride and DHEAS independently of BW SDS, BMI SDS and IGF-1 SDS.

Conclusion: ICPP girls born SGA more likely exhibited hypo-HDL-C and born LGA presented with metabolic healthy obesity, characterized by higher BMI SDS with an adequate metabolic profile. Higher DHEAS was not associated with increased cardiometabolic risk excluding the impact of birth size and current state of nutrition in ICPP girls.

RFC9.5

Pubertal milestones in Prader-Willi syndrome: Is there a role of genetic subtypes and *MKRN3* status?

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Background: Subtle phenotypic differences have previously been described among children with varied genetic subtypes of Prader-Willi syndrome (PWS) – 15q11-q13 paternal microdeletion, maternal uniparental disomy (mUPD), and rare imprinting center defects. The *MKRN3* gene, located on 15q11.2, is a master regulator of pubertal initiation and is a candidate gene for abnormal pubertal development in PWS.

Objective and Hypotheses: We hypothesized that the abnormal pattern of pubertal development in PWS may be associated with altering *MKRN3* expression in individual genetic subtypes.

Method: We investigated 37 individuals with PWS (18 females, 19 pubertal) currently aged 11.1 years (median; 5.4 – 18.8 years, 5th – 95th percentile). All these patients started growth hormone treatment early in life at 0.9 years (median; 0.3 – 4.0 years, 5th – 95th percentile). We used MS-MLPA and Sanger sequencing to investigate individual genetic subtypes and determine *MKRN3* expression and sequence. Moreover, we evaluated age at pubarche (PH2) and at pubertal onset (B2 or testicular volume 4 ml; gonadarche), subsequent puberty progression and skeletal maturation.

Results: From the 37 probands, 23 had PWS caused by 15q11-q13 microdeletion and the remaining 14 had mUPD. Regardless of the genetic subtype, all children with PWS started with pubarche (adrenarche) early at -2.4 ± 1.3 SDS (mean ± SD) of appropriate age ($p < 0.0001$). In girls with PWS, the mean chronological age at pubarche was 7.4 years (-3.4 ± 1.1; SDS ± SD), and in boys 9.4 years (-2.1 ± 0.8). But those children had normal mean age at gonadarche (-0.2 ± 1.3 SDS). In girls with PWS, the mean chronological age at gonadarche was 10.3 years – similar to the healthy population (0.3 ± 1.0; SDS ± SD), and in boys 11.0 years (-0.7 ± 1.0). The bone age at gonadarche tended to be advanced by 0.5±1.1 years ($p = 0.07$), but there was not significant correlation between skeletal advancement and age of pubertal onset ($r = 0.4$, $p = 0.12$). The subsequent pubertal progression was slow and only exceptionally lead to spontaneous achievement of full pubertal maturation.

Conclusions: Children with PWS, regardless of the genetic subtype and the *MKRN3* status, have precocious pubarche and normal age at gonadarche, however they show insufficient subsequent pubertal progression. The bone age is a poor predictor of pubertal onset.

RFC9.6

Craniopharyngiomas diagnosed as incidentalomas - Results of KRANIOPHARYNGEOM 2007

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Purpose: Childhood-onset craniopharyngiomas (CP) are diagnosed due to clinical symptoms (symCP) or incidentally (incCP). In childhood-onset CP, studies on history before CP diagnosis have revealed symptoms and complaints related to CP, which were documented in CP patients' records with a median duration of 5 months prior to CP diagnosis. We investigated clinical manifestations and outcome in incCPs and symCPs.

Methods: IncCP were discovered in 4 (3m/1f) and symCP in 214 (101m/113f) CP recruited 2007–2014 in KRANIOPHARYNGEOM 2007. Age, sex, height, body mass index (BMI), tumor volume, degree of resection, pre- and postsurgical hypothalamic involvement/lesions, pituitary function and outcome were compared between both subgroups. The Pediatric Quality of Life (PEDQOL) and the German daily life ability scale Fertigkeitenskala Münster-Heidelberg (FMH) questionnaires were used to analyze health-related quality of life (QoL) and functional capacity, respectively.

Results: Reasons for imaging in incCP were cerebral palsy, head trauma, nasal obstruction, and tethered-cord syndrome, whereas headache (44%), visual impairment (25%), and growth retardation (17%) lead to imaging in symCP. Tumor volume at diagnosis was smaller in incCP (median 2.39 cm3; range: 0.14–4.10 cm3) when compared with symCP (15.86 cm3; 0.002–286.34 cm3). Age, gender, BMI, height, hydrocephalus, tumor location, and hypothalamic involvement at diagnosis of incCP were within the range of these parameters in symCP. Complete resections were achieved more frequently (3/4 patients) in incCP when compared

with symCP (20%). Surgical hypothalamic lesions were distributed similar in incCP and symCP. Irradiation was performed only in symCP (33%). No noticeable differences were observed concerning survival rates, endocrine deficiencies, BMI, height, functional capacity and quality of life of the 4 incCP cases when compared with the symCP cohort.

Conclusions: IncCP are rare (1.8%) and characterized by lack of endocrine deficiencies, resulting in normal height and BMI, no hydrocephalus, and smaller tumor volume at diagnosis when compared with symCPs. Outcome of the observed incCP is similar with symCP. Based on our findings, we conclude that headache, visual impairment, growth retardation, neurologic symptoms, weight gain, symptoms of central diabetes insipidus, and disturbances of pubertal development are frequent symptoms observed in CP at the time of diagnosis. A long duration of history is typical with regard to reduced growth rates and weight gain. IncCP cases occur with low frequency especially in CP patients with tumors of low tumor volume and without hydrocephalus at the time of diagnosis. In incCP, outcome was similar to symCP patients.

GH and IGFs

RFC10.1

Clinical and biochemical predictors of Permanent Growth Hormone Deficiency (pGHD) at retesting

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Background and Aims: Retesting subjects treated with GH throughout childhood at attainment of final height is of importance to identify those having pGHD and needing replacement treatment during transition years and adulthood, and to avoid overtreatment of GH sufficient subjects.

This study aimed at evaluating the clinical and biochemical features of patients diagnosed of isolated idiopathic (II) GHD in childhood at retesting to verify the prevalence of permanent and transient GHD (tGHD), and the clinical outcomes. We also explored the possible predictors of pGHD.

Methods: We retrospectively evaluated 55 subjects (30 females; mean age 15.3+/-1.56yr) who were retested using the GHRH+ arginine stimulation test (ATT). Subjects having pGHD and tGHD were compared. At diagnosis all patients underwent an ATT as first test followed by glucagon (59%), L-Dopa (20%), clonidine (6%) or GHRH+ATT (16%) tolerance tests. Auxological and biochemical parameters, bone age at diagnosis, at 6 and 12 months from the start of replacement therapy and at retesting were recorded. Possible associations with the features of the pituitary gland at MRI at diagnosis, and best GH peak at diagnosis, and at retesting were evaluated.

Results: The prevalence of pGHD was 16.3%. Both catch-up growth in the first year of therapy and total height gain at final stature were greater in the pGHD group that had also a greater BMI at diagnosis, at 6 and 12 months on GH therapy compared with the tGHD group. They had also a more pronounced and persistent bone age delay during GH therapy. Subjects with pGHD had a smaller pituitary volume at MRI than the tGHD group, and morphological changes in the pituitary gland were more frequently found. The levels of the GH peaks at diagnosis correlated with the GH peak at retesting. IGF1 and IGFBP3 at diagnosis were lower in the pGHD. At discontinuation of therapy, the biochemical marker that best differentiated the subgroups was IGFBP3 (pGHD 3285.80±505.18ng/ml vs tGHD 4297.67±477.68ng/ml, $p<0.05$) as a potential marker of persistent GHD in the age of transition.

Conclusions: Permanent GHD is not frequent among patients diagnosed of IIGHD in childhood. However, they do seem to have some distinctive features that if confirmed in a larger series could help identify which subjects need retesting and possibly further GH treatment. Furthermore, the correlation between peak GH at testing at diagnosis, and at retesting using the GHRH+ ATT confirms the diagnostic and predictive potential of this combined test.

RFC10.2

Severe primary IGF1 deficiency diagnosed by a standardized IGF1/ IGFBP3 generation test: The Belgian experience

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Background/Aim: Over the past 6 years, the IGF1/ IGFBP3 generation test (IGFGT) has been used in Belgium in a standardized form to identify children with severe primary IGF1 deficiency (SPIGFD). In this study, the discordance of the IGF1 and IGFBP3 responses during an IGFGT and the prevalence of SPIGFD were analyzed in a cohort of children with short stature (height SDS < - 2) and presenting with low (below lower reference limit) serum IGF1 level and normal stimulated GH peak (> 7 μg/L).

Methods: In total, 56 (35 male) children aged between 1.3 and 14.8 years (median 7.5) underwent an IGFGT. Only 34 IGFGT

were analyzed, because of non-persisting low serum IGF1 values and/or an underlying chronic disease in 22 children. Morning serum IGF1 and IGFBP3 concentrations were measured by the IDS-iSYS assay before and after 7 daily injections of GH (0.05 mg/kg bodyweight somatotropin) in the evening. An abnormal IGF1/IGFBP3 response was defined by a stimulated value remaining below gender and age specific basal reference limits. SPIGFD was defined by a low basal IGF1 together with a IGF1 response < 15 µg/L and a IGFBP3 response < 400 µg/L during the IGFGT.

Results: In 16/34 (47%) children, a normal basal serum IGF1 by the IDS-iSYS assay was measured and paralleled with a normal serum IGFBP3 in 13 cases. Twelve (67 %) of the 18 children with a confirmed low basal IGF1 had a low serum IGFBP3, 6 (33 %) had an abnormal IGF1 response and the same 6 cases had an abnormal IGFBP3 response, whereas 6 had a IGF1 response < 15 µg/L, 5 had a IGFBP3 response < 400 µg/L and 4 had both responses below the defined limits. Genetic studies in 3 of these 4 cases confirmed a pathogenic heterogenous GHR gene mutation (c.899 dup p. and c.876G>T) in 2 cases and a pathogenic PTPN11 mutation in another case.

Conclusion: In short children with persistent low IGF1 values and a normal stimulated GH peak, a low IGF1 status could be confirmed in only half of the cases using the IDS-iSYS assay. In those children, a 100 % concordance between low stimulated IGF1 and low stimulated IGFBP3 levels was observed during a standardized (high dose and prolonged up to 7 days) IGF1/ IGFBP3 generation test, permitting finally the biochemical diagnosis of a severe primary IGF1 deficiency in 12 %.

RFC10.3

A rare *HESX1* variant in a patient with congenital hypopituitarism

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Background: Congenital hypopituitarism (CH) is characterized by a deficiency of one or more pituitary hormones. Mutations in the genes coding for transcription factors, such *HESX1*, involved in the development of the pituitary, determine a highly variable phenotype which may include severe midline defects, septo-optic dysplasia and other congenital abnormalities. A small number of *HESX1* variants have been identified in humans. The phenotype shows always a GH deficiency, often associated with other pituitary hormone deficiencies in addition to ectopic posterior pituitary, mid-line abnormalities, micropenis, and polydactyly. We report a case of a newborn with congenital hypopituitarism due to a rare mutation of *HESX1* who presented with hypoglycemia and micropenis at birth.

Case Report: The patient was born at term to consanguineous parents after an uncomplicated pregnancy. Presentation at birth: weight 2.850 kg, length 49 cm, head circumference 34.1 cm, large anterior and posterior fontanels, diastasis of rectus abdominal muscles, micropenis and bilateral cryptorchidism, jaundice and transient hypoglicaemia. Serum thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, growth hormone (GH), testosterone, and insulin-like growth factor I (IGF-I) were undetectable. Free thyroxine was 1.10 ng/dl (0.89-1.76) and serum cortisol was 0.7 µg/dl (4.3-22.4), Ultrasound showed both testes located in the inguinal canal. The brain MRI showed the absence of the anterior pituitary with normal posterior pituitary and pituitary stalk, normal optical chiasm and no midline abnormalities. Hydrocortisone replacement (10 mg/m^2/day) was started immediately followed by L-Thyroxine (9 µg/kg/day). At the age of 9 months, he started GH treatment. At the age of 2.7 years he underwent left orchidopexy. Right orchidopexy is scheduled. Genetic investigation identified a rare pathogenetic homozygous variant c.325C> T p. (arg109*) in *HESX1*, and a heterozygous variant of uncertain significance (c.19C> p. (arg7cys) in *PROP1*. This *HESX1* variant was reported in only one patient who presented panhypopituitarism, hypoplastic adenohypophysis, ectopic neurohypophysis and interruption of the pituitary stalk. Our patient is currently on replacement therapy with L-Thyroxine (2.4 µg/kg/day), GH (0.023 mg/kg/day), hydrocortisone (12 mg/m^2/day). During the 3 years follow-up he had a catch-up growth, no adrenal crisis, and just one hypoglycemic episode post surgery.

Conclusions: We reported a case of a rare homozygous pathogenic *HESX1* variant characterized by hypopituitarism, absent anterior pituitary, normal posterior pituitary, stalk and optic nerves. These data might help to better understand the genotype-phenotype correlation in patients with homozygous *HESX1* variants, which, according to the current knowledge is still not clear.

RFC10.4

Recombinant PAPP-A2 induces sex-specific increases in body weight and length and changes in bone microstructure in adolescent mice with longitudinal growth reduction induced by Pappa2 deletion

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Deficiency of pregnancy-associated plasma protein-A2 (PAPP-A2), a protease that regulates IGF-1 availability, causes postnatal growth failure and changes in bone size and density in humans and mice. The present study aimed to determine the effects of daily administration (from PND5 to PND35) of

recombinant murine (rm) PAPP-A2, in comparison to rmGH and rmIGF1, on mouse auxology and bone microarchitecture in homozygous Pappa2 knock-out (ko/ko) mice of both sexes. Hormone treatment increased body weight and length in a drug, genotype and sex-dependent manner, with rmPAPP-A2 resulting in weight and length increases up to 10% and 2%, respectively, in Pappa2ko/ko males and up to 15% and 11%, respectively, in Pappa2ko/ko females. Hormone treatment also increased relative femur density and weight in a drug, genotype and sex-dependent manner, with Pappa2ko/ko males exhibiting a significant increase in relative femur density, and Pappa2ko/ko females showing significant increases in both relative femur density and weight after rmPAPPA2 administration. Morphometric analysis of bone by Microcomputed Tomography (μCT) revealed that rmPAPP-A2 administration in Pappa2ko/ko males increased femur trabecular separation, trabecular thickness and cortical area fraction, and normalized trabecular number and cortical thickness. No effect of treatment on femur microarchitecture was observed in females. In summary, daily administration of recombinant PAPP-A2 from PND5 to PND35 increases body weight and length in Pappa2ko/ko mice, and changes bone morphometry in a manner suggestive of prolonged bone development. These effects depend on sex and provide important insights into PAPP-A2 efficacy as potential therapy for growth failure and the comparison to treatment with rmGH or rmIGF1 will be presented.

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RFC10.5

Evaluation of health-related quality of life and problem behavior in adults born small for gestational age treated with growth hormone during childhood in comparison with untreated controls

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Background: Being born small for gestational age (SGA) has been associated with a reduction in health-related quality of life (HRQoL) and more problem behaviour. Growth hormone (GH) treatment, which leads to a significant improvement in adult height (AH), improves HRQoL and decreases problem behavior in SGA children. However, such results are very limited in SGA adults who were treated with GH during childhood.

Objective: To assess HRQoL and problem behavior in adults born SGA who were treated with GH during childhood in comparison with age-matched untreated controls.

Methods: The study group consistent of 4 different groups: adults born SGA treated with GH during childhood (SGA-GH), adults born SGA with persistent short stature (SGA-S), adults born SGA with spontaneous catch-up growth to a normal adult height (SGA-CU) and adults born with normal birthweight and birthweight (AGA). HRQoL was assessed using TNO-AZL Adults Quality of Life questionnaire (TAAQOL), which consists of 45 items and contains twelve scales; scales were scored from 0-100, 0 indicating the lowest HRQoL. Problem behaviour was assessed using Adolescent Behavior Check List (ABCL). It consists of 113 questions divided in eight subscales and 3 main scales; total problem, externalizing and internalizing problem behavior. Scales were scored from 50-70, 70 indicating the greatest problem behavior.

Results: The group consisted of 335 subjects: 105 SGA-GH, 50 SGA-S, 77 SGA-CU, and 103 AGA. Mean age at follow-up was 28.6 (SGA-GH), 31.8 (SGA-S), 32.7 (SGA-CU) and 32.7 years (AGA), resp. Mean adult height SDS was -1.6 (SGA-GH), -2.4 (SGA-S), -0.2 (SGA-CU) and 0.4 (AGA), resp. Eighty percent of SGA-GH were content with their adult height compared to fifty-six percent in SGA-S ($p<0.001$). There was no difference in cognitive function, vitality, positive emotions and all other TAAQoL subscales in SGA-GH compared to SGA-S and SGA-CU. No difference between motor function, sleep, social function, daily activities and depressive emotion was found between SGA-GH and AGA.

We found no difference in all ABCL subscales in SGA-GH compared to SGA-S. Negative correlation was found between adult height SDS and ABCL total problem score (-0.27, $p<0.001$). Positive correlation was found between adult height SDS and TAAQoL vitality score (0.18, $p<0.001$) and positive emotions score (0.17, $p<0.001$).

Conclusion: SGA-GH were more content with their adult height compared to SGA-S. No differences were found in HRQoL & problem behavior between SGA-GH, SGA-S and SGA-CU. On particular subscales, HRQoL & problem behavior was not different in SGA-GH compared to AGA.

RFC10.6

Growth hormone deficiency in adult survivors of childhood brain tumors treated with irradiation

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Introduction: Brain tumors are the most common solid neoplasm in children, and treatment often includes high-dose irradiation of the central nervous system (CNS). Although not universal, growth hormone deficiency (GHD) is a very common endocrine late effect after CNS irradiation in childhood. The consequences of GHD in adults are many e.g., reduced bone mineral density, fatigue, decreased lean body mass and adiposity, which implies that adults with severe GHD should be offered substitution with growth hormone.

Aims: 1) To determine the frequency of GHD in adult long term survivors after CNS irradiation for a brain tumor in childhood 2) To detect undiagnosed GHD in survivors after CNS irradiation in childhood 3) To assess if proton therapy is associated with less GHD than photon therapy.

Methods: The study group comprised population based five-year survivors from two health regions in Denmark treated for a brain tumor in childhood with CNS irradiation in the period 1997–2015. Medical charts from all survivors were reviewed for endocrinological and other health data. Irradiated survivors, where a GH test at final height had not been performed, were invited to an Insulin Tolerance Test (ITT) or a Growth Hormone-releasing hormone-arginine test if ITT was contraindicated.

Results: Forty-one survivors (22 females) with a median age of 21.7 years at follow up (range 15.1-33.8 years) and 14.8 years since diagnosis (range 5.1-23.4 years) had received CNS irradiation of 12-61 Gy. GHD was detected in 26 (63%) of 41 survivors. In total, 17 %, 15 % and 15 % had two, three and four hormonal deficiencies, respectively. Eighteen of 21 patients had already confirmed GHD after reaching final height. Sixteen of 20 patients with no GH test at final height accepted the invitation to a GH test (participation rate 80%), and 8 (50%) were found to have GHD. Of the 41 irradiated survivors, 11 had received proton irradiation and 30 photon irradiation. GHD was diagnosed in 73 % of patients treated with proton- and in 60 % of patients treated with photon irradiation, respectively.

Conclusion: In this study, a high frequency of undiagnosed GHD in survivors with no GH test at final height were identified. The results reinforce the importance of screening for GHD at final height in survivors of childhood brain tumors with prior exposure to cranial irradiation. In this small study the frequency of GHD was similar in patients treated with proton and photon irradiation.

Late Breaking

RFC11.1

Six-months of treatment with exenatide improves glycemic control, but does not affect endogenous intact GLP-1 concentrations in adolescents with obesity

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Introduction: When used to treat obesity, glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RA) improve both BMI and metabolic health. Liraglutide is approved by both the EMA and FDA for the treatment of pediatric obesity, from 12 years and older. However, 26 weeks after discontinuation of liraglutide, the weight lost during treatment is regained. Prolonged exogenous stimulation of hormone-specific receptors may influence endogenous hormonal regulation. Treatment with the GLP-1RA liraglutide has been shown to both suppress and enhance endogenous concentrations of GLP-1 in adults. It is still unknown what effects GLP-1RA have on endogenous hormonal systems in children and adolescents with obesity. If GLP-1 is suppressed, it may contribute to a more pronounced hunger after discontinuation. For these reasons, we measured the effect of the GLP-1RA exenatide on secretory patterns of endogenous intact GLP-1 as well as insulin, proinsulin, C-peptide, glicentin, glucagon and glucose in adolescents with obesity.

Method: The Combating JUvenile Diabetes and Obesity (Combat-JUDO) trial was a 6-month multi-center, randomized, double-blinded, parallel, placebo-controlled trial (clinicaltrials.gov: NCT02794402). Participants were randomized to receive either exenatide (n = 22) or placebo (n = 22) for six months. Complete sample sets were available for 19 patients in the exenatide group and 18 in the placebo group. Venous blood was collected in EDTA tubes during an oral glucose tolerance test (OGTT) at the beginning of the study and after six months of treatment. Intact endogenous GLP-1 was measured by chemiluminescent enzyme-linked assay (Mercodia, Uppsala, Sweden) which has no reported cross-reactivity with exenatide. Insulin, proinsulin, C-peptide, glicentin and glucagon were measured using ELISA (Mercodia).

Results: Basic characteristics of the participants have been published previously. There was no difference in age, BMI, sex, glycaemic status or Tanner staging between the groups.

Treatment with exenatide significantly lowered glucose levels during the OGTT ($p < 0.0001$). Insulin secretion had a later peak after treatment (60 minutes), compared to before (30 minutes). No other differences in insulin were seen during the OGTT. Fasting proinsulin (mean difference -4.961 +/- 1.409 pmol/L, $p=0.0024$) and the proinsulin to insulin ratio (mean difference -0.03842 +/- 0.01190, $p=0.0047$) were both lowered following treatment. Intact endogenous GLP-1, glucagon, glicentin and C-peptide were not affected by treatment.

Conclusion: Six months of treatment with exenatide improves glycemic control and lowers proinsulin, but does not affect endogenous GLP-1 in adolescents with obesity, making it an interesting candidate for pharmacological treatment of pediatric obesity.

RFC11.2

Dynamics of meal-related plasma asprosin levels

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Background: Asprosin is an adipokine involved in glucose homeostasis and its plasma levels physiologically increases in fasting conditions and decreases with refeeding. In non-diabetic children and adolescents with obesity, insulin resistance (IR) and impaired fasting glucose (IFG) seem to influence the physiological variation in meal-related asprosin levels 120 minutes after an oral glucose load (Corica et al. doi:10.3389/fendo.2021.805700). No data are available on plasma asprosin levels at 60 minutes after a meal in children and adolescents with obesity.

Objectives: To evaluate the dynamics of asprosin secretion at fasting and 60 and 120 minutes after meal intake, with particular interest in the trend of asprosin levels at 60 minutes with respect to fasting and 120 minutes levels

Methods: Seventy-nine obese subjects were recruited (aged 11.5 ± 2.6 years). Children underwent clinical and biochemical assessments, including oral glucose tolerance test (OGTT). Monophasic or biphasic blood glucose shape trends were assessed. IR was defined as HOMA-IR > 2.5 in prepubertal children and > 4 in pubertal subjects. IFG was defined as fasting plasma glucose between 100 and 125 mg/dL. Asprosin serum levels were measured by an ELISA at fasting and at 60-minute and 120-minute OGTT timepoints. Applying Mc Wolfe's non-parametric test, trends in asprosin levels among fasting, 60-minute and 120-minute OGTT timepoints were assessed in the entire study population as well as in subgroups divided according to the presence of IR, IFG and glucose shape trend.

Results: A significant change in asprosin levels between 0, 60 and 120 minutes was demonstrated in the entire study population. Specifically, evaluation of meal-related asprosin dynamics documented that the increase between fasting and 60-minute levels and the decrease between 60-minute and 120-minute levels were significant (p=0.004). The same trend in asprosin levels was also documented among subjects with IFG (p=0.024), IR (p=0.037), and those with a monophasic glucose shape pattern (p=0.021). The variation of asprosin levels was not significant among non-IFG and non-IR patients and among those with a biphasic glucose curve pattern.

Conclusions: The analysis of the dynamic of asprosin levels carried out on three assessments in obese children with IFG and/or IR and/or a monophasic glucose shape pattern, supporting the hypothesis of a potential impairment of meal-related asprosin levels in these subjects. These results suggest that an altered asprosin secretion might be an early biomarker of impaired glucose regulation and IR.

RFC11.3

Predictors of kidney damage development in children with metabolically healthy and metabolically unhealthy obese phenotypes

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Background: A close association has been reported between obesity and renal damage in adults, but evidence in childhood is still limited.

Methods: We retrospectively studied 396 children and adolescents with obesity. Clinical, biochemical, and instrumental evaluations were performed. Patients were stratified according to the metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO) phenotypes. Kidney damage was defined as the presence of reduced eGFR and/or proteinuria and/or hypertension.

Results: Children with kidney damage had higher BMI-SDS values and an increased prevalence of Non Alcoholic fatty liver disease (NAFLD) than those without kidney damage (2.30±0.51 vs. 2.14±0.63 and 62.4% vs. 35.5%, p=0.012 and p<0.0001, respectively). As markers of inflammation, they also showed higher levels of platelets, white blood cells, and neutrophils than those without kidney damage (p=0.038, p=0.017, and p=0.037, respectively). More, higher Homeostasis model assessment of insulin resistance (HOMA-IR) values were found in subjects with kidney damage compared to those without kidney damage (4.58±3.47 vs. 3.38±1.96, p<0.0001). As expected, patients with MUO phenotype showed a worse cardiometabolic profile than those with MHO phenotype (all p<0.0001). MUO patients also showed a higher prevalence of NAFLD compared to MHO subjects (80% vs. 59.5%, p =0.003). They also had an OR to show kidney damage of of 1.92 (CI 1.22-3.01, p=0.005) after adjustment for age, sex, BMI-SDS, and HOMA-IR. Patients with MUO having kidney damage showed higher prevalence of NAFLD and increased HOMA-IR values than those without kidney damage (65.2% vs. 34.8%, p <0.0001; 5.33±3.19 vs. 4.09±2.02, p=0.015, respectively). Inflammation markers such as platelets, white blood cells, and neutrophils were also found to be higher in these patients compared to those without kidney damage (p=0.015, p=0.039, and p=0.04, respectively). More, significant differences were reported for uric acid, fasting glucose, fasting insulin, HOMA-IR, total cholesterol, and LDL cholesterol levels in MHO children with kidney damage compared to peers without kidney damage (all p<0.05). Children with MHO phenotype showed an OR of 1.05 (CI 1.00-1.09, p=0.028) to show kidney damage after adjustments for confounders.

Conclusion: Children with obesity showed an increased risk of early kidney damage. Although this risk has been found to be higher in subjects with MUO phenotype, it should be not underestimated in children with MHO profile because of their adverse cardiometabolic risk profile predisposing to obesity-related comorbidities development over time.

RFC11.4

Are GnRH agonists beneficial in final adult height after 8 years old? Data from a Portuguese National Digital Platform of idiopathic Central Precocious Puberty

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Objective: Central precocious puberty (CPP) is a common condition in pediatric endocrinology practice. Gonadotropin-releasing hormone agonists (GnRHa) treatment is safe, but the real effect on final height and the ideal timing for treatment remains controversial. The purpose of the authors was to evaluate a nationwide representative group of CPP Portuguese girls treated with GnRHa, assess the effectiveness of treatment and the growth outcome before and after 8 years of age.

Design and Methods: Nationwide retrospective longitudinal study evaluated data from Portuguese girls with CPP who completed GnRHa treatment, between January 2010 and 2021. Auxological and clinical characteristics were analyzed and compared according to the age at the beginning of treatment.

Results: Of the 400 patients diagnosed with CPP, we assessed 134 girls in this study. Patients were divided into early (<8 years, n=48) and later treatment group (≥ 8 years, n=86). Duration of treatment was higher in the early group (p=0.001). In all patients, height-SDS for chronological age (CA) tended to decrease during the study (p=0.005; p=0.038), while height-SDS for bone age (BA) had a continuous increase (p=0.086; p=0.012). Similar patterns were observed in later treatment group. In early treatment group, both height-SDS for CA and BA increased throughout the study (height-SDS for CA: p=0.828 and p=0.821; height-SDS for BA: p=0.450 and p=0.001). BA advancement decreased since baseline to final treatment (p=0.008) and last visit (p=0.034), and an increase in predicted adult height (PAH) was observed in both groups (early treatment group, p=0.032; later treatment group, p=0.04). Height gain was higher in the early group, but the difference between groups was not statistically significant (p=0.056).

Conclusions: This study showed a benefit of the treatment in terms of growth outcomes demonstrated by an increase of height-SDS for BA and PAH, and a decrease in BA advancement in both groups. Moreover, height at last visit was higher than the initial PAH and GnRHa treatment was still effective even after 8 years of age in girls with CPP.

RFC11.5

Dasiglucagon Treatment Over 21 days in Infants with Congenital Hyperinsulinism Results in Glycaemic Stability and Reduces Requirement for Intravenous Glucose

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Background: Congenital hyperinsulinism (CHI) is a chronic and complex rare endocrinopathy with dysregulated insulin secretion causing severe and recurrent hypoglycemia resulting in adverse neurologic and developmental sequelae in children. Current treatment options are limited and often inadequate to treat CHI. Dasiglucagon (DASI), a glucagon analog administered by subcutaneous continuous infusion, has demonstrated reduction in glucose infusion rate (GIR) in Part 1 of a randomized placebo-controlled trial over a 48-hour period in neonates and infants with CHI.

Study Design: We report efficacy and safety of DASI in Part 2 of this phase 2/3 trial in children with CHI aged ≥7 days to <1 year requiring intravenous glucose infusion rates (GIR) > 10 mg/kg/min. Following completion of Part 1 of the study, all participants continued open label DASI for an additional 21 days (Part 2). Outcomes included the ability to reduce intravenous glucose infusion, total daily carbohydrates and hypoglycaemia frequency (<70 and <54 mg/dL by self-monitored blood glucose (SMBG) and continuous glucose monitoring (CGM). Safety markers included hyperglycaemia (SMBG >180 mg/dL), tolerability and adverse events (AE).

Study Results: All 12 children (age 0.5-10.7 months, mean 2.4) enrolled in Part 1 continued into Part 2. Baseline GIR for 12 hours prior to study initiation was 15.7 ± 4.5 mg/kg/min (mean ± SD). In Part 1, DASI resulted in a significant reduction in GIR (treatment difference: -5.2 [-8.3;-2.1] mg/kg/min, p=0.0037) versus placebo (55% decrease). In Part 2, DASI enabled reduction or discontinuation of intravenous glucose infusion in 10 out of 12 children. Seven of them, who did not require pancreatectomy, were completely weaned-off. CGM measures of hypoglycaemia trended lower with a reduction in median time <70 mg/dL from 7.0% to 5.2% (week 1 to 3) and <54 mg/dL, 1.9% to 0.88% (week 1 to 3). There was no increase in hyperglycaemia. DASI was well tolerated with skin rashes and gastrointestinal disturbance reported commonly as AE but not requiring discontinuation of treatment. No serious AE were reported.

Conclusions: The use of continuous subcutaneous infusion of dasiglucagon in a 21-day open-label trial in infants with CHI suggests that dasiglucagon may reduce intravenous glucose requirements, time in hypoglycaemia and enabled discontinuation of intravenous glucose in most infants, thus obviating the need for subtotal pancreatectomy for glycaemic stability. In combination with results from Part 1, these data support the efficacy and safety of DASI as a potential novel treatment for CHI.

RFC11.6

Genotype, phenotype characteristics and long-term follow-up of patients with Vitamin D Dependent Rickets Type IA (VDDR1a): A nationwide multicentre retrospective cross-sectional study

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Background: Vitamin D Dependent Rickets Type IA (VDDR1a) is an autosomal recessive disorder characterized by defects in the biosynthesis of its active form 1,25 dihydroxyvitamin D due to the mutations in the CYP27B1 gene encoding for the enzyme 1α-hydroxylase.

Objective and Hypotheses: To evaluatethe clinical characteristics, molecular genetics aetiology and long-term outcome of a large nationwide cohort of VDDR-Ia from Turkey.

Method: In this nationwide multi-centre retrospective cross-sectional study we collected data from around the country using a web-based research network, CEDD-NET for paediatric endocrinology. Presenting symptoms, family history, gender, age of diagnosis, anthropometric measurements, presence of skeletal deformity, serum Ca, P, ALP, PTH, 25 (OH) vitamin D level, urinary ca/creatinine ratio and radiological findings were collected from the paediatric endocrine centres using a structured dataset disseminated through the CEDD-NET. Molecular genetics analysis results for which a molecular genetic analysis was applicable were collected. Clinical and biochemical characteristics and their relationship with molecular genetics analysis, treatment strategies and long-term outcomes of patients were recorded. Data collected from the paediatric endocrine centres were analysed using IBM-SPSS software.

Results: In total 128 patients (55 F, 73 M) with VDDR1a were recruited. The median age of the diagnosis was 2.0 years. The most common presenting complaints were skeletal deformity (n=48), short stature (n=46), and delay in walking (n=42), The most common mutations detected in molecular genetics analysis were a splice donor sitemutation (c.195+2T>G) (n=38), followed by a 7-bp duplication mutation 1319–1325dupCCCACCC(Phe443Profs*24) (n=20) and the missense p.192K>E(c.574A>G) mutation (n=19), suggesting Turkey serving as a mutational hot spot or founder effect for the relevant variants. All patients were treated using an active form of vitamin D, calcitriol, at a mean daily dose of 56±27 pg/kg and calcium replacement once required. After an average duration of 6 years for calcitriol therapy, patients' height SDS improved from the baseline (-2.2±1.6) to the latest follow-up visit (1.6±1.4 SD) during the study period ($p<0.001$) suggesting a favourable long-term outcome. No severe side effect has been reported in the short-term and long-term follow-up undercalcitriol therapy.

Conclusion: In this nationwide multi-centre retrospective cross-sectional study on the VDDR1a most common three mutations accounted for about half of the cohort suggesting Turkey to be a mutational hotspot or founder effect for the relevant variants. Long-term follow-up data revealed improvement in height outcome with no severe complications suggesting a safe and effective therapy with calcitriol treatment.

Top 20 Posters

T1

Measurement of 11-oxo-androgens, a novel biomarker, in females with clinical signs of premature adrenarche

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Introduction: Adrenarche is characterized by the activation of androgen precursors which are released from the zona reticularis of the adrenal gland. Dehydroepiandosterone (DHEA) is a weak androgen and its conversion to slightly more potent androgens such as Dehydroepiandosterone- sulfate (DHEA-S) is thought to be responsible for the clinical signs of adrenarche. Premature adrenarche is one of the most common endocrine abnormalities causing concern among peripubertal children and their parents. Recent studies have demonstrated that adrenal production of 11-oxygenated steroids such as 11-ketotestosterone, 11 hydroxyandrostenedione, and 11-beta- hydroxytestosterone are also potent adrenal androgens that can bind to androgen receptors and therefore likely play a role in the clinical picture of adrenarche.

Objective: The objective of the study is to determine if levels of 11-oxo androgens can be used as a new more sensitive biochemical marker for diagnosis of premature adrenarche in females.

Methods: A chart review study was conducted that looked at laboratory and anthropometric data of female patients who presented with history of symptoms associated with premature adrenarche before 8 years of age.

Results: A total of 28 subjects were collected. Of the 16 subjects who had normal DHEA and/or DHEA-S, 12 (75%) had elevated 11 oxoandrogens (defined as one or more). We also noted that 11-ketotestosterone and 11- hydroxyandrostenedione were elevated more consistently than 11-hydroxytestoterone.

Conclusions: Seventy five percent of patient with normal DHEA/DHEA-S had elevated 11-oxo androgens, indicating that their symptoms are likely related to the effect of oxo androgens as opposed to simply DHEA/DHEA-S. Therefore, 11-oxo androgens could be used as novel biomarkers to evaluate premature adrenarche for patients in whom previous biochemical evaluation yielded inconclusive results.

T2

Conditional PTEN knockout in mouse osteoprogenitor cells impacts bone structure and turnover

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Background: Bone development and remodeling are controlled by the phosphoinositid-3-kinase (PI3K) signaling pathway. We investigated the effects of downregulation of phosphatase and tensin homolog (Pten), a negative regulator of PI3K signaling, in osteoprogenitor cells.

Methods: Femura, tibiae and bone marrow stromal cells (BMSCs) from mice with Cre-inducible Pten knockdown in cells expressing the transcription factor Osterix/Sp7 (Pten cKO) and Cre negative control mice were compared. Bone phenotyping was performed via μCT and 3-point bending test. Number of osteoclasts and osteoblasts was determined by tartrate resistant acid phosphatase (TRAP) immunohistochemistry. Proliferation of BMSCs was measured by counting Hoechst and Ki-67 stained cells. In vitro adipogenic and osteogenic differentiation was determined via Oil Red O and alkaline phosphatase staining, respectively. Bone turnover was assessed by ELISA detecting CTX and P1NP and intraperitoneal Calcein injections 2 and 5 days prior to sacrifice.

Results: We detected a higher trabecular bone volume/total volume (BV/TV) and higher bone mineral density (BMD) in Pten cKO of both sexes, while BV/TV and BMD was lower in cortical bone. Biomechanical analysis revealed a significantly higher maximum force (3.7fold, $P = 0.0003$ for males) and elasticity of Pten cKO femura. Pten cKO bones from male mice displayed less osteoclasts (0.7fold) and more osteoblasts (2.0fold, $P = 0.0006$) per bone surface compared to controls. Bone turnover markers P1NP and CTX were significantly increased both in Pten cKO male and female mice. The percentage of bone marrow fat was higher in male mice (1.4fold, $p = 0.007$), but not in female Pten cKO mice compared to controls. An increase in the proliferation rate of male (1.8fold), but not female BMSCs from Pten cKO mice compared to controls was detected. While there was no significant difference in adipogenic differentiation in vitro, osteogenic differentiation capacity was significantly enhanced in BMSCs from both, male and female, Pten cKO mice. Evaluation of bone dynamics revealed significantly higher P1NP and CTX serum levels in Pten cKO mice compared to controls. A trend towards increased mineralized surface per bone surface and bone formation rate was observed in Pten cKO but not Cre negative bones of 38 week old mice.

Conclusion: Conditional Pten knockout in osteoprogenitor cells increases both, bone stability and elasticity, and leads to increased proliferation and osteogenic differentiation of bone marrow stromal cells. Bone regeneration is preserved in older Pten cKO mice.

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T3

Association Between Non-invasive Diagnostic Methods of Liver Fibrosis and Type 2 Diabetes in Pediatric Patients With Non-alcoholic Fatty Liver Disease

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Background and Purpose: The prevalence of non-alcoholic fatty liver disease (NAFLD) in children has been increasing associated with insulin resistance. However, there is a scarcity of related studies in children with NAFLD with type 2 diabetes mellitus (T2DM) compared to adults. We conducted this study to investigate the association between non-invasive diagnostic methods of liver fibrosis and T2DM in pediatric patients with NAFLD.

Methods: We enrolled a total of 152 patients aged <18 years with NAFLD, and compared their data according to the presence of T2DM. We evaluated fibrosis by transient elastography (TE, FibroScan®), and calculated the following fibrosis scores for each patient: NAFLD fibrosis score (NFS), AST: platelet ratio index (APRI), Fibrosis-4 (FIB-4) index, and pediatric NAFLD fibrosis index (PNFI).

Results: In the NAFLD–T2DM group, the NFS and mean controlled attenuation parameter in FibroScan were significantly higher than those in the nondiabetic group. The receiver operating characteristic (ROC) curve values for predicting the presence of T2DM were 0.78 for NFS, 0.64 for FIB-4, 0.62 for PNFI, and 0.61 for APRI. The cutoff HbA1c levels for predicting fibrosis progression in APRI, NFS, and PNFI were 5.7% [area under the curve (AUC) 0.74], 6.4% (AUC 0.71), and 6.4% (AUC 0.55), respectively. In the multivariate analysis, hepatosteatosis on abdomen sonography, NFS, FibroScan F, and APRI were independently associated with T2DM risk.

Conclusions: We significantly characterized non-invasive fibrosis markers and elastography in pediatric NAFLD with T2DM compared with the nondiabetic group. We suggest evaluating the progression of fibrosis in the prediabetic stage in children using a combination of these non-invasive methods.

T4

Does Socioeconomic Status Play a Role in Paediatric Insulin Pump Access? A Systematic Review

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Background: Continuous Subcutaneous Insulin Infusions (CSII) or insulin pumps improve overall glycaemic control in paediatric populations. Children's access to CSII may partly depend on socioeconomic status (SES), healthcare systems, and funding structures.

Aim: The aim of our systematic review was to evaluate whether SES affects children's access to CSII, across various countries with different types of healthcare provision.

Methods: We searched MEDLINE for peer-reviewed articles published between 1st January 2002 and 5th April 2022. Search-term groups comprised 'insulin pump / CSII', 'paediatric', and 'socioeconomic'. Neither language nor geographical restrictions were applied. Studies were eligible for inclusion when (1) all participants were under 21; (2) data on insulin pump access were available; and (3) SES data on participants having an insulin pump were provided. Two independent authors examined titles, abstracts, and studies. Results were corroborated. We extracted study design and location, data collection dates, number of participants on insulin pumps and not on insulin pumps (i.e. control group), SES measures used, relationship between SES and pump access, as well as whether insulin pumps were publicly funded. Individual study quality was assessed using an abbreviated and adapted version of the JBI Critical Appraisal Tools.

Results: Our search identified 203 studies of which 20 were included. Ten studies were classified as 'high', eight as 'medium', and two as 'low' quality. Participants on insulin pumps totalled 37,650 (34,661 in control groups). All data was collected between 2001 and 2019. Thirteen studies were conducted in North America, six in Europe and one in Oceania. Seven studies took place in countries with nationwide government-funded insulin pump programs. The main measures of SES were based on deprivation or equity indices, annual family income, parental education, and access to health insurance. Nineteen studies reported either lower insulin pump access among children from lower SES backgrounds or higher insulin pump access among children from higher SES backgrounds. One 'medium' quality study reported no difference in insulin pump access based on SES. One 'low' quality study reported lower proportion of insulin pump access among children from higher SES backgrounds.

Conclusion: Participants from lower SES backgrounds were less frequently on insulin pumps, regardless of the healthcare funding structure of their country. Other factors such as ethnicity and physician bias may also contribute to disparities in insulin pump access. Addressing these aspects may also contribute to better glycaemic control in paediatric populations.

T5

Genetic Variations in Early Onset Obesity: Experience from southern California

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Introduction: Early onset of obesity has very severe consequences for the rest of the life which leads to morbid obesity as adults, dyslipidemia, hypertension, diabetes mellitus, sleep apnea and fatty liver disease. Recently, various genetic panels have been available and are quickly becoming a standard of care to screen children with genetic panel for obesity. However, most of these variations in ethnically diverse populations have not been extensively studied.

Methods: We collected buccal swab specimens from children with excessive weight gain in the first two years of life without history of hypotonia. The subjects were enrolled from the Endocrine clinics of Children's Hospital of Orange County. Genetic panel of obesity was performed as a part of Uncovering Rare Obesity® Program by Prevention Genetics labs. The ethnic background of the subject for predominantly Hispanic with the BMI percentile of a greater than 99% or more than two standard deviations above the mean.

Results: 18 different children were found to have at least one variation in the genes linked to early onset obesity. Out of the 18 majority of these variation were classified under interpretation as "uncertain". Only one variation of *PCSK1* gene was classified as "risk" and this subject was heterogenous (het) for c.661A>G, p.Asn221Asp change. The gene variation, which was likely pathogenic was het for c.3082+1G>T change leading to a GT donor in the *VPS13B* gene. 10 out of 18 subjects had mono-allelic variation in these gene. 2 subjects had biallelic variations, 4 subjects had variations in 3 different genes. 1 subject had variations in 4 genes and 1 in 5 genes. Some of the commonly seen gene variation in our cohort was as follows:- 2 subjects were het for the c.1996G>A,p.Val666Met in the PLXNA4 gene; 2 subjects were het for c.2050C>T,p.Pro684Ser in the RAI1 gene; 2 subjects were het for c.2105T in the PCNT gene, 2 subjects were also het for c.806T>A, p.Ile269Asn in the MC4R gene. Bardet-Biedl syndrome (BBS) or Alström syndrome related genes were found in 7 out of 18 subjects.

Conclusion: Majority of gene variations in these children with early onset severe obesity are reported as "uncertain". As more children will be identified with various gene mutations the phenotype-genotype link might be established. Another important thing to note is that in most children had single allelic variations. However 8/18 had polygenic variations. In ~ 40% had gene variations in the BBS or Alström syndrome related genes pathway.

T6

Circulating GDF15 Concentrations in Girls with Low Birth Weight and Precocious Pubarche: Effects of Prolonged Metformin Treatment

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Background: Low birth weight (LBW) followed by a rapid postnatal catch-up in weight predisposes individuals to a central distribution of body fat, which is reverted by metformin. Growth-and-differentiation-factor-15 (GDF15) plays an important role in the regulation of energy homeostasis, reducing food intake and lowering body weight. We aimed to assess whether GDF15 concentrations are raised by long-term metformin treatment in LBW/catch-up girls with precocious pubarche (PP, pubic hair before age 8 years), and whether they relate to changes in endocrine-metabolic variables, body composition and abdominal fat partitioning.

Methods: Circulating GDF15 was determined in 32 LBW/catch-up girls with PP randomly assigned to receive metformin for 4 years (n=16; 425 mg/d for 2 years, then 850 mg/d for 2 years) or to remain untreated (n=16). Thirty patients were included in the final analysis (n=15 in each study arm), after excluding basal outliers. Endocrine-metabolic variables, body composition (by absorptiometry) and abdominal fat partitioning (by MRI) were assessed at start and yearly during the follow-up.

Results: Circulating GDF15 concentrations increased significantly in LBW-PP girls only after 3 and 4 years on metformin. GDF15 levels associated negatively with insulin, HOMA-IR, androgens, body fat and visceral fat.

Conclusion: Prepubertal intervention with metformin reduces central adiposity and insulin resistance in girls with reduced prenatal growth. GDF15 could be among the mediators of such metformin effects, especially over the long term.

T7

Efficacy and safety of once-weekly somatrogon in pediatric subjects with growth hormone deficiency: lack of impact of anti-drug antibodies

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Objectives: Somatrogon, a long-acting recombinant human growth hormone (GH) consisting of the amino acid sequence of human GH (hGH) and three copies of the carboxy-terminal peptide (CTP) of human chorionic gonadotropin, is approved by the EMA for treatment of children with GH deficiency (GHD). In this phase 3 study, children with GHD received either somatrogon or Genotropin. The impact of testing positive for anti-drug antibodies to somatrogon (ADA+) on the efficacy and safety of somatrogon was evaluated.

Methods: In the 12-month main study, subjects were randomized to once-weekly somatrogon (0.66 mg/kg/week) or once-daily Genotropin (0.24 mg/kg/week). After the main study, subjects could enroll in an open label extension (OLE), where all subjects received somatrogon (0.66 mg/kg/week). Samples to assess ADAs were collected quarterly during the main study and every 6 months during the OLE. Using electrochemiluminescence assays, samples were initially assessed for anti-somatrogon ADAs; ADA+ samples were further assessed for anti-hGH and anti-CTP ADAs. Neutralizing ADAs (NAb) to somatrogon and hGH were identified in assays measuring inhibition of somatrogon/hGH-stimulated cell proliferation. Subjects with ≥1 ADA+ result were compared with subjects with no ADA+ samples (ADA−).

Results: By Month 12, 84/109 (77.1%) somatrogon-treated subjects had ≥1 ADA+ result; most were anti-hGH+. Two of the 84 subjects tested NAb+ for somatrogon. At OLE Month 12, of the 212 subjects (108 subjects had received Genotropin in the main study), 114 (53.8%) had ≥1 ADA+ result; most ADA samples were anti-hGH. No additional subjects tested NAb+ for somatrogon while 3 subjects tested NAb+ for hGH. ADA status had no effect on growth parameters (**Table**). Being ADA+ was associated with numerically higher mean IGF-1 SDS values and greater changes from baseline but there was considerable overlap between ADA+ and ADA− subjects (**Table**). The presence of ADAs to somatrogon did not affect the incidence of treatment-emergent adverse events (AEs), serious AEs, or AEs of special interest; there was no association between the incidence of AEs and ADA titer.

Conclusions: ADA+ did not affect the efficacy or safety of somatrogon.

T8

Caregiver Burden in Bardet-Biedl Syndrome: a Survey of Obesity and Hyperphagia Impacts

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Background: Hyperphagia, or pathologic insatiable hunger, and early-onset obesity are prevalent clinical features of Bardet-Biedl syndrome (BBS), a rare genetic disorder. While hyperphagia and obesity have broad impacts on individuals with BBS and their caregivers, the extent of this burden is not well characterized.

Methods: This multicountry cross-sectional survey of caregivers of individuals with BBS was conducted to quantify the burden and impact of severe obesity and hyperphagia on patients and caregivers. Eligible respondents were caregivers ≥18 years old who had cared for ≥6 months individuals with a diagnosis of BBS who had obesity or were in the ≥95 weight percentile and had hyperphagia (uncontrollable hunger). The survey comprised several observer- and caregiver-reported outcome instruments, including the Impact of Weight on Quality of Life-Kids (IWQOL-Kids, parent proxy; score range, 0-100, with a score of 100 having the least impact on quality of life), the Symptoms of Hyperphagia (SOH), and the Impacts of Hyperphagia (IOH) questionnaires.

Results: A total of 242 caregivers in Canada, Germany, the United Kingdom, and the United States completed the survey (mean [standard deviation (SD)] age, 41.9 [6.7] years; 54.1% male; mean [SD] age of individuals with BBS, 12 [3.7] years; 64% male). Hyperphagia contributed to a BBS diagnosis in 230 of 242 individuals (95%). From the IWQOL-Kids, caregivers reported obesity impacted health-related quality of life (HRQOL) for those in their

Table. Growth and ADA results at OLE Month 12

	Soma/Soma		Geno/Soma	
Mean (SD)	**ADA+ (n=91)**	**ADA− (n=18)**	**ADA+ (n=38)**	**ADA− (n=69)**
Annual height velocity, cm/year	8.10 (1.86)	7.47 (1.38)	8.44 (1.94)	8.14 (1.83)
Change in height SDS	1.29 (0.61)	1.19 (0.56)	1.57 (0.74)	1.17 (0.58)
IGF-1 SDS	1.28 (1.29)	0.49 (1.14)	1.48 (1.07)	1.20 (1.21)

Clinicaltrials.gov:NCT02968004; EudraCT:2016-003874-42

care, especially as it related to body esteem (mean [SD], 40.9 [18.3]), social life (41.7 [18.1]), and physical comfort (41.9 [17.5]). From the SOH, caregivers observed hyperphagic behaviors multiple times a day, such as negotiating for food (89.6%) and waking up asking or looking for food at night (88.4%). Of the 181 children, hyperphagia caused difficulty with focusing in school in 97.7%, and BBS symptoms caused 82.3% of children to miss ≥1 day of school over a week. From the IOH, hyperphagia had at least moderate impacts on individuals with BBS, with leisure/recreational activities (61.5%), mood/emotions (55.8%), and sleep (53.7%) affected. Similar moderate-to-severe impacts of hyperphagia on caregiver mood (56.6%), sleep (46.6%), and relationships (48.0%) were reported.

Conclusions: Hyperphagia and obesity have substantial negative impacts on the HRQOL of individuals with BBS and their caregivers/families. This study improves the understanding of the burden of hyperphagia and BBS and highlights the value of identifying effective interventions to alleviate symptoms of hyperphagia to improve HRQOL of these individuals and their caregivers and families.

T9

Exosomal miRNA profile in children with small for gestational age; potential biomarker for catch – up growth

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Objective: The mechanism underlying postnatal growth failure and catch up growth in small for gestational age (SGA) is poorly understood. This study attempted to identify exosomal miRNA signature associated with catch – up growth in SGA children.

Methods: A total sixteen SGA children and 10 appropriate for gestational age (AGA) children included in this study. Exosomal miRNA was analyzed with next generation sequencing (NGS). Profiling exosomal miRNA was performed in 5 SGA with catch up (SGA – CU), 6 SGA – non CU, and 5 AGA children. Differentially expressed miRNA were analyzed between SGA and AGA groups.

Results: Exosomal miRNAs profile was clearly divided into three groups. The exosomal miRNAs expression profile of SGA – nonCU was apparently different than that of SGA – CU and AGA. Twenty two miRNAs were differentially expressed between SGA – non CU and AGA, while 19 miRNAs between SGA – nonCU and SGA –CU were differentially expressed. Whereas 6 miRNAs were differentially expressed between SGA – CU and AGA. MiR-874-3p was upregulated and miR-6126 was downregulated in both SGA – non CU and SGA – CU. Therefore, these two miRNAs might be biomarkers for SGA. Compared to SGA-CU and AGA, miR-30c-5p, miR-363-3p, miR-29a-3p and miR-29c-3p were upregulated in SGA – nonCU, and miR-629-5p and miR-23a-5p were downregulated. These six miRNAs might be associated with growth failure in SGA – non CU.

Conclusions: SGA children without catch up growth have a distinct exosomal miRNA expression profile compared with AGA and SGA children with catch up growth. Exosomal miRNAs could serve as novel biomarkers helping to resolve the mystery of catch – up growth mechanisms.

T10

Aromatase Inhibitor (anastrazole) versus placebo delays bone age maturation in prepubertal children with Silver Russell or Prader-Willi Syndrome and pathological adrenarche

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Background: Silver Russell syndrome (SRS) is a rare imprinting disorder with prenatal and postnatal growth retardation and feeding difficulties. The main molecular causes are loss of methylation of the 11p15.5 imprinting control region (*H19/IGF2*) and maternal uniparental disomy of chromosome 7. Prader-Willi syndrome (PWS) is a complex neurodevelopmental imprinting disorder with neonatal muscular hypotonia, failure to thrive to insatiable appetite, short stature and impaired cognitive function, secondary to molecular anomalies in the 15q11q13 region. In both syndromes, rapid bone age maturation can occur even in the absence of central puberty during pathological adrenarche. Androgens after aromatisation in estrogens are leading to bone maturation and can produce premature epiphyseal fusion. There is currently no drug with a pediatric authorization capable of limiting the advance in bone maturation secondary to adrenarche.

Aromatase inhibitors, used for the treatment of hormone-dependent cancers, block the transformation of androgens into estrogens. Third generation inhibitors, such as Anastrozole, have been used in a few clinical trials to limit bone maturation and improve final height, notably in children treated with growth hormone (GH) due to a GH deficit. Nevertheless, the data reported do not include children with pathological adrenarche.

Objective: This study evaluates the effectiveness of an aromatase inhibitor during pathological adrenarche in prepubertal children with SRS or PWS to delay their bone age maturation.

Methods: The study included 25 prepubertal patients with SRS or PWS, treated with GH. "Pathological" adrenarche was defined either by an SDHEA value higher than the normal values according to age, or by pubic hair, associated with a bone age at least equal to the chronological age. Patients were randomized double-blind with 2 treatment arms: Anastrazole (1 mg/day) versus placebo, for a period of 18 months. The primary endpoint was the rate of progression of bone maturation, assessed on hand and wrist X-rays.

Findings: Bone age progresses by 9.5 months (0-41 months) in the Anatrazole group and by 12 months (0-30 months) in the

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Placebo group when the bone age is read according to the method based on Greulich and Pyle atlas (p=0.43). When the BoneXpert computer-automated bone age determination method is used, bone age increases significantly more, in 18 months in the Placebo group than in the Anastrazole group (absolute difference of 8.46 months) (p=0.01). No serious adverse effects were observed.

Conclusion: Anastrazole, an aromatase inhibitor, is effective in slowing bone maturation during pathological adrenarche in patients with SRS or PWS.

T11

Factors associated with authoimmune thyroid diseases in children with diabetes mellitus type 1

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Objective: to determine risk factors of co-existing thyroid autoimmunity in children with type 1 diabetes mellitus (T1DM).

Material and Methods: 48 children with combined autoimmune pathology (45 – with T1DM and autoimmune thyroiditis and 3 – with T1DM and Grave's disease) – main group, age 12.51±3.57 years) and 99 patients with only T1DM (comparison group, age 11.76±3.05 years) were recruited. Groups were comparable in age (p=0.19) and T1DM duration (p=0.66). We assessed CTLA4 gene for rs231775 (+49 A/G) variant, PTPN22 gene for rs2476601 (+1858C/T) variant and microsatellite repeat in exon 5 of MICA class I gene. Evaluation of anthropometric parameters; biochemical blood parameters; glycosylated hemoglobin (HbA1c), vitamin D, thyroid hormones, antibodies to thyroid peroxidase (anti-TPO), glutamate decarboxylase (GAD) and zinc transporter8 (ZnT8) levels was carried out. Results were processed using Statistica 10 and Excel 10.

Results: Statistically significant difference in the frequency of CTLA4 genotypes +49A>G was found between patients with combined autoimmune pathology and isolated T1DM: AG and GG genotypes increased three-fold the risk of autoimmune thyroid diseases (OR=2.94, 95% CI: 1.13-7.68). Patients of the main group had higher prevalence of combinations of A5.1/A5.1 genotype of the MICA gene with certain genotypes at loci +49A/G of the CTLA4 gene and +1858C/T of the PTPN22 gene. In particular, autoimmune thyroid pathology was more likely in patients with combination of CTLA-4 +49 A/G GG genotype and MICA gene A5.1/A5.1 genotype (OR=19.40, 95% CI: 2.35-160.22); combination of PTPN22 +1858C/T CT and TT genotypes and A5.1/A9 of the MICA gene (OR = 4.01, 95% CI: 1.11-14.46).

Children with polyglandular autoimmune pathology showed higher prevalence of severe vitamin D deficiency (level <10 ng/ml) (OR = 4.26, 95% CI: 1.53-11.82). Among the factors, associated with co-existing autoimmune thyroid diseases we also detected female gender (OR=3.08, CI 1.48-6.36), high levels of GAD antibodies (>50 U/ml) (OR = 2.66, CI: 1.27-5.56) and ZnT8 antibodies (>1500 U/ml) (OR=4.57, CI: 1.43-14.62).

Conclusions:

1. Co-existing autoimmune thyroid diseases in children with T1DM were associated with severe vitamin D deficiency, female gender, high levels of GAD ant ZnT8 antibodies.
2. We have demonstrated that a distinct association exists between polyglandular autoimmune pathology and carrying of G allele of CTLA-4 at loci +49 A/G; combinations of genotype A5.1/A5.1 of the MICA gene with GG genotypes at loci +49A/G CTLA4 or CT and TT genotypes at loci +1858C/T of the PTPN22 gene.

T12

Assessment of non-alcoholic fatty liver disease with non-invasive indices in adolescents with polycystic ovary syndrome

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Context: Polycystic ovary syndrome (PCOS) is a complex disorder affecting women from adolescence until menopause. PCOS in adolescent years shares common features with clinical presentation in adulthood, including the adverse metabolic profile. Non-alcoholic fatty liver disease (NAFLD) is a spectrum of hepatic changes, from liver steatosis to severe inflammation and fibrinogenesis.

Objective: To assess NAFLD in an adolescent sample diagnosed with PCOS, using non-invasive indices.

Patients: The study included 87 Caucasian adolescent girls (40 controls and 47 PCOS patients), aged 12.28-18.62 years (mean=15.20, SD=1.40) recruited from the Center for Adolescent Medicine and UNESCO Chair in Adolescent Health Care, First Department of Pediatrics, School of Medicine, National and Kapodistrian University of Athens, at the Aghia Sophia Children's Hospital.

Methods: Adolescents' somatometric data were recorded and biochemical and hormonal parameters were measured with commercial methods. Fatty liver index (FLI), Liver fat score (LFS), Lipid accumulation product (LAP), Hepatic steatosis index (HSI) and PCOS hepatic steatosis index for obese individuals (PCOS-HS), Visceral adiposity index (VAI), FIB-4 index, NAFLD fibrosis score (NFS), AST to Platelet ratio index (APRI), BARD score, and BAAT score were calculated by given equations to assess liver steatosis and fibrosis. Imaging studies were also performed; specifically liver ultrasound to assess steatosis and Fibroscan for fibrotic changes.

Results: Class I NAFLD was detected by ultrasound in 13.5% of all adolescents, 22.7% of PCOS patients and 6.1% of controls

(p=0.046). ALT levels were not significantly different between PCOS patients and controls; 15% of all adolescents had ALT>22U/L but only one adolescent had ALT>44U/L. LFS, FLI, HSI and ALT/triglycerides ratio were worse in PCOS patients than controls (p=0.019, 0.007, 0.004, 0.009 respectively). For VAI, LAP and PCOS-HS the differences were not statistically significant. Fibroscan stiffness and IQR were not significantly different between PCOS patients and controls (p=0.570 and 0.496 respectively) and only 3 adolescents of each group (PCOS patients and controls) had Fibroscan® values indicative of hepatic fibrosis (≥7.9kPa). Neither of the calculated scores for hepatic fibrosis (FIB4, NFS, APRI, BARD and BAAT) were more affected in PCOS patients than controls.

Conclusion: Data about PCOS and NAFLD in adolescents are scarce. Lack of ideal and safe diagnostic methods for NAFLD and lack of consensus for pediatric population's diagnostic algorithm create heterogeneity in the literature. This is the first time a study uses such a variety of methods to measure NAFLD in adolescents with PCOS.

T13

Impact on predicted adult height and basal gonadotropin levels through triptorelin 6-month formulation in patients with central precocious puberty

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Background: Triptorelin, a gonadotropin-releasing hormone (GnRH) agonist, is available as 1-, 3-, and 6-month formulation for treatment of central precocious puberty (CPP). The triptorelin 22.5mg as 6-month formulation, which has recently been approved for use in CPP and offers greater convenience to children by reducing the injection frequency, but related research is very limited. The aim of this study was to study on the impact of 6 month formulation on predicted adult height (PAH) and changes in gonadotropin levels including related variables.

Methods: Total 42 patients (33 girls and 9 boys) with idiopathic central precocious puberty who were treated with triptorelin 6-month formulation for more than 12 months were enrolled. Auxological parameters including chronological age (CA), bone age (BA), height (cm and SDS), weight (kg and SDS), taget height (TH), and Tanner stage were evaluated at baseline, 6, 12, 18 and 24 months of treatment. In addition, hormonal parameters including serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol for girls and testosterone for boys were analyzed at the same interval.

Results: The mean age at the initiation of treatment was 8.6 years old (8.3 years for girls, 9.6 years for boys). The mean evoked LH level from GnRH stimulation test at diagnosis was 15.47 ± 9.94 IU/L. No progression of the Tanner stage of the breast was observed during treatment in all females and testis volume remained unchanged in males. Compared to the time at diagnosis, LH, FSH, estradiol, and testosterone were significantly reduced. In particular, the basal LH levels were well suppressed to less than l.0 IU/L and the LH/FSH ratio was less than 0.66. During treatment, the BA/CA ratio was kept steady, and although not statistically significant, it showed a decreasing trend (1.15 at baseline, 1.14 at 18 month, 1.11 at 24 month). PAH SDS increased during the treatment as 0.77±0.79 at baseline, 0.87±0.84 at 6 month, and 1.01±0.93 at 12 month of treatment with a significant increase in PAH-TH SDS (p<0.001). No adverse effect was observed during treatment.

Conclusion: The triptorelin 6-month formulation not only suppressed the pituitary-gonadal axis stably, but also showed improvement in PAH. Considering convenience and effectiveness, a significant shift to long-acting formulations is expected in the future.

T14

CCDC149: A Novel Gene Associated with Multiple Pituitary Hormone Deficiency

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Background: Idiopathic hypogonadotropic hypogonadism (HH) is highly genetically heterogeneous. To date, about 50 causative genes have been identified, estimated to account for up to 50% of hereditary cases. With next generation sequencing (NGS) technology now in wide clinical use, it is increasingly possible to determine the underlying genetic etiology of isolated and combined pituitary hormone deficiencies.

Objective: We report a case of two siblings with consanguineous parents, presenting with HH, growth hormone deficiency (GHD), intellectual disability and obesity in whom we performed NGS aiming to identify a genetic etiology.

Methods: Clinical, biochemical and hormonal assays as well as endocrine stimulation studies were performed, followed by whole exome sequencing (WES) and Sanger sequencing.

Patients: A 19-year-old male was referred for evaluation of short stature and hypogonadism with small intra-scrotal testes (2 ml), no pubic hair (P1), and micropenis. In addition, he had cognitive impairment, strabismus, obesity and marked acanthosis nigricans. Sense of smell was preserved. His sister was 16 years old at the time of presentation and similarly demonstrated short stature, delayed puberty (B1P2), cognitive impairment, strabismus and obesity.

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Results: Hormone assays and endocrine stimulation tests revealed GHD and HH in both siblings. Using WES, we identified a likely pathogenic homozygous point mutation in the gene *CCDC149*: c.847G>T;p.Gly283* creating a stop codon in the 9th exon, in both siblings. The father was found to be heterozygous for the variant. Their mother passed away several years earlier however her sister was likewise found to be a heterozygous carrier. Several bioinformatics models identified the mutation as an extremely rare and likely pathological variant not previously reported in general population databases such as gnomAD. This gene codes for a highly preserved protein whose function in humans is presently unknown, although functional studies in the nematode C. elegans, suggest a possible association with ciliopathies such as in Bardet-Biedl syndrome.

Conclusion: We describe for the first time a homozygous variant in the *CCDC149* gene associated with congenital hypopituitarism. Further investigation is required to determine the function of this gene and confirm its role in this genetic disorder.

T15

Secondary Oxidized DEHP Metabolites May Participate in the Progression from Isolated Premature Thelarche to Central Precocious Puberty or Early Puberty

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Objective: Urine phthalic acid esters (PAEs) are one of estrogen-mimetic EDCs. Many studies have suggested that urinary phthalic acid esters (PAEs) are closely related to central precocious puberty (CPP) and isolated premature thelarche (IPT), but there is no study between urinary PAEs and the progression of IPT. This study is to explore the influence of PAEs on the progression of IPT to CPP or early puberty (EP).

Methods: Patients with IPT (74) admitted to the Department of Endocrinology of Shenzhen Children's Hospital from December 2018 to August 2019, who had been asked to be followed up regularly for one year. The girls were followed clinically every 3 months. During the follow-up period, girls was divided into transformed group and untransformed group. In order to identify independent risk factors affecting significantly the progression of IPT to CPP/EP, we performed a binary logistic regression analysis (forward LR stepwise method) with the progression of IPT to CPP/EP as the dependent variable. The independent variables were those shown to be significant ($p < 0.05$) in the comparison between two groups (breast Tanner stage, mean ovarian volume, the sun of secondary oxidized Di-(2-ethylhexyl) phthalate(DEHP) metabolites (Σ_4DEHP, Σ_4DEHP= MEHHP+MEOHP+MECPP+MCMHP)), and other factors that may be clinically correlated (basic LH, IGF-1 SDS, uterine diameter).

Result: IPT girls were successfully followed up in 61 cases, 39 cases in the untransformed group and 22 cases in the transformed group. The transformed group had significantly higher ovarian volume and breast Tanner stage than that in the untransformed group (all $p<0.01$). The transformed group had significantly higher secondary oxidized DEHP metabolites (MECPP, MEHHP, MEOHP, MCMHP) than that in the untransformed group (all $p<0.01$). There were no significant difference in other PAEs between the two groups ($p>0.05$). Among the 61 IPT girls, breast Tanner stage (OR=3.75(1.08-13.01)), Σ_4DEHP (OR=3.12(1.33-7.27)) were independent risk factors for the progression of IPT.

Conclusions: Exposure to low level of DEHP for a long time. IPT girls may progress to CPP/EP more possibly. The higher breast Tanner stage is, the more possibly IPT was progressed to CPP/EP.

T16

The Relationship Between Leptin, Kisspeptin, Irisin, Myostatin and Omentin Levels and Fat Tissue at Puberty

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Introduction: The hypothalamo-pituitary system is activated as puberty begins and GnRH release occurs as well as the synthesis of many hormones. These hormones cause changes on muscle development, body fat distribution. In this study, changes in miyostatin, irisin, kisspeptin, omentin and leptin levels and the relationship of these changes with physical properties and fat tissue were investigated.

Material and Method: A total of 150 healthy children; between the ages of 8 and 16; with equal distribution of boys and girls; were included in the study. Serum irisin, omentin, leptin, kisspeptin and myostatin levels were analyzed by ELISA method.

The study was supported by the Scientific Research Projects Commission of Atatürk University with the code TTU-2020-8610.

Results: Serum leptin level was 322.27 ± 773.64 μL in girls and 228.89 ± 713.84 μL in boys. The serum omentin level was 37.2 ± 16.47 ng/ml in boys and 31.25 ± 17.84 ng/ml in girls, and there were significant differences between genders, respectively ($p<0.001$, <0.05). In addition, irisin hormone ($p=0.015$) and leptin hormone increased statistically significantly as Tanner stage increased in female cases ($p<0.05$).

When the relationship between the anthropometric measurements of the cases and biochemical values of the cases is evaluated; in male cases; between irisin and hip circumference ($p<0.001$) and BMI ($p=0.024$), between leptin and hip circumference ($p=0.005$) and BMI ($p=0.001$) statistically significant relationship was observed. No correlation was found between other parameters. Also, when investigating the relationship between these hormones; a highly significant positive relationship was found between myostatin and kisspeptin and omentin, and between kisspeptin and irisin ($p<0.001$). Further, a statistically significant positive relationship was observed between kisspeptin and omentin ($p=0.002$) and leptin ($p=0.043$).

Conclusion: In addition to increases in height, weight, BMI, waist, hip circumference, waist/hip circumference ratio, there were significant increases in FSH, LH and E2 levels as puberty progresses. While the waist/hip circumference ratio was higher in boys, indicating central fat deposition in boys. Also, the fact that

serum omentin levels were found to be lower and serum leptin levels higher in girls during puberty, emphasizes that serum omentin and leptin levels at puberty are affected by gender.

T17

Impact on predicted adult height and basal gonadotropin levels through triptorelin 6-month formulation in patients with central precocious puberty

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Background: Triptorelin, a gonadotropin-releasing hormone (GnRH) agonist, is available as 1-, 3-, and 6-month formulation for treatment of central precocious puberty (CPP). The triptorelin 22.5mg as 6-month formulation, which has recently been approved for use in CPP and offers greater convenience to children by reducing the injection frequency, but related research is very limited. The aim of this study was to study on the impact of 6 month formulation on predicted adult height (PAH) and changes in gonadotropin levels including related variables.

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Conclusion: The triptorelin 6-month formulation not only suppressed the pituitary-gonadal axis stably, but also showed improvement in PAH. Considering convenience and effectiveness, a significant shift to long-acting formulations is expected in the future.

T18

SF1next study: spectrum of SF-1/NR5A1 gene variants in this large international cohort

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Background: Loss-of-function variants in the NR5A1 gene are frequent causes of 46,XY differences of sex development (DSD). To date, the Human Gene Mutation Database contains 291 NR5A1 variants, most of which are missense (69%). Mouse models demonstrated the effect of loss of SF-1 on sex development, but the interactome of SF-1 is huge and an explanation for the broad phenotype is still missing. Controversies exist as: a) in vitro transactivation assays of NR5A1-regulated genes show contradictory results for several variants, b) in vitro modelling of heterozygous variants does not show a dominant negative effect, c) several variants are present in combination with other DSD-related gene variants of unknown significance. We aimed to describe the genotype in the largest possible international SF-1/NR5A1 cohort to allow future identification of phenotype-genotype clusters.

Methods: After recruiting cases through the I-DSD registry and through contacting researchers from previous publications on SF-1, collaborators entered genotype data in a REDCap database. Gene variants were identified by single gene analysis, next generation sequencing (NGS) and/or comparative genomic hybridization array. We performed variant classification according to guidelines from the American College of Medical Genetics and Genomics. Collaborators of SF1next study group are listed here: https://www.dropbox.com/s/wza2bud5naw2ftd/SF1next%20study%20group.pdf?dl=0.

Results: Among 107 individuals (90% 46,XY, 8% 46,XX, 1% 47,XXY, 1% 47,XYY), we found 78 different NR5A1 variants, of which 28 were novel (11/28 missense, 8/28 delins, 3/28 nonsense, 2/28 silent, 2/28 small deletions or insertions). All but 6 were heterozygous (72/78, 92%). Variants were scattered throughout the whole NR5A1 gene, mostly in the DNA-binding (33/78, 42%) and the ligand-binding domain of the protein (28/78, 36%). We classified 59/78 (76%) variants as pathogenic/likely pathogenic and 16/78 (20%) as variants of unknown significance. Additional gene variants (e.g. DHX37) were identified in 26/107 (24%) individuals using various methods (52% single-gene analysis, 33% NGS).

Conclusion: Novel variants are still identified in the NR5A1 gene. Further studies are required to explain the broad phenotype of SF-1 individuals. Current targeted approaches have limitations as they may not detect additional gene variants. In the future, individuals who have loss-of-function SF-1 variants may have to be re-evaluated with newer methods, e.g. NGS.

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T19

Impaired gonadal function among pediatric Fanconi anemia patients following hematopoietic stem cell transplantation

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Background: Gonadal dysfunction and fertility impairment are some of the many clinical manifestations described among patients with Fanconi anemia (FA). Many who receive hematopoietic stem cell transplantation (HSCT) suffer additionally from infertility due to gonadal damage from their preparative regimen. The effect of HSCT on gonadal insufficiency and fertility potential among children with FA is largely unknown.

Methods: We performed a retrospective analysis of male and female patients with FA who had pubertal and hormonal data from their follow-up visits at CCHMC from July 1990 to June 2020 to evaluate the incidence of primary ovarian insufficiency (POI) and testicular failure (TF) among transplanted patients. We defined POI in pre-pubertal females as undetectable anti-Mullerian hormone (AMH) and in pubertal females as follicle stimulating hormone (FSH) >20 mIU/L, or undetectable AMH with absent menstrual periods. Among pubertal males, TF was defined as FSH >20 mIU/L and/or luteinizing hormone (LH) >10 mIU/L. Inhibin B (pg/mL) levels were also collected as markers of spermatogenesis and fertility recovery.

Results: Median follow-up time after HSCT for the entire cohort was 6.18 years (range 0.05-30.4 years). Among 57 transplanted female FA patients, we identified POI among 30 (52.6%) female patients who developed POI at any time point from HSCT. The media age at diagnosis was 13.82 years (range 5.78-26.86 years) and the median time after HSCT for diagnosis was 3.81 years (range 0.58-13.99 years). Among 41 male patients, we identified TF in 20 (48.4%) patients, at a median time of 5.2 years (range 0.73-30.4 years) from HSCT. Among all patients with POI, AMH levels negatively correlated with time from transplant (r^2 = 0.21, p = 0.001). Additionally, FSH levels did not increase significantly with time from HSCT among female POI patients, (r^2=0.01, p=0.26). In contrast, FSH increased significantly with time from HSCT among male patients (r^2=0.17, p=0.005). Inhibin B levels also declined among male patients who had gonadal insufficiency following HSCT (r^2=0.14, p=0.01).

Conclusions: POI and TF are prevalent among FA patients who have undergone HSCT. AMH declined among female patients diagnosed with POI after HSCT. AMH may serve as a more precise marker for POI diagnosis among female FA patients who have undergone HSCT. Increasing FSH and decreasing inhibin B correlated with time from HSCT among male FA patients. Because of the latency to gonadal insufficiency following HSCT, extended timepoints may be needed among these patients to monitor gonadal function.

T20

Sensitivity to thyroid hormones and cardiometabolic risk in euthyroid obese children: a cross-sectional study

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Background: The typical biochemical phenotype related to obesity, that is high serum thyrotropin (TSH) within normal range, low/normal free thyroxine (FT4) and increased free triiodothyronine (FT3) levels, can be interpreted as a resistance to thyroid hormones. It is unclear the role played by thyroid hormones in the pathogenesis of metabolic derangement associated with obesity.

Aim: To investigate the association between thyroid hormones sensitivity and cardio-metabolic risk factors in a cohort of euthyroid obese youths.

Material and Methods: This is a single-center, cross-sectional, observational study on children with euthyroid obesity. Each patient underwent clinical and auxological examination and laboratory workup including an Oral Glucose Tolerance Test (OGTT) and the measurement of serum TSH, FT4, FT3 and lipid profile. We measured the parameters representing central and peripheral sensitivities to thyroid hormones (Thyroid Feedback Quantile-based Index (TFQI), TSH Index (TSHI), Thyrotroph Thyroxine Resistance Index (TT4RI), Parametric Thyroid Feedback Quantile-based Index (PTFQI) and FT3/FT4 ratio, respectively), and we compared them in different subgroups of patients according to the TSH level, the presence/absence of insulin resistance and the severity of obesity; finally, we evaluated the association with some cardiometabolic risk factors.

Results: Four hundred ninety-one Caucasian euthyroid obese children and adolescents (age 9.93±2.90) were recruited. Two hundred twenty-five subjects (45.8%) had a high-normal TSH level (TSH 2.3-5.0 mU/L), 315 subjects (64.2%) were severe obese (BMI standard deviation (SD) > 2.5 according to the WHO reference). Two hundred sixty-one subjects (53.1%) had insulin resistance defined by HOMA-IR > 2.5 in prepubertal children and > 4 in pubertal ones. Severe obese children as well as subjects with high-normal TSH had higher FT3/FT4 ratio values comparing with those with BMI < 2.5 SD and with low-normal TSH values, respectively. There were no differences in indices of thyroid hormones sensitivity between children with insulin resistance and those normoinsulinemic. On regression analysis, BMI-SD was positively associated with FT3/FT4 ratio values (B= 2.202, p<0.001); area under the glucose curve and area under the insulin curve were positively associated with TT4RI (B= 1.110, p=0.034; B= 7.670, p=0.001 respectively); HDL values was negatively associated with TSHI values (B= -9.140, p=0.005).

Conclusions: Higher values in resistance to thyroid hormones indices are associated with an unfavorable metabolic phenotype related to obesity. These evidences could suggest the potential role of sensitivity to thyroid hormones in the development of metabolic diseases.

Poster Category 1

Adrenals and HPA Axis

P1-1

Collection of salivary steroids in children under conditions replicating home sampling

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Background: Measurement of salivary glucocorticoids is an accepted method for testing adrenal function and is gaining popularity as it offers a non-invasive collection technique, enabling sampling in the community or home environment, allowing tailored capture of steroid circadian rhythm and improved patient experience. However, there is little data on stability during home collection and sampling methods in young children. Current salivary collection techniques require active patient participation or present a choking hazard and are therefore unsuitable for very young children.

Objectives: To compare salivary glucocorticoids sampled using different collection techniques (Salivette Cortisol, passive drool and SalivaBio); assess the stability of salivary glucocorticoids under different storage conditions replicating home collection; evaluate the time taken for salivary glucocorticoid collection and assess caregiver acceptability when comparing the SalivaBio and a new salivary collection device designed for infants and young children (SalivaBio swab encased in an infant pacifier "SaliPac").

Methods: Six healthy adults collected salivary samples using a Salivette, passive drool and SalivaBio on retiring for bed, soon after waking and at 3pm for five days. Saliva was stored at 4°C, room temperature and 50°C for 24, 48, 72 hours and a week to replicate potential postage conditions. Salivary cortisol and cortisone concentrations were measured by LCMS. Mean time to collect 1ml saliva and caregiver acceptability using the SalivaBio and SaliPac was assessed in 30 children <6 years in a single-site prospective feasibility study.

Results: There was no significant difference in salivary cortisol and cortisone concentrations using the three different collection methods. Salivary cortisol and cortisone were stable for 72 hours when at room temperature and refrigerated (4oC), with cortisone stable at 4°C and cortisol at room temperature out to a week. High temperature accelerated degradation. Repeated freeze-thaw cycles did not cause significant degradation. In children <6 years the SalivaBio and SaliPac were well tolerated and collected sufficient saliva for salivary steroid analysis in under four minutes. There was no significant difference in time taken for salivary collection between SalivaBio and SaliPac. There was a high level of acceptability in caregivers, who felt confident they could successfully perform salivary collection at home using the SalivBio or SaliPac.

Conclusions: Salivette, passive drool and SalivaBio collect comparable salivary cortisol and cortisone concentrations, which are stable under conditions that replicate home collection and SaliPac is an acceptable device for salivary sampling in young children.

P1-2

Growth evaluation by applying the QEPS growth model in patients with CAH

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Objective: Patients with congenital adrenal hyperplasia (CAH) seldom achieve their target height. Early adrenarche may accelerate bone age maturation and affect adult height. The QEPS-growth-model have been used for developing growth references and investigating healthy/pathological growth, however, not before used in individuals with endocrine disorders. This study aimed to evaluate growth patterns in CAH-patients with the QEPS-model.

Methods: Longitudinal growth-data were collected from 25 CAH-patients (13 girls) at Lithuanian University of Health Sciences Hospital[1]. The QEPS-model[2] was used, and the model's growth-functions and estimates were compared with the GrowUp1974Gothenburg cohort, used for both Swedish growth reference and when developing the QEPS-growth model.

Results: The CAH-patients were similar with the GrowUp1974cohort in birth characteristics and parental heights, except CAH-patients being longer at birth. The CAH-patients had faster tempo of growth as shown by both shorter E-timescale (E-growth function in QEPS-model representing mainly foetal/infancy growth) and earlier onset of pubertal growth. The specific pubertal height gain was lower in CAH-patients and their adult height was lower than expected from parental heights, details in Table 1.

Conclusion: The QEPS-model has now for the first time been used and proven to characterize growth patterns in patients with CAH. CAH-patients had distinct different growth patterns when

Table 1.

Variable	Mean CAH girls (n13)	Mean Gothenburg girls (n1165)	p–value	Mean CAH boys (n12)	Mean Gothenburg boys (n1174)	p–value
Gestational age (weeks)	39.08	39.78	0.221	39.42	39.68	0.258
Birth length (cm)	51.50	49.95	0.005	53.45	50.53	< 0.001
Birth weight (kg)	3.238	3.410	0.096	3.659	3.515	0.164
Mother's height (cm)	166.6	166.1	0.386	166.9	166.8	0.473
Father's height (cm)	179.9	180.1	0.456	179.8	179.5	0. 437
Etimescale[1]	0.89	1.01	< 0.001	0.80	1.01	< 0.001
Emax (cm)	61.26	62.85	<.0.036	60.14	65.07	< 0.001
Qmax2 (cm)	97.50	97.59	0.484	109.50	104.05	0.010
AgeP5%[3] (years)	8.60	9.87	< 0.001	9.97	11.82	< 0.001
Age at peak height velocity (years)	10.39	11.84	< 0.001	11.92	13.69	< 0.001
Pmax[4] (cm)	8.87	12.80	< 0.001	10.86	17.38	< 0.001
Tmax[5] (cm)	158.10	167.26	< 0.001	169.43	180.53	< 0.001

1=Tempo of the exponential (E) growth function. 2=Quadratic growth function from before birth until adult height. 3=Age at 5% (onset) of pubertal growth. 4=Specific pubertal height gain. 5=Calculated total/adult height.

compared with a healthy reference population, including faster tempo of growth during infancy/early childhood and puberty with earlier onset, lower specific pubertal gain, resulting in shorter adult height.

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P1-3

Blood pressure (BP) status in Congenital Adrenal Hyperplasia (CAH) – longitudinal analysis of real world data from the I-CAH registry

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Introduction: Data on BP in children with classic congenital adrenal hyperplasia (CAH) is inconsistent.

Aim: To assess the trend in BP throughout childhood using data from the International CAH registry and compare this to normative data from the American Academy of Paediatrics (AAP).

Method: This retrospective multi-centre study included 37 centres from 20 countries. BP data was analysed by Lambda-Mu-Sigma (LMS) modelling to create smoothing reference curves. We subtracted the AAP median BP for age from the I-CAH registry median BP for age, and conducted Bayesian multiple change point analysis to assess the age at which BP in the two populations converged.

Results: A total of 546 patients (53% girls, 86% prescribed Fludrocortisone) with 6357 visits between 1988-2021 were available for analysis and 3181 visits had BP measurements available. Each centre contributed a median of 12 patients (Interquartile Range (IQR) 5, 23), with data from a median of 6.0 years (IQR 3.2, 12.7) follow up per patient. Median age at visit was 5.4 years (IQR 2.4, 10.6), maximum age at visit was 19.9 years, and median number of visits available per patient was 5 (IQR 2, 9).

When compared against AAP normative BP values, the difference in median BP for age decreased with a clear plateau in both sexes. Systolic BP was higher in 1 year old CAH patients by 17.5 mmHg in boys and 13.6mmHg in girls, decreasing to a plateau of 6.2mmHg higher after age 7.7 years in boys and 5.3mmHg after age 13.3 years in girls. Diastolic BP was 22.9mmHg higher in boys and 18.3mmHg higher in girls at the age of 1 year, decreasing to a plateau of 3.2mmHg higher after age 6.7 years in boys and 3.3mmHg higher after age 6.3 years in girls.

Conclusions: Analysis of real world data shows BP in children with classic CAH to be higher than normative values at an early age, but to plateau at age 8 years in males and 13 years in females to a level marginally higher than reference values. The difference was greater in diastolic BP at early ages, but greater in systolic BP after plateau. The impact of higher BP at these young ages on vascular modelling and long term cardiovascular risk in CAH is unknown and warrants further investigation. Further analysis with covariates within this data set is ongoing, seeking to clarify other determinants of BP in CAH.

P1-4

Glucocorticoid-induced adrenal insufficiency: morning plasma cortisol values safely assess recovery of the HPA axis in pediatrics

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Background and Objectives: Chronic administration of synthetic glucocorticoids affects 1% of the world population and is responsible for secondary adrenal insufficiency for 40% of the patients. In pediatrics, glucocorticoid-induced adrenal insufficiency (GI-AI) diagnosis is based on the Low Dose Synacthen Test (LD-SST). Screening for glucocorticoid-induced adrenal insufficiency implies medical and economical costs due to the necessity of an intravenous line and medical survey. As glucocorticoids are widely prescribed in pediatrics, we aimed to define morning cortisol thresholds to predict either normal or pathologic responses to the LD-SST in order to avoid unnecessary tests.

Methods: Data from patients aged from 6 months to 18 years old who underwent a LD-SST following administration of glucocorticoids for at least 3 weeks between 2016 and 2020 were recorded. According to the practices in our hospital, adrenal insufficiency was defined as a cortisol plasma level 20 minutes after 1µg of Synacthen inferior to 500 nmol/L.

Results: Of the 91 patients included, 60% were diagnosed with glucocorticoid induced adrenal insufficiency. Morning cortisol plasma levels were significantly associated with the results of LD-SST (ANOVA, $p<0.0001$). Using a ROC curve (AUC 0.78), we defined two thresholds of morning plasma cortisol levels. A morning plasma cortisol level under 144 nmol/L managed to predict GI-AI with a specificity of 94% whereas GI-AI can be ruled out when morning plasma cortisol value is superior to 317 nmol/L with a sensitivity of 95%.

Conclusions: Morning cortisol values can be a safe tool to screen adrenal insufficiency after prolonged glucocorticoid treatment in children. Utilization of those thresholds could avoid 50% of LD-SST.

P1-5

Urinary steroid metabolite ratios: sex- and age-dependent changes and use for the differential diagnosis of inborn steroidogenesis disorders

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Background: Biochemical ratios of precursor-to-product urinary steroid metabolites have been proposed as surrogate markers of steroidogenic enzyme activity to aid the differential diagnosis of inborn disorders of steroidogenesis. Using ratios rather than total amounts facilitates analysis of single spot urine samples, more convenient than 24-h urine collections for young children. Previous studies examining the utility of these biochemical ratios have been limited by small numbers and primarily compared single patient groups to healthy controls. Here, we established sex- and age-dependent variability in urinary steroid ratios from birth to adulthood, established their discriminative ability to differentiate healthy from inborn steroidogenic disorders and also differentiate distinct steroidogenic disorders from each other.

Methods: Urine samples were collected from 829 healthy controls and 178 patients with genetically confirmed inborn disorder of steroidogenesis (CYP21A2 n=27, CYP11B1 n=12, POR n=36, CYP17A1 n=30, HSD3B2 n=22, SRD5A2 n=51). 32 urinary steroid metabolites were quantified using GC-MS. 14 previously published diagnostic biochemical ratios of urinary metabolites were examined. To characterise age-related variability, 10 age groups were compared: <1month (n=115), 1-3months (n=72), 3-6months (n=76), 6-12months (n=42), 1-4years (n=96), 4-10years (n=44), 10-18years (n=24), 18-30years (n=67), 30-50years (n=165), >50years (n=94). To characterise age- and sex-related variability, 3 age groups were compared: <6months (n=249; 126 male, 123 female), 6months-16years (n=220; 125 male, 95 female) and >16years (n=360; 138 male, 222 female). The 97.5th percentile of healthy was used as an upper reference limit for the purposes of diagnosing abnormalities.

Results: Data distribution for all ratios was highly skewed. No subgroups showed a normal distribution, less than half showed a log-normal distribution. Distinct ratio patterns were observed for childhood and adulthood, some also showing distinct patterns in early infancy; times of major changes in steroid ratios were 3 months of life and onset of puberty. Observed age-related differences were of greater statistical significance than sex-related differences. Biochemical ratios showed a lack of specificity when values for all patient groups were compared for each biochemical ratio. Discriminative ability was improved through scaling calculated ratio values to a healthy reference value. Using a simple interpretation algorithm, ratios performed with 100% sensitivity (patient vs. healthy), 89.9% sensitivity (correct diagnosis) and 80% specificity. CYP21A2, POR and CYP17A1 deficiencies were challenging to differentiate.

Conclusion: We present considerations required for establishing appropriate reference ranges, challenges of using established biochemical ratios for the analysis of urinary steroid metabolome data and propose a simple algorithm for the diagnosis of inborn steroidogenic disorders.

P1-6

Clinical and Genetic characterization of primary adrenal insufficiency in Sudanese children

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Background: Primary adrenal insufficiency (PAI) in children is an uncommon condition. Diagnosis is usually challenging especially in resource limited settings where facilities for antibodies and genetic testing are constrained. Many genetic etiologies have been reported in children with PAI due to congenital adrenal hyperplasia (CAH) and Allgrove syndrome are the commonest identified genetic causes to date in Sudan. Studies from Africa are rare and here we describe for the first time the clinical presentation and genetic etiologies of PAI in Sudanese children.

Patients and Methods: Thirty-six patients from twenty-nine Sudanese families (22 males and 14 females) with undiagnosed forms of PAI were included in this series. Diagnosis was based on clinical presentation of PAI paired with biochemical finding of low cortisol and high ACTH, +/- a negative response to synacthen stimulation. Candidates with clinical and genetic diagnosis of CAH and Allgrove syndrome were excluded. Gene sequencing (CGS) of commonly causative genes: MC2R, MRAP, CYP11A1 and STAR, was followed by whole exome sequencing (WES) in affected individuals and family members (where available), if they were mutation-negative on CGS. WES results were confirmed by Sanger sequencing.

Results: Hyperpigmentation was the commonest symptom at presentation detected in all patients while adrenal crisis was not

uncommon. We were able to identify the genetic etiology in 19/36 patients with a clinical diagnosis of PAI with mutations discovered in NNT (n=5) including a novel, synonymous splice causing variant seen in more than one family (T731=), MC2R (n=1), AIRE (n=4) including a 5 exon deletion, in two families, ABCD1 (n=4), NROBI (n=1), CYP11A1 (n=1), CYP11B1-CYP11B2 fusion (n=3), of which NNT mutations are the commonest in our patients.

Conclusion: CGS of "commonly causative" genes was of limited use in this cohort with NNT, ABCD1 and AIRE variants more common in this population. In addition, the study highlighted the importance of considering "silent" mutations in rare disease. Determining the etiology of adrenal insufficiency can be challenging, due to poor phenotype-genotype correlation and WES is invaluable in this. PAI in Sudan has heterogeneous etiology and gaining a genetic diagnosis is priceless to the patient and family, helping to guide the management and provide vital information on the prognosis.

P1-7

Management of mineralocorticoid deficiency in Congenital Adrenal Hyperplasia – a single centre study

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Introduction: Glucocorticoid replacement has been the main focus of research in congenital adrenal hyperplasia (CAH). However, few studies have focused on mineralocorticoid replacement.

Aim: Evaluation of mineralocorticoid replacement in a large cohort (n=124) with CAH recruited retrospectively over a 10-year (2010-2020) period.

Methods: We recruited 124patients (71female, 53male) with biochemically proven 21-hydroxylase deficiency CAH who required fludrocortisone and presented over a 10-year period. The types of CAH (simple-virilising [SV] and salt-wasting [SW]) were classified according to their presentation and genotypes.

Hypertension was defined as systolic BP (SBP)≥95 centile or diastolic BP (DBP)≥95 centile. We referred to the Second Task Force on Blood Pressure Control in Children for 0-12months and height and age percentile chart for blood pressure for ages >12months.

Results: Mean plasma renin activity (PRA) in the first 3months of life was 44.87±47.75nmol/l/h (reference range 0.6-12nmol/l/h) and reduced to 14.9±15.97nmol/l/h after one year on treatment. A high mean dose of fludrocortisone 259.31±106.47mcg/m2/day was required during the first 3months. This was reduced to 200.13±69.87mcg/m2/day after one year, with a further reduction to 57.76±19.97mcg/m2/day. Eighty-eight patients (71%) required sodium (mean dose 6.94±2.99mmol/kg/day) during the first 3months, with a gradual reduction over time. By 2years of age, 12% still required sodium. Sixty patients met the criteria for a diagnosis of hypertension. The mean dose of fludrocortisone in the hypertensive group was higher than the non-hypertensive group (113.42±48.87mcg/m2/day c.f. 97.94±40.90mcg/m2/day; p=0.009), with a lower mean PRA in the hypertensive group (4.45±4.32nmol/l/h c.f. 13.02 ± 8.48nmol/l/h; p=0.018).

We stratified the patients into SV (n=33) and SW (n=67) forms of CAH. The timing of starting fludrocortisone were not significantly different between the two (SV:1.94±3.08years c.f. SW:1.58±2.87years; p=0.448). PRA concentrations were higher in the SW group during the first year although the difference did not achieve statistical significance (35.98±366nmol/l/h c.f. 18.76±17.43nmol/l/h; p=0.243). Additionally, the dose of fludrocortisone was higher in the SW group in the first year (229.37±91.01mcg/m2/day c.f. 176.62±58.03mcg/m2/day; p=0.007).

This study confirms the established practice at our centre of commencing fludrocortisone at a higher dose and titrating according to the PRA and blood pressure. Periodic assessment is also recommended by the Endocrine Society Clinical Practice Guideline 2018. The PRA should be kept within the normal range to prevent hypertension. In patients without SW, sodium should be weaned early, with a view to later reducing fludrocortisone doses if possible.

P1-8

Evolution of the Short Synacthen Test over a decade - a single UK centre's experience

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Background: The Short Synacthen Test (SST) is the most popular test of adrenal insufficiency (AI) worldwide. The current SST protocol at Sheffield Children's Hospital (SCH), UK, recommends measurement of serum cortisol at baseline, then 30- and 60-minutes post stimulation, with a peak cortisol of >429nmol/L constituting a pass. Our practice has evolved to consider near-pass results as "borderline" and patients may be treated with stress dosing steroids only, rather than full replacement.

Methods: We conducted a retrospective analysis of all SSTs performed at SCH from 2011-2019. The number of SSTs performed annually, test indication, Synacthen dose administered (low: 1mcg or standard: 145mcg/m2), cortisol results, timing of peak cortisol, patient's steroid history and management outcome were extracted from laboratory records and patient notes. A peak cortisol between 350 and 429 nmol/L was categorised as borderline.

Results: We analysed 1275 SSTs over the nine-year period. The number of SSTs being performed annually has increased 54%, from 114 to 175, but the incidence of AI has remained constant

(~40 cases/year). Over the study period the proportion of SSTs performed to diagnose steroid induced adrenal suppression increased from 34% to 58%, with 47.4% passing the SST and 15.6% considered borderline. The proportion of tests performed using the standard dose (SDSST) has increased annually from 26% at the start of the study period to 100%. Timing of peak cortisol was dependant on SST dose: 58% of low dose SSTs peaking at 30mins and 96% of SDSSTs at 60mins. Sampling only at 60mins during the SDSST would have resulted in two additional failed SSTs (both in the borderline category), but a cost saving of ~£1000/year. Peak cortisol results were borderline in 122 (9.6%) patients. This proportion remained relatively constant over the study period (mean 9.7%, range 5.4%-15.0%). Management of "borderline" patients depended on the clinical scenario; with their pre-test probability for AI, cortisol result, and steroid history all playing a role. Use of stress-dosing rather than full steroid replacement has not resulted in any adverse events to date.

Discussion: Our SST requests, Synacthen dose and interpretative practice have evolved over the last decade. The number of SSTs conducted each year continues to increase without a change in the incidence of AI. Our data suggest this is due to increasing concern about adrenal suppression secondary to steroid use, however there was a low diagnostic yield of AI requiring replacement glucocorticoid for this indication

P1-9

Identification of a novel CYP11B2 variant in a family with varying degrees of aldosterone synthase deficiency

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Background: Isolated aldosterone synthase deficiency is a rare autosomal recessive disorder caused by pathogenic variants in CYP11B2. To date, more than forty different pathogenic variants in the CYP11B2 gene causing isolated aldosterone synthase deficiency have been identified. We report on a novel pathogenic CYP11B2 variant.

Case Report: The second child (male) of consanguineous, healthy parents, presented shortly after birth with severe signs of aldosterone deficiency. Initial biochemical analysis showed hyponatremia, hyperkalemia and metabolic acidosis. After ruling out glucocorticoid deficiency with a cosyntropin stimulation test, isolated mineralocorticoid deficiency or pseudohypoaldosteronism was suspected. Additional biochemical work-up revealed hyperreninemic hypoaldosteronism and clearly elevated aldosterone precursors, confirming the biochemical diagnosis of isolated aldosterone synthase deficiency.

Genetic Analysis: Initial genetic analysis revealed a novel heterozygous variant of unknown significance in exon 3 of the CYP11B2 gene Chr8: NM_000498.3:c.400G>A p.(Gly134Arg). The heterozygous variant seemed an insufficient explanation for the observed phenotype of our patient. Because the variant was located in a large region of homozygosity, another set of primers was designed which led to the discovery that the c.400G>A variant was in fact present in the homozygous state. The initially used primers had also recognized and amplified the highly homologous region of the CYB11B1 gene, leading to false negative results.

Segregation analysis on the patients asymptomatic parents and sister revealed that the mother and sister were heterozygous carriers but, surprisingly, the patient's father appeared homozygous for the novel CYP11B2 variant. Biochemical evaluation of the father indicated subclinical enzyme impairment, characterized by low aldosterone and elevated aldosterone precursors.

In Silico Analysis: To gather more arguments for pathogenicity of the c.400G>A variant, in silico analyses were performed. Gly at position 134 is highly conserved across species and appears to be an exposed residue in the Cytochrome P450 domain of CYP11B2. The variant is predicted to be deleterious by multiple pathogenicity prediction methods. Protein modelling using PyMOL predicted that p.(Gly134Arg) has a positively charged appendicle in close proximity to the putative steroid product egress route, which probably influences protein-substrate dynamics. These findings support the pathogenicity of the reported novel homozygous CYP11B2 variant.

Conclusion: We report on a novel variant in CYP11B2 associated with varying degrees of isolated aldosterone synthase deficiency in the same family. Initial genetic analysis was complicated by homology of the CYP11B2 and CYP11B1 genes. In silico analyses, including protein modelling, provided additional evidence for pathogenicity of this novel variant.

P1-10

Outcomes of the low dose short Synacthen test in infancy

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Background: The hypothalamic-pituitary-adrenal (HPA) axis may be suppressed at birth. In most infants this is tolerated well. HPA testing in infancy often generates 'abnormal' results although abnormalities of the HPA may not be identified and cortisol measurements often 'normalise' over time.[1]

Aim: To contribute to the evidence base on neonatal HPA activity by reporting outcomes of infants age < 1 year tested with the low dose short Synacthen test (LDSST: Synacthen 500ng/1.73m2, sampling at 0', 15', 25', 35') between 2013-2020 at a tertiary children's hospital. Infants with low cortisol during critical illness, prolonged jaundice, recurrent hypoglycaemia and following high dose glucocorticoid use in intensive care were tested.

Methods: Gestation at birth, age at testing and gender were recorded. Maximum cortisol concentrations were: 'normal', ≥450nmol/L; 'suboptimal' 350-449nmol/L treated with 'sick day' hydrocortisone, during periods of stress only; 'abnormal', <350nmol/L, treated with daily hydrocortisone.

Results: Data from 31 (21M) infants, age 0.2 months (±0.3 months) at time of first LDSST were included. 15/31 (48.4%) received daily hydrocortisone, 9/31 (29.0%) received sick day only. Preterm infants were more likely to 'fail' (Table 1).

A second LDSST performed 0.9 ±0.9 years later was abnormal in 6/24 (25%) infants, of whom two had normal results on subsequent tests. In 20/24 (83.3%) infants in whom the cortisol peak was <450nmol/L on the first LDSST, a normal test result was documented at the age of 1.3 ± 1.1 years.

After two years, four infants are treated with daily hydrocortisone, none have a diagnosis for adrenal insufficiency.

Discussion: Cortisol responses to LDSST are frequently impaired, particularly in preterm infants. Long-term hydrocortisone treatment may inhibit the normal maturation of this hormone pathway. Regular re-evaluation of the adrenal axis is essential.

Reference

1. Tan et al. (2018) Arch Dis Child

P1-11

Low-dose ACTH Stimulation Test: Comparison of Cortisol Response at 30, 40, and 60 Minutes

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Background: Low-dose adrenocorticotropic hormone stimulation test (LDST) is commonly used for evaluating the adequacy of hypothalamo-pituitary-adrenal axis functions. However, there is still no standardization between protocols used in different centres.

Objective: To contribute to the optimal time of highest cortisol response in the LDST in children.

Design: A prospective study of LDST resultsperformed on children with clinical suspicion of adrenal insufficiency.

Method: Cortisol concentrations were measured at baseline, 30, 40, and 60 minutes after intravenous administration of 1 μg tetracosactide. Basal cortisol levels were also assessed by using liquid chromatography-mass spectrometry (LC-MS/MS). Adrenal insufficiency was defined as a stimulated cortisol level <18.1 μg/dL (500 nmol/L).

Table 1. Results of the LDSST according to gestation

Gestation	Extremely preterm (<28 weeks)	Very preterm (28-<32 weeks)	Moderately preterm (32-<37 weeks)	Term (≥ 37 weeks)	Total (n)
First LDSST					
Passed	0 (0%)	0 (0%)	0 (0%)	7 (37%)	7(23%)
Suboptimal	1 (25%)	0 (0%)	2 (40%)	6 (32%)	9 (29%)
Failed	3 (75%)	3 (100%)	3 (60%)	6 (32%)	15 (48%)
Infants tested	4	3	5	19	31
Second LDSST					
Passed	2 (50%)	2 (66%)	4 (80%)	10 (83%)	18 (75%)
Suboptimal	0 (0%)	0 (0%)	1 (20%)	1 (8%)	2 (8%)
Failed	2 (50%)	1 (33%)	0 (0%)	1 (8%)	4 (17%)
Infants tested	4	3	5	12	24

Table 1. The probabilities of LSDT yield at 30, 40, and 60 minutes after administration of tetracosactide

	LDST Pass (n)	Number of Patients Who Would Need Additional Sample to Prevent One False Positive LDST Result, n	Sensitivity by whole test, Probability LDST Pass Changes, %
30 min in addition to 0	85	24	78%
40 min in addition to 0	98	11	90%
60 min in addition to 0	95	14	87%
40 min in addition to 0 and 30	101	8	93%
60 min in addition to 0 and 30	102	7	94%
60 min in addition to 0 and 40	106	3	97%

Results: 135 patients (61girls, mean age 9.98±5.93 years) were included. Cortisol response was adequate at any time point in 80.7% (n=109) of patients. In the case of a single measurement after stimulation, 62.9% (n=85) of the patients had an adequate response at 30.th minute, 72.6% (n=98) at 40.th minute, and 70.4% (n=95) at 60 minute (p=0.04). In the case of one measurement at the 40.th minute, 8 patients (7.3%) who had an adequate response at 60.th minute, would have been misdiagnosed. In this condition, delta cortisol (0 to 40) value above 9.3 μg/dL reduces the probability of LDST result being false-negative by a negative predictive value of 95.5%. The threshold basal cortisol value predicting a negative LDST result in the immunoassay method was determined as >6.5 μg/dL (69.2% sensitivity/74.3% specificity) and >6.1 μg/dL (59.1% sensitivity/78% specificity) by LC-MS/MS method (p= 0.0001).

Conclusions: In the LDST, sampling at the 40th and 60th minutes after stimulation minimizes the false-positive LDSTs, and in the case of a single measurement, the 40.th minute sampling reduces false-negativity compared to the 30.th and 60.th minutes.

P1-12

Novel Homozygous Mutation in a Boy with Pseudohypoaldosteronism Type 1

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Pseudohypodosteronism type 1 (PHA-1) is an inherited disease caused by the resistance of peripheral tissues to aldosterone, leading to severe salt loss in infants. This rare disease is caused by mutations in the amiloride-sensitive epithelial sodium channel subunits (ENaCs). Loss-of-function mutations in ENaCs lead to PHA-1, which is associated with neonatal salt wasting. PHA1 can be transmitted as autosomal dominant and recessive forms. Patients with the autosomal dominant form of PHA1 have milder symptoms and more renal involvement. The autosomal recessive form of PHA1 is more severe and resistant to mineralocorticoids is seen in several organs such as the kidney and colon, sweat and salivary glands.

Case report: Here we report a severe form of the disease that resulted in the death of several children in the family. Our patient was the seventh child in the family and the result of a first degree cousin marriage. The first, third, fourth children of the family, who were boys, and the sixth child of the family, who was a girl, died shortly after birth from PHA1, respectively. These children were hospitalized in another city. The second child of the family is a girl and the fifth child of the family, who is a boy, is healthy and alive.

Our patient weighed 3,500 grams at birth and had a height and head circumference 51 and 35.5 cm, respectively.

The patient had severe vomiting and poor feeding from the second day of birth and transferred to the NICU. Due to the death of previous children and the history of PHA1 in his family, the necessary studies were performed. ACTH and other sex steroids were in the normal range. Renin and aldosterone levels were very high. Serum potassium was 9 meq / l and sodium was 110 meq / l. His skin was not hyperpigmented and he had a normal external genitals. At the age of 5, he is 109 cm tall and weighs 18 kg and his growth and development is normal.

Genetic study: In this patient, a novel homozygous missense mutation (c.1497G>C) in exon 10 of SCNN1A gene was identified, changing Glutamine 499 to Histidine (p. Gln499His). Sanger sequencing was used to validate the detected variant. Segregation analysis using Sanger sequencing revealed that both parents showed heterozygosity at the mutation position.

Conclusion: Identifying this mutation can help diagnose new patients with Pseudohypoaldosteronism Type 1.

P1-13

Clinical characteristics and pubertal development in Greek girls with premature adrenarche

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Background: Premature adrenarche (PA) is characterized by the appearance of pubic and axillary hair associated with an increase in adrenal androgen production, in the absence of central puberty, steroidogenic enzyme defects, or virilizing tumors, before the age of 8 years in girls and 9 years in boys. Studies have shown increased likelihood of PA for children with obesity and those born small for gestational age (SGA).

Aim: To assess the correlation between PA in girls and age at puberty onset. Furthermore, to investigate whether girls with PA were born SGA, the association with their body mass index (BMI) and if the age at puberty onset was correlated with bone age advancement (BAA) and mother's age of menarche.

Methods: Data from 81 prepubertal females with clinical signs of androgen action and elevated serum androgen levels were analyzed retrospectively from their medical records. Student's t-tests or Anova were used for the comparison of means between groups. Correlations between variables were evaluated using Pearson's correlation coefficient.

Results: Eighty-one prepubertal females with mean age 7.22 ±1.08 years were evaluated. Of those, non-classic CAH was diagnosed in seven girls and were excluded from our study. Mean BMI z-score was 1.44±1.04, 22 (29.7%) were obese, defined as BMI z-score ≥ 2, 23 (31.1%) were overweight (1<BMI z-score<2) whereas 29 (39.2%) were of normal weight. Birth weight data were available for 66/74 children. Five girls (7.58%) were born SGA. Mean age of adrenarche was 6.60±1.16 years, mean bone age was 8.27±1.37 years and the mean BAA was 0.972±0.831 years at baseline. Mean age at puberty onset was 8.99±1.14 years. The majority of girls (54.1%) entered puberty within normal range of age (9.99±0.79), whereas 25.7% in early normal range (8.56±0.25) and 20.3% had precocious puberty (7.62±0.34). The mean age of menarche of the mothers was 12.3±1.33 years. No significant correlation was found between age at adrenarche and BAA, however girls who developed early puberty had a greater BAA at diagnosis of PA (p=0.017). Moreover, overweight/obese girls had a greater BAA (p=0.018). Furthermore, there was a positive correlation with girls' puberty onset and mothers' age of menarche (r=0.308, p-value=0.019).

Conclusion: Children with PA tend to have increased BMI, advanced bone age and enter puberty earlier than general population. Advanced bone age seems to correlate with early onset of puberty. No significant correlations were found between PA and SGA.

P1-14

Demographic, Clinical, Hormonal And Genetic Characteristics Of Children And Adolescents With Congenital Adrenal Hyperplasia Due To 11-Beta Hydroxylase Deficiency

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Introduction: 11-beta hydroxylase deficiency(11β-OHaseD) is the second frequent congenital adrenal hyperplasia(CAH) form. This study aimed to determine demographic and genetic characteristics and final height, to evaluate the long term clinical follow-up of children&/adolescents with 11β-OHaseD.

Material and Methods: The study is designed as a multicenter, national, retrospective. 60 cases from 11 Pediatric Endocrinology Center were included.

Results: The mean diagnosis of age was 3.5±4.3(0.0-16.5) years. The mean follow up period was 7.7±4.9(0.8-20.0) years. 47 cases had karyotype data and 55.3%(n:26) was 46 XX. 87%(n=41) of these cases were brought up compatible with karyotypic gender. 77% of all cases(n=46) had consanguinity between parent. 64%(n=38) had similar disease in family. The complaints at first approval were ambigious genitalia [35%(n=21)], pubic hair [23%(n=14)], sibling with CAH [12%(n=7)], macrogenitalia [8%(n=5)]. At first admission the mean weight&height&BMI SDS were 0.82±1.75(-3.80-4.35), 0.57±1.96(-3.60-5.38), 0.42±1.65(-4.50-2.92) respectively. The mean bone age at first admisson was 7.7±4.9(0.2-17.0). The median pubertal stage was Tanner Stage III. 18.2%(n=10) axillary hairs, 20%(n=12) hypospadias, 8%(n=5) cordea, 37%(n=22) labioskrotal fusion were explored at first admission. 17% case had precocious puberty (treated with GnRH analogs). 32%(n=19) had surgical operations [18%(n=11)cliteroplasty and/or vaginoplasty, 8%(n=5)hysterectomy+ooferectomy, 5%(n=3)testicular prosthesis, 3%(n=2) correction of

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hypospadias]. 8% of all cases(n=5) developed adrenal REST tumors, and these cases had treated with high doses glucocorticoids with 25.0±9.6(12-36) months [40%(n=2) total recovery, 40%(n=2) partially recovery, 20%(n=1) growth in REST tumor (treated with testicular sparing surgery)]. 32% of all cases(n=19) had final height [final height SDS -2.25±2.0(-7-0.94)]. 45% of all cases (n=27) had CYP11B1 gene analysis [74%(n=20) homozygous, 11%(n=3) heterozygous, 4%(n=1) combined heterozygous mutation and 7%(n=2) had deletion].

Conclusion: In our study, we found that cases with 11β-OHaseD could still be diagnosed late. Therefore, we found that height potentials were negatively affected. We thought that it is important to provide genetic counseling and prenatal diagnosis for other children, especially after a child with a diagnosis of CAH is born in families with consanguinity. As a result, the compilation of the results obtained from the cases followed up with the diagnosis of CAH can provide significant improvements in the follow-up of the newly diagnosed cases.

P1-15

Growth from birth to adult height in patients with classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency: A collaborative study

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Objective: To evaluate growth in patients with classical CAH.

Patients and Methods: Retrospective, longitudinal and multicentric study of patients with classical CAH due to 21-hydroxylase deficiency who had achieved adult height (AH).

Excluded: boys with simple virilising forms(SV)>1-year at diagnosis. Normative Control Group: Millennials Longitudinal Growth Study(2018).

According to age at pubertal growth spurt (PGS)onset, patients were considered: very-early, early, intermediate, late and very-late maturers.

PGS was considered normal if height Z-Score (HZS) at PGS-onset was similar (±0.5) to AH Z-Score.

Results: 50 patients(37 females); 41 salt-wasting.

During the first year of life a decrease in height SDS was observed.Three groups of patients were identified according to their growth pattern from the first year:

Group1: Regained growth until PGS onset, normal PGS, AH Z-Score>-2 and AH Z-Score-mean parental height(MPH) Z-Score>-1.

Group2: Non-regained prepubertal growth and normal PGS: HZS(PGSonset–3 years)< 0.5.

Group3: Accelerated prepubertal growth with disrupted PGS: HZS(PGS onset-3years)>1. All presented advanced bone age(BA) related to chronological age(>1year).

Six patients were non-classifiable.

AH Z-Score: non-statistically different in patients with and without salt wasting forms. Significantly lower in very-early maturers(-1.90±0,60) versus intermediate(-0,79±0,92) and very-late maturers(-1,16±0,40).

Testosterone and androstenedione values were higher in Group3 versus Group1 at 7-years and at PGS-onset.

No correlation was observed between hydrocortisone doses and HZS.

Conclusions:

- Globally, loss of HZS were observed during the first year of life with partial recovery until PGS-onset
- Auxological evaluation is a useful tool for monitoring disease management
- The observed growth pattern heterogeneity is partially explained by hydrocortisone doses and biochemical control.

Table 1. HZS at different time-points.

	NN	1-year	3-years	7-years	PGS-onset	2nd year of PGS	AH	AH-MPH
Group1 n=19	0,36±0,79	-1.77±1.0	-0.99±0.94	-0.50±0.98	-0.44±0.98	-0.32±0.90	-0.53±0.75	-0.07±1.02
Group2 n=11	0,10±0,59	-2.11±1.51	-2.26±0.79*	-1.91±0.70*	-1.81±0.71*	-1.68±0.62*	-1.67±0.42*	-1.04±1.19*
Group3 n=14	0,23±0,81	-1.90±1.70	-1.43±0.96	-0.25±1.06	0.25±1.06	-0.34±1.35	-2.06±1.01*	-1.39±0.85*
All sample n=50	0.24±0.77 (-1.46,2.8)	-1.84±1.34 (0.57,-6)	-1.40±1.01 (2.22,-3.45)	-0.65±1.15 (1.92,-3.19)	-0.53±1.20 (1.87,-2.90)	-0.64±1.12 (1,69,-3.89)	-1.31±1.07 (1.11,-4.14)	-0.68±1.19 (2.31,-3.37)
Hidrocortisone (mg/m2/day) n=39		21.1±5.1 (37.7,13.5)	18.1±4.9 (30.8,7.4)	19.06±3.7 (26.3,10.6)	16.7±4.6 (33,7.6)	15.9±4.3 (25,6.6)		

Mean±SD;(max,min).*p<0.05 vs group1

AH was 156.5±5.3cm(168.5-139.1)in women and 168.6±7.4cm(185.1-159.0) in men.

P1-16

Long-term follow-up of three male siblings with a novel *NNT* pathogenic variant causing primary adrenal insufficiency

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Nicotinamide nucleotide transhydrogenase (NNT) is expressed in the heart, thyroid, and testicles, where it maintains the balance of reactive oxygen species in the mitochondria. It is linked, by an insufficiently described mechanism, to primary adrenal insufficiency (PAI) with or without mineralocorticoid insufficiency and several extra-adrenal manifestations (i.e. gonadal adrenal rest tumors, cardiomyopathy, hypothyroidism, and precocious puberty). A comprehensive and chronologically detailed clinical long-term follow-up of three siblings with a novel pathogenic variant in the *NNT* gene is presented.

A novel homozygous frameshift pathogenic variant c.1575dup in the *NNT* gene was identified in 3 males (age 21.6, 20.2, and 4.2 years at final clinical evaluation) by whole-exome and confirmatory Sanger sequencing. Both parents were heterozygous for the variant and in good general health at the age of 45 and 43 years.

PAI was diagnosed in the two eldest brothers after an Addisonian crisis at the age of 1.4 and 1.1 years, respectively. Cascade sibling screening led to the identification of PAI by an ACTH stimulation test in the third sibling at the age of 4.5 months in the asymptomatic stage. A normal urinary steroid profile, performed by gas chromatography-mass spectrometry, was determined in this patient. Following the PAI diagnosis, no further adrenal crises were determined. The average hydrocortisone dose for the whole follow-up in the two eldest patients was 16.6 mg/m^2 body surface and 13.0 mg/m^2 in the youngest. None had impaired mineralocorticoid secretion.

Thyroid function and morphology were normal. Echocardiography revealed no structural or functional heart abnormalities. Adolescent patients had a normal start of puberty (aged 11–12), while pubertal progression to Tanner 5 stage was prolonged to 19–20 years. The final testicular volume was 15 mL and testicular endocrine function (testosterone, inhibin B, basal and GnRH-stimulated LH and FSH) was normal in both. No adrenal rest tumors were identified by ultrasound. In the eldest two patients, bone mineral density in the range of osteopenia was identified.

Presented data suggest that adrenal impairment in NNT deficiency is progressive, thus early hormonal testing might not rule out this condition. *NNT* gene is a good candidate gene for neonatal screening panels and could prevent life-threatening Addisonian crises in these patients. Early genetic testing is required in siblings of patients with the determined mutation. Presented results identify pubertal progression dysregulation and decreased bone mineral density as additional extra-adrenal manifestations in NNT disfunction.

P1-17

Expanding the phenotype of deglycosylation disorders: Adrenal Insufficiency and Micropenis in NGLY1-CDDG

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Background: NGLY1 encodes the enzyme N-glycanase that catalyzes protein deglycosylation in the process of protein degradation. Loss of function mutations in NGLY1 lead to a disorder of N-linked deglycosylation which is a rare multisystemic disease. The typical phenotype includes intellectual disability, liver dysfunction, muscular hypotonia, involuntary movements and decreased or absent tear production. Adrenal insufficiency has been previously reported in only two cases. Micropenis has not been reported yet.

Case Report: A 5.6-year-old child was evaluated due to gradual darkening of the skin and more frequent falls. He is a product of pregnancy with intrauterine growth retardation, birth at 38 weeks and birth weight 2,558 grams. He achieved normal milestones until age 1.6 years and then experienced regression in his speech. Myoclonic seizures followed shortly afterward and treatment with sodium valproate and later levetiracetam was started. EEG was compatible with myoclonic epilepsy. MRI showed normal white matter myelinization and brain structure. The parents noticed darkening of the skin and mucous membranes 6 months prior to his referral with more frequent falls.

Physical examination revealed general darkening of the skin and mucous membranes. Weight 17.8 kg WSDS -0.69, height 109 cm HSDS -0.6, BMI 15 BMI SDS -0.35, head circumference 50 cm. Normal heart, chest, and abdomen exam. The testes were both in the testicular sac, 3 mL in volume, stretched penile length 3 cm (<3.5SDS), Tanner 1.

Cortisol levels were undetectable at baseline and after ACTH stimulation. All other adrenal metabolites were low as well and ACTH levels were very high at baseline. Treatment was started with hydrocortisone and fludrocortisone with gradual improvement in his general condition.

A next generation sequencing panel for epilepsy genes revealed a previously unreported homozygous variant c.-17_12del in

NGLY1classified as likely pathogenic by Varsome database. Pathogenicity was confirmed by high-resolution mass spectrometry determination of dried blood spot aspartylglycosamine (a diagnostic biomarker for NGLY1-CDDG) revealing a level 5.7 standard deviations above controls.

Conclusion: Mutations in NGLY1 are rare and adrenal insufficiency has been reported only in the minority of the cases. The increased mortality reported in this disorder during intercurrent illness might be attributable to undiagnosed adrenal insufficiency. This is the first report of micropenis in NCLY1-CDDG.

P1-18

Very early and atypical presentation of Triple A (Allgrove) syndrome

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Background: Triple A (Allgrove syndrome) is a rare, autosomal recessive disorder characterized by the alacrimia, achalasia, and adrenal insufficiency triad. Alacrimia starts in early infancy, while achalasia and adrenal insufficiency appear subsequently during childhood or adulthood. We are presenting an infant with very early and simultaneous clinical manifestations of triple A syndrome.

Case Presentation: An 11-month-old male infant was admitted to the neurological department for evaluation of muscle hypotonia and developmental delay. Mother reported child limpness, feeding problems, and failure to thrive since 6 months of age. Before admission, child had daily fevers for two months due to repeated pneumonia. On admission, clinical examination showed a failure to thrive (weight 6040 g – Z score < -3SD), pale skin with hyperpigmentation in the lumbar region, and abdominal distension without organomegaly. Neurological examination revealed generalized muscle weakness with reduced spontaneous motor activity. He cried without tears since birth.

Baseline investigations revealed normal complete blood count, serum creatinine, and salt wasting (serum Na 125 mmol/l, K 6.2 mmol/l, urine Na 30 mmol/L). Based on clinical presentation, and initial laboratory results, neurologist suspected Allgrove syndrome, and referred the patient to the endocrinology department. ACTH concentration was 886 pg/ml, with basal serum cortisol of 165 nmol/l, which failed to increase during the Synachten test (in 30 and 60 minutes cortisol levels were 157 and 159 nmol/l, respectively), while 17-OHP was low throughout the test. Diagnosis of primary adrenal insufficiency was established, and hydrocortisone and fludrocortisone therapy were initiated. Ophthalmic evaluation revealed reduced tear production and local therapy with artificial tears was introduced.

Due to swallowing difficulties and repeated vomiting, barium study was performed, and severe stenosis of the lower esophageal sphincter, as well as dilatation of the upper esophagus, were revealed. A diagnosis of achalasia was made and later managed with esophagomyotomy. Molecular genetic testing conducted at the Dresden University of Technology confirmed a compound heterozygous mutation in the AAAS gene: p.Ser263Pro (paternal mutation) and c.787T>C (maternal mutation).

Conclusion: Given the rarity and high phenotypic heterogeneity, early identification of the Triple A syndrome is challenging. According to the current state of literature, the mean age of onset of the first symptom is between 2 and 13 years. Our patient was 6 months old when the triad of signs presented, making him the youngest child with Allgrove syndrome reported so far.

P1-201

Gene chimeras involving *CYP21A2* and *TNXB* genes in spanish patients with congenital adrenal hyperplasia (CAH)

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Background-Aim: Gene rearrangements between *CYP21A2*, *TNXB* and their homologous pseudogenes (*CYP21A1P*,*TNXA*) result in chimeric genes, responsible for the CAHX syndrome. CAHX patients show CAH and Ehlers-Danlos syndrome (EDS) symptoms. Three CAHX chimeras with different clinical severity are described: CH1 (including 120bp deletion in exon 35), CH2 and CH3. The small size and few series reported so far warrant further studies in other populations.

Aim: To learn about the number of CAH Spanish patients at risk of having CAHX chimeras, their distribution, and clinical manifestations in three tertiary hospitals.

Methods: Molecular analysis:

1. *CYP21A2* chimeras junction-site determination: intra or downstream to the gene
2. Multiplex Ligation Probe Amplification (MLPA) to detect CH1-chimeras
3. Heterodimers detection after *TNXB* (ex34-ex37)-PCR and electrophoresis to detect CH1 in retrospective samples
4. Sequencing of *TNXB* exons 40,41,43 for CH2,CH3-chimeras

Medical history review and clinical evaluation were performed in 20 patients.

Results:

- CAH patients carrying alleles "at risk" of CAHX chimeras

Among the 4284 CAH patients (classical, nonclassical and hyperandrogenism) analyzed in our laboratory since 1995, 404

were carrying, at least, one *CYP21A2* deletion allele. In 185, junction-site was located before *CYP21A2*-exon 6. In 219 (54.2%) deletion extended downstream and may involve TNXB. MLPA performed in 114 patients revealed 27 (23.7%) CH1-chimeras. Heterodimers detection approach performed in 36 samples detected four CH1-chimeras. Sequencing of *TNXB* exons detected 20 CH2 and five CH3-chimeras.

- CAHX chimeras distribution and clinical evaluation

HVA (6/6): Intragenic *CYP21A2* chimeras were more frequent (71%, $p<0.05$) in this area. Only one CH2 patient with no clinical symptoms was detected.

HLP (7/10 revised): CAHX chimeras were detected in four patients (2 CH1 and 2 CH2). A CH2 patient showed EDS-related clinical symptoms without hypermobility (Beighton score:2/9). One patient with EDS manifestations was negative.

HMV (7/7): five chimeras were detected. Three patients carried CH1 (two with clinical signs -luxations and cronic artralgy-) and two carried CH2, one with EDS signs, the other with Perthes disease.

Conclusions: CAHX chimeras distribution is different in our population (CH1: 21.8% vs 39%, CH2: 15% vs 32%, CH3: 3.8% vs 1.5%). A not homogeneous geographic distribution was observed, as well (1.8%, 7.4% and 9.3% in different areas).

As a dominant disease CAHX should be also considered in carriers and nonclassical forms.

MLPA, first approach allowing the systematic search of CAHX chimeras, only detects CH1. *TNXB* sequencing must be performed to discard CAHX. A heterodimer approach to detect CH1 chimeras was useful to investigate retrspective DNA samples.

P1-202

Abstract Withdrawn

P1-203

P450 oxireductase (POR) regulates blood brain (BBB) maturation by mediating retinoic acid (RA) metabolism in a model of the human BBB

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Background: The blood-brain barrier (BBB) is a multicellular neurovascular unit (NVU) that allows selective passage of necessary molecules into the central nervous system (CNS) while limiting the entry of neurotoxins and most drugs. A cross talk with pericytes and neural cells mediates the acquisition of tight junctions (TJs) in brain microvascular endothelial cells (BMECs), which limit the paracellular passage of solutes, thereby regulating CNS homeostasis. However, the mechanisms by which NVU cells communicate to mediate TJ formation remains a mystery. Retinoic acid (RA), a key signaling molecule during vertebrate embryonic development, is commonly used to enhance functional barrier properties in in vitro BBB models. However, its physiological relevance and affected pathways are not fully understood. P450 oxidoreductase (POR) acts as an electron donor for microsomal cytochromes, thereby regulating their enzymatic activity.

Aim: To study the role of POR in the functional development of BBB properties.

Methods: We generated iPSC-derived brain microvascular endothelial-like cells (iBMECs) derived from both, POR-deficient (PORD)patients and CRISPR/Cas9-mediated POR-depleted isogenic lines (PORM), to study the role of POR in BMEC acquirement of functional barrier properties.

Results: We demonstrate that POR is expressed at the BBB and in iBMECs and is enzymatically active in control iBMECs while severely attenuated in PORD iBMECs. An analysis for the TJ relevant markers ZO-1, GLUT-1 and CLDN-5 showed a control-like expression of ZO-1, GLUT-1 and CLDN-5 in PORD iBMECs. PORM iBMECs exhibited non-continuous expression of ZO-1, decreased expression of GLUT-1 and no detectable CLDN-5.

Studies on iPSC differentiation to iBMECs with a gradient of RA concentrations demonstrate that PORD and PORM iBMECs fail to develop functional barrier properties under higher RA concentrations and suggest that POR is necessary for the RA-dependent acquisition of TJs and barrier functions.We tested RA-dependent changes in gene expression within each cell line by calculating the differentially expressed genes (DEGs) as the fold change of each RA concentration compared to iBMECs differentiated without

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RA. DEGs were then further filtered by their base means. Control iBMECs showed a gradual dose-dependent increase in RA-induced number of DEGs. Contrarily, PORD iBMECs showed an increased number of DEGs that was apparent already at the lower RA concentrations. This was further accentuated in the PORM iBMECs.

Conclusion: We demonstrate that POR regulates RA homeostasis, and that POR-deficiency leads to accumulation of RA within iBMECs, resulting with impaired expression of TJs and consequently to dysfunctional development of barrier properties.

P1-204

Reduced cognitive function in children with classical 21-hydroxylase deficient congenital adrenal hyperplasia (21OHD-CAH)

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Background: In the absence of a national screening program for congenital adrenal hyperplasia (CAH), children are often diagnosed late, when unwell with salt-wasting crisis or hypoglycemic symptoms. In 21-hydroxylase deficient CAH (21OHD-CAH), girls usually present with a disorder of sex development (DSD) and are thus diagnosed earlier than boys who present with salt-wasting.

Aim: to investigate the global intelligence of children with classical congenital adrenal hyperplasia and to evaluate the relation between intelligence quotient (IQ), sex and age at diagnosis

Patients and Methods: Patients with 21OH-CAH were evaluated for cognitive function by the same psychologist in a single center.

IQ was assessed using the Wechsler Intelligence Scale for Children (Wechsler Preschool and Primary Scales of Intelligence (WPPSI)) and the Khos Block Design Test for preschool children.

Degrees of intellectual disability or normal intelligence were defined according to IQ value, a child with an IQ < 70 being considered to have intellectual disability.

Epi-info7 software was used to collect the data and perform statistical tests.

Results: Sixty-six patients (18 boys and 48 girls, M: F ratio 0.4) with classical 21OHD-CAH deficiency were evaluated. Girls were both diagnosed earlier and started treatment earlier than boys: median (range) 17.5 (1-540) vs 45 (8-1645) days.

Mean (SD) age at IQ evaluation was 7.8±3.4 years, with no difference in age at IQ evaluation between girls and boys (7.5±3 vs 8.8±4 years, p=0.2).

Mean IQ was 78 ±18.8 in all children. The distribution of patients was:

- 20 <IQ<34 (Severe intellectual disability): 2 (3%)
- 34<IQ<49 (Moderate intellectual disability): 4 (6%)
- 50<IQ<69 (Mild intellectual disability):16 (23%)
- 70<IQ<85: (Low intelligence): 22 (33%)
- 85<IQ<99: (Low-average intelligence): 14 (21%)
- 100<IQ<114 (Above average intelligence): 9 (13.5%)

IQ was significantly higher in girls than boys - mean (SD) 80.1±16.5 vs 65.9±20.6 (p< 0.02). Also, there was a correlation between IQ and age at diagnosis and start of treatment (ρ: -0.29 IC 95%[-0.4972 ; -0.0516], p< 0.02).

Conclusion: Children with 21OHD-CAH deficiency usually have lower IQ than the general population, with boys more severely affected than girls. This is probably related to delayed diagnosis in the absence of DSD in boys, and the consequent delay in starting treatment. Our findings underline the importance of implementing a neonatal screening program for CAH in all the countries where this condition is relatively common.

P1-205

Exploring the growth curves of 248 Chinese patients aged 0-3 years with salt-wasting 21-hydroxylase deficiency

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Background: To construct the growth curves of body length and weight for Chinese patients from birth to 3 years with salt-wasting 21-hydroxylase deficiency (SW 21-OHD), changes in body mass index (BMI) will also be described, so as to explore the growth pattern of these special patients and guide the monitoring of early growth.

Methods: The body length and weight data of SW 21-OHD patients aged 0-3 years who visited in 4 hospitals across our country before December 2021 were collected. The LMS method was used to smooth the growth curves, values of percentile and Z-score curves were calculated and then generated growth curves.

Results: 248 patients were included, of which 128 (51.6%) cases were male and 120 (48.4%) cases were female. A total of 624 length and 711 weight values were obtained for male patients, while 633 length and 772 weight values for female. For male and female patients, their average birth length was all 50.00 cm, their average birth weights were 3.37 ± 0.32 kg and 3.32 ± 0.34 kg, respectively. The body length of both male and female patients was impaired mostly at 19-24 months old (-0.83 SDS and -0.96 SDS, respectively), their lowest weight was observed at 10-12 months (-0.74 SDS) and 19-24 months (-0.80 SDS), respectively. In addition, we found that the BMI of male patients was close to the overweight threshold at 36 months old. Finally, we successfully construct the

growth curves of body length and weight for Chinese patients aged 0-3 years with SW 21-OHD.

Conclusion: The growth of length and weight of patients with SW 21-OHD has its particularity, and attention should be paid to weight control while pursuing normal growth of length. Our growth curve will facilitate the assessment of growth in the management of patients with SW 21-OHD.

Keywords: congenital adrenal hyperplasia; 21-hydroxylase deficiency; salt-wasting type; growth curve

P1-206

Primary adrenal insufficiency in a patient with biallelic *QRSL1* mutations

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Background: Biallelic *QRSL1* mutations cause mitochondrial "combined oxidative phosphorylation deficiency-40" (COXPD40). COXPD40 has been reported invariably lethal in infancy. Adrenal insufficiency was weakly reported and investigated among seven previously reported patients with COXPD40.

Objective: We report clinical, biochemical, molecular, and functional characteristics of a patient with adrenal insufficiency due to COXPD40.

Methods: The medical history and adrenal function tests were examined. Genetic analysis was performed using whole-exome sequencing. Mitochondrial function was tested using mitochondrial membrane potential (MMP) and superoxide dismutase (SOD) enzyme assays.

Results: An 8-year-old boy was investigated for adrenal insufficiency. He had also mild developmental delay, sensorineural hearing loss, hypertrophic cardiomyopathy, nephrocalcinosis, elevated parathyroid hormone and creatine kinase, and lactic acidosis. Biallelic novel *QRSL1* variants (c.300T>A;Y100* and c.610G>A;G204R) were identified.Oxidative damage in mitochondria was shown by reduced MMP and SOD assays in the patient compared to controls ($p<0.0001$). Adrenal function tests revealed a "primary adrenal insufficiency other than congenital adrenal hyperplasia" (non-CAH PAI) with an isolated glucocorticoid deficiency. In the 8-year follow-up, having the longest survival of reported COXPD40 patients, he had preserved mineralocorticoid functions and gonadal steroidogenesis.

Conclusion: Biallelic *QRSL1* mutations can cause non-CAH PAI. Adrenal functions should be monitored in mitochondrial disorders to improve clinical outcomes.

P1-207

Clinical and genetic characteristics of androgen insensitivity syndrome

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Background: Androgen insensitivity syndrome (AIS) is a common 46XY disorders of sex development (DSD), which is mainly caused by mutations in the androgen receptor (AR) gene. The clinical manifestations vary among patients, depending on residual androgen receptor activity.

Methods: Five patients with different degrees of masculinization of external genitalia were selected as the research objects. As well as the detailed medical history and physical examination of the five patients were collected, relevant laboratory and imaging examinations were carried out. At the same time, the peripheral blood of the patients and their parents was collected for genetic testing.

Results: AR gene variants were found in all five patients, and none of them were reported, namely c.401dupA (p.P135Afs23), 1350bp deletion mutation, c.2505C>G (p.Y835X), c.1747T>C (p.F583L) and c.610G>T (p.E204X)

Conclusion: Patients with ambiguous external genitalia should be alert to the possibility of AIS, and ultimately need to be confirmed by genetic testing, so as to achieve the purpose of early diagnosis and early intervention, and provide convenience for the patient's family to conduct genetic counseling.

P1-208

Targeting melanocortin type 2 receptor (MC2R) with peptides for the treatment of congenital adrenal hyperplasia

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Congenital adrenal hyperplasia (CAH) is a common disorder of steroid production mainly caused by a mutated CYP21A2 gene, causing 21-hydroxylase deficiency (21OHD). CAH due to 21OHD requires lifelong mineralocorticoid (MC) and glucocorticoid (GC) therapy. But, from the location of the enzyme block in the steroid production and increase of adrenocorticotropic hormone (ACTH) which stimulates the melanocortin type 2 receptor (MC2R) in the

adrenal, excessive adrenal androgen production remains a challenging side effect for CAH even under MC and GC treatment.

We modeled the interaction of ACTH with MC2R and designed peptides to understand ACTH binding and activation of MC2R. A model of MC2R was made using the recently described structure of MC4R protein. We docked the ACTH into the MC2R structure using AUTODOCK-VINA and performed Molecular dynamics simulations to study the ACTH-MC2R interactions. Details of ACTH binding to MC2R provided hints for the design of better peptides to block ACTH-MC2R interaction.

We have analyzed the MC receptors and aligned the sequences of MC1R, MC2R, MC3R, MC4R, and MC5R to study the similarities and differences between these receptors. Sequence analysis identified two specific regions that are distinct for MC2R compared to other MC receptors and are also critical for the binding of ACTH to MC2R. Several rounds of peptide design were performed that use 4, 6, and 8 residues as linear as well as circular peptides for targeting MC2R. A sequence optimization of peptides and ACTH residues was performed to improve the peptide binding to MC2R and to improve peptide stability. Several of our designed peptides competed well with ACTH for binding to MC2R and inhibited the interaction of ACTH with MC2R. Downstream signaling of ACTH binding to MC2R was also inhibited by designed peptides.

We have modeled the binding of ACTH to MC2R and designed antibodies that could target the ACTH-MC2R interaction and signaling. A new round of peptide design was made to improve upon our previous attempts to create more specific and tighter binding peptides to MC2R that can be used to block ACTH-MC2R interaction. Further improvements to create potent and stable peptides will further our understanding of ACTH-MC2R interaction as target for treatment of CAH caused by CYP21A2 deficiency.

P1-209

Systematic review of cortisol levels during acute illnesses in children and young people not known to have glucocorticoid deficiency

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Importance: Current practice of doubling or trebling the basal glucocorticoid (GC) replacement dose during acute illnesses in children and young people (CYP) with GC deficiency is extrapolated from research in adults and not based on robust evidence. Endogenous cortisol levels during acute illnesses in CYP without GC deficiency can provide insight for optimal GC stress dosing for CYP with GC deficiency.

Objective: To summarise published evidence for endogenous cortisol levels during a range of acute illnesses in CYP not known to have GC deficiency.

Data source: Using PRISMA guidelines, a literature search was conducted of publications between 1 January 2000 to 30 June 2020 from CINAHL, Cochrane library, Cochrane Database of Systematic Reviews, Embase and Medline.

Study Selection: Two reviewers independently screened the abstracts for eligibility criteria and resolved differences by joint discussion. Inclusion criteria were: common acute illnesses; age 1 month to 18 years; basal blood cortisol levels within 48 hours of presentation. Exclusion criteria were: fewer than 5 subjects; subjects known to have GC deficiency or treatment with potential influence on cortisol levels.

Data Extraction and Synthesis: Two separate pairs of reviewers extracted and checked data for predefined fields. Cortisol values in traditional units were converted to SI units (nmol/l) and reported as mean and standard deviation (SD). Overall weighted means and pooled SDs were calculated.

Main Outcomes and Measures: Primary outcome was mean cortisol level and spread for controls and for patients in different illness groups.

Results: From 345 records screened, 15 studies were included. All were hospital based, 14 were prospective observational, one was part of a trial and five had controls. Mean cortisol levels were higher in all acute illness groups (n=689) than in controls (n=175) (811.10 vs 288.04, p<.001). Levels were highest in bacterial meningitis (mean 1281.26) and were over 3-fold higher than controls in severe gastroenteritis (mean 1094.00). Among the subgroups with sepsis, those with shock had lower cortisol levels than those without (mean 768.09 vs 1021.30, p=.002) but levels in survivors did not differ from non-survivors (mean 842.75 vs 686.84, p=.503).

Conclusions and Relevance: In children and young people, circulating cortisol levels are higher during acute illness compared to controls and vary across the range of illnesses. Further study is required to optimise GC stress dosing tailored to the nature and severity of the acute illness.

P1-210

Congenital Adrenal Hyperplasia due to 21-hydroxylase deficiency: the correlation of 17-hydroxyprogesterone stimulated concentrations with genotype for the identification of the molecular defect- A study of 526 cases

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Introduction: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by impairment of one of the enzymes involved in the steroidogenesis pathway. CAH due to

21-hydroxylase deficiency (21-OHD) is attributed to mutations of the *CYP21A2* gene and is distinguished into classic [salt wasting (SW), simple virilizing (SV)] and non-classic form. Herein we present a) the genetic investigation of 526 subjects with suspicion of 21-OHD in the last four years and b) the correlation of 17-hydroxyprogesterone (17-OHP) concentrations after ACTH stimulation test in heterozygotes and genotypically negative individuals.

Patients and Methods: 526 subjects (75% girls, 25% boys) with a mean age of 9 years (3 days-77 years) were referred for genetic analysis of the *CYP21A2* gene. The majority of referrals were due to premature adrenarche.

Sanger sequencing *CYP21A2* gene was carried out in all individuals (and parents when available). MLPA analysis was also performed when duplication/deletion was suspected. A total of 950 parents were analyzed.

Two different approaches were applied for the correlation of 17-OHP concentrations, i. Difference 17-OHP(60′) – 17-OHP(0′) and ii. Sum 17-OHP(30′)+17-OHP(60′) with genotype.

Results: Genetic diagnosis of CAH was achieved in 30% of cases (22% compound heterozygotes and 7.8% homozygotes). 37% of the referrals were found to be heterozygotes (16% heterozygotes for a classic and 84% for a non-classic *CYP21A2* mutation). 2.5% harbored a *CYP21A2* duplication. No mutation was identified in 31% of the cases. Genotyping of the parents identified 29/950 (3%) compound heterozygotes/homozygotes for the non-classic form of 21-OHD.

Table 1 presents the % of the cases where genotype correlates with the 17-OHP values. It should be stated that the best correlation of 17-OHP concentrations and genotype is provided by the p.P30L (94.1%) while the c.*13G>A shows a poor correlation with 17-OHP concentrations (60%) for both approaches tested.

Discussion: The two different approaches for the correlation of stimulated 17-OHP concentrations and genotype cannot successfully distinguish the heterozygotes and the genotypically negative examined individuals highlighting the importance of molecular genetic analysis in order to confirm the clinical diagnosis, patient prognosis and genetic counselling.

P1-211

Effect of maternal steroid medication prescribed during pregnancy on neonatal adrenal function

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Background: There is limited data supporting concerns that systemic corticosteroids, prescribed in pregnancy for maternal health reasons, can suppress the neonatal Hypothalamic-Pituitary-Adrenal (HPA) axis. Our study aimed to determine if neonates born to mothers on long-term or high dose steroids are at risk of adrenal suppression.

Methodology: Neonates who underwent assessment of adrenal function over a seven-year period (July 2014-June 2021) at our tertiary neonatal unit in Sheffield, UK, were identified from laboratory records. Current guidance recommends a standard-dose short synacthen test (SST) after 24 hours of age for neonates born to mothers receiving ≥7.5mg/day prednisolone for 28 consecutive days in the 3rd trimester (cohort 1). This replaced previous guidance in 2019, which advised taking three random cortisol levels 8 hours apart on day three of life (cohort 2). A normal SST was defined as a peak cortisol >430nmol/l. Data regarding maternal steroid formulation, dose and duration, along with neonatal demographic data and outcomes were obtained through retrospective case note review.

Results: Over the study period 56 babies underwent assessment of adrenal function due to maternal steroid use during pregnancy. Gestational age ranged from 28-41 weeks. Steroid data were obtained from 38 mothers. The equivalent dose of prednisolone ranged from 5mg to 40mg taken for between one month to the entire pregnancy.

Of the 18 neonates in cohort-1, three had a suboptimal response to Synacthen stimulation, with a peak cortisol between 318-348 nmol/L. All were managed with 'sick day rule' hydrocortisone rather than starting on steroid replacement. Mother-1 received 60-80mg/day IV hydrocortisone for 3 weeks, followed by 4 weeks of 15-20mg/day prednisolone, with delivery at 36+5 weeks. Mother-2 received 20mg/day prednisolone from 24 weeks gestation and

Table 1.

Correlations between genotype and stimulated 17-OHP concentrations

Genotype	Number	17-OHP(60′)-17-OHP(0′) Cut-off for heterozygotes >3.6ng/μL	17-OHP(60′)+17-OHP(30′) Cut-off for heterozygotes >10.1ng/μL
p.P30L/N	17	16 (94.1%)	16 (94.1%)
p.V281L/N	55	44 (80%)	49 (89.1%)
p.P453S/N	19	16 (84.2%)	16 (84.2%)
c.*13G>A/N	15	9 (60%)	9 (60%)
N/N	123	77 (62.6%)	46 (37.4%)

delivered at 32+4 weeks. Dose and duration of steroids was unavailable for mother-3, who delivered at 35+3 weeks. Baby-1 & -3 had a normal repeat SST after 6 weeks, baby-2 was lost to follow-up following transfer to another unit. Of the 38 neonates in cohort-2, 16 underwent a subsequent SST all of whom demonstrated a normal response.

Conclusion: Whilst the majority of babies born to mothers using corticosteroids in pregnancy have normal adrenal function, some may be at risk of transient adrenal suppression. Dose and duration may play a role. Further studies detailing normal adrenal function in neonates and the effect of maternal steroids use in pregnancy are required to inform in whom HPA-axis assessment maybe necessary, the best method of assessment and interpretation.

P1-212

Molecular analyses of a virilized newborn. Implications in clinical management

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Background-Aim: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by defects in the steroidogenic pathway of the adrenal cortex. In their most severe forms, they produce adrenal insufficiency and virilization of external genitalia when involving the terminal enzymes of the cortisol and aldosterone synthesis pathway (21-hydroxylase (21-OHD, OMIM#201910) and 11-hydroxylase (11-OHD, OMIM#202010) deficiencies). Mutations of *CYP21A2* gene (Cr6p21.33) account for 95% of cases, meanwhile mutations in *CYP11B1* (Cr8q24.3) are the second cause (3-5% of cases). It is characterized by an accumulation of 11-deoxycorticosterone (DOCA) with mineralocorticoid activity. Both genes have tandem homologous regions, *CYP21A2* (*CYP21A1P* pseudogene) and *CYP11B1* (*CYP11B2* gene), therefore specific molecular approaches are required.

We describe a newborn with CAH whose genotyping was useful in the clinical management.

Case Presentation: Newborn from a consanguineous family with extremely virilized external genitalia: thin micropenis, bilateral cryptorchidism and hyperpigmented scrotal sacs. QF-PCR and karyotype: 46XX. Biochemical parameters: Testosterone 14.60ng/mL; 17-OHP 17.31nmol/L; cortisol 3.4µg/dL; DHEA-S 5.57µg/mL; androstenedione >10ng/mL; aldosterone 982pg/mL. Treatment with hydrocortisone and fludrocortisone was started. No salt wasting was evidenced. An embryonal rhabdomyosarcoma with bone marrow and regional lymph nodes infiltration was detected at 5 months.

Molecular Analyses: Molecular analyses were performed by gene-specific PCR followed by Sanger sequencing of the overlapping fragments of *CYP21A2* and *CYP11B1*. Allele-specific oligonucleotide (ASO) hybridizations and gene doses analysis by MLPA were done to detect the recurrent alterations of *CYP21A2*. Allele segregation was established through parental DNA analyses.

Results: *CYP21A2* genotyping detected non-severe alleles: c.955C>T (p.Gln319*) in a gene duplicated allele and c.844G>T (p.Val282Leu) in compound heterozygosity. *CYP11B1* analysis was carried out and a frameshift alteration c.50_51delins (p.Ser17*) that results in stop codon was detected in homozygosity. Both parents, asymptomatic, were found to be carriers. This non-previously described alteration may be considered pathogenic as it is a null variant in a recessive disease with a loss-of-function mechanism. Mineralocorticoid was discontinued. Post-treatment values: DHEA-S 1µg/mL; cortisol 9.9µg/dL; plasma renin activity 9.6ng/mL/h; DOCA 23.0ng/dL and 11-deoxycortisol in the normal range.

Conclusions: The informativity of gene analyses along with a good genotype/phenotype relationship in CAH facilitates the diagnosis, prognosis and treatment adequacy, even in the absence of pretreatment whole biochemical data or when analytical interferences (not infrequent in direct immunoanalyses of steroids in the neonatal period) difficult the interpretation of results.

An expert evaluation of molecular findings and their proper stratification is essential when complex genetic loci, reluctant to massive approaches, are investigated.

P1-213

Alterations in glucocorticoid metabolism as a possible cause of hypertension in childhood obesity

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Introduction: Childhood obesity is associated with alterations in hypothalamus-pituitary-adrenal axis activity. We tested the hypothesis that multiple alterations in the metabolism of glucocorticoids are required for the development of hypertension in children who become overweight.

Methods: Timed spot urine for targeted gas chromatography-mass spectrometry steroid metabolome analysis was collected from (1) overweight/hypertensive children (n=38), (2) overweight/non-hypertensive children (n=83), and (3) non-overweight/non-hypertensive children (n=56). Excretion rates and enzyme activities were calculated from the measured steroid levels.

Results: The mean (±SD) age of participants was 10.4±3.4 years, and 53% of them were male. Their results are displayed in the table. Group 1 and group 2 had higher excretion rates of cortisol and corticosterone metabolites than group 3, and group 1 had

Table.

Outcome	Group			P value		
	Overweight & hypertensive (1)	Overweight & non-hypertensive (2)	Non-overweight & non-hypertensive (3)	1 vs. 2	1 vs. 3	2 vs. 3
Excretion rates (in µg/mmol creatinine · m2 body surface area)						
Cortisol	7.6 (5.3-12.2)	6.9 (4.9-9.6)	6.3 (4.5-8.2)	0.11	0.03	0.54
Sum of cortisol metabolites	869 (631-1,352)	839 (609-1,123)	608 (439-834)	0.27	0.001	0.007
Sum of corticosterone metabolites	72 (48-137)	69 (51-124)	51 (36-77)	0.99	0.008	0.002
Sum of 5α-reduced metabolites	329 (218-407)	252 (178-326)	205 (142-286)	0.04	0.009	0.27
Sum of 5β-reduced metabolites	176 (133-278)	196 (142-251)	169 (118-222)	0.89	0.17	0.14
Enzyme activities						
Global 11β-HSD activity	0.56 (0.44-0.67)	0.47 (0.42-0.59)	0.60 (0.49-0.75)	0.13	0.16	<0.001
Relative 5α-/5β-reductase activity	1.56 (1.18-2.17)	1.23 (1.02-1.56)	1.47 (1.01-1.84)	0.004	0.06	0.69
CYP3A4 activity	2.13 (1.65-2.72)	2.46 (1.95-3.13)	2.43 (1.96-3.04)	0.05	0.02	0.49
20α-HSD activity	0.57 (0.47-0.73	0.59 (0.49-0.72)	0.53 (0.47-0.61)	0.69	0.08	0.001
11β-hydroxylase activity	27.5 (21.5-37.1)	25.1 (17.5-33.2)	23.4 (15.3-31.6)	0.16	0.005	0.13
Global 17-hydroxylase/17,20-lyase activity	0.72 (0.44-1.62)	0.86 (0.34-1.86)	0.61 (0.29-2.05)	0.62	0.52	0.28
Global 17α-hydroxylase activity	0.13 (0.09-0.20)	0.14 (0.11-0.18)	0.12 (0.10-0.17)	0.14	0.83	0.05

a higher excretion rate of naive cortisol than group 3. Furthermore, groups differed in cortisol metabolism, in particular in the activities of 11β-hydroxysteroid dehydrogenases, as assessed from the ratio of cortisol:cortisone metabolites (group 2 < group 3), 5α-reductase (group 1 > group 2 or 3), and CYP3A4 activity (group 1 < group 2 or 3).

Discussion: The sequence of events leading to obesity-associated hypertension in children may involve an increase in the production of glucocorticoids, downregulation of 11β-hydroxysteroid dehydrogenase type 1 activity, and upregulation of 5α-reductase activity, along with a decrease in CYP3A4 activity and an increase in bioavailable cortisol.

P1-214

Development and validation of simultaneous quantification of urinary catecholamines and free metanephrines by UHPLC-MS/MS method

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Background: Neuroendocrine tumors from adrenal and extra-adrenal chromaffin cells are characterized by overproduction of catecholamines (CA), leading to the increase of urinary O-methylated metabolites (uO-Met) excretion, reliable biomarkers for the initial screening, diagnosis and monitoring of patients with pheochromocytoma and paragangliomas (PPGLs).

Objective: To develop and validate a UHPLC-MS/MS method for the simultaneous quantification of Epinephrine (EPI), norepinephrine (NE), dopamine (DA), metanephrine (MN), normetanephrine (NMN) and 3-methoxytyramine (3MT).

Methods: UHPLC-MS/MS system (Shimadzu Nexera 20A-AB Sciex QTRAP®6500 system). 15 minutes run; ESI+. Method performance was validated for recovery, linearity, precision and accuracy, ion suppression and carry over. Lower limit of detection (LLD): signal/noise ratio 3. Lower Limit Of Quantitation (LLOQ): lowest concentration with CV% <20% (recovery between 80 and 120%). We included 24hs urine samples from 6 patients with confirmed tumor [Group 1; 4 PPGLs and 2 neuroblastoma (NB)], and Group 2, 10 patients with clinical suspicion of neural crest cells tumors (5 with molecular diagnosis). Median age and range 20.5 (0.2 to 49) years. Results from patients were evaluated according to reference ranges from Peitzsch et al. (1).

Results: Recoveries ranged from 90 to 110%; intra- and inter-CVs% from 2 to 15%; linearity coefficient >0.9900. Analytical range, LLOD and LLOQ (Relative Standard deviation, RSD%) for each analyte are shown in the table.

Analyte (ug/L)	Analytical range	LLOD	LLOQ (RSD%)
EPI	0.75–135	0.30	0.75 (8.7)
NE	1.50–270	0.90	1.50 (8.7)
DA	20–3600	1.57	20 (9.3)
MN	25–650	1.12	25 (2.9)
NMN	31.3–812.5	7.4	31.3 (5.4)
3MT	25–650	0.64	25 (2.0)

In Group 1, NMN was elevated in all patients, NE in 4, while EPI and MN was elevated in 1/6. Of note, DA was elevated in 2/6 and 3MT in 5/6. In group 2, CA were within normal range in all patients, however, we observed that uO-Met were elevated in the 4 patients with confirmed molecular diagnosis.

Conclusions: We developed and validated an UHPLC-MS/MS method for the accurate simultaneous measurement of urine

endogenous CA as well as their respective free uO-Met metabolites. The preliminary results suggest that our method enables the confirmation of the tumor presence in patients with PPGLs and NB. It would be interesting to explore the usefulness of free uO-Met measurement by our method in a larger cohort of patients with clinical suspicion of neuroendocrine pathologies.

Reference

(1) Peitzsch et al. doi: 10.1016/j.cca.2012.12.03.

P1-215

Salt-Wasting CAH phenotype as a result of the *TNXA/TNXB* Chimera 1 (CAH-X CH-1) and the severe *IVS2-13A/C>G* in *CYP21A2* gene

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Background: Genetic diversity of mutations in the *CYP21A2* gene is the main cause of the monogenic Congenital adrenal hyperplasia (CAH) disorder. On chromosome 6p23.1, the CYP21A2 gene is partially overlapped by the *TNXB* gene and reside in tandem with their highly homologous corresponding pseudogenes (CYP21A1P and TNXA), which leads to recurrent homologous recombination.

Methods and Results: The genetic status of a family of Cypriot origin is presented. The index case concerns the female (46, XX) neonate originally assigned as male as she presented with severe (Prader 5) virilization and subsequently diagnosed with the salt-wasting (SW) form of CAH based on biochemical and hormonal findings. Genetic defects in the *CYP21A2* and *TNXB* genes were investigated by Sanger, multiplex ligation-dependent probe amplification (MLPA) and a real-time PCR assay. The neonate carried in compound heterozygosity the *TNXA/TNXB* chimeric gene complex (termed CAH-X CH-1) that results in a contiguous *CYP21A2* and *TNXB* deletion and in her second allele the severe IVS2-13A/C>G in *CYP21A2*.

Conclusions: The classic SW-CAH due to 21-hydroxylase deficiency may result from various complex etiological mechanisms and such can involve the formation of monoallelic *TNXA/TNXB* chimeras found in trans with other *CYP21A2* pathogenic variants. By identifying the correct CAH genotypes for a given phenotype, should be able to assist clinicians in prenatal diagnosis, appropriate treatment and genetic counseling.

P1-216

Salivary Cortisol in Children with Congenital Adrenal Hyperplasia and Different Treatment Regimens

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Background: Children with classical congenital adrenal hyperplasia (CAH) require glucocorticoid replacement. The measurement of cortisol and steroid precursors in saliva is particularly suitable for pediatric endocrinology. Data on salivary cortisol measurements in patients with CAH is limited.

Objective and Hypothesis: The cortisol in saliva shows a circadian rhythm even under steroid substitution. This is independent of the treatment regimen.

Method: In this retrospective analysis of 22 patients with salt-wasting CAH, we aimed to investigate the kinetics of cortisol in saliva in relation to the treatment regimen. Saliva samples were obtained in the morning, at noon and in the evening, always before intake of hydrocortisone and fludrocortisone.

Results: We analyzed 153 daily profiles (459 samples) of salivary cortisol from 22 patients. The following values were found in the total group (median and 25th/75th percentiles): morning 3.9 ng/ml (1.35 – 21.6), noon 1.7 ng/ml (0.7 – 5.35) and evening 1.15 ng/ml (0.6 – 2.6). The reverse-circadian treated children showed the following values: morning 3.3 ng/ml (1.15 – 14.5), noon 1.4 ng/ml (0.65 – 5.05) and evening 0.9 ng/ml (0.53 – 2.05). Non-reverse-circadian treated children: morning 5.1 ng/ml (1.43 – 30.0), noon 1.8 ng/ml (0.9 – 5.38) and evening 1.45 ng/ml (0.6 – 4.08). Our study shows a difference between cortisol in the morning compared to noon/evening. The values show similar levels at noon and evening. However, the values in the morning are higher. These findings are independent of the therapy regimen (total group, reverse circadian or non-reverse-circadian treatment). In reverse circadian treated children, the morning values are (statistically non-significantly) lower compared to other regimens.

Conclusion: Cortisol follows a circadian rhythm even under different therapy regimens. With a half-life of hydrocortisone of a few hours, the higher concentrations of cortisol in the morning cannot be explained sufficiently by pharmacokinetics. Assuming that the pharmacokinetics are the same during the day and at night, the cortisol level should be the lowest in the morning. One possible cause could be a different metabolisation of hydrocortisone at different times of the day. The role of corticosteroid binding globulin (CBG) in this context remains unclear. CBG could be subject to circadian rhythmicity and circadian binding capacity. The physiological ACTH peak, which is also present in patients with CAH, causes increased hepatic clerence of cortisol. Patients with CAH regularly have elevated ACTH levels. This could be also a partial explanation for the reduced cortisol clearance during the night.

P1-217

Precocious pubarche in girls - A clinical sign for underlying hyperandrogenic disease

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Background: Precocious pubarche (PP), defined as the development of pubic hair before 8 years of age in females could be the first sign of a hyperandrogenic condition.

Aim: The purpose of the study was to analyze the etiology of premature androgenization of girls with a history for PP and to evaluate their clinical, laboratory and ovarian ultrasound profile.

Material and Methods: A total of thirty-nine girls with a history of PP were enrolled in this 5-year retrospective study at a tertiary medical center. The mean age of all included participants was 14.2±3.0 years (7-20 years). Data was collected on anthropometry, clinical features of hyperandrogenism and menstrual irregularities. Hormonal and metabolic markers were assessed and HOMA-IR was calculated. Ovarian ultrasound was performed. The overweight/obesity prevalence was defined according to IOTF age- and gender-specific BMI cut-offs.

Results: The historical data of PP was associated with a subsequent diagnosis of non-classic congenital adrenal hyperplasia (NCCAH) in 51.3% of the girls (n=20, mean age 13.8±3.6 years), polycystic ovary syndrome (PCOS) in 20.5% of the participants (n=8, mean age 14.9±2.1 years) and idiopathic PP in 28.2 % (n=11, mean age 14.5±2.4 years). NCCAH girls were significantly shorter (152.5±13.1 cm) compared to the PCOS (161.4±2.3 cm, p=0.038) and idiopathic PP girls (160.7±4.0 cm, p=0.033), respectively. Clinical symptoms of hyperandrogenism were present more often in NCCAH patients compared to the other two groups but only the presence of hirsutism reached a significantly higher rate (95.0%NCCAH vs. 75%PCOS vs. 45.5%idiopathic PP, p=0.005). Menstrual irregularities were found in 91.8% of girls with idiopathic PP compared to 35% of NCCAH (p=0.022) and 37.5% of PCOS patients (p=0.05), respectively. The overall prevalence of overweight/obesity was 20.5% and mean body weight and BMI did not differ between groups. No significant between-groups differences were found in the parameters of lipid and glucose metabolism. Testosterone and androstenedione levels were similar for all participants. Basal 17OHProgesterone levels were significantly higher in NCCAH females compared to the idiopathic PP girls (2.01±0.85 vs. 1.11±0.83 ng/ml, p=0.009) and correlated with the development of hirsutism (r=0.445, p=0.014). Polycystic ovaries were demonstrated in 15.4% of all participants, with a significantly higher rate in PCOS girls (50%) in comparison to NCCAH (5%, p=0.007) and idiopathic PP patients (9.1%, p=0.032).

Conclusion: PP in girls could be a warning sign of a pathologic hyperandrogenic condition and should be evaluated by endocrinologists.

P1-401

Increased basal levels of 17- Hydroxyprogesterone in the COVID era: Must we change the cut-off point to request acth test?

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Background: 17-hydroxyprogesterone (17-OHP) basal levels greater than 2ng/ml has been related to the need to request an ACTH test to dismiss non-classic congenital adrenal hyperplasia. We have seen an increase in baseline levels in 2021 compared to 2020.

Objectives: To determine how many of the tests that were requested due to a high basal 17-OHP value, were positive. Assess the need to modify the cut-off points to request an ACTH test. To determine the possible relationship of the increase in basal levels of 17-OHP with the BMI SDS.

Material and Methods: retrospective descriptive study of all patients who underwent an ACTH test between January 1, 2020 and December 31, 2021, in a region of northern Spain. We analyze: sex, age, Tanner stage, BMI SDS, baseline 17-OHP and ACTH test results and main reason for requesting. The test was considered: diagnostic with a peak of 17-OHP at 60 minutes higher than 15 ng/ml, and suggestive if 10-15ng/ml. Laboratory method for the determination of 17-OHP: chemiluminescence immunoassay in Maglumi 2000 Analyzer (Snibe-Diagnostic). The trial meets the quality criteria certified by EQAS QCNet (BioRad-Laboratories, Inc, UK).

Results: 149 ACTH tests were performed, 45 in 2020 and 104 in 2021. 116 women (77.9%). Mean age: 10.1 years (range 2.2-15.9 years). 114 had already started puberty. 21 BMI>2SDS. Main reason for requesting the ACTH test: elevated baseline 17-OHP 38%(20% in 2020, 45% in 2021), accelerated bone age (>2 years)48%, pubarche 9%. Mean baseline 17-OHP was 2.93ng/ml(±3.6ng/ml), median 1.26ng/ml(range 0.1-26ng/ml) in 2020 and 2.67ng/ml(range 0.56-16.2ng/ml) in 2021, difference not statistically significant (p 0.67), but clinically relevant. ACTH test results: mean peak at 60 minutes was 4.98ng/ml(range 0.1-64). The determination of baseline 17-OHP was above 2ng/ml in 61 patients, and above 4ng/ml in 24. But only in 7 cases the test was positive (diagnostic or suggestive), all them with basal 17OHP>4ng/ml. This cut-off point shows a higher specificity with the same sensitivity. Comparing 2020 with 2021, we found no difference in BMI SDS (p 0.27). Relationship between BMI SDS and basal 17OHP was not confirmed (p 0.81).

Conclusions: Our study confirms a significant increase in the number of ACTH tests performed, as well as in the basal level of 17-OHP in the last year. A baseline value of 17-OHP greater than 4ng/dl seems to be the most appropriate as the main indicator of the need to perform the test.

P1-402

Glucose regulation and cardiovascular health in children and young people with primary adrenal insufficiency

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Background: Hypoglycaemia and poor cardiovascular outcomes are described in children and young people (CYP) with primary adrenal insufficiency (PAI). In this study, we described cortisol exposure during hydrocortisone replacement therapy, glucose regulation by continuous glucose monitoring (CGM) and cardiovascular function. Here, we present the final study data.

Methods: CYP with PAI underwent CGM for 7 days using Dexcom G6. Vascular health was assessed from measurements of carotid intima media thickness (CIMT) and flow mediated dilatation (FMD). Office blood pressure (BP) and where possible, ambulatory blood pressure monitoring (ABPM) were performed. HOMA-IR was determined from fasting insulin and glucose concentrations. Data were analysed by the independent t-test and Mann Whitney U tests.

Results: 26 (15M) CYP with PAI (Addison's disease n=4, congenital adrenal hyperplasia (CAH) n =21, and PAI of unknown aetiology n =1;) aged 9.4±5.1 years were recruited. Hydrocortisone doses were 11.0±4.4mg/m2/day, height SDS -0.04±1.21 and BMI SDS 0.89±1.36. Mean glucose levels were higher in the PAI group than in reference data from a healthy paediatric population (6.01±0.55mmol/L vs 5.47mmol/L±0.36, p<0.001).1 Coefficient variability did not differ between PAI and reference data (p = 0.409), however, the percentage of time >8.8mmol/L and 7.7mmol/L was significantly higher (p<0.001).

In 7/25 (28%) CYP systolic BP was >95th centile, and diastolic BP >95th centile in 4/25 (16%). ABPM was tolerated in only nine participants: 1/9 had a systolic BP >90th centile and 3/9 showed loss of nocturnal dipping of BP, a known risk factor of cardiovascular disease. CIMT measurements were obtained in 20 participants and was ≥95th centile in 5 (25%). FMD was measured in 18 participants and was low in 6 (33%). HOMA-IR was raised in 4/14 (28.6%) in whom it was measured.

Conclusion: Cardiovascular studies, such as ABPM and vascular ultrasound scanning can be poorly tolerated in CYP leading to challenges in obtaining full datasets. Poor cardiovascular outcomes have been reported in adults with childhood onset PAI. Our data suggest that cardiovascular morbidity may have its onset in childhood, through disrupted glucose metabolism, vascular dysfunction, raised blood pressure and insulin resistance. If these findings are confirmed in larger studies, it might be that early intervention in childhood, to modify these risk factors, may improve long term outcomes.

Reference

1 Shah, V.N., et al., Continuous Glucose Monitoring Profiles in Healthy Nondiabetic Participants: A Multicenter Prospective Study. J Clin Endocrinol Metab, 2019. 104(10): p. 4356–4364.

P1-403

Outcomes of treatment in pediatric Cushing`s disease

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Objective: The first line of treatment for Cushing`s disease (CD) is transsphenoidal surgery (TSS), whose effectiveness range is from 70 to 90%. If surgical treatment is unsuccessful or recurrence appears, radiation treatment (RT) is the next therapeutic option, which effectiveness range is also 90%, but the hypopituitarism rate as side effect of treatment is higher.

Aim: Analysis of recurrence rates of CD and side effects after successful treatment according to therapeutic option.

Design: We conducted a retrospective analysis of 90 pediatric patients with CD who underwent treatment between 1992 and 2020.

Methods: Patients were divided into 2 groups according to therapeutic option: 1 group - underwent TSS only [n=55], 2 group – underwent RT on one of the steps of treatment [n=35]. Patients who underwent TSS as 1st line of treatment and were tested in the early postoperative period [n=61] were also divided on 2 groups according to developed adrenal insufficiency: 1 group – patients who developed adrenal insufficiency [n=38], and 2 group - patients without [n=23].

Results: Recurrence rate after successful treatment was 11% [10/90]. In the group after TSS recurrence rate was 14% [8/55], in the group after RT – 6% [2/35]. Time to recurrence was statistically different after TSS compared to radiosurgery (mean time to recurrence after TSS was 3,3 years, after RT – 6 years; P=0.007, Kaplan–Meier analysis).

In the group with developed adrenal insufficiency in the early postoperative period recurrence rate was 13% [5/38], in the group without – 14% [4/23]. Time to recurrence was statistically shorter in the group with developed adrenal insufficiency (mean time to recurrence in the 1st group was 2,65 years, after RT – 3,56 years; P=0.04, Kaplan–Meier analysis).

The frequency of growth hormone deficiency after TSS was 49% [27/55] and after RT was 91% [32/35]; hypothyroidism was diagnosed in 45% after TSS [25/55] and in 60% [21/35] after RT; gonadotrophin deficiency - in 27% after TSS [13/55] and in 48% [17/35] after RT. Diabetes insipidus was diagnosed only after TSS. Analysis of side effect of treatment showed that the frequency of growth hormone and gonadotrophin deficiency was statistically higher after radiosurgery (p<0,01, Kruskel—Wallis ANOVA test).

Conclusions: Therapeutic option has an impact on time to recurrence, not on recurrence rates. Adrenal insufficiency in the early postoperative period couldn`t be used as a predictor of long-term remission. The frequency of growth hormone and gonadotrophin deficiency was statistically higher after radiosurgery compared to TSS.

P1-404

Steroid metabotyping in treated infants with classical congenital adrenal hyperplasia by chromatography-mass spectrometry analysis

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Objective: Cluster analysis of urinary steroid metabolome analysis obtained by gas chromatography-mass spectrometry (GC-MS) for treatment monitoring of infants with classic salt-wasting CAH.

Methods: We evaluated metabolome analysis of spot urine samples of 60 young children ≤4 years of age (29 females) with classic CAH due to 21-hydroxylase deficiency treated with hydrocortisone and fludrocortisone. Subjects were divided into groups (metabotypes) by hierarchical clustering using the Euclidean distance and Ward's linkage algorithm.

Results: Three unique metabotypes were generated. Metabotype #1 (N=15 (25%)) showed high urinary androgen and 17OHP concentrations, metabotype #2 (N=28 (47%)) revealed adequate metabolic control, and metabotype #3 (N=17; 28%) demonstrated suppressed adrrenals. The metaboltypes did not differ in age, sex, weight and height.

The daily hydrocortisone doses and urinary concentrations of cortisol and cortisone metabolites did not differ between all metabotypes. Metabotype #2 had highest daily dose of fludrocortisone (75±44 µg vs. 50±25 µg and 50±23 µg in metaboltypes #1 and #3, respectively; p=0.016).

Receiver operating characteristic curve analysis showed that pregnanetriolone (11-O-PT, area under the curve (AUC) 0.967, cut-off 308 µg/L), pregnanetriol (PT, AUC 0.936, cut-off 731 µg/L) and the ratio PTO/ tetrahydrocortisone (THE) (AUC 0.899, cut-off 0.175) were most suitable of separating metabotype #1 from #2.

For metabotypes #2 vs. #3, the 11-oxygenated androgen metabolite 11-hydroxyandrosterone (11-OH-AN, AUC 0.983, cut-off 24.2 µg/L), the ratio 11-OH-AN/ THE (AUC 0.97, cut-off 0.015) and PT (AUC 0.956, cut-off 194 µg/L) were most suitable.

Conclusion: Metabotyping helps to monitor treatment of infants with CAH. This method allows classification in under-, over-, and adequate-treated young children.

P1-405

Body composition in children and adolescents with non-classic congenital adrenal hyperplasia and risk for metabolic syndrome components – an observational study

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Context: Non-classic congenital adrenal hyperplasia (NCCAH) diagnosed in childhood, whether treated or untreated, could pose an increased risk of obesity and metabolic derangements in adolescence and early adulthood. Both sustained hyperandrogenism and chronic glucocorticoid therapy may affect body composition. However, little is known about the body composition of subjects with NCCAH and its contribution to the development of adverse metabolic outcomes.

Aim: To explore the interaction between muscle-to-fat ratio (MFR) and metabolic syndrome components in pediatric subjects with NCCAH.

Methods: This retrospective, observational study was conducted in a tertiary center. The study group comprised 75 subjects with NCCAH (26 males [61 hydrocortisone-treated and 14 untreated]) and 50 subjects with premature adrenarche (PA, 8 males). The control group comprised 134 healthy sex- and age-matched subjects (41 males) with normal puberty landmarks. Body composition was measured by bioelectrical impedance analysis (BIA, Tanita MC-780 MA and GMON Professional Software), and MFR z-scores were calculated. Stepwise linear regression models were applied to evaluate explanatory variables for MFR z-scores, blood pressure percentiles, lipid profiles and glucose metabolism. Variables entered into the models included: sex, socioeconomic position (SEP) index, family history of obesity, age (at diagnosis and BIA), perinatal characteristics (gestational age, birthweight z-scores), hydrocortisone exposure (mean dose, treatment duration, cumulative dose) and MFR z-scores (for metabolic syndrome components).

Results: The median age [interquartile range] was 7.5 years [5.3, 8.8] at NCCAH diagnosis, and 12.3 years [8.9, 15.4] at BIA. The median cumulative hydrocortisone dose was 7620 mg/m^2 [2547, 12903]. Subjects with NCCAH had higher mean BMI z-scores compared to controls (0.47±0.97 vs. -0.19±1.04, P<0.001) and lower median MFR z-scores (-0.74 [-1.06, -0.14] vs. -0.37 [-0.99, 0.15], P=0.045), with no significant differences between NCCAH and PA groups. Linear regression models and their explanatory variables: MFR z-score (r^2=0.253, P<0.001) - SEP index (B=0.348, P=0.003), birthweight z-score (B=-0.258, P=0.013) and duration of hydrocortisone treatment in years (B=0.048, P=0.023); systolic BP percentile (r^2=0.166, P<0.001) - MFR z-score (B=-9.75, P<0.001); TG/HDL ratio (r^2=0.116, P=0.024) - MFR z-score (B=-0.300, P=0.024); no significant variables were found for glucose.

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Conclusions: Our findings suggest that youth with NCCAH have a body composition characterized by an imbalance between muscle and fat tissue, placing them at increased risk for early-onset cardiometabolic derangements. It is reassuring that glucocorticoid therapy in pediatric patients with NCCAH aimed to alleviate androgen overproduction does not appear to adversely affect body composition.

P1-406

Salt-wasting in newborns due to adrenal dysfunctions other than 21 OH Congenital adrenal hyperplasia (CAH): a single center experience

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Introduction: salt wasting is a potentially life-threatening condition in the newborn period. Other than 21 OH-CAH other rarer adrenal causes should be considered in the differential diagnosis

Objective: to report the laboratory, clinical features, management and genotype of a series of consecutive patients who showed up at our Center for a salt wasting syndrome in the last 32 years, excluding patients with 21 OH CAH.

Patients and Methods: we retrospectively collected data of 20 children managed in our hospital from 1989 to 2021.

Results: Overall, the mean age at presentation was 19,9 ± 16,2 days of life (1-56 days). Symptoms at presentation were poor growth (80%), vomiting (50%), feeding difficulties (35%), hypotonus (30%), dehydration (30%). At the onset severe hyponatremia (sodium <130 mmol/L) was present in all cases and hyperkalemia (> 7 mmol/L) in 50% of patients. The molecular analysis confirmed the suspected diagnoses in all cases. 35% of children resulted affected by pseudohypoaldosteronism type 1 r (PHA1r), 35% by aldosterone synthase deficiency (ASD), 20% by pseudohypoaldosteronism type 1 r (PHA1s) and 10% by X-linked adrenal hypoplasia congenita (AHC). Although natremia was not significantly different in patients grouped by diagnosis, a significant difference in potassium levels between PHA1s patients (10.6±0.7mmol/l) versus the others (6.8±0.8 mmol/L) ($p < 0.001$) was found. Moreover in PHA1s patients the time onset of symptoms was significantly earlier (5.5 ±2.6 days of life) than the others (23 ± 16 days of life) ($p<0,001$). According to the pathophysiology of the diseases, all patients with ASD and AHC had high plasma renin levels and low aldosterone levels; conversely, patients with PHA1r and PHA1s showed elevated levels of both. One case was initially suspected for ASD but finally was diagnosed by AHC at 21 months of life when he developed glucocorticoid deficiency.

Conclusions: we found a relative higher incidence of ASD and PHA1r compared to the results of a recent Italian study (Bizzarri C et al. Ital J Pediatr. 2016); PHA1s patients showed an earlier and more severe onset of symptoms associated with life threatening hyperkalemia. In our experience, in patients with hyponatremia, with or without severe hyperkalemia, the adrenal function evaluation should be part of the diagnostic work up even in patient who were already screened for 21 OH-CAH at birth. Early molecular analysis confirmation by a Next Generation Sequencing targeted gene panel could be helpful especially in cases with clinical and laboratory features overlap (AHC, ASD).

P1-407

Agreement between Acth-low test and Insuline Tolerance Test in Patients with Risk Factors for Central Adrenal Insufficiency

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Background: Central adrenal insufficiency (CAI) is a potential life-threatening condition and a prompt diagnosis represents a clinical challenge; indeed, the Insulin Tolerance Test (ITT), gold standard for CAI diagnosis, can be contraindicated in some conditions. Aims were to evaluate the diagnostic value of the ACTH low test (ACTH-LT) compared to the ITT and to identify eventual determinants (primary diagnosis, risk factors, symptoms, baseline cortisol, hypothalamic-pituitary defects) as predictors of a pathological cortisol peak.

Methods: 64 patients (n=41males, n=23females) underwent ITT and ACTH-LT between 2010 and 2021 (mean distance 18months) for suspected CAI. According to primary diagnosis, patients were categorized as: tumoral (n=29), multiple-pituitary defects (n=16), idiopathic GHD (n=12), others (n=7). Exclusion criteria were distance between the tests>8years, being on GC therapy, insulin resistance, failure to halve glycemia after ITT. Risk factors considered were brain surgery, brain radiotherapy and prolonged glucorticoids-GC administration. Potential CAI symptoms were defined as asthenia, recurrent headache and/or fatigue. Baseline characteristics are summarized in Table 1.

Results: Thirty-nine patients had pathological cortisol peak values at the ITT(<18μg/dL);ACTH-LT was pathological in 18/39(<16μg/dL), borderline in 14/39(16-22μg/dL) and normal in 7/39. Agreement between ACTH-LT and ITT was 0.83(Cohen's K 0.51,95% CI:0.26-0.75), with a sensitivity of 88%(44/50), a specificity of 64%(9/14), a positive predictive value of 0.89(44/49) and a negative predictive value of 0.60(9/15). Peak cortisol levels to ACTH-LT were lower in patients with symptoms compared to subjects without them [15.2(IQR 11.3-18.3μg/dL) vs 17.7(IQR 14.5-19.8μg/dL),p=0,017]. No significant differences were found between ITT and ACTH-LT cortisol peak values in pubertal/prepubertal children, subjects with or without risk factors and different primary diagnosis.

Conclusion: Preliminary results demonstrate that the ACTH-LT is suitable for screening purposes, but not for final confirmation of CAI in our cohort. Further studies are needed to better define which factors influence the ACTH-LT response and its diagnostic value for clinicians.

Characteristics	n.(%)	Median[1st–3rd quartile]
Pre-pubertal at ITT	13(20.3%)	
Post-pubertal at ITT	51(79.7%)	
Age at ACTH-LT(years)		13.9[12.8-16.6]
BMI-SDS at ACTH-LT		1.0[0.3–2.0]
Baseline cortisol(μg/dL)		9.9[8.0–13.0]
Cortisol peak(μg/dL)		18.2[15.2-21.3]
Cortisol peak yes-symptoms(μg/dL)		15.6[13.4-19.1]
Cortisol peak no-symptoms(μg/dL)		18.6[15.8-22.1]
Age at ITT (years)		14.6[12.2-16.9]
BMI-SDS at ITT		0.9[0.2–2.0]
Baseline cortisol(μg/dL)		9.3[6.9-13.5]
Cortisol peak(μg/dL)		16.9[13.8-19.4]
Risk Factors	45(70.3%)	
Symptoms	17(26.6%)	

P1-408

Diverse clinical features, genetic etiologies, and histopathological features of adrenal neoplasms in children and adolescents

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Purpose: Adrenal neoplasms (ANs) are rare endocrine neoplasms in children, and etiopathogenesis and prognosis of pediatric ANs remain obscure. This study investigated clinical features, histopathological features, genetic etiologies and prognosis of ANs.

Methods: This study included 33 ANs patients diagnosed from March 1997 to April 2021. Clinical features and endocrine findings were collected by retrospective medical chart review. The histopathological features were assessed using the Weiss scoring system. Molecular analysis was performed by Sanger sequencing according to the patients' phenotype.

Results: Among 33 patients, adrenocortical carcinoma (N = 9, 27.3%) and pheochromocytoma (N = 9, 27.3%) were the most common, followed by adrenal adenoma (N = 5, 15.2%) and ganglioneuroma (N = 3, 9.1%). The median age at diagnosis was 7.8 years (range, 0.8–17.8 years). There was no metastasis at diagnosis, however, ANs recurred in 6 patients. All patients survived during the follow-up period. The most common presenting symptom was precocious adrenarche (N = 13, 39.4%), followed by hypertension (N = 11, 33.3%) in all patients with pheochromocytoma, adrenal incidentaloma (N = 6, 18.2%), and Cushing syndrome (N = 4, 12.1%). Molecular etiologies were identified in 12 patients: Li-Fraumeni syndrome (N = 5), 21-hydroxylase deficiency (N = 3), and von Hippel-Lindau syndrome (N = 4). The mean Weiss score was 1.5 ± 1.6. Weiss scores was not significantly different between adrenocortical carcinoma and pheochromocytoma (2.6 ± 1.9 vs. 1.1 ± 1.2, P = 0.094), however, the score of ganglioneuroma was higher than that of phenochromocytoma (3.5 ± 0.7 vs. 1.1 ± 1.2, P = 0.036). Weiss score of Li-Fraumeni syndrome was significantly higher than the other ANs (3.2 ± 1.6 vs. 1.1 ± 1.4, P = 0.013). The maximum diameter of tumor was 5.3 ± 1.9 cm, which showed no significant correlation with the Weiss score (r = 0.141, P = 0.464).

Conclusions: In this study, adrenal carcinoma and pheochromocytoma were most frequent in children and adolescents with ANs. In patients with genetic etiologies, tumor screening and for other organs and genetic counseling are necessary.

P1-409

Clinical, laboratory and body composition profile of young female patients with non-classic congenital adrenal hyperplasia

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Background: Non-classic congenital adrenal hyperplasia (NCCAH) is a genetic disorder characterized by hyperandrogenism associated with potential metabolic alterations and changes in body composition and bone mineral parameters.

Aim: The purpose of this pilot study was to evaluate the clinical and biochemical characteristics in association with bone mineral parameters and body composition in female patients diagnosed with NCCAH in comparison to female age-matched healthy controls.

Material and Methods: A total of forty-five females, aged 10-27 years, were enrolled in this study at a tertiary medical center, including twenty-seven patients with NCCAH (mean age 16.6±3.5 years) and eighteen healthy controls (mean age 15.2±2.1 years). Data was collected on anthropometry, clinical features of hyperandrogenism (hirsutism, acne, alopecia) and menstrual irregularities, and ovarian ultrasound was performed. Hormonal and metabolic markers were assessed and HOMA-IR was calculated. The overweight/obesity prevalence was defined according to IOTF age- and gender-specific BMI cut-offs. Dual-energy X-ray absorptiometry (DXA) was used to determine bone mineral density (BMD), bone mineral content (BMC), fat and lean mass, and fat distribution.

Results: The clinical symptoms of hyperandrogenism were significantly more common in NCCAH girls. Hirsutism was present in 96.3% of the NCCAH females and 50.0% of the controls, p<0.0001, while acne and alopecia were defined in 92.6% and 66.7% of the NCCAH patients, respectively, compared to 44.4% and 22.2% of the healthy females (pacne<0.0001 and palopecia=0.003). No significant difference was found in the rate of

menstrual disorders between groups. The overall prevalence of overweight/obesity was 22.2% and mean body weight, BMI and waist circumference did not differ between NCCAH females and healthy controls. No significant difference was found in the parameters of lipid and glucose metabolism between the groups, but BMI correlated with triglycerides (r=0.384, p=0.009). Testosterone, androstenedione and basal levels of 17OHProgesterone were significantly higher in NCCAH females (p<0.05 for all). Polycystic ovaries were detected by ultrasound in 4.4% of all participants, without significant difference between groups. No differences in bone mineral parameters, body composition and fat distribution were found either. However, %fat mass was associated with insulin concentration (r=0.303, p=0.05) and the presence of hirsutism (r=0.305, p=0.049).

Conclusion: NCCAH in young females is characterized by clinical and biochemical hyperandrogenism associated with insignificant changes in BMD and body composition.

P1-410

Neonatal Screening for Congenital Adrenal Hyperplasia in Saudi Arabia: A Retrospective, Descriptive study

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Background and Aims: A congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders in which enzymes in the cortisol biosynthesis pathways are interrupted by gene mutations. More than 90% of CAH, is caused by 21-hydroxylase (21OHD) deficiency. The 17α-hydroxylase (17OHD) deficiency one of the less common forms of CAH, can result in significant morbidity and mortality if left untreated, thus making early diagnosis essential. In Saudi Arabia, research related to CAH is limited. Hence, this study aimed to examine the incidence and the associated clinical characteristics of neonatal CAH at Prince Sultan Military Medical City, Saudi Arabia, and provide evidence-based guidance for its application in CAH screening.

Methods: This retrospective, descriptive study, was conducted in April 2022 at Pediatric Endocrinology Department, Prince Sultan Military Medical City, Riyadh, Saudi Arabia. We reviewed the screening database in search of babies with suspected CAH, that is, altered birth- weight adjusted 17-hydroxyprogesterone (17-OHP) values at screening.

Results: A total of 54,940 newborns were screened from January 2019 to April 2022; among them, 169 CAH cases were detected, yielding an incidence of 1:325. Compared to females (38.1%), a higher percentage of males (67.7%) were diagnosed with CAH. The mean 17-OHP of the study population was 89 ± 32.4, gestation period 31.8 ± 12.5, and bodyweight of 1762 ± 367 g. Female infants have a lower mean 17-OHP value (75 ± 23.1) than males (93 ± 26.2). No significant changes were found in the bodyweight of male infants (1767g) and female infants (1759 g). Compared to other regions of Saudi Arabia, a higher percentage of (65.7%) of the CAH-positive case diagnosed in the Riyadh region.

Conclusion: The present findings highlighted the need for CAH screening by the public health care system in Saudi Arabia. Further, focused and evidence-based interventions, extensive collaborative studies, or meta-analyses are essential to determine the life-saving benefits of screening.

Keywords: Neonatal screening, congenital adrenal hyperplasia, incidence, Saudi Arabia

P1-411

Prevalence and Incidence of Congenital Adrenal Hyperplasia in Denmark – a nationwide cohort study

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Aim: Increased clinical attention toward less severe cases of congenital adrenal hyperplasia (CAH) may affect both incidence and prevalence. In this nationwide population-based cohort study, we estimate incidence, prevalence, and age at diagnosis of CAH according to subtype and sex.

Patients and Methods: Individuals registered with a diagnosis of CAH during 1977 to 2018 were identified in the Danish National Patient Registry, by genetic data and via the National neonatal screening program (n=3368). If registered at an endocrine, pediatric or gynecological department, medical records were reviewed to validate the CAH diagnosis (n=1876).

Results: Combined, 462 individuals (females: n=290) had CAH with the following distribution of subtypes: salt-wasting (SW): n=222 (103 males), simple virilizing (SV): n=59 (21 males), non-classic (NC): n=142 (34 males), other subtypes: n=24, and unknown subtype: n=15.

The average incidence of CAH was 1.9 per 1,000,000 females and 1.2 per 1,000,000 males.

Among newborns, the maximum average prevalence of females and males diagnosed with CAH was observed during 1967-2011 and 1967-2016, respectively, being 15 per 100,000 females and 9 per 100,000 males. During the same period, and stratified according to subtype, SW CAH occurred with a prevalence of 6.3 and 5.5 per 100,000 newborn females and males, respectively. SV CAH occurred with a prevalence of 2.0 and 1.1 per 100,000 newborn females and males respectively and NC CAH occurred with a

prevalence of 5.6 and 1.8 per 100,000 newborn females and males, respectively. Females and males with SW-CAH were diagnosed at a median age of 6 days, IQR [1-10] and 10 days, IQR [8-20], respectively and with a significant decrease of three days among males ($p<0.0001$), after introduction of the neonatal CAH screening program.

The median age at diagnosis of SV CAH was 5.4 years, IQR[2.5-9] and 5.14 years, IQR[4.4-6.9] in females and males, respectively ($p = 0.73$) and for NC CAH 15.6 years, IQR[8.0-22.6] and 9.5 years, IQR[7.2-23.2] in females and males, respectively ($p = 0.26$).

Conclusion: We identified the entire Danish cohort of individuals with CAH and estimated a total maximum average prevalence of 15 CAH females per 100,000 newborn females, which is higher than in previous studies, and 9 CAH males per 100,000 newborn males. Males with SV-CAH and NC-CAH suffer significantly from non-diagnosis compared to females. Individuals with NC-CAH are diagnosed late.

P1-412

A single centre experience of aromatase inhibitors to limit bone age advancement in pre-pubertal boys with adrenal disorders causing androgen excess

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Introduction: Anastrozole, an aromatase inhibitor, prevents the conversion of androgen to oestrogen, which is required for the adolescent growth spurt and the attainment of peak bone mass. Anastrozole may help minimise bone age (BA) advancement in conditions associated with adrenal androgen excess, such as congenital adrenal hyperplasia (CAH) and premature adrenarche.

Objectives:

1. To describe baseline characteristics and BA parameters of patients with CAH and premature adrenarche treated with anastrozole.
2. To describe the safety profile of anastrozole.

Methods: Retrospective data collection of patients with CAH and premature adrenarche (with BA advancement >2 years) treated with anastrozole. BA was calculated using the Tanner Whitehouse method and/or by Bonexpert Software.

Results: Eleven male patients with classical or non-classical CAH secondary to 21-hydroxylase deficiency received 1mg anastrozole once daily, in addition to hydrocortisone (mean dose 13.66 mg/m2/day), with or without fludrocortisone. All patients were pre-pubertal at treatment initiation; six have since entered puberty, with three requiring GnRH analogue treatment. Anastrozole was started at a mean age of 7.96 years. The mean BA advancement at the start of treatment was 4.37 years. Three patients have recently commenced treatment, so no follow-up data are available. One patient has stopped treatment, with a final height at his mid-parental height. Seven patients remain on anastrozole, with a mean treatment length of 3.55 years. The average change in BA per year was 0.16 years. Liver function was normal in all eight patients who underwent testing. Total cholesterol concentrations were normal in nine patients who were tested. Triglyceride concentrations were elevated in two. Nine patients are known to have a normal bone mass following DEXA scans.

Three male patients with premature adrenarche received anastrozole at a mean age of 9.03 years, with a mean BA advancement of 2.82 years. The average change in their BA per year was 0.49 years. All three patients had a normal bone mass, normal total cholesterol concentrations, but with raised triglyceride concentrations.

Discussion: Children with CAH may display a very advanced BA, whilst receiving appropriate doses of hydrocortisone. Some children with premature adrenarche have an advanced BA, in the absence of underlying pathology. Anastrozole treatment in childhood appears to be particularly effective at minimising further BA advancement in CAH. If stopped before the adolescent growth spurt, it may facilitate achievement of target height. It has few side-effects, with no changes in liver function, total cholesterol or bone density reported in these patients.

P1-413

Incidence and severity of Coronavirus Disease 2019 (COVID-19) in children with primary and secondary adrenal insufficiency during the pandemic in Italy

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Background: Adrenal insufficiency (AI) is a rare condition caused by an inadequate production of glucocorticoids. Preliminary data in adults suggest that AI could be associated with an increased susceptibility to infections; moreover, AI patients are at risk to develop a severe course of infectious diseases and to experience a life-threatening adrenal crisis. The aim of our study is to evaluate the severity and the outcome of COVID-19 in pediatric AI patients in comparison to subjects affected with other endocrinopathies not involving adrenal gland.

Patients and Methods: This was a retrospective, multicenter study involving 11 Italian tertiary-centers of pediatric endocrinology. Data regarding symptoms, severity and duration of the disease, the need to increase the dose or receive parenteral administration of hydrocortisone and the outcome were collected through a telephone interview and review of patient's medical files. From March 2020 to October 2021, 80 children with a history of COVID-19 were collected: 49 subjects affected by AI (42 primary AI, 7 central AI) and 31 subjects as controls.

Results: Mean age was comparable between patients and controls (11.4±4.4 years vs 10±3.5 years, respectively). The frequency of signs/symptoms during COVID-19 in AI patients was as follows: fever 68%, rhinorrhea 34%, headache 34%, sore-throat 30%, cough 28%, anosmia/ageusia 21%. Less common symptoms were characterized by arthralgia, abdominal pain, diarrhea and vomiting. The severity of infection was comparable between patients and controls: paucisymptomatic 40.8% vs 25.8%; mild 55.1% vs 61.3%; severe 4.1% vs 12.9%, respectively (Chi-square=0.19). Time between the first positive nasopharyngeal swab and the first negative one in patients vs controls was: ≤15 days, 39% vs 56.6%; >15 days, 61% vs 43.3%, showing a tendency to longer infection in AI children, although this difference did not reach statistical significance (Chi-square=0.14). In 64% of AI patients the dose of hydrocortisone was increased during the infection and in 6.4% parenteral hydrocortisone was needed. 94% of AI subjects did not require hospitalization while only 6% were hospitalized with a complete recovery in 100% of cases. Within the entire cohort of AI subjects, 2 children (4%) experienced an adrenal crisis during infection. No fatal events occurred.

Conclusion: Our data, suggest that children with AI adequately treated are not at increased risk of severe course of COVID-19. In comparison to controls, subjects with AI have a slightly longer duration of the disease, although this data need to be confirmed on larger sample of patients.

P1-414

A short intragenic inversion in *CYP11B1* gene involved in a 46,XX virilizing congenital adrenal hyperplasia: interest of cross-use of targeted massively parallel and Sanger sequencing

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Background: Steroid 11-β hydroxylase deficiency is the second most frequent cause of adrenal hyperplasia (CAH) with autosomal recessive inheritance. Girls have importantly virilized external genitalia at birth, and boys display precocious pseudopuberty. Unlike others enzymatic deficiency involved in CAH, there is no salt wasting during infancy but patients develop hypertension. Because of more than 90% of homologous sequence between *CYP11B1* gene (11-β hydroxylase) and *CYP11B2* gene (aldosterone synthase), Sanger sequencing remains the gold-standard method. Here, we report a patient with an 11-β hydroxylase deficiency in whom classical Sanger failed to identify a structural molecular variant, revealed by additional investigation using massively parallel sequencing (MPS) and an adapted Sanger technique.

Case: The patient is the second child of non-consanguineous parents, born with atypical external genitalia without palpable gonads (Prader IV), and karyotype 46,XX. The high level of 11-deoxycortisol (206.5 nmol/L) was pathognomonic of the 11-β hydroxylase deficiency (> 40 nmol/L). Surgery of genitals was undertaken, as well as a treatment by hydrocortisone and nicardipin.

Molecular Characterization: Sanger sequencing revealed only one heterozygous short indel (NM_000497.4:c.331_332delinsC ; p.(Met111Argfs*22)), inherited from the father. In the absence of identification of a second mutation, *CYP11B1* was sequenced by targeted DNA sequencing (custom design SeqCap EZ (Roche NimbleGen®) on a Nextseq 500 (Illumina®)). The in-house bioinformatic pipeline also failed in the identification of a second variation. Alignments files visualization by IGV® revealed incompletely aligned and abnormally distant read pairs. By looking at the non-aligned base pairs, we identified a short intragenic inversion of 598bp, involving exons 5 and 6 (NM_000497.4:c.892_1121+7inv; 1121+8_1121+9del). We designed a specific Sanger sequencing method flanking the breakpoint regions in the inverted allele to confirm the variant.

Discussion: We here report the first short intragenic inversion in *CYP11B1*. It may conduce to an aberrant truncated protein or absence of protein. Classical pre-sanger molecular amplification dropped out the inversion-carrying allele as did the bioinformatic pipeline used for MPS. In the face of evidence of a defect in CYP11B1 (based on clinical and hormonal data), the specific visualization of the reads obtained by MPS and imperfectly aligned on *CYP11B1* was necessary to reveal the molecular mechanism missed by classical technologies. A specific strategy by Sanger sequencing allowed its characterization. Our analysis thus allow personalized genetic counseling.

P1-415

Basal cortisol measurements in the prediction of low-dose ACTH stimulation test outcomes

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Background: Low-dose adrenocorticotropic hormone stimulation test (LDST) is widely used to assess patients for adrenal insufficiency. However, the predictive power of basal cortisol for the performance of LDST is not clear.

Objective: To determine the appropriate basal serum cortisol cutt-off values that predict a positive or negative LDST.

Design: A single-centre retrospective study to investigate LDSTs measuring baseline, 40th and 60th min cortisol concentrations after intravenous administration of 1 μg of synthetic ACTH.

Method: All the LDSTs of patients suspected of AI between November 2016 and February 2022 were included. A positive LDST (suggesting AI) was defined as a stimulated peak cortisol level <18.1 μg/dL (500 nmol/L). The associations between serum basal and peak cortisol levels in LDST were analysed and the diagnostic precision of basal serum cortisol concentrations for LDST performance was evaluated by ROC analysis.

Results: A total of 646 LDSTs performed on 537 (237 girls, median age 9.2±5.8 years) patients were evaluated. 215 LDSTs (33.3%) failed to show adequate cortisol response. Diagnoses leading to the use of LDST were: history of pituitary tumour, cranial radiotherapy or neurosurgery (n= 94, 17.5%); presence of one or more pituitary hormone deficiencies (n= 287, 53.5%); history of exogenous long-term glucocorticoid use (n= 99, 18.4%); and clinical suspicion of AI (n= 57, 10.6%). In the group that passed the LDST (n= 431, 66.8%) the mean basal cortisol was 9.9±4.7 μg/dL (273±129.6 nmol/L); in the failed group (n= 214, 33.2%) was 6.0±3.7 μg/dL (165.5±102 nmol/L) (p<0.0001). The mean basal ACTH level was 28.0±22.0 pg/mL in the passed group and 30.0±26.0 pg/mL in the failed group and this relationship is statistically insignificant (p=0.3089).

The threshold basal cortisol value predicting a negative LDST result was determined as >6.8 μg/dL (189.5 nmol/L), having a sensitivity of 70%. Values above this threshold had a negative predictive value of 82.3%.

Conclusions: As a result of this unique study with large sample size carried out on a pediatric population, we determined serum basal cortisol of > or ≤6.8 μg/dL that can be used to confirm or exclude adrenal Insufficiency (AI) less invasively. Assessment of basal cortisol can reduce the need for LDST and can save cost and time.

P1-416

The assessment of the usefulness of morning cortisol and DHEAS concentration levels in the diagnosis of central adrenal insufficiency in pediatric patients - preliminary results

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The diagnosis of central adrenal insufficiency (CAI) is challenging. The most popular diagnostic tool in pediatric population remains low-dose (1 μg) cosyntropin (LDC) test. Nevertheless, there is still a need for the CAI markers that might be used on an outpatient setting as a first-line screening. In adult patients morning cortisol and dehydroepiandrosterone sulphate (DHEAS) has been postulated as a possible markers. The aim of the study was to evaluate the usefulness of basal morning serum cortisol and DHEAS assessment to diagnose CAI in the pediatric population.

Material and Methods: In 94 pediatric patients suspected to have CAI basal cortisol and DHEAS levels were assessed, and LDC and was performed.

Results: On the basis of LDC test 9 patients were diagnosed with CAI (group 1, maximal cortisol level < 140 ng/mL), in 70 CAI was excluded (group 2, maximal cortisol level > 200 ng/mL), in the rest the test results indicated partial CAI. Basal morning cortisol

level was significantly lower in group 1, than in group 2 (33.3 vs. 112.1 ng/mL, p=0.04) as well as DHEAS level (16.8 vs. 86.5 μg/mL, p=0.00007). Despite these differences, it was not possible to determine the value of the cut-off point for any of the parameters.

Conclusion: In pediatric patients with CAI basal morning cortisol and DHEAS levels are significantly lower than in patients with normal adrenal function. Nevertheless, due to the impossibility of drawing a cut-off point, they cannot replace stimulation tests.

P1-417

A patient with autoimmune polyglandular syndrome type 1 with atypical presentation

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Background: Autoimmune polyglandular syndrome type 1 (APS-1) is a rare multisystem disorder due to mutations in the autoimmune regulator gene (AIRE). APS-1 usually is characterized by a triad of hypoparathyroidism, primary adrenal insufficiency (PAI) and chronic mucocutaneous candidiasis. In the absence of the classic triad, the diagnosis becomes obscure and is often delayed.

Case Presentation: We report a 12 years old girl from consanguineous marriage born from 2nd pathologic pregnancy (antibiotic treatment due to mother's pneumonia) at term, with birth weight of 3000 g. The patient had chronic nail and oral candidiasis with unknown duration. After the age of 7 years she had recurrent episodes of vomiting, abdominal pain and carving for salty foods. During one of the occasions, she experienced generalized seizure. Laboratory tests showed severe hypoglycemia (BGL 1.0 mmol/l), metabolic acidosis (BE -24.1 mmol/l), hyponatremia and hyperkaliemia. She was transferred to our Expert center for rare endocrine diseases. The diagnosis of adrenal crisis due to primary adrenal insufficiency was made. After intensive care and acute treatment, she was started initially with oral Hydrocortisone and Fludrocortisone. At age of 8 years 6 months the patient presented with severe megaloblastic anemia and thrombocytopenia. At admission hemoglobin level was 26 g/l, MCV 93.1 fl and platelet count was 53x109/l. Treatment with vitamin B12 and folic acid was implemented with good effect. The patient underwent gastroscopy that led to the diagnosis of atrophic gastritis. During the continuous follow up calcium and phosphorus levels were in the referent ranges, and the patient did not demonstrate any other autoimmune conditions. APS-1 was suspected based on PAI, vitamin B12 deficient anemia and candidiasis. Blood samples were sent for molecular analysis. AIRE gene screening revealed homozygous state for LRG_18t1:c[769C>T](p.Arg257*) mutation, which is frequently reported as the cause of APS-1. The patient is regularly followed and so far, she has not developed further autoimmune conditions.

Conclusion: The presented patient demonstrates the need to actively screen patients with one autoimmune condition for APS-1 at the first presentation in order to prevent omission of affected individuals and adverse events from delayed treatment.

Bone, Growth Plate and Mineral Metabolism

P1-19

Bone mass and biomarkers in young women 3 years after intensive nutrition therapy for severe anorexia nervosa

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Purpose: Anorexia nervosa (AN) increases the risk of impaired bone health, low areal bone mineral density (aBMD), and subsequent fractures. This study investigated the long-term effects on bone and biomarkers in young women with AN.

Methods: Twenty-five Swedish female AN patients, median age 21.0 years (16.1 to 24.3 years), median BMI 15.4 kg/m2, were included, 22 patients completed a high-energy in-patient treatment for 12 weeks, 20 of these were followed-up after 3 years. Bone mass and body composition were measured by dual-energy X-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT), and DXA and laser before and after 12 weeks of nutrition therapy, and after 3 years. C-terminal collagen cross-links (CTX), osteocalcin, bone-specific alkaline phosphatase (BALP), leptin, and sclerostin, were analyzed at the same time points. An age-matched comparison group of 17 healthy women was recruited for the 3-year follow-up.

Results: Body mass index (BMI) and fat mass increased from baseline to 3 years in women with AN. Median total body aBMD among the AN patients remained stable over 3 years, but was significantly lower compared to healthy controls after 3 years. Trabecular volumetric BMD (vBMD) decreased during the first 12 weeks and over 3 years despite stable BMI and was significantly lower in AN patients than the controls. The trabecular vBMD was decreased in 42% of the AN patients and in 6% of the healthy controls. Median serum sclerostin decreased from 31.7 to 24.6 pmol/L

after 12 weeks of nutrition therapy (p=0.033) and further decreased to 19.0 pmol/L over 3 years (p=0.042). From baseline to 3 years, median BALP increased from 8.0 to 15.0 µg/L (p=0.0029), but osteocalcin was stable. Median serum CTX decreased from 1.24 ng/mL at baseline to 0.34 ng/mL at the 3-year follow-up (p<0.0001). Leptin increased during nutrition therapy before decreasing at 3 years. There were no associations between the change in sclerostin from baseline to 3 years and the changes in other bone turnover markers, aBMD, or vBMD.

Conclusions: This longitudinal study demonstrated low aBMD in AN patients compared to healthy controls and a reduction in trabecular vBMD at the 3-year follow-up despite stable BMI, reduced sclerostin levels, and changes in bone turnover markers usually associated with increased bone mass. Our findings highlight the importance of early detection and organized long-term follow-up of bone health in young women with a history of AN.

P1-20

Report of the first paediatric case of hypercalciuric hypocalcaemia managed with simultaneous parathyroid and kidney transplantation

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Background: Calcium-sensing receptors (CaSR) located on parathyroid glands and kidneys act to regulate serum calcium levels. Inherited hypocalciuric hypercalcaemia and autosomal dominant hypercalciuric hypocalcaemia are due to inactivating and activating CaSR mutations respectively. We present the immediate and medium term postoperative clinical course of the first paediatric patient with hypercalciuric hypocalcaemia managed with a simultaneous parathyroid and kidney transplantation after failure of medical therapy.

Case Presentation: A 1 year-old Caucasian girl, with no family history, presented with hypocalcaemic convulsions with a corrected calcium of 1.42 mmol/L [2.19-2.69 pmol/L], undetectable PTH <0.5 pmol/L [0.95 – 5.7 pmol/L], normal vitamin D levels and high urinary calcium creatinine (Ca:Cr) ratio (5 mmol/mmol). Renal ultrasound detected bilateral nephrocalcinosis. Molecular analysis identified an activating mutation of CaSR (c.2528C>A p.A843E).

Initial management consisted of 1-alphahydroxycholecalciferol and calcium but increasing urinary Ca:Cr ratios worsened nephrocalcinosis. Hypocalcaemic seizures were poorly controlled so daily subcutaneous injections of recombinant PTH was introduced at 1.5y and subsequent subcutaneous PTH infusion was started at the age of 2.5 years via an insulin pump.

PTH infusion improved hypercalciuria but hypocalcaemia management remained challenging with hypocalcaemic seizures and progressive metabolic bone disease. She presented with slipped bilateral upper femoral epiphyses at 10.6y.

Renal function remained normal until age of 9, before deteriorating to end stage kidney disease at the age of 11.3y (eGFR 10ml/min/1.73m2) needing haemodialysis and listed for transplant. The etiology of this remains uncertain as renal ultrasound showed bilateral cortical cysts but with no signs of nephrocalcinosis or nephrolithiasis. At 11.8y she simultaneously received a kidney and a parathyroid gland from her father who did not carry any pathogenic variations in the CaSR.

Postoperatively, PTH infusion and calcium supplementation was recommenced and weaned with the aim to maintain corrected serum calcium just below the normal range. This was to stimulate the endogenous PTH graft production (peak level 28 ng/L [10-65 ng/L]). At 22 weeks post transplantation the PTH pump could be completely stopped although she remained on calcium and vitamin D supplementation. 2 years post transplantation there was evidence of parathyroid transplant failure with hypocalcaemia and inappropriately low serum PTH (19 ng/L). Alfacalcidol was reintroduced, however the urinary Ca:Cr ratio remained low (0.7).

Conclusion: The case highlights the benefits and clinical course of a paediatric patient with an activating mutation in the CaSR managed with a simultaneous parathyroid and kidney transplantation.

P1-21

Etiological analysis of hypophosphatemia: A single-center experience

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Background: Hereditary hypophosphatemia (HH), is a rare condition related to decreased renal tubular phosphate reabsorption. Although X-linked hypophosphatemia (*PHEX* mutation) is the most frequent cause of HH, recent advances in the next-generation sequencing (NGS) techniques enable the identification of various genetic etiologies.

Our study aims to determine the molecular etiology of patients with hypophosphatemia and to identify new candidate genes.

Subjects and Methods: Forty-one patients (19 males) from 32 unrelated families were included in the molecular analyses except two cases in whom family did not give consent. Initially, the *PHEX* gene was sequenced, if the result was negative, MLPA (Multiplex Ligation-dependent Probe Amplification) analysis for *PHEX* was performed. A targeted gene panel, including all known HH genes,

was carried to the patients with normal *PHEX* gene or isolated hypophosphatemia without any rickets findings.

Results: Genetic cause in any of the known genes was detected in 34 patients from 26 families in the study group. *PHEX* gene variants were identified (five novel) in 18 patients from 14 unrelated families (18/39;46%) which included 5 nonsense, 3 missense, 3 splice-site, 1 in-frame deletion, 1 deletion, and 1 duplication. Novel variants in the *PHEX* gene were c.1382_1391del, c.958_960del, c.1111_1112insTT. A novel exon 2 deletion and also, a novel exon 4-12 duplication of the *PHEX* gene were revealed by MLPA.

SLC34A3 gene variants were the second most common 18% (7/39) molecular defect in our cohort. Six homozygous and one heterozygous mutations were detected including double homozygous variants (c.1335+2T>A and c.756G>A) in three patients from two families. Novel variants in *SLC34A3* were c.1267G>A and c.1435del. On the *SLC34A1* gene, a compound heterozygous (a novel c.457G>T and previously reported c.1484G>A) and a heterozygous (c.272_292del) variants were also detected (2;5%).

The variants in *FAM20C* (1;2,5%), *CLCN5* (1;2,5%), *SLC2A2* (1;2,5%) and *DMP1* (3;7,5%) genes were the other known defects detected in our cohort. The c.26del variant in the *ENPP1* gene (1;2,5%) was also novel. We could not find any genetic etiology in 5 patients (5/39;%13). The evaluation of whole exome sequencing is pending for these patients.

Conclusions: The application of MLPA and NGS techniques in addition to single gene sequencing revealed a molecular etiology in 87% of our cohort. MLPA had the additive value of 5% to explain the molecular pathology. Although *PHEX* gene defects were the most frequent genetic cause for hyphophosphatemia, NGS demonstrate rarer molecular etiologies in the majority of the remaining patients.

P1-22

Resolution of severe constipation following a switch from calcium carbonate to recombinant human PTH therapy: A case report

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Hypoparathyroidism is treated with oral calcium carbonate and vitamin D analogues to increase serum calcium levels. Recombinant human parathyroid hormone (rhPTH) therapy can be considered in patients with poorly controlled hypocalcaemia or side effects to conventional treatment. Constipation, a known side effect of calcium carbonate, is often easily managed with simple laxatives. We describe resolution of severe constipation by changing conventional treatment to rhPTH.

A female patient, diagnosed with 22q11 deletion and hypocalcaemia during the neonatal period, was managed with calcium supplements. She developed constipation at 4-years-old when she was commenced on Movicol. Strategies such as star charts and reward systems were also trialled. Unfortunately, the patient developed soiling and management was escalated to Picolax and then Botox and manual extraction. The patient was referred to endocrinology at 6-years-old and was commenced on Alfacalcidol, which improved her bowels for a short period. Calcium supplements were weaned at the age of 6.5 years, as the patient found them difficult to take with her constipation. Overtime, Alfacalcidol was increased to 85nanogram/kg/day and her vitamin D levels were optimised. At 9-years-old, the patient experienced seizure-like activity and was found to have an adjusted calcium level of 1.82mmol/L (2.15-2.74), phosphate level of 2.21mmol/L (0.97-1.94) and inappropriately low PTH of 2.2pmol/L (1.1-6.9). She was re-commenced on oral calcium, but control remained poor (adjusted calcium ranged from 1.58 to 2.02mmol/L and phosphate ranged from 1.85 to 2.58mmol/L) and she was requiring regular surgical intervention for constipation. She was admitted at 12 years of age for rhPTH (Terrosa) therapy subcutaneously. The dose was initiated at 0.31micrograms/kg/dose twice daily and increased in stages to 0.40micrograms/kg/dose twice daily. Table 1 shows improvement of bone biochemistry following rhPTH. Her bowel movements have improved. She has remained on oral laxatives but has not required surgical intervention to date since starting rhPTH.

Recombinant human PTH therapy can be used successfully to wean calcium supplements and reduce severe complications secondary to the oral medication. It also improves compliance and overall bone biochemistry.

Table 1. shows bone biochemistry before and after rhPTH treatment

Level	Pre-rhPTH	3 days post-rhPTH	2 weeks post-rhPTH	4 weeks post-rhPTH
Calcium mmol/L (2.15-2.74)	1.59	1.92	2.27	2.43
Adjusted calcium mmol/L (2.15-2.74)	1.67	1.94	2.17	2.31
Phosphate mmol/L (0.81-1.61)	2.76	2.39	1.54	1.63
Parathyroid hormone pmol/L (1.1-6.9)	1.9	NA	NA	NA
Urine calcium/ creatinine ratio mm/mmCr (0-0.6)	0.07	NA	0.49	NA

NA=Not Available

P1-23

Comparison of adult height prediction models against the average height of the Mexican population

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Background: Adult height prediction models (AHP) were designed several decades ago based on the Caucasian population, hence they are not adapted to our population's characteristics and secular changes. Technological advances have improved the accuracy of bone age (BA) reading through automated analysis, which has been incorporated into new AHP models, but have not been evaluated in the Mexican population.

Objective: Identify which AHP model best fits the average height of the Mexican population.

Methodology: This is an analytical cross-sectional study in which 1,173 healthy children were included between the ages of 5 and 18. AHP for each participant was performed using projected height (PH), Bayley-Pinneau (B&P), Tanner-Whitehouse-2 (TW2) and the automated BoneXpert model, with both manual BA reading taken by experts and the automated BoneXpert method. The best model was considered the one showing the least difference according to the average height of adults in Mexico City (men 167.1 cm and women 155.2 cm), considering the secular trend.

Results: It was observed that all AHP models tend to overestimate between 3.2 and 11.4 cm in men and between 1.7 and 6.2 cm in women. In the Table 1 we shown the differences between manual and automated readings for each AHP model.

HP, projected height; B&P, Bayley-Pinneau; TW2, Tanner-Whitehouse-2; cm, centimeters; SDS, standard deviation score.

Conclusions: The BoneXpert model best fits the characteristics of our population. On the other hand, reading of BA by experts may improve model prediction compared to automated reading. However, inter-observer variability may cause significant differences in predictions that can be reduced by the higher accuracy of automated reading.

P1-24

SIADH as presenting feature of foramen magnum stenosis in a 2-month-old infant with achondroplasia (ACH): case report and discussion on management of infants with ACH in order to reduce the risk of serious complications

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Background and Aim: Achondroplasia is the most common skeletal dysplasia and is associated with serious complications such as foramen magnum stenosis (FMS). Current guidelines in Germany recommend polysomnography at 2-3 months and

Table 1. Comparison of AHP with manual and automated reading of BA

	Males n 683				
	Manual		Automated		
Model	Mean ±SDS	Rank (cm)	Mean ±SDS	Rank (cm)	p Value
HP	177.3 ± 11.2	138.1-232.7	175.5 ±7.7	155.7-205.2	0.001
B&P	178.5 ± 8.0	151.2-211.5	178.5 ± 6.9	163.1-211.5	0.948
TW2	175.2 ± 6.7	155.3-204.5	175.1 ± 6.6	158.7-204.7	0.675
BoneXpert	170.3 ± 5.9	149.3-195.4	171.5 ± 5.9	151.2-192.3	0.001
	Females n 490				
	Manual		Automated		
Model	Mean ±SDS	Rank (cm)	Mean ±SDS	Rank (cm)	p Value
HP	157.9 ± 7.0	132.9-189.0	160.3 ± 6.6	136.1-191.8	0.001
B&P	159.1 ± 7.2	138.6-179.7	160.8 ± 6.8	140.7-180.7	0.014
TW2	160.2 ± 6.7	134.8-181.3	161.4 ± 6.7	136.4 180.5	0.014
BoneXpert	156.9 ± 6.1	136.9-174.1	158.8 ± 5.8	138.1-175.0	0.001

cranial imaging at 6-9 months of life in achondroplasia, whereas American Academy of Pediatrics recommends to evaluate every infant with achondroplasia for cranio-cervical junction risks via neurologic examination, polysomnography and neuroimaging either with computerized tomography (CT) or magnetic resonance imaging (MRI) as soon as the diagnosis is recognised. Here we present an infant with achondroplasia and FMS who presented with syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to significant FMS and myelocompression. Our aim is to draw attention to the early presentation of a life-threatening complication of achondroplasia and to discuss the optimal timing of cranial MRI.

Case Report: A 2-month-old boy with prenatally diagnosed achondroplasia was referred to our university hospital due to disordered breathing and altered consciousness. On physical examination, the patient was apathic, pale, hypotonic and hypothermic (34.8°C) and had typical features of achondroplasia. Shallow breathing with nasal flaring and suprasternal retractions and deep sighing was compatible with central apnoea, blood gas analysis revealed respiratory acidosis. The patient was intubated in our paediatric intensive care unit. Laboratory investigations revealed severe hyponatremia (114 mmol/l) and hypochloridaemia (82 mmol/l) with normal glucose and urea levels and high urinary sodium-output (131.8 mol/mol Cr). The diagnosis of SIADH was made based on low serum osmolality (237 mOsm/kg) in the presence of high urine osmolality (431 mOsm/kg) and treatment was started. An emergency CT showed a high-grade stenosis at the cranio-cervical junction, subsequent MRI demonstrated myelocompression (AFMS 4b). The patient underwent decompression surgery the next day. A prompt improvement of laboratory parameters was observed after operation with an increase in serum osmolality (290 mOsm/kg) and a decrease in urinary sodium extraction (42 mol/mol Cr). Spontaneous breathing after extubation was sufficient but only reduced spontaneous motor activity of the extremities was observed in the course, hence a high-level spinal injury can be assumed.

Conclusion: Clinicians should be aware of SIADH as a presenting sign of FMS in children with achondroplasia. Further discussion is needed regarding improved family education and timing of screening recommendations including neuroimaging especially in children who did not receive polysomnography.

P1-25

Efficacy and safety of bisphosphonate treatment in pediatric patients with osteoporosis caused by immobilization

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Introduction: Osteoporosis is medical condition commonly associated with immobilization in children, which can lead to a vicious cycle of disability, worsening osteoporosis, and recurrent fractures. Currently, bisphosphonates are widely used as a standard therapy in children with osteoporosis, but there are limited data on efficacy according to its dosage and duration. We aimed to evaluate efficacy of bisphosphonate treatment according to the dosage and duration in pediatric patients with osteoporosis due to immobilization.

Method: We reviewed medical records of pediatric patients who were diagnosed with osteoporosis due to immobilization rated as Gross Motor Function Classification System (GMFCS) grade V, and who received bisphosphonate therapy with regular check-up for at least 1 year. The dosage and duration of the treatment, biochemical laboratory measurements, data of bone densitometry, and the occurrence of side effects were collected.

Results: Subjects were 21 children. The average duration of bisphosphonate treatment was 2.0 ± 0.9 years, and mean cumulative dose per body weight of bisphosphonate was 7.7 ± 2.5 (mg/kg/year). After the treatment, mean lumbar spine bone mineral contents (BMC) significantly increased from 14.20 ± 8.58 (g) to 19.38 ± 9.89 (g) ($p<0.05$), lumbar spine bone mineral density (BMD) significantly increased from 0.40 ± 0.14 (g/cm2) to 0.49 ± 0.14 (g/cm2) ($p<0.05$), and height-adjusted lumbar spine BMD Z-score also showed improvement from -2.66 ± 1.66 to -1.66 ± 1.38 with statistical significance ($p<0.05$). The cumulative dose and the duration of treatment were not related to its efficacy, but increasing average dose per body weight in each cycle (mg/kg/cycle) showed significant effects on increasing change in height-adjusted lumbar spine BMD z-score (regression coefficient $\beta = 1.065$, $p <0.05$).

Discussion: BMC, BMD, and height-adjusted BMD z-score significantly increased after bisphosphonate treatment in pediatric patient with osteoporosis due to immobilization. Independent of cumulative dosage and duration, the efficacy of bisphosphonate treatment increased significantly as average dose per body weight in each cycle increased. Further studies with sufficient number of subjects and long term follow-up observation are needed.

P1-26

Outcomes of four patients with osteonecrosis after one-year pamidronate treatment

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Background: Osteonecrosis (ON) is bone death caused by inadequate blood supply resulting in demineralization and trabecular thinning and, subsequently, mechanical failure. Although the pathophysiology of ON is not fully understood, the use of high-dose glucocorticoid (GC) is one of the triggers. Furthermore, its optimal management remains uncertain. The use of

bisphosphonates (BP) for the treatment of ON has been reported, however, data on outcomes are limited.

Method: The patients who were evaluated in our unit regarding ON during the last two years were included. Data regarding clinical, laboratory, and imaging studies MRI, and bone mineral density measurements (BMD) were recorded before and one year after treatment (reevaluation). The severity of the clinical picture was assessed using Common Terminology Criteria for Adverse Events (CTCAE) criteria (between 1 (asymptomatic) and 5(death)). Patients were treated with pamidronate (1mg/kg/day, with a maximum dose of 60 mg/day, for two days, quarterly) and, when needed, calcium, vitamin D, and physiotherapy.

Results: There were four female patients (Patient 1, acute lymphoblastic leukemia treated with bone marrow transplantation; Patient 2, immune thrombocytopenic purpura, Patients 3 and 4, systemic lupus erythematosus) aged between 10 and 17 years. Only Patient 1 was prepubertal. According to CTCAE, ON was consistent with Grade 3 (Severe symptoms; limiting self-care activities of daily living; elective operative intervention indicated) and multifocal in lower limbs in all of them. Surgical core decompression in Patient 4, which had been performed before pamidronate, did result in clinical improvement. All of them had been treated with high-dose GC. None of them had any fractures. Calcium, phosphorus, alkaline phosphatase (ALP), vitamin D, and parathyroid hormone levels were normal in all patients before, during, and one year after pamidronate administration. The BMD SD scores were all normal for P1, P2, and P4. Patient 3 had a normal BMD SD score (1.2 SDS) before treatment, but it increased to 2.9 SD score at reevaluation. No other side effects related to the use of bisphosphonates were observed. At the time of reevaluation, the lesions were stable on MRI and their clinical condition was consistent with Grade 1 according to CTCAE (Asymptomatic; clinical or diagnostic observations only; intervention not indicated).

Conclusion: Pamidronate may be an effective treatment for the improvement of symptoms related to ON.

P1-27

Effects of pharmacological inhibition of BCL-2 on linear bone growth

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Introduction: The survival rates for childhood cancer have significantly increased over the past decades but the management of treatment-related complications remains challenging. Thus, the introduction of novel drugs requires careful investigation of potential off-target side effects. The developing skeleton is severely affected by the anticancer treatment which may result in growth retardation and short stature. Venetoclax is a selective Bcl-2 inhibitor which is under investigation in pediatric cancer clinical trials. However, there are no data regarding the potential side-effects of venetoclax on the bone tissue.

Objectives: The overall aim was to investigate the effects of venetoclax on bone growth. Mitochondrial activity and the Bcl-2 pathway are crucial during bone development, we hypothesized that venetoclax might suppress bone growth by inhibiting Bcl-2 in the growth plate.

Methods: (a) Culture of ATDC5 cells: The chondrogenic ATDC5 cells were cultured with venetoclax (0.625-2.5 μM) or DMSO and cell viability was assessed after 48 or 72 hrs with the CellTiter-Glo® Luminescent Cell Viability Assay. (b) Culture of fetal rat metatarsals: E20 rat metatarsals were cultured ex vivo with venetoclax (1 nM-10 μM) for 12 days (n=15). Photos and length measurements were taken at designated time-points to monitor growth and histomorphometric analysis was performed. (c) In vivo studies: Female NMRI nu/nu mice (7-week-old, n=4-5) were treated with venetoclax (100 or 200 mg/kg via oral gavage) or vehicle for 14 days. X-rays were taken to evaluate longitudinal bone growth and changes in the growth plate were assessed with histomorphometry.

Results: Venetoclax decreased cell viability in ATDC5 cells after 48 or 72 hrs culture. Venetoclax-treated metatarsals showed decreased growth from day 0 to day 12 compared to the control group (2.5 μM: 65.4 ± 3.4 % vs control 76.4 ± 1.5%, $p<0.05$; 5 μM: 20.2 ± 1.4 % and 10 μM: 9.5 ± 1.1% vs control 76.4 ± 1.5%, $p<0.001$). Furthermore, the height of resting + proliferative zone and the size of hypertrophic cells were significantly reduced in the venetoclax groups. Venetoclax in the highest dose significantly reduced tibia growth in vivo ($p<0.05$) and both doses reduced growth plate height compared to vehicle (100 mg/kg: 130.2 ± 3.3 μm, $p< 0.01$; 200 mg/kg: 130.6 ± 4.9 μm, $p< 0.05$ vs vehicle: 151.4 ± 4.9 μm).

Conclusion: Our findings show that venetoclax impairs chondrogenesis and induces growth retardation. Based on these, further investigations will enable the identification of the mechanisms involved in the observed side-effects on bone.

P1-28

Pain as an onset symptom in hereditary hypophosphatemic rickets with hypercalciuria, a case report

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We report a case of hereditary hypophosphatemic rickets with hypercalciuria (Hereditary Hypophosphatemic Rickets with Hypercalciuria, HHRH) in a 13-year-old boy, referred for evaluation due to the onset of bilateral knee pain for about two years. Pain was intermittent and walking limiting and negatively affected quality of life. Negative family history of bone/joint pathologies and kidney stones. The parents are consanguineous (first cousins), have normal stature and no history of bone and mineral disorders.

Physical examination revealed normal height and weight. There were no skeletal deformities.

Hypophosphatemia was found on blood tests (2.7 mg/dL, normal for age 3.30-5.70) associated with high urinary excretion of phosphates (reduced TRP) and high urinary excretion of calcium (6.1 mg/ kg/day, normal <4 mg/kg /day). There were also elevated 1,25-vitamin D values (141 pg/mL, normal value 42-95 pg/mL)

with inhibited parathyroid hormone (14 pg/mL, normal 15-65 pg/mL) and normal alkaline phosphatase values for the pubertal stage. The concentration of intact FGF23 was undetectable (<5 pg/ml, normal value 23.2- 95.4 pg/mL) in the patient's serum.

X-rays of the knees showed no obvious signs of rickets. The ultrasound of the urinary tract was normal, excluding the presence of nephrocalcinosis / nephrolithiasis.

MRI of the distal femoral epiphyses disclosed abnormalities that were consistent with rickets.

Genetic analysis PHEX gene was carried out negative. The FGF23-independent hypophosphatemia pattern directed the diagnostic suspicion towards a form of tubulopathy. Possible diagnostic hypotheses were, HHRH, Dent disease, Fanconi syndrome, or idiopathic familial hypercalciuria.

Genetic analysis showed a homozygous mutation of the variant c.448 + 1G> A in the SLC34A3 gene, pathogenetic for hereditary hypophosphatemic rickets with hypercalciuria.

The accurate diagnosis of HHRH has important therapeutic implications. In our patient, phosphate therapy caused complete remission of symptoms after about 2 months from the start of therapy with normalization of the urinary calcium.

In patients with HHRH, unlike other forms of rickets, the addition of active vitamin D can create complications, such as hypercalcemia, nephrocalcinosis, and renal damage.

P1-29

Don't forget the bones: incidence and risk factors of Metabolic Bone Disease in a cohort of preterm infants

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Background and Aim: Metabolic Bone Disease of Prematurity (MBD) is a condition of reduced bone mineral content (BMC) compared to the expected for gestational age (GA). Preterm birth interrupts the physiological process of calcium (Ca) and phosphorus(P) deposition that occurs mostly in the 3rd-trimester of pregnancy, leading to an inadequate bone mineralization during intrauterine life (IUL). After birth, an insufficient intake of Ca and P carries on this alteration, resulting in overt disease. Despite advances in neonatal intensive care, MBD is still frequent in preterm infants, with an incidence of 16-23% in Very-Low-Birth-Weight (VLBWI, BW<1500g), and 40-60% in Extremely-Low-Birth-Weight (ELBW, BW<1000g) infants. Several risk factors are associated with MBD (e.g. malabsorption, parenteral nutrition (PN), bronchodysplasia (BPD), necrotizing enterocolitis, and chronic medications). The aim of this study was to evaluate incidence of MBD in a cohort of VLBWI and the role of some risk factors.

Material and Methods: VLBWI of a GA≤32weeks were assessed between 3rd-5th weeks of life. Subjects were classified as increased risk (G1) if P≤4.5mg/dl or ALP≥900UI/L, or standard risk (G2) if P≥4.5mg/dl and ALP≤900UI/L. GA, BW, days on PN and invasive ventilation, and occurrence of BPD were evaluated. Differences between G1-G2 were evaluated using t-test for continuous variables and $\chi 2$-test for categorical variables. The statistical significance was fixed at 0.05.

Results: We enrolled 238 VLBWI (107male, 52 at increased risk(G1). Mean P(mg/dl) and ALP(UI/L) were 4.2±1.04vs6.15±0.93 in G1 and G2 respectively($p<0.001$). G1-subjects have lower GA (28.53±1.99vs29.38±1.94 weeks, $p<0.01$) and BW (1019.87g±243.57vs 1162.23g±245.16, $p<0.001$). Moreover, they needed a longer PN support (25.35days±10.51 vs 20.54days±13.55, $p<0.05$) and invasive ventilation (7.46 days±9.27 vs 3.41days±10.05, $p<0.01$). G1 presented a higher incidence of BPD (36.5% vs 20.4%, $p=0.026$). At linear regression analysis, BW and PN resulted as independent predictor of increased risk ($p=0.001$, $p=0.040$, respectively). Preventive strategy led to a reduction in NP, LOS and invasive ventilation (930, 1674 and 744 cumulative days respectively).

Conclusions: VLBWI have an increased risk of MBD. Low BW is correlated with alteration in BMC due to an insufficient provision of Ca and P during IUL. Moreover, despite advances in neonatal nutrition and care, is still difficult to guarantee an adequate amount Ca and P in VLBWI. Further studies are needed to explore the pathophysiological mechanisms underlying MBD in order to implement preventive strategies and reduce the incidence of this complication.

P1-30

Vitamin D may facilitate Clock/Bmal1-DNA interactions in a Vitamin D receptor-independent fashion

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Background: The Clock/Bmal1 transcription factor heterodimer regulates the circadian activities of many biological systems, including the hypothalamic-pituitary-adrenal (HPA) axis, by trans-activating or trans-repressing downstream target genes. 1,25 Dihydroxy Vitamin D (Vitamin D), a sterol hormone that is activated by exposure to sunlight, plays a fundamental role in maintaining calcium and phosphorus homeostasis. Recent evidence suggests that the nuclear vitamin D receptor (VDR) interacts with the Clock component of the heterodimer, thereby influencing the binding of the latter onto the regulatory regions of its target genes

in a circadian fashion. However, direct influence of vitamin D on the transcriptional activity of the Clock/Bmal1 has not been investigated as yet. Direct influence of the steroid hormone cortisol on the interaction of the heterodimer with double stranded (ds) DNA was previously shown.

Objective and Hypotheses: To investigate in silico the potential role of light-activated vitamin D in the Clock/Bmal1 heterodimer complex-generated circadian biorhythms. For comparison, cortisol was studied in parallel.

Methods and Results: The complex of Clock/Bmal1 was modeled via conventional molecular modeling techniques and used to perform molecular docking experiments for vitamin D and cortisol. Experimentally determined structures and the constructed models were then used for molecular docking with ZDOCK version 3.0. Molecular systems were subjected to unrestrained Molecular Dynamics simulations (MDS) using the Gromacs suite, version 4.5.5. MDS took place in a SPC water-solved, periodic environment. Water molecules were added using the truncated octahedron box extending 7Å from each atom. Molecular systems were neutralized with counter-ions as required. For the purposes of this study, all MDS were performed using the NVT ensemble in a canonical environment, at 300 K, 1 atm, and a step size equal to 2 femtoseconds for a total 100 nanoseconds simulation time. An NVT ensemble requires that the Number of atoms, Volume, and Temperature remain constant throughout the simulation. We found that upon vitamin D and cortisol binding, the two alpha-helices bend inward from the network of the established hydrogen, van de Waals, and weak bonds. Notably, vitamin D formed more bonds than cortisol, thus, achieving a more stable docking conformation with dsDNA than the latter.

Conclusions: Our results indicate that vitamin D levels may enhance Clock/Bmal1-dsDNA interactions, potentially serving in an ultrashort positive feedback loop between this hormone and the circadian clock during the morning hours.

P1-31

Osteogenesis imperfecta: the effectiveness of bisphosphonates

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Osteogenesis imperfecta (OI) is a rare genetic disease characterized by bone fragility and an increased risk of fractures. Intravenous bisphosphonates are the current gold standard for the treatment of OI: the aim of this therapy is an increase in Bone Mass Density (BMD) and a consequent reduction in pathological fracture rates. Currently, the only bisphosphonate approved in Italy for pediatric population is neridronate, infused in hospital once every four months.

In San Raffaele Hospital (Milan) 14 children with OI are currently being treated, seven of which with neridronate therapy with an average of 7.5 years of treatment. Patients treated with neridronate are showing an increase of BMD greater than the one expected for their normal skeletal growth (which is 3.5-5.7% per year): we observed an increase of 16-20% in the first year of therapy, 8-20% in the following years. These children also had a decrease in bone turnover with significant reductions in total serum ALP, urinary calcium, NTx and CTx. Those markers started to decrease in the first 3-4 months of therapy, so they could be considered useful as an early sign of the effectiveness of bisphosphonate therapy. We found a reduction in the incidence of fractures, averaging from 1.24 pre-treatment fractures per patient/year to 0.73 fractures during treatment per patient/year; in addition, many of the fractures that occurred during treatment were less severe and occurred for more severe trauma than the pre-treatment ones. One patient, that had the highest number of fractures, did not have a marked improvement with bisphosphonate therapy. We did not observe an increase in height in SDS in most of our patients, indicating that it is unclear how much bisphosphonate treatment affects growth. The therapy was well tolerated by our patients with no significant adverse effects.

Our data are in line with many randomized and controlled studies about the effectiveness of bisphosphonates in OI, showing that BMD increases and biochemical markers of bone turnover decrease compared to the absence of treatment. The data about the reduction of fracture rate are conflicting in many studies: the effectiveness is still uncertain since it is difficult to distinguish the true effects of bisphosphonates by the effects that come from skeletal growth and the protective measures applied to prevent trauma. Further randomized, placebo-controlled clinical trials will be needed to evaluate the effectiveness of bisphosphonates in reducing the incidence of fractures in patients with OI.

P1-32

Six-year clinical outcome of enzyme replacement therapy for patients with perinatal lethal and infantile hypophosphatasia in Korea

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Hypophosphatasia (HPP) is a genetic skeletal disease caused by loss-of-function mutations of ALPL encoding tissue-nonspecific alkaline phosphatase (TNSALP). The clinical presentation of HPP varies greatly, ranging from stillbirth without bone mineralization to findings in later life, such as delayed walking, short stature, skeletal deformities, bone pain, and pathologic fractures. The diagnosis is based on clinical examination, radiographic findings, biochemical parameters of reduced ALP activity, elevated serum and urine levels of TNAP substrates, and molecular analysis of the ALPL gene. The prognosis for the prenatal/infantile form is poor, with approximately 50% of patients dying within the first year of life from respiratory failure. Asfotase alfa, a bone-targeted, recombinant TNAP, has recently been developed to treat HPP complications. We describe the clinical features, biochemical findings, molecular analysis, and clinical experience of treatment with asfotase alfa over 6 years in patients with perinatal and infantile HPP

in Korea. Patients received asfotase alfa with dose of 2 mg/kg three times weekly subcutaneously. All patients survived and the radiographic findings, laboratory findings, developmental milestones and respiratory function were improved. Injection site reactions were the most frequent adverse events, however, no serious adverse events were noted. Our results add support to the safety and efficacy of treatment with asfotase alfa for HPP patients. A persistently low ALP level in patients with unspecified diagnoses could be a key to diagnose HPP. Since 2020, health insurance for treatment with asfotase alfa has begun to apply for HPP patients in Korea on the condition that the treatment start and stop criteria are met. Accurate diagnosis and prompt treatment play an important role for avoiding preventable morbidity and premature mortality in patients with HPP.

P1-33

Primary or secondary bone fragility? This is the question

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Background: Pediatric osteoporosis is a condition which can stem from genetic causes (primary osteoporosis), from systemic diseases or from the chronic use of drugs that alter bone metabolism (secondary osteoporosis). Obesity affects bone health in several ways, including bone remodeling, proinflammatory cytokine production and bone marrow microenvironment alteration. We describe the case of a boy who presented spontaneous vertebral fractures.

Clinical History: F. is a full-term child born from unrelated parents. Nothing relevant was present in his clinical history until the age of 9 when F. started suffering from pain in the dorsal and lumbar region, in the absence of trauma. Physical examination was normal, except for severe obesity (BMI > 99°), and vitamin D deficiency for which he began oral supplementation (1000 IU/day). Given the aggravation of pain which made independent walking impossible, a magnetic resonance imaging (MRI) of the spine was performed. As a result, a wedging and bone edema of L1 was revealed. At the Dual-energy X-ray absorptiometry (DXA) assessment: Z-score -2.4. An orthopedic immobilization corset was recommended. MRI performed after three months showed new vertebral collapses, and DXA documented further reduction in BMD (Z score -3.2). F. was referred to the pediatric endocrinologist who performed blood test to exclude the most common causes of secondary osteoporosis and increased oral vitamin D supplementation to 2500 IU/day. Bone remodeling markers were found to be normal. Considering the severity of the clinical picture, it was decided to perform a genetic investigation of the genes related to bone fragility and to start intravenous infusion of neridronate at a dose of 1 mg/kg. The genetic analysis was done through a NGS-targeted panel including the main known genes affecting syndromic and non-syndromic bone fragility. A rare variant of the exon 10 of the LRP5 (NM_002335), c.2236C>T, p.(Arg746Trp) was found. This variant not reported in public population databases (PM2), occurs in a gene in which missense variants are common cause of disease (PP2) and is predicted 'deleterious' in silico (PP3). Two months after the infusion, F. showed marked clinical improvement and started walking again. F. will perform two more neridronate infusions quarterly, and lateral spine X-ray and DXA will then be reassessed. Although the genetic bases of constitutional forms of bone fragility remain incompletely understood, tailored molecular testing represents the ultimate resource for the assessment and decision making in complex cases.

P1-218

Pubertal increment in insulin resistance is negatively associated with lumbar bone mineral density in 18-year-old males independently of body composition

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Aim: Insulin resistance is known to be closely related to the development of obesity and type 2 diabetes, whereas transient insulin resistance is part of the physiological developmental processes during pubertal years. However, insulin resistance might have detrimental effect on growing bone and bone mineral accrual. The aim of the present study was to identify whether increase in insulin resistance during pubertal years contribute to bone mineral characteristics in young adult males independently of body composition parameters.

Methods: Data from 85 boys were included into this retrospective cohort-based longitudinal observational study. Boys were studied annually during their pubertal years (12 years at baseline) and at follow-up at the age of 18 years. Anthropometry, bone age, fasting blood samples, body composition, and total body and lumbar spine bone mineral characteristics were measured. Insulin resistance was determined by homeostatic model assessment of insulin resistance (HOMA-IR). To determine the effect of changes in HOMA-IR during pubertal years as longitudinal predictor to fixed bone mineral outcome variables at the age of 18 years, multiple regression analyses with were performed. All models were adjusted to potential confounding variables.

Results: Increment in HOMA-IR was negative independent predictor of lumbar spine bone mineral areal density (β = -0.202, p = 0.005) and lumbar spine bone mineral apparent density (β = -0.235, p = 0.005) after adjustment to body composition related and other justified confounding variables.

Conclusions: Increment in insulin resistance during pubertal years has potential detrimental effect on lumbar spine bone mineral density accrual independently of body composition parameters. Further studies are necessary to clarify whether monitoring HOMA-IR through puberty may identify subjects having increased risk for low peak bone mass and possible osteoporosis in future.

P1-219

Use of Zoledronic acid in children with sickle cell disease: a single centre experience

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Children with sickle cell disease (SCD) often suffer from back pain and present with vertebral changes, but the use of bisphosphonates is poorly reported. We present our experience on treating six children with SCD with Zoledronate in a tertiary paediatric endocrinology and haematology centre.

Population: Six children with SCD were treated with zoledronate infusions between the years 2016-2021. All children had a history of significant mid or lower back pain and vertebral abnormalities.

Methods: Bone mineral density (BMD) was recorded in whole body less head (WBLH), lumbar spine (LS) by dual energy X-ray absorptiometry (DXA) and bone mineral adjusted density (BMAD) of the LS was calculated. A z-score <-2 was considered to be low. 4/6 had magnetic resonance imaging (MRI) of the spine. Zoledronate was given at 0.05 mg/kg/dose every six months as an intravenous infusion.

Results: Six children (age 12-17years, females=3) received treatment. 5/6 were given > 3 doses of zoledronate. All had vertebral changes, the morphologies consisted of loss of vertebral height or biconcavities. MRI confirmed vertebral plate depressions, but there was no increased STIR signal indicating acute vertebral fracture.

4/6 children reported reduction in back pain, while pain remained unchanged in 2/6. Three children had at least one abnormally low BMD parameter at the start of treatment, of which one had also chronic kidney disease (CKD) and another had parathyroid adenoma and 2/6 had delayed puberty. After 1 year of treatment BMD z-score normalised in two of them and improved in the third. Also, the vertebral changes remained stable and there was remodelling in 1 vertebrae.

Conclusion: The diagnosis of osteoporosis in children with SCD is complicated by multiple factors. Back pain could be due to sickle cell crisis and vertebral compressions due to infarcts causing avascular necrosis or may represent osteoporotic changes. Pain improved in the majority of our cohort. Excluding the two children with CKD and parathyroid adenoma, BMD z-scores were within normal or only slightly reduced. Despite at least a year on Zoledronate, vertebral changes remained stable and only 1 vertebral shape improved, indicating that they are most likely features of the underlying SCD and not osteoporotic fractures.

P1-220

Hypocalcemia as the Initial Presentation of Type2 Bartter Syndrome: A Family Report

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Context: Bartter syndrome (BS) is a group of rare autosomal-recessive tubulopathies characterized by hypokalemic, hypochloremic metabolic alkalosis in which the primary defect is a deficiency of transporters involved in sodium chloride reabsorption. Type 2 BS results from a defect in the renal outer medullary potassium channel encoded by the KCNJ1 gene. Type 2 BS presents with polyhydramnios, intrauterine growth retardation, prematurity, failure to thrive, polyuria, hypercalciuria, and life-threatening episodes of dehydration. Hypocalcemia is a very rare presenting symptom of BS, with only a few published cases reporting it as the initial manifestation of type 2 BS.

Objective: To describe a child who presented with hypocalcemic seizure at the age of 2.3 years that was first related to vitamin D deficiency and high-phosphate soft drink consumption.

Methods: Whole exome sequencing (WES) was used to evaluate the biochemical abnormalities of the proband.

Results: We identified a previously described homozygous missense mutation c.212C>T, p.T71M in the KCNJ1 gene associated with type 2 BS. Six additional family members with the same mutation and diagnosed clinically with BS are also reported, 2 presenting with hypocalcemia associated with vitamin D deficiency.

Conclusion: This report expands the clinical spectrum associated with KCNJ1 mutations and emphasizes the role of WES in unsolved cases of hypocalcemia when genetic disease is suspected. It also highlights the hazardous effects of phosphate-containing soft drinks on calcium metabolism.

P1-221

Association between early-puberty girls' bone maturation and linear growth in Shenzhen City: a retrospective study

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Purpose: To describe and analyze association between early-puberty girls' bone maturation and linear growth in Shenzhen City.

Methods: Girls diagnosed as "Early-onset puberty" without drug intervention were collected from Shenzhen Children's Hospital From January 2016 to December 2020. Artificial intelligence (AI) system was used to evaluate bone age. The girls were divided into groups according to age and bone age, ΔBA/ΔCA and the progress of height SDS were described and analyzed respectively. LMS Chartmaker method was used to draw percentile curves to describe pattern of bone maturation and linear growth.

Results: A total of 498 girls were included in the study. The average age of initiation of breast development was 8.1±0.5 years old. LMS method was used to construct growth curves along with EP girls' bone age and chronological age seperately, and were compared with normal girls'. As for growth curve along with bone age, it showed a pattern of attenuation growth from 7 to 9 years old and showed a turning point of upward catch-up growth at 11 years old, the linear growth curve of EP girls approached to the normal growth curve after 11.The bone age of peak height velocity was between 11.5 and 12.0 years old.Meanwhile, Nearly half of the patients reached to significant rapid progress of bone age over chronological age (median of ΔBA/ΔCA > 2) before bone age 8 years old. But the progression of bone age over age showed a trend of slowing down.

As for growth along with Chronological age, it showed a similar pattern as normal girls' from 7 to 10 years old. The average height of EP girls were taller than normal girls, but the difference started to narrow down after 10 years old. ΔBA/ΔCA declined slightly along with chronological age.

Conclusions: Girls of early-onset puberty have their own pattern of growth and bone maturation.At bone age from 7 to 11 years old, the rate of bone maturation was faster and the growth of height was attenuated with the increase of bone age.After 11 years of bone age, with the increase of bone age, the progress of bone maturation slowed down, and the height began to catch up and approached to the normal growth curve.

P1-222

Infantile Hypercalcemia Type 2 Due to Novel Mutation in SLC34A1 Gene

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Introduction: The SLC34A1 gene encodes the NaPi-IIa cotransporter, which plays an important role in phosphate reabsorption in the kidney proximal tubule. Inactivating mutations of this gene cause nephrolithiasis and osteoporosis, together with clinical pictures such as hypophosphatemic rickets type 1, Fanconi renotubular syndrome type 2, and infantile hypercalcemia type 2.

Case: A 40-day-old male patient presented with medullary nephrocalcinosis and hypercalcemia. He was born at 35 weeks, 2660 g. It was learned that the patient had hyperechogenic kidneys and oligohydramnios on antenatal ultrasonography (USG), and a combined heterozygous mutation in the SLC34A1 gene was detected in the amniotic fluid sample at the 21st gestational week. There were no signs of developmental delay and dehydration in his physical examination. At the time of admission, he had hypercalcemia, lower limit phosphorus level, increased alkaline phosphatase, low parathormone, and hypercalciuria. 25OHD level was normal. In urinary USG, renal parenchyma echogenicity increase and millimetric stones in the renal medulla were detected. 24-hour urine protein level was normal, urine protein electrophoresis and urine glucose were negative, and proximal tubulopathy was excluded. Oral phosphorus solution at a dose of 30 meq/kg/day was started. In the follow-up of the patient, hypercalcemia and hypercalciuria regressed and returned to the normal range.

In the family screening of the patient, a novel variant in the SLC34A1 gene was detected in the father {c.1256G>A (p.S419N) (p.Ser419Asn)(heterozygous)} and mother {IVS6+1G>A (c.644+1G>A)(heterozygous)}. The patient's genetic result, clinical and laboratory findings were found to be compatible with infantile hypercalcemia type 2. In his brother, crystalloid was detected in his urinary USG, his laboratory values were normal and he had no complaints. In the genetic analysis, the same variant changes were detected in the same gene as the patient.

Conclusion: SLC34A1 mutation may present with different clinical manifestations. Despite the absence of significant low phosphate and phosphaturia in our case, success was achieved with the phosphorus treatment that was initiated. Therefore, this mutation should be considered in children with hypercalcemia close to the lower limit of normal or with slightly low phosphorus levels, as in our case. Although the patient's sibling has the same variant changes, the fact that there is no hypercalcemia and only kidney crystalloid can be considered that mutations in this gene may cause a wide spectrum of disease.

P1-223

Real-world data in children with achondroplasia after licensing of Vosoritide

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Background: Achondroplasia (ACH), caused by a pathogenic variant in the fibroblast growth factor receptor 3 gene (FGFR3), is characterized by severe growth failure and may be associated with multisystemic complications. The clinical phenotype is variable and relates to deformity of rhizomelic shortened legs, and myelon compression at cranial base and spine. Recent guidelines are published for diagnostic workflow, neurosurgical, orthopaedic and otorhinolaryngological interventions. Vosoritide, an analog of C-type natriuretic peptide, has been developed for the treatment of short stature in children with achondroplasia, and was approved by the EMA in August 2021 for ACH treatment. In a collaborative approach, we present epidemiological data characterizing the current practice of multidisciplinary treatment in Portugal, Austria, and Germany.

Patients: Medical history and clinical data were obtained routinely as standard of care from 575 children with ACH aged <17 years. Auxological data, safety of Vosoritide therapy and QoL data will be prospectively collected during routine visits.

Results: Since October 2021, Vosoritide had been started in 164 (29%) children: 80 aged 2-6y. (49%), 56 (34%) aged 7-11 y. and 28 (17%) aged >11y. At time of report in April 2022 all patients continued drug therapy. Related to the whole achondroplasia group 19% received a cranial decompression surgery and 8% limb lengthening.

Outlook: (1) To facilitate data collection, an achondroplasia-specific list of items has been inserted in the web-based registry CrescNet. (2) Prospective data acquisition by a multicenter approach aims to increase greater patient safety and longitudinal evaluation of treatment response.

P1-224

High vitamin deficiency throughout childhood. Inma-asturias cohort. Spain

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Background: Vitamin D (25OHD) insufficiency is becoming a public health issue. Adequate 25OHD status during pregnancy may influence the health status of the offspring.

Objective: To evaluate the levels of 25OHD from gestation to 12 years, assessing seasonality and intake.

Material and Methods: Data were obtained from 485 pregnant mothers recruited in Asturias between 2004-2007 and their children from of the Environment and Childhood [INfancia y Medio Ambiente] (INMA) Project, a population-based birth cohort study. Maternal 25OHD levels were analyzed at 12 weeks' gestation and in infancy at 4, 8, and 12 years, as well as maternal age, gestational weeks, gender, seasonality, and vitamin D intake.

Results: The mean maternal age was 32 years (range 18-42). 94.1% of the newborns were term and 47.6% girls. The median of 25OHD in pregnancy was 27.40 ng/ml (range 6.4-66.9), at 4 years 20.90 ng/ml (range 2.77-49.80), at 8 years 25.25 ng/ml (range 8.56-53) and at 12 years 23.00 ng/ml (range 11.00-67.00), being lower in winter and spring, with normal levels of calcium and phosphorus in all of them. The percentages in each of the ages according to the groups of plasma 25OHD levels (Deficiency <20 ng/ml; Insufficiency: 20-29.9 ng/ml; Sufficiency ≥30 ng/ml) are shown in Table 1. The results were presented to the cohort before the age of 8 years, which could have influenced the better 25OHD status at that age, although this was not maintained at 12 years. A statistically significant relationship was found between 25OHD in pregnancy and at 4 and 12 years (rPearson 0.192 and 0.219). The median intake of vitamin D in the diet adjusted for calories in

Table 1. Status of 25OHD in INMA-Asturias Cohort.

	N	25OHD Deficiency (< 20 ng/ml) (%)	25OHD Insufficiency (20-29,9 ng/ml) (%)	25OHD Sufficiency (≥30 ng/ml) (%)
12 weeks' gestation	453	27.4	35.3	37.3
4 years	283	52.7	38.5	8.8
8 years	254	24.0	45.3	30.7
12 years	170	29.4	48.8	21.8

pregnancy was 5.02 μg/day (range 1.57-20.95), at 4 years 2.60 (range 0.96-9.94) and at 8 years 5.13 (range 2.06-12.22), without association with 25OHD levels.

Conclusions: A high frequency of deficient and insufficient levels of 25OHD was detected both in pregnant women and throughout childhood. The estimated intake was lower than recommended in most of the cohort. Periodic nutritional recommendations are necessary for an adequate 25OHD status in childhood.

P1-225

Nephrolithiasis and hypoparathyroidism with normocalcemia – detecting a new mutation solves the mystery

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We report on a 17-year-old patient with hypoparathyroidism which was noticed during the diagnosis of a first renal colic a year and a half ago. At that time, a prevesical ureter stone on the right could be depicted sonographically, which disappeared spontaneously. Initially calcium levels in serum and urine were reported to be normal. However, a slight hypercalcemia and hypercalciuria as well as high normal vitamin D levels without vitamin D substitution were detected intermittently between age 15.5 and 17 years. In addition, hypophosphaturia was repeatedly measured. The family history was unremarkable.

Based on this clinical and laboratory constellations, we initiated a gene panel analysis for hypoparathyroidism. We detected a compound heterozygous mutation in the CYP24A1 gene comprising the variants c.1226T>C (p.Leu409Ser) on one allele and c.1434G>A (p.Trp478ter) on the other allele. Genetic analysis of the parents is underway. The variant c.1226T>C (p.Leu409Ser) is listed in the databases as a pathogenic mutation, while the other variant c.1434G>A (p.Trp478ter) is novel. However, the latter leads to a premature stop codon, which makes a pathogenic effect likely.

Homozygous or compound-heterozygous mutations in the CYP24A1 gene are described as the molecular cause of autosomal recessive type 1 hypercalcemia (HCINF1). As a result of mutations of the 1,25(OH)2D-24-hydroxylase cytochrome P450 (CYP24A1) the degradation of 1,25(OH)2D3 into inactive metabolites is impaired. 1,25(OH)2D3 increases bone resorption, renal calcium and phosphorus reabsorption, and intestinal calcium and phosphorus absorption. Elevated calcium levels associated with elevated serum 1,25(OH)2D3 consecutively lead to PTH suppression.

The clinical manifestations largely depend on the age at diagnosis. Infants may be asymptomatic or may show insufficient weight gain, vomiting, dehydration, lethargy and hypotonia. In contrast, adults with CYP24A1 mutations most frequently present with nephrocalcinosis and/or nephrolithiasis. As additional features abdominal pain, nausea, constipation, pancreatitis, hypertension and neuropsychiatric symptoms are described. The degree of hypercalcemia and symptoms can vary from mild and intermittent to severe. Patients manifesting in infancy usually present with severe courses. Our patient shows a mild and intermittent hypercalcemia with flank pain, nephrolithiasis and borderline arterial hypertension. She is treated with a urin-alkalizing drug and a sufficient daily drinking volume.

Long-term management is focussed on eliminating or minimizing symptoms of hypercalcemia and reducing hypercalciuria, but therapeutical options are limited. Low-calcium and vitamin D diet was started in our patient and is the cornerstone of therapy to minimize the risk of nephrocalcinosis and nephrolithiasis.

P1-226

FGFR3 gene mutation causes hypochondroplasia via autophagy inhibition

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Background: Fibroblast growth factor receptor 3 (FGFR3) is a negative regulator of skeletal development. Gain-of-function point mutations in FGFR3 are responsible for hypochondroplasia (HCH), one of the most common forms of dwarfism in humans. Autophagy is an evolutionarily conserved catabolic process, which is indispensable for cell homeostasis maintenance and stress responses. Dysregulation at the level of autophagic activity consequently disturbs the chondrocyte viability in the growth plate and mediates the onset and progression of multiple bone diseases, including HCH.

Objective: The role of autophagy in HCH and its underlying molecular mechanisms remain elusive. The study aimed to explore the potential role of FGFR3 gene mutation-regulated autophagic activity in the pathogenesis and treatment of HCH.

Methods: We describe a de novo mutation in FGFR3 (G382D) in a patient with HCH. We characterize the impact of the variant on autophagy signaling using a mouse model with the corresponding genome-edited variant FGFR3 (V376D) and support these findings using ATDC5-FGFR3(G382D) cell lines.

Results: We found that mutant activated FGFR3 inhibited the autophagic activity of chondrocytes both in vivo and in vitro. Proteomic analysis in the FGFR3 (V376D, corresponding to human source G382D) mouse model revealed significantly upregulation of HSPB6 expression. Furthermore, we found that HSPB6 inhibited autophagy via activating the ERK/p-ERK signaling pathway. Consistently, in vitro, we found that mutations are critical for ATDC5 cells proliferation and autophagy regulation. Transient transfection of HSPB6 and targeted inhibition of ERK partially rescued FGFR3-mediated inhibition of ATDC5 cells proliferation and autophagy, and the rescue effect was more pronounced by combined treatment.

Conclusions: Our findings reveal that mutant activated FGFR3 inhibits the autophagic activity through activating ERK/p-ERK signaling pathway by increasing the HSPB6 expression level, which may play an essential role in the pathogenesis and treatment of HCH.

P1-227

Primary Hyperparathyroidism caused by a Mutation of the Vitamin D Receptor Gene

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Objective: To present a patient with hypercalcemia caused by a parathyroid adenoma and a deletion of the VDR gene.

Case clinic: The case is that of a 13-year-old male who presented with hypercalcemia, muscle weakness, nephrocalcinosis, two pathological fractures and a family history of nephrocalcinosis. Physical examination was unremarkable, except the presence of a fracture of the left femur.Laboratory findings: Total serum calcium 14.4 mg/dl (8.5 a 10.2 mg/dL), ionic calcium 4.24 mmol/l (1.20-1.38 mmol/l), serum phosphate 3.3 mg/dl (4.0 a 7.0 mg/dl.), urinary calcium normal, serum PTH 233 pmol/L (10 a 55 pg/mL), alkaline phosphatase 390 U/L (86-315 U/L.), 25 (OH)D 18 ng/ml (20 y 40 ng/mL), 1-25(OH)D 189 pg/ml (15,2 – 90,1 pg/mL). Left femoral x-ray with fracture. Bone densitometry showed vertebral and hip osteoporosis. Scintigraphy with sestamibi revealed a right lower parathyroid adenoma. A heterozygous C2 T>C mutation of the VDR gene was found. The parathyroid adenoma was removed surgically with resolution of the hypercalcemia.

Conclusion: VDR Gene mutations can lead to secondary parathyroid adenomas and hypercalcemia.

P1-228

Effect of burosumab treatment on phosphate metabolism and bone health in patients with X-linked hypophosphatemic rickets (XLH). Preliminary data within an Italian sample

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XLH is the commonest inherited form of rickets. Impaired regulation of fibroblast growth factor 23 (FGF23) due to PHEX gene mutation leads to reduced tubular reabsorption of phosphate (TmP/GFR) and 1,25-dihydroxyvitamin D (1,25(OH)2D) synthesis with hypophosphatemia. Patients show rickets and osteomalacia, bone and muscular pain, stunted growth, and reduced quality of life. We report preliminary data on burosumab therapy in a selected sample of Italian patients.

Patients and Methods: We enrolled 15 patients with XLH confirmed by PHEX gene mutation (age 11.1±4.3 yr; 8 M, 7 F) receiving conventional treatment (inorganic oral phosphate salts and calcitriol or alphacalcidol) from 8.2±4.3 yr. Conventional treatment was stopped for 7-10 days and then burosumab (Crysvita, Kyowa-Kirin, Japan) was started (at entry 0.4-0.8 mg/kg/d; maintenance 1.2-1.4 mg/kg/d, s.c. every two weeks). In all patients serum phosphate and TmP/GFR were measured at baseline and after 6 and 12 months of burosumab. In all patients intact FGF23 plasma levels (DiaSorin, Liaison, Saluggia, Italy) and serum 1,25(OH)2D levels (RIA, IDS, UK) were measured at entry, too. In growing patients (n=10) rickets severity score (RSS, Thacher TD, 2019) was assessed at baseline and after 12 months. In adolescents (n=5) approaching growth cessation and epiphyseal fusion Womac score was assessed at baseline and after 6 months of burosumab.

Results: At entry, all patients had hypophosphatemia (2.1±0.4 mg/dL) and reduced TmP/GFR (1.7±0.5 mg/dL). After 6 months: serum phosphate 3.3±0.4 mg/dL, D57%, p<0.0001; TmP/GFR 2.9±0.5 mg/dL, D71%, p<0.0001. After 12 months: serum phosphate 3.0±0.5 mg/dL, D43%, p<0.0001; TmP/GFR 2.6±0.5 mg/dL, D53%, p<0.0001. Mean intact FGF23 plasma levels and serum 1,25(OH)2D levels was 122.4±74 ng/mL (in all patients >40 ng/mL) and 27.4±7.7 pg/mL (nv 20-120 pg/mL), respectively. RSS and Womac score improved significantly (5.9±1.6 to 2.6±0.8, p<0.0001) and (71.2±8.1% to 34.8±5.6%, p<0.0001), respectively. Injection-site reaction was reported in one patient. No other adverse effect was observed.

Comments: After transition to burosumab the improvement of serum phosphate and RSS was greater than that observed during the conventional therapy. Biochemical effect on serum phosphate

and TmP/GFR was maintained after 12 months of burosumab treatment. RSS and Womac score were effective to assess bone health in children and adolescents with XLH receiving burosumab treatment, respectively.

P1-229

Neurological symptoms leading to Pseudohypoparathyreoidism 1B (iPPSD3)

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Background: Pseudohypoparathyroidism is a rare congenital disorder presenting with variable symptoms and features. Since 2016 a new international nomenclature subclassifies the different forms of pseudohypoparathyreoidism as inactivating PTH/PTHrP signalling disorders (iPPSD). Pseudohypoparathyreoidism 1A (iPPSD2) and 1B (iPPSD3) are mainly characterized by resistance of parathyroid hormone (PTH) with high serum PTH levels and thyrotropin (TSH) resistance. In both forms, iPPSD2 and 3, cerebral calcifications can be found. As these patients may develop hypogonadotropic hypogonadism and growth hormone deficiency, puberty and height velocity of patients should be closely monitored.

Case Presentation: We present a four-year-old boy, hospitalised with the suspected diagnosis of epilepsy. He showed clinical features reminding of absence seizures and musculoskeletal convulsions. As ionized calcium concentration was very low at several occasions (0.84 mmol/l, range: 1.0-1.9 mmol/L) hypocalcemia was found to be the cause of the recurrent absences.

The patient presented with an excessive high level of PTH (515 pg/mL, range: 15-65 pg/mL)) as well as with high serum phosphate levels (2.91 mmol/L, range: 1.05-1.8 mmol/L). We started to substitute calcium (2 g/day) and alfacalcidol (50 ng/kg per day). In order to avoid hypercalciuria and consecutive nephrocalcinosis we closely monitored serum calcium levels as well as urine levels of calcium and phosphate.

Due to macrosomia and normal cognitive development, we suspected pseudohypoparathyreoidism 1B. On genetic investigation, a hypermethylation of *NESP55* and a hypomethylation of *NESPAS/GNASXL* in the *GNAS* locus were found. This pattern has already been described and associated with the diagnosis of pseudohypoparathyreoidism 1B. The assessment of the DNA of patient`s parents with regard to a potential UPD20 is underway. In addition, we plan a MRI to reveal cerebral calcifications.

Conclusion: Hypocalcemia may cause neurological symptoms such as seizures. A thorough work-up of the calcium-phosphate metabolism including genetic analysis is necessary to define the etiology of the disorder such as PHP1B (iPPSD3) in the presented case.

P1-230

CLEIDOCRANIAL DYSPLASIA: A 3 Generations Family with a Novel Mutation, and Growth Hormone treatment

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Background: Cleidocranial dysplasia (CCD) is a very rare dominantly inherited autosomal bone disorder mainly characterized by hypoplasia or aplasia of clavicles, failure of cranial suture closure, dental anomalies, short stature, and other changes in skeletal patterning and growth. Heterozygous loss-of-function mutations cause the majority of the abnormalities in the run-related transcription factor 2 gene (RUNX2). This gene is located on chromosome 6p21 and its function is linked to osteoblast differentiation and chondrocyte maturation.

We report a 3 generations family with a novel RUNX2 mutation.

Case Report: A 12-year-old boy, a descendent of a consanguineous indigenous Brazilian family, was sent to our hospital by his dentist, after short stature, high palate, impacted supernumerary teeth, and persistent temporary milk teeth. On examination, his height was 135cm (-2.27 SDS, according to WHO standards), and a sitting height/ height of 0.53. He had facial dysmorphism with parietal bossing. His Tanner staging was prepubertal. A full skeleton X-ray revealed a broadening of the frontal and lambdoid sutures, hypoplastic clavicles, wide pubic symphysis with ossification delay, rhizomelic shortening of upper and lower limbs, and hand bone abnormalities. There were no vertebrae malformations. Bone age and bone mineral density looked normal. Blood laboratory tests showed normal thyroid function, renal function, ionized calcium, phosphate, magnesium, 25-hydroxyvitamin D, parathyroid hormone, and alkaline phosphatase. IGF-1 was 64ng/mL (NR: 49-487 ng/mL) and IGF-BP3 was 5.8 μg/mL (NR: 2.7-8.9 μg/mL).

The molecular analysis detected a novel heterozygous mutation NM_001024630.3p.T155P (c.477A>C) in the RUNX2 gene. As his father and his paternal grandfather also presented short stature [160cm (-2.27 SDS), and 155cm (-2.95 SDS), respectively] and several skeletal abnormalities, genetic testing was performed, and the same mutation was found.

A clonidine stimulation test preceded by testosterone priming was performed on the boy and the peak growth hormone (GH) response was 9.0 μg/L (NR: > 7 μg/L). Because of his short stature, GH therapy was started at 30 μg/Kg/day, with a good response in one-year time [147cm, (- 2.07 SDS)], and no adverse side effects.

Discussion: CCD is diagnosed clinically (short stature with severe dental and clavicles anomalies) and supported by X-ray. Molecular genetic analysis reveals a RUNX2 mutation in about 70% of the cases. Data on GH treatment for CDC are minimal. In our patient, it has been hopeful, but we are aware of the need for randomized controlled trials involving more patients.

P1-231

A Case Report of Vitamin D-Dependent Rickets Type 2A Without Alopecia

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Introduction: Vitamin D-dependent rickets type 2A (VDDR2A) is a rare autosomal recessive disease that caused by mutations in the vitamin D receptor (VDR) gene.Hypocalcemia, high alkaline phosphatase, secondary hyperparathyroidism, high 1.25-OH vitamin D (1.25-OHD) levels despite normal 25-OH vitamin D (25-OHD) levels are diagnostic.The clinical signs are rickets, short stature, recurrent lung infections and total/subtotal alopecia.Here, we present a case of VDDR2A without alopecia.

Case: A 1.5-year-old male patient was admitted because of inability to walk.It was learned that he was born on term with 3150 gr and there was no consanguinity between his parents.On physical examination, height: 6 cm (-2.07 SDS), weight:10.6 kg (-0.73 SDS), body mass index:18.35 kg/m2 (1.08 SDS), his anterior fontanelle had closed, wide wrists, rachitic rosaries, and he did not have alopecia.The laboratory findings were as followed; calcium: 6.1 mg/dl, phosphorus: 3.5 mg/dl, alkaline phosphatase: 1313 IU/L, parathormone: 454 pg/ml, 25-OHD: 9.45 ng/ml, 1.25-OHD: 23.26 pg/ml, urinary calcium/creatinine: 0.03.Oral calcium lactate 75 mg/kg/day and intravenous calcium gluconate 4x1 ml/kg (elementary calcium 36 mg/kg/g) treatments were started. 150.000IU vitamin D stoss was given. The patient,whose hypocalcemia did not improve despite these treatments, was started 2x0.5μg calcitriol treatment. A diagnosis of VDDR was considered in this case due to long-term treatment-resistant hypocalcemia, need for high-dose calcitriol (3x5 μg), and relatively increased 1.25-OHD compared to 25-OHD. The genetic analysis revealed that C.803T>C (p.Ile268Thr) homozygous in the 8th exon of the VDR gene.Our case had a high calcitriol dose requirement until the age of 3.5 (16.5 μg/day).The patient, who is currently 11 years and 9 months old, has normal anthropometry and normocalcemia and normal urinary calcium/creatinine ratio while receiving 4x7 g calcium lactate (60 mg/kg/g) and calcitriol 3x1 μg (56 ng/kg/g) treatments. However, his BMD score is observed to be shifted towards osteosclerosis.

Results: The phenotype-genotype correlation has been defined in cases with VDDR2A.Although it has been reported that the changes in the ligand binding site have a milder course and generally do not cause alopecia, as in our case, the dose of calcitriol, which provides normocalcemia, was high inconsistently with the mild clinical course.Although alopecia is helpful in the diagnosis in VDDR2A cases, it should be kept in mind that it will not be seen in some cases, and the phenotype-genotype relationship may show case-specific differences in each case.

P1-232

Beyond genetics: Three sisters with pseudoypoparathyroidism 1A

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Pseudohypoparathyroidism (PHP) is an hereditary disorder characterized by resistance to parathyroid hormone (PTH) and in varying degrees to TSH, GHRH and FSH/LH, and caused by loss-of-function mutations in the GNAS gene, encoding the membrane protein Gs-alpha. Pathognomonic of these patients is a dysmorphic phenotype, called Albright's Osteodystrophy, which includes short stature, obesity, round face, mental delay, subcutaneous ossifications and brachydactyly. The most frequent subtype is PHP 1A, caused by maternal segregated mutations. The aim of our report is to describe, starting from the case of three sisters, the enormous phenotypic variability of this pathology.

Three sisters came to our observation for hyperparathyroidism and hypothyroidism. The oldest, met at the age of 4, presented hypocalcemia, hyperparathyroidism, congenital hypothyroidism, mild psychomotor delay, brachydactyly, stature on the low normal limit (15°P), and moderate excess weight. The second, met at the age of 6, presented hyperphosphatemia, hyperparathyroidism, acquired hypothyroidism, brachydactyly, round face and moderate obesity. In the end, the youngest, met at the age of 1, was affected by congenital hypothyroidism, hyperparathyroidism, severe short stature (-2.9 SD), and moderate obesity.

In the suspicion of PHP, a GNAS study was carried out, calcitriol was started and levothyroxine was continued, with monitoring of calcemia, phosphorus, PTH and thyroid hormones. The clinical exome study revealed heterozygous deletion in GNAS with maternal segregation (c.118_139 + 51del), never described in literature before, with consequent diagnosis of PHP 1A. Despite the identical genotype, the three patients, in addition to a different onset of disease from a clinical-auxological and biochemical-hormonal point of view, presented, during the follow-up, significantly different clinical course and complications. In fact, the older sister has, to date, only a short stature (-2.26 SD) and mild mental retardation; the second sister has a stature in the range but developed osteorarefactions and osteosclerosis of the hands and feet which required orthopedic management and in the end, the youngest, presents a remarkably early onset (before 2 years of age) of severe obesity, short stature and diffuse subcutaneous ossifications.

These cases are emblematic because demonstrates how pseudohypoparathyroidism is a very heterogeneous pathology, with considerably different presentation, course and type of complications from patient to patient, even among close relatives with the same genotype. The study of the GNAS gene, which in our case has allowed us to identify a mutation with maternal segregation never described in literature before, is fundamental for the diagnostic confirmation and the consequent multidisciplinary management.

P1-418

Serum Bone Markers and Its Associations with Measures of Bone Health in Adolescents with Alpha-thalassemia Requiring Frequent Blood Transfusion

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Background: People with thalassemia have decreased bone mineral density (BMD). Whereas a growing body of research has demonstrated associations between circulating bone markers and BMD in many conditions, such data in adolescents with alpha-thalassemia who required frequent blood transfusion (BT) are limited.

Objective: To evaluate the associations between measures of bone health and serum bone markers in adolescents with alpha-thalassemia who required frequent BT.

Methods: Adolescents with alpha-thalassemia were recruited from thalassemia clinic. Inclusion criteria were i) ages 10-21 years, ii) received blood transfusion ≥6 times/year, iii) regularly followed up in our clinic, iv) BMI z-score > -2 to < -2, and v) apparently healthy. Participants were excluded if they had uncontrolled conditions or received medications affecting bone metabolism. L1-4 spine (LS) and whole-body less head (WB) BMD were measured using Lunar Prodigy DXA. BMD z-score was converted using instrumental software. Trabecular bone score (TBS) was calculated using iNsight™ software to determine microarchitecture of the lumbar spine. Fasting serum osteocalcin, c-terminal telopeptide (CTX) and LDL-c, a recently emerged osteoclast inhibitor, were served as bone markers.

Results: Thirty-two participants were enrolled to the study [45% male, mean age (±SD) 14.2±3.0 years, height z-score -0.1±0.25, BMI z-score -0.1±1.2, Tanner stage 3.5±1.5, pre-transfusion hemoglobin (PTHb) 8.8±0.8 g/dL]. Twenty-five (78%) participants had hemoglobin H-Constant Spring. Average BT volume was 113±32 mL/kg/year. Mean TBS, LSBMD and WBBMD z-scores were -0.04±0.30, -1.45±1.11 and -1.23±0.78, respectively. The prevalence of BMD z-scores <-2 at both measured sites was 19%. PTHb correlated with TBS (r=0.491, p=0.008), however, the association was insignificant in regression models. Ferritin did not correlate with TBS, BMD at both sites nor serum bone markers. CTX z-score (β±SE: 0.31±0.13; p=0.032), but not OC z-score or LDL-c, was positively associated with LSBMD z-score independent of BMI and height z-scores, Tanner stage and 25OHD. However, the association became insignificant after further adjusting for PTHb (p=0.066). LDL-c (β±SE: -0.02±0.01; p=0.024) negatively and CTX (β±SE: 0.20±0.08; p=0.029) positively associated with WBBMD in the fully adjusted model.

Conclusions: Elevated CTX is associated with increased LSBMD and WBBMD in adolescents with alpha-thalassemia who required frequent BT. Further, we also found an association between LDL-c and WBBMD. Thus, LDL-c could be an alternative low-cost screening for bone health in this population.

P1-419

Early-Stage Radiological Markers of Endothelial Dysfunction and Cardiovascular Findings in Patients with Osteogenesis Imperfecta and Their Genotype-Phenotype Correlations: A Case-Control Study

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Introduction: Osteogenesis imperfecta (OI) is a disease related to collagen synthesis or fuctions. Collagen is found in many areas of the cardiovascular system. Endotelial dysfunction can be detected at an early stage before the symptoms become evident by non-invasive radiologic methods such as flow-mediated dilatation (FMD), carotid intima-media thickness (CIMT), and ventricular functions measurements, which may serve as indicators of endothelial dysfunction. This study aimed to compare early-stage radiological markers of endothelial dysfunction and cardiovascular diseases and to assess the correlations of these parameters with genotype.

Results: Thirty(14girls/16boys) OI cases from 24 different families were evaluated. In the molecular analyzes; There were pathogenic variants in the COL1A1 gene in 18(60%) cases, in the COL1A2 gene in 3(10%) cases, in both COL1A1 and COL1A2 genes in 1(3.3%) case, in the FKBP10 gene in 4(13.3%) cases, in the SERPINF1 gene in 2(6.7%) cases and in the P3H1 gene in 2 (6.7%) cases.

Ventricular dysfunction indicators (right and left ventricular myocardial performance indices[RVMPI&LVMPI]) were statistically significantly higher in the OI group than in the control group. The cases were analyzed according to molecular variants, there was no difference between gene variants in terms of RVMPI and LVMPI. In terms of right ventricular diastolic function indicators (tricuspid A&E waves), there was no significant difference between the OI group and the control group, while the E/A ratio was statistically significantly lower in the OI group. There was no difference between the groups in terms of mitral E wave, however, a statistically significant decrease was in the A wave OI group. CIMT was low and FMD was high in the OI group, these differences were statistically significant. According to molecular variants; There was no difference in terms of FMD and CIMT.

Conclusions: This study propounded that patients with OI without clinical signs of the cardiovascular system may have ventricular and endothelial dysfunction in the early period.

Table 1. Endothelial dysfunction indicators in cases

	Oİ(n:30)	Healty control(n:30)	
Mitral E(cm/s)	90,53±17,44	96,67±12,58	p>0.05
Mitral A(cm/s)	50,43±10,28	57,7±13,1	p<0.05
E/A	1,86±0,52	1,73±0,31	p>0.05
Tricuspid A	52,13±12,56	47,07±10,1	p>0.05
trE/A	1,31±0,26	1,51±0,33	p<0.05
LVMPI	0,41±0,10	0,22±0,08	p<0.05
RVMPI	0,38±0,13	0,24±0,84	p<0.001
CIMT	0,42±0,06	0,34±0,46	p<0.001
FMD%	7,00±3,06	12,14±1,99	p<0.001

P1-420

Skeletal phenotype in patients with the monogenic Mulibrey nanism disorder

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Background: Mulibrey nanism (MUL) is a monogenic growth disorder with typical craniofacial features, perimyocardial heart disease, infertility and predisposition to tumors. MUL is caused by mutations in the TRIM37 gene encoding TRIM37 protein possessing E3 ubiquitin-ligase activity.

Objective and Hypotheses: MUL patients have pre- and postnatal growth failure with an average birth length SDS of -3.1 and birth weight SDS of -2.8. Clinically, patients are gracile with relative macrocephaly, thin extremities and narrow shoulders. Facial features include triangular face with high, broad forehead and low nasal bridge. Fibrous dysplasia of long bones has been observed in up to 25% of the patients but the full spectrum of skeletal features remains unknown. We conducted a cross-sectional study in order to further clarify the skeletal phenotype.

Methods: The study included altogether 33 patients with MUL, aged 4.5-48 years (14 females and 19 males, median age 16.7 years) undergoing routine check-ups at the Children's Hospital. Radiographs of the long bones and spine were assessed for skeletal features. Hospital records were reviewed for clinical characteristics, bone health and fractures.

Results: Radiographic analysis confirmed significant skeletal abnormalities related to MUL. Skeletal changes were present in all patients. The vertebral bodies were anomalous in all patients with ceased growth. The vertebral bodies were high, with an increased ratio between the vertical diameter and the sagittal diameter. Vertebral endplates were concave. The long bones were slender. The metaphyses were broad in comparison with the narrow diaphyses. Bowing of long bones was observed in all patients. Bowing of the radius was most frequent, observed in 31/33 (94%) of patients, followed by bowing of the fibula in 25/33 patients (76%). The cortices of the long bones were thick in all 33 patients and the medullary cavities were narrow. Cortical thickness was most pronounced in the femur and radius. Radiographic changes of fibrous dysplasia were found in 19/33 patients (58%); changes were monostotic in 63% and polyostotic in 37%. Fibrous dysplasia was equally frequent in females and males. Altogether 14/33 patients (42%) had a history of fractures.

Conclusions: Our study confirms that in addition to short stature, patients with MUL have a specific skeletal dysplasia. The characteristic features include high vertebral bodies, slender and curved long bones with thick cortex and narrow medullary cavity, and a high prevalence of fibrous dysplasia and fractures. Our findings suggest an important role for TRIM37 in cellular functions governing skeletal homeostasis.

P1-421

Novel *ACAN* Variants in Eight Chinese Families with Short Stature and Literature Review

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Context: *ACAN* gene is located at 15q26.1 and encodes aggrecan, which is a critical proteoglycan component of cartilage extracellular matrix. Heterozygous variants in *ACAN* are associated with short stature, premature growth cessation, and impaired bone maturation. A comprehensive understanding of the genetic and clinical characteristics of patients with *ACAN* mutations helps to improve the overall management of an individual.

Objective: We sought to analyze eight Chinese short stature children with heterozygous *ACAN* mutations and perform a literature search to firstly summarize the phenotypic spectrum, secondly elucidate the effects of age, sex and mutation type on the height of *ACAN* mutations carriers, and finally investigate the treatment outcome of growth-promoting therapy.

Patients and Methods: Eight probands from unrelated families were genetically evaluated by Whole-Exome Sequencing (WES). Subsequently, we reviewed the literature to summarize the clinical characteristics, genetic findings, and the efficacy of growth-promoting therapy in *ACAN*-positive individuals.

Results: We identified seven novel *ACAN* mutations and one recurrent variant. Patients in our center showed somewhat hypertelorism (4/8), broad nose (4/8), long philtrum (2/8), flat nasal bridge (2/8), brachydactyly (1/8) and short neck (1/8). Besides, the variants in the *ACAN* gene might display high penetrance. Combined with the literature review, we found that Hands/feet deformity (50%), spinal deformity (36.26%), and head/neck deformity (30.49%) were more often observed in the patients with *ACAN* heterozygous mutations. Truncating variants had a more severe effect on height, and height was weakly negatively correlated with age at diagnosis. Individuals had received growth-promoting therapy with variable levels of height SDS score improvement.

Conclusion: This study further expands the variation spectrum of the *ACAN* gene and suggests that facial dysmorphic features are not prominent in Chinese short stature population. In addition, patients who receive growth-promoting treatment before puberty may reap better therapeutic benefits, while also being aware of the duration of treatment.

P1-422

A heterozygous variant of CYP3A4 in a Chinese boy with Vitamin D-dependent rickets type 3

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Background: Vitamin D-dependent rickets type 3 (VDDR3) is a rare autosomal dominant inheritance disease, which is caused by the gain-of-function mutation in CYP3A4 (c.902T>C p.Ile301Thr).

Case Presentation: We report the case of a 32-month-old boy presented with discomfort of both knee-joints, poor mobility, and gait abnormality when running. Laboratory examinations revealed low concentrations of serum calcium, phosphorus, and 25-OHD, as well as high levels of PTH and ALP. X-ray films showed brush-like changes in the pelvis and lower extremities. The medical data of the patient was collected and analyzed. We used whole exon sequencing to detect the pathogenic gene and found a variant in CYP3A4, a heterozygous single nucleotide change (c.902T>C p.Ile301Thr) which was further confirmed using Sanger sequencing. However, this variant was not found in his parents. After several months of oral vitamin D treatment, the pathological changes improved in X-ray films.

Conclusion: This was the first reported case of VDDR3 in China. The clinical features of VDDR3 are mainly skeletal abnormality and impaired growth, and its diagnosis depends on serum levels of 25-OHD and 1,25-(OH)2D levels, as well as whole exon sequencing. No effective treatment has been found yet, and there is lack of evidence on the safety of large doses of oral vitamin D. As such, regular follow-up visits are essential during treatment.

P1-423

A case report investigating hereditary hypophosphataemic rickets with hypercalcuria (HHRH), a suspected novel mutation and the FGF23 'red herring'

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Objective: To explore the clinical manifestation of a case of hereditary hypophosphataemic rickets with hypercalcuria (HHRH), describe a potentially novel mutation and identify key learning points in the diagnosis and management.

Background: Inherited forms of hypophosphoatameic rickets such as XLH have phosphaturia, often mediated by elevated FGF-23 levels and low or inappropriately normal 1,25 OHD levels. Conversely, in HHRH, loss of function mutations in the SLC34A3 gene, which encode the proximal renal tubule sodium phosphate co-transporter, prevent proximal tubule phosphate re-absorption; the FGF-23 levels are low and the 1,25 Vitamin D levels are elevated, resulting in hypercalciuria. Treatment is with oral phosphate only as active vitamin D is contraindicated due to the risk of nephrocalcinosis.

Case Report: A female infant presented at 12 months old with rickets. There was no family history of metabolic bone disease. The co-existing Vitamin D deficiency was corrected. Initial investigations also showed a low phosphate 0.47nmol/l (1.42-1.99mmol/l), normal calcium 2.33mmol/l (2.20-2.60mmol/l), elevated ALP 1140IU/L (142-336iu/l), inappropriately normal PTH 1.9pmol/l (1.5-7.6pmol/l) and an elevated 1,25 OHD 187pmol/l (20-120pmol/l). Further investigations demonstrated phosphate loss (TmP/GFR 0.9mmol/l) (1.15 - 2.44), with an initially reported high FGF-23 1073RU/ml (<100). The urine calcium: creatinine ratio could not be calculated due to a low urine creatinine (urine calcium 1.08, urine creatinine <1). Due to delays in genetic test results, she was presumed to have FGF-23 mediated hypophosphataemic rickets and commenced on oral phosphate and low doses of activated Vitamin D.

Subsequently the genetics report demonstrated a homozygous mutation on SLC34A3 gene (NM_080877.2: c.1211G>C p.(Gly404Ala) Location: GRCH37(hg19) Chr:9:140129059) with confirmed biparental inheritance. This has been classed as a variant of uncertain significance until functional mRNA analysis is undertaken. Based on these genetic results alfacalcidol was discontinued. The FGF-23 result was re-visited, which identified, the C-terminal fragment had been measured (which has a longer half-life), rather than the biologically active molecule 'intact' FGF-23.

Conclusion: Clues to the diagnosis of HHRH include an elevated urine calcium: creatinine ratio, elevated 1,25 Vitamin D and a normal FGF23. The learning points here include measuring 'intact' FGF-23 and not to overlook a urine calcium in the presence of an undetectable urine creatinine. Genetic testing is crucial in the diagnosis of hypophosphataemic rickets to ensure appropriate therapy. This potentially novel mutation is undergoing functional analysis in an effort to further understand the genotype phenotype relationship.

P1-424

Therapeutic approach to primary hyperparathyroidism: A case-report from one pediatric endocrinology center

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Primary hyperparathyroidism is a condition characterized by one or more hyperfunctioning parathyroids leading to hypercalcemia and inappropriately normal or elevated levels of parathyroid hormone (PTH). Clinically it can occur asymptomatically or manifests with osteopenia, increased risk of pathological fractures, nephrolithiasis, gastrointestinal symptoms (vomiting, constipation, abdominal pain) or asthenia.

We report the case of A.L.M, a 15-year-old female who went to the Emergency Department of our Hospital for abdominal pain and nausea, also complaining appearance of asthenia since few weeks.

The biochemical screening showed as only noteworthy alteration a hypercalcemia (Ca tot. 12.6 mg/dl) confirmed in a second sample (Ca 12.8 mg/dl) 7 days apart and associated with high levels of PTH (207 pg/ml) with normal phosphoremia and 25OH vitamin D.

She was sent to our attention and subjected to further investigations that led to an ultrasound finding of hyper vascularized hypoechoic nodular formation at the lower margin of the left thyroid lobe. Tecnetium-99 Parathyroid Scintigraphy confirmed an "area of hyperaccumulation compatible with parathyroid adenoma".

It was also documented by lumbar and total-body DEXA a bone mineral density below the expected range for age (z-score -1.3) and a normal abdominal ultrasound. Although there was no familiarity for endocrinological diseases, molecular analysis of RET gene was performed, resulted negative.

Treatment consisted of parenteral fluid therapy, subsequently shifted enterally, in combination with diuretic treatment with Furosemide. For the scarce calcemic control (13.6 mg/dl) and the resumption of gastrointestinal symptoms, associated with the appearance of bone pain, therapeutic attempt with Cinacalcet was performed. It brings simultaneous reduction in calcium serum levels (11.5 mg/dl), that made possible to discontinue diuretic treatment.

The girl was then subjected to surgery for remove the adenoma and to improve its accuracy, intraoperative dosage of PTH (from 456 to 74 pg/ml) was performed. The subject undertook post-surgical supplementation with Calcium and 1,25OH vitamin D, progressively reduced until suspension in about 2 months.

Although very rare in pediatric age, primary hyperparathyroidism from parathyroid adenoma is a diagnosis to consider in patients with PTH-dependent hypercalcemia.

Unfortunately, medical treatment not always can control symptoms, so that in our patient it was necessary to use off-label Cinacalcet, a calcimimetic drug used in pediatric patients with secondary hyperparathyroidism from chronic kidney failure. Our experience demonstrates the effectiveness of this drug even in the treatment of a primary hyperparathyroidism in pediatric age in the absence of significant side effects.

P1-425

Association between mothers, breast milk, and infants vitamin D at 2 weeks of age in Japan

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Introduction: Breast milk is a perfect food, but it can be deficient in vitamin D. In the Danish study, vitamin D was correlated in mothers, breast milk and not in breast milk and infants. We investigated the correlation between mother, breast milk, and infants vitamin D levels in Japan.

Materials and Methods: This study included 84 pairs of mothers and 2-week-old infants born at the Iizuka Hospital and Vitamin D including D2, D3, 25(OH)D2 and 25(OH)D3 in mothers, foremilk, hindmilk and infants were determined by LC-MS/MS. We defined D2+D3 as VD and 25(OH)D2+25(OH)D3 as VDOH.

Results: We observed seasonal variation in VD and VDOH, with high summer and low winter levels in mothers and breast milk. Both VD and VDOH showed a correlation between mothers, breast milk and infants. However, because infants VD and VDOH were correlated with the proportion of formula, analysis of 24 pairs of fully breastfed infants showed no correlation between breast milk and infants. We found that there was a mothers/breast milk and mothers/infant VD and VDOH correlation, but there was no breast milk/infants VD and VDOH correlation as previously reported.

Discussion: It may appear that the correlation between breast milk and infants is not so small as to be due to the abundance of VD and VDOH in breast milk.

Conclusions: In Japan, infants vitamin D was dependent on the proportion of fomula, and there was no correlation between breast milk and infants vitamin D.

P1-426

Epidemiology of Childhood Fractures in Bulgaria: A Retrospective Survey

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Objectives: The results from several European studies done during the last 25 years show that fractures are common in childhood with the highest incidence in pubertal years. Fractures are more prevalent among males, and the distal arm is the most common location. The role of the body weight as a risk factor for fractures in childhood is still unclear and under debate.

Methods: A survey about fracture history and the presence of concomitant skeletal or chronic illnesses have been conducted at 14 high schools in the city of Varna, Bulgaria, among students 16-19 years of age. The survey was completed correctly by 2513 students (1291 girls, 1106 boys, 116 without sex assignment) - 415 filled in electronically (Google forms) and 2098 on paper. All forms were filled in by a parent or by a parent and the student together.

Results: A total of 612 students (24% of all, 57% males) had fractured during childhood - 257 females (20% of females) and 337 males (30% of males), with a total incidence of 13.1/1000/years. Reported 195 males (58%) with 1 fracture, 86 (26%) - 2 fractures and 56 (16%) - 3 or more fractures. More than half of the fractures among males (57%) happened between 12–16 years of age. Among females, 179 (69%) had 1 fracture, 51 (20%) - 2 fractures and 27 (11%) - 3 or more fractures; 50% of all fractures among females between 10-14 years of age. The most common fracture site is the upper limb (72% in boys, 65% in girls), lower limb (20% boys, 27% girls), 8% in both sexes with other locations (clavicula, ribs, skull, etc). Girls with overweight/obesity are 9% in those without fractures, 10% in those with 1 fracture, 15% in those with 2 or more fractures and 21% in those with 4 or more fractures. Boys without fractures are overweight/obese in 16% and those with 3 or more fractures in 22%. Those with fractures (8% boys,17% girls) had other musculoskeletal complaints/problems – most often knees (33%, 30%), scoliosis (21%, 16%), lower back pain (14%, 18%). The same complaints with similar distribution are reported by 7% of the boys and 13% of the girls without fractures.

Conclusions: We present the first Bulgarian study on the epidemiology of childhood fractures. The results are comparable to those published earlier from other countries. More data is needed to reveal the role of adipose tissue on bone metabolism and bone strength.

P1-427

The mutation of the FGFR3 gene causes familial acanthosis nigricans with hypochondroplasia syndrome

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Objective: Acanthosis nigricans (AN) is characterized by velvety and papillomatous pigmented hyperkeratosis of the flexures and neck. Mutations in fibroblast growth factor receptor 3 (FGFR3) gene have been identified as one of the causes of skeletal dysplasia with AN. However, there have been few reports about familial AN with hypochondroplasia. Here we report a familial case with FGFR3 gene mutation.

Case Reports: A 16-year-old boy with no significant past medical history was referred to our institution because of short stature. He was born at term by spontaneous vaginal delivery and his birth weight was 3370g. His height, weight, and BMI were 139.10cm (SDS -2.74), 3.06kg (SDS -1.39) and 18.76 (SDS -0.06), respectively. His testicular volume was 4.0 ml and Tanner stage I for pubic hair. His bone age was estimated to be 10.5 years old (SDS -0.55) based on Greulich-Pyle method. The patient presented relative macrocephaly and upper-to-lower body-segment ratio (1.4) indicated abnormal body proportion. In the developmental state, there was no intellectual disability but poor growth. He presented hyperpigmentation with a velvety texture, which could be suspected as acanthosis nigricans on the neck, axilla, trunk and abdomen. Acanthosis nigricans was confirmed by histopathological study of a 4mm punch biopsy from the abdominal region. Fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR) were within normal range. The growth hormone stimulation test induced by insulin and arginine showed a growth hormone peak of 14.57 ng/ml. The characteristics of short stature and generalized hyperpigmentation were observed not only in the patients but also in the mother and grandfather. Genetic studies for hypochondroplasia using genomic DNA extracted from peripheral lymphocytes was conducted, and the genetic tests confirmed the presence of a mutation in the FGFR3 mutation. The proband had a heterozygous mutation of c.1949delinsTTCT, which lead to the p.[(Lys650Ile;Lys650_Thr651insLeu)] mutation at the protein level. The same mutation was detected in a heterozygous state in the mother and grandfather.

Conclusion: We describe a family with AN caused by an autosomal dominant mutation in the FGFR3 gene. Therefore, the mutations of FGFR3 should be taken into consideration in patients with AN accompanying hypochondroplasia.

P1-428

Extra-articular calcification in an adolescent boy: where history is paramount

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A 15-year-old boy, an active sportsperson, presented to an orthopaedic surgeon with a painful left elbow. He had no history of preceding trauma, had full range of motion of his elbow and was systemically well. Imaging demonstrated extra articular calcification at the distal humerus. Serum phosphate was elevated at 2.53mmol/L [1.10-1.80] with calcium 2.48mmol/L [2.10-2.60] and tubular reabsorption of phosphate of 94.6% [82-100%]. He was then referred for endocrine assessment, where a history of short tooth roots was elicited. A diagnosis of hyperphosphatemia due to a mutation in GALNT3 was suspected. Dietary phosphate restriction was commenced. Additional investigations revealed a 9mm of calcification medial to the greater tuberosity of left hip and nephrocalcinosis on renal ultrasound. A phosphate binder (Sevalmer) was added, aiming to reduce calcification.

Over the following eight months, significant enlargement of the elbow lesion occurred, with worsening pain, reduced mobility limiting sporting activity, accompanied by deterioration of mental health. Serum phosphate remained elevated 2.22 mmol/Lwith a calcium in the normal range 2.31 nmol/L, low FGF23 13.6 ng/L [23.2 – 95.4 ng/L] with tubular reabsorption of phosphate 98.04% [82-100%]. Radiologic imaging confirmed significant increase in calcification at both left elbow and left hip. Surgical resection was undertaken, due to worsening symptoms with marked joint restriction. Other medical interventions being trialled or considered include acetazolamide (carbonic anhydrase inhibitor), NSAIDS or glucocorticoid as anti-inflammatory agents, IL1 blockade (Anakinra), Monoclonal antibody against IL-1Beta or anti-mineralisation therapies with sodium thiosulfate.

Hyperphosphatemia Familial Tumoral Calcinosis is a rare, disabling disorder characterised by ectopic calcifications, painful swellings and enamel hypoplasia with bulbous tooth roots (1, 2). Periarticular calcification leads to pain, reduced range of movement and impaired physical function(1). It is caused by autosomal recessive inheritance of a pathological variant in either the gene encoding FGF23, GALNT3 or KLOTHO (1-3), with resultant deficiency of/or resistance to the phosphate regulating hormone fibroblast growth factor 23(1,3). Less common features include small vessel calcification, testicular microlithiasis and angioid streaks of the retina(1-3).

The case underlines the importance of a careful history, the unusual history of short tooth roots enabling rapid confirmation of the genetic diagnosis. The main aim of treatment is to reduce serum and urinary phosphate and to reduce pain, though there is no definitive cure (1, 4). Lesion resection is reserved for where the condition affects activity of daily living but may have variable outcomes (3, 4).

P1-429

Progressive pseudorheumatoid dysplasia as a cause of short stature

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Introduction: Progressive pseudorheumatoid dysplasia (PPRD) is a rare genetic bone disorder characterised by the progressive degeneration of articular cartilage leading to pain, stiffness, joint enlargement and short stature. PPRD occurs due to a mutation in cellular communication network factor 6 (*CCN6*)/Wnt1-inducible signalling protein 3 (*WISP3*) gene, encoding a 354 amino acid signalling factor involved in BMP/WNT signalling and mitochondrial function. Diagnosis is based on clinical and radiographic findings and confirmed by genetic analysis.

Case: A female, born with normal birth weight to consanguineous parents, presented at 4 years with a waddling gait, mild cavovarus foot deformity with restricted joint movements. She had poor growth from age 5. At age 11.7 years, when referred to Paediatric Endocrinology, her height was -2.33 SDS, BMI +3.0 SDS, head circumference +1.1 SDS. She had restricted extension of fingers, elbows, knees and ankles. She attained menarche at 13 years; (near) final height was 136cm (-4.0 SDS). She had autoantibody-negative insulin-dependent diabetes mellitus with low C-peptide. Her developmental milestones, hearing and vision were normal. Mother was 157.8 cm, father's height was unknown. Maternal grandmother suffered from arthritis. Two cousins had insulin-dependent diabetes.

Results: She was initially investigated by neuromuscular and rheumatological teams. MRI brain and spine were initially normal; EMG suggested muscle pathology with normal creatinine kinase and muscle biopsy. Inflammatory markers were normal with radiological abnormalities. Bone age was 13 years at chronological age 11.1 years. IGF-1 was 138 mcg/L (101-576.3) and IGFBP3 2.7 mg/L (2.4-6.1). Skeletal survey at 12 years was suggestive of PPRD and showed loss of joint space and widened metaphyses but no erosion in several joints. Vertebrae showed platyspondyly with anterior ossification defects, and supracetabular lipping of the iliac bones. Skeletal dysplasia gene panel analysis showed a previously reported pathogenic homozygous c.210C>A (p.Cys70*) nonsense variant in *CCN6/WISP3*. Further family testing was recommended but declined.

Discussion: PPRD presents usually between ages of 3 to 6 years with slowing growth and progressive involvement of the metacarpophalangeal (MCP), proximal (PIP) and distal interphalangeal (DIP) joints, wrists, elbows, knees, shoulders, and ankle joints. PPRD can be initially misdiagnosed as juvenile rheumatoid arthritis but is distinguished on radiographic analysis and the absence of inflammatory joint disease. This diagnosis is important to avoid unnecessary immunosuppressant therapy. This case emphasises the usefulness of radiographic skeletal survey as an investigative tool in short stature, even without disproportion.

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P1-430

Importance of early detection of familial hypomagnesemia in preventing neurological handicap

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Background: Hereditary hypomagnesemia with secondary hypocalcemia (HSH) is a are autosomal recessive disorder which presents in early infancy with generalized convulsions, or other symptoms related to increased neuromuscular excitability. Several mutations in the TRPM6 gene have been described. Early diagnosis is an effective means of preventing the inevitable neurocognitive sequelae which occur in the absence of appropriate treatment.

Objective: We report on three cases of HSH from one family, with different diagnostic circumstances and neurodevelopmental outcomes.

Family Study: The proband is a girl, born to consanguineous parents, who presented aged 4 months with psychomotor delay and convulsions. Investigations (reference range) showed serum calcium 1.6 (2.2-2.6) mmol/L, phosphate 1.45 (1.2-2.6) mmol/L, alkaline phosphatase 270 (70-450) IU/L, parathormone (PTH) 18 (10-65) pg/m, 25 (OH) Vit D 24 (30-80) ng/ml Initial diagnosis was of dietary vitamin D deficiency, given the absence of prophylaxis and the low serum vitamin D level.

She was hospitalized again at 6 months with generalize convulsions with fever, and was found to have pneumococcal meningitis, which was successfully treated with antibiotics. The infant was put on Sodium Valproate 30mg/kg/day but her developmental delay progressed and the convulsions persisted, despite addition of a second anticonvulsant. At one year, further investigations showed PTH 18 ng/L), calcium 1.69 mmol/L, phosphate 1.54 mmol/L, and severe hypomagnesemia at 0.22 (0.7-1.1) mmol/L with reduction in fractional magnesium excretion at 0.7 (2-4)%. After administration of intravenous magnesium and calcium followed by high-dose oral magnesium at 45 mg/kg/day (2.28 mg/kg/day) the convulsions ceased. Genetic studies confirmed a missense mutation in the TRPM6 gene. Now aged 10 years, the girl is not attending school, and suffers from a severe movement disorder with learning difficulties.

The second child was diagnosed antenatally as an affected homozygote on chorionic villous sampling and was treated with magnesium supplementation immediately after birth. Aged 8 years he is attending normal school, with normal growth and development. The third and fourth children, twins, were unscreened but clinically unaffected. The fifth child, also unscreened, presented at one month with an afebrile convulsion, serum magnesium 0.3 mmol/L and received treatment. Aged 3 years he is not displaying any developmental problems.

Conclusions: Hypomagnesemia should always be considered in infants with persistent and refractory hypocalcemia. Early diagnosis of HSH avoids neurological sequelae and immediate magnesium measurement is recommended in symptomatic hypocalcemia when parents are consanguineous.

P1-431

Kenny-Caffey Type 2 syndrome (KCT2S) as a rare cause of hypoparathyroidism causing neonatal seizures

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We report a male patient born small for gestational age (birth weight 2090 g, -2.97 SDS; birth length 43.5 cm, -3.37 SDS), with dysmorphic features (triangular face, low-set, posteriorly rotated ears, pectus excavatum, large anterior fontanel) who presented with seizures at the age of 4 weeks.

The child was treated with antiepileptic drugs (Levetiracetam, Midazolam, Phenobarbital, carbamazepine) for 1 year until a severe hypocalcemia (Calcium 6.4 mg/dl, ionised calcium 0.78 mmol/L) was discovered. Retrospectively, this hypocalcemia has already been present in the setting of his first seizure but not at birth. A further diagnostic work up revealed a low PTH (6.9 pg/ml), elevated inorganic phosphate (8.3 mg/dl) and normal vitamin D levels.

A part from hypoparathyroidism, he had elevated liver enzymes (GOT 151 U/l, GPT 111 U/l, GGT 121 U/l), papillary oedema, short stature (61.5 cm height at age 1 year, -6.46 SDS), underweight (BMI at age one year, 13.2 kg/m2, -3.02 SDS) and a wide opened anterior fontanel (1.5x1.5 cm). These findings guided us to the clinical suspicion of a KCT2S, confirmed by the genetic analysis revealing a heterozygous de novo missense variant in the gene FAM111A (c.928A>C). This variant has so far not been reported in the literature.

KCT2S is an autosomal dominantly inherited extremely rare (prevalence <1 / 1 000 000) primary bone dysplasia syndrome characterized by growth retardation, cortical thickening and medullary stenosis of the long bones, delayed anterior fontanelle closure, hypocalcaemia due to congenital hypoparathyroidism and facial dysmorphism. Additional manifestations include ocular and dental anomalies, hypoplastic nails and neonatal liver disease.

Since the introduction of a treatment with 1-alpha-calcidiol and calcium (current dosage 750 mg Calcium, 0.9 mcg 1-alpha-calcidiol/day) the calcium levels have normalised and the antiepileptic therapy could be stopped without any further seizures. EEG was normal. Liver enzymes decreased, but stayed elevated (stop of carbamazepine, liver disease in KCT2S). Papillary oedema persisted although normalised calcium (maybe ocular phenotype of KCT2S). Weight development became better under therapy (BMI at 2 years -0.95 SDS), growth remained poor (height at 2 years: 65.4 cm, -7.12 SDS). No dental or nail anomalies. Neurocognitive development is normal.

Conclusion: Hypocalcaemia is an important differential diagnosis in the setting of seizures. A rare cause of neonatal seizures can be a congenital hypoparathyroidism. We describe a patient with a KCT2S with a so far not described mutation in the FAM111A gene.

P1-432

Effects of COVID-19 pandemic on serum vitamin D concentration in Korean children

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Purpose: Vitamin D deficiency (VDD) is very common nowadays in children as well as in adults, probably due to decreased exposure to sunlight. COVID-19 pandemic resulted in school closure and decreased outdoor activity in children, which lead to lower chance for exposure to sunlight. It was reported that the higher level of visceral fat was associated with the lower vitamin D levels in children. The aim of this study is whether body mass index (BMI) affect serum vitamin D concentration during COVID-19 pandemic.

Methods: BMI and serum 25-hydroxy cholecalciferol (vitamin D) concentration were measured in 1429 children (6 to 11 years of age) between August in 2017 and July in 2018 for pre-COVID-19, 1204 children who lived in urban area of Korea between August in 2020 and July in 2021 for post-COVID-19. Student's t-test and correlation analysis were applied to analyze the relationships between BMI and serum vitamin D concentrations.

Results: The BMI standard deviation score (SDS) was 0.15±1.15 kg/m^2 and 0.51±1.59 kg/m^2 in pre-COVID-19 and post-COVID-19, respectively ($p<0.01$). The serum vitamin D concentrations were 16.9±7.0 ng/mL and 21.2±7.7 ng/mL in pre-COVID-19 and post-COVID-19, respectively ($p<0.01$). The BMI SDS was 0.11±1.27 kg/m^2 and 0.56±1.78 kg/m^2 in pre-COVID-19 and post-COVID-19 in boys, respectively ($p<0.01$). The serum vitamin D concentrations were 18.4±6.7 ng/mL and 21.6±7.8 ng/mL in pre-COVID-19 and post-COVID-19 in boys, respectively ($p<0.01$). The BMI SDS was 0.16±1.11 kg/m^2 and 0.46±1.40 kg/m^2 in pre-COVID-19 and post-COVID-19 in girls, respectively ($p<0.01$). The serum vitamin D concentrations were 16.4±7.1 ng/mL and 20.9±7.6 ng/mL in pre-COVID-19 and post-COVID-19 in girls, respectively ($p<0.01$).

Conclusions: This retrospective data suggest that the prevalence of VDD in Korean children during COVID-19 pandemic seemed to decrease, despite of increased BMI. Considering that the target group was children living in urban areas, it is thought to suggest that sufficient vitamin D were taken during COVID-19 pandemic.

P1-433

Challenges in the management of infantile hypophosphatasia: revisiting the importance of supportive therapy in limited-resource settings

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Background: Infantile hypophosphatasia (HPP) is an ultra-rare condition that may lead to debilitating morbidity and mortality. The prevalence of HPP in Indonesia is unknown. Enzyme replacement therapy or asfotase alfa, a bone-targeted recombinant alkaline phosphatase, can improve clinical outcome and prognosis of the patients, particularly those with severe type of HPP. The complications of HPP may be life-threatening and contribute to higher mortality in younger infants. In the absence and unavailability of asfotase alfa in Indonesia, supportive therapy becomes a sole management strategy in children and young infants with HPP.

Objective: To demonstrate clinical manifestation, complications, supportive management and its outcomes of the first reported case of infantile hypophosphatasia in Indonesia.

Case: A 7-month-old boy was admitted to the ICU due to severe pneumonia and prolonged fever. He was born prematurely at 36 weeks, 3640 gram from consanguineous parents. Since age 2 months, he was frequently hospitalised due to pneumonia. He had growth failure and global developmental delay. During hospital admission, his weight was 5800 gram and length was 58.5 cm (-5.69 SDS; U/L ratio 1.9), grade I hypertension, and fever. Physical examination showed enlarged fontanelle, microcephaly, chest deformity, and hypotonic extremities. Laboratory showed normal renal and liver tests, low thyroid function, hypercalcemia (serum Ca 11.2 mg/dL; ionised Ca 1.46 mmol/L), low serum ALP (10 U/L), increased serum B6 (>100 ng/mL) with normal magnesium, phosphate, and vitamin D25-OH. Echocardiography and head ultrasound were normal. Renal ultrasound showed nephrocalcinosis. Bone survey revealed multiple rib fractures, rickets-like appearance, and 'tongues of radiolucency' sign. He was diagnosed with hospital-acquired pneumonia, hypophosphatasia, and hypothyroid. Medical treatment included ventilatory support, levothyroxine, and intravenous antibiotics. During the current hospitalisation, he was put on tracheostomy and still ventilator-dependent due to bronchomalacia and airway clearance disorder. Genetic test showed homozygous ALPL mutation (c.98C>T (p.Ala33Val) and c.1099T>A (p.Ser367Thr)). Counseling was given to the parents with the most recent and feasible options of management. Ventilatory support strategy such as home ventilation becomes the most possible option to maintain the continuation of care and prolong the patient's survival.

Conclusion: The first reported case of infantile HPP in Indonesia showed significant and life-threatening complication such as persistent ventilator-dependent respiratory failure. Given the situation that asfotase alfa is not available in Indonesia, supportive management has become the only strategy to improve clinical outcomes and prognosis in the patient.

Diabetes and Insulin

P1-34

Early treatment of neonatal diabetes with oral glibenclamide suspension (Amglidia®) in an extremely preterm infant: evidence for efficacy, safety and easiness

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Background: Early treatment of neonatal diabetes with sulfonylureas has shown to improve neurodevelopment, beyond the demonstrated efficacy on glycemic control. Several barriers still prevent its use as an early treatment in preterm babies including the limited availability of a suitable galenic form of glibenclamide. Recently, an oral suspension of glibenclamide (Amglidia®) has been approved for use in EU.

Methods: We adopted Amglidia® 6mg/ml for the early treatment of neonatal diabetes due to an homozygous variant of KCNJ11 gene c.10C>T ; p.(Arg4Cys) in an extremely preterm infant. Amglidia® was administered via nasogastric tube and diluted in maternal milk at a final concentration of 1mg/1mL during the inpatient treatment, and administered orally at discharge.

Results: A female infant was born at 26+2 weeks' gestation after C-section for chorioamnionitis (birthweight 750g (10thcentile)). On day 1 she presented with persistent hyperglycemia (>200mg/dL) and was started on insulin drip through a central catheter (0.01U/kg/h with an initial low glucose intake [4.5g/kg/d]) until day 41 of birth, when insulin was suspended for glucose normalization. On day 45 (32+5 weeks), due to a new raise of blood glucose (>400mg/dl) she was started on glibenclamide (Amglidia® 6 mg/mL) at the dose of 0.02mg/kg/day (in two daily administrations) via nasogastric tube. At 3 months of birth she was switched to oral Amglidia 0.6mg/ml at the dose of 0.008mg/kg/day with a progressive tapering off. The choice of glibenclamide suspension was due to the simplicity of drug administration and the possibility of the fine-tuning of dose titration. The patient exhibited a mean daily growth of 11g/kg/day during the treatment and glibenclamide was progressively weaned off and suspended at month 6 of birth (weight 4.9 kg [5th – 10th centile], M3 of corrected age). During the treatment, the patient exhibited a stable glucose profile within the range 4-8mmol/L in the absence of hypo or hyperglycemic episodes with 2-3 blood glucose tests per day.

Retinopathy of prematurity (ROP) screening showed Stade 2 in ZoneII ROP at 32 weeks, with spontaneous regression at 45 weeks, while on glibenclamide.

Conclusion: This is the first report of the successful use of Amglidia® in an extremely preterm infant and supports the responsiveness of beta-cell to glibenclamide at this gestational age. Amglidia® was efficacious, safe and easy to administer enterally/orally and could be regarded as part of the treatment for hyperglycemia even in very preterm babies due to its beneficial effects on the metabolic and neurodevelopmental side.

P1-35

Does parental food choice preferences impact on metabolic control of children with type 1 diabetes?

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Introduction: Diet plays a key role in the management of type 1 diabetes (T1D), thus nutritional education is a cornerstone in T1D therapy. The integration of nutrition knowledge into nutritional behavior may help parents inculcate a healthy lifestyle to their children. However, parents' diet and its potential impact on metabolic control of the disease of their children have been scarcely analyzed. This study was aimed to examine whether parents' food choices may influence metabolic control of their children with T1D.

Patients and Methods: Food Choice Questionnaire in Spanish population (FCQ-SP) was conducted to assess main caregivers of children with T1D eating behaviors. The questionnaire measures eight motivational dimensions: mood, health, natural content, sensory appeal, weight control, convenience, familiarity and price. Patients' HbA1c was determined during medical consultation. Demographic, anthropometric and clinical data were registered on the same day that the questionnaire was taken from the parents, after informed consent. Significance was established in p-value<0.05.

Results: Fifty-five T1D patients (35 girls; 51%), with a median age in years of 12.9 (9.8-14.5), were recruited. 41 (73.2%) patients had closed-loop insulin pumps. 33 (60%) have shown HbA1c levels of <7.5%, while only 17 (30.9%) had a time in range of >70%. Main caregivers were mothers, median age 44 (40-48) years. Significant positive correlation was found between Hb1Ac and

R values of correlation study								
	Convenience	**Familiarity**	**Health**	**Mood**	**Natural content**	**Price**	**Sensorial appeal**	**Weight control**
BMI (z-score)	0.109	0.102	0.142	0.162	0.084	0.312*	0.209	0.304*
Insulin dose (UI/kg/day)	0.269	-0.311*	0.253	0.065	-0.045	-0.037	0.283*	0.094
Hb1Ac	-0.020	0.303*	0.250	0.030	0.110	-0.021	0.287*	0.070

*indicates significant correlation ($p<0.05$).

familiarity and sensory appeal (R:+0.287 and R:+0.303 respectively). Furthermore, insulin needs (UI/kg/day) showed a positive significant correlation with sensory appeal and negative with familiarity (R:+0.283 and R:-0.311) and Z-score BMI with price and weight control (R:+0.312 and R:+0.304). No correlation was found with other motivational dimensions.

Conclusions: Children with T1D whose parents choose food for their sensorial appeal have higher insulin needs and HbA1c. When food is chosen by familiarity, children have higher HbA1c levels and use less amount of insulin. These data provide new insights into the food choices of parents of children with T1D and support the importance of personalized nutritional education to acquire glucose control promoting nutritional habits.

P1-36

Human umbilical cord derived mesenchymal stem cells alleviate T1DM model via TGFBI-mediated T cells proliferation

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Type 1 diabetes mellitus is autoimmune T cells mediated destruction of β-cells. Mesenchymal stem cells (MSCs) are considered a promising treatment for T1DM due to the strong immunosuppressive and regenerative capacity. However, the comprehensive mechanism is still unclear. Our previous study indicated that the transforming growth factor beta-induced gene (TGFBI) is highly expressed in human umbilical cord derived mesenchymal stem cells (hUC-MSCs), which is also implicated in T1DM. Thus, our study aimed to investigate TGFBI mediated immunomodulatory properties of hUC-MSCs in the treatment of T1DM.

In this study, a stably knockdown TGFBI lentiviral vector was successfully constructed and transfected into hUC-MSCs to obtain sh-TGFBI-MSCs. MSCs transduced with the control lentivirus were also referred as negative control (sh-NC-MSCs). To evaluate the role of TGFBI in the treatment effects of hUC-MSCs in T1DM mice, sh-TGFBI-MSCs and sh-NC-MSCs were intravenously administered to STZ-induced T1DM mice. We found that silencing TGFBI significantly abrogated the therapeutic effects of hUC-MSCs on T1DM model. Histologic analysis performed via H&E and insulin immunohistochemical staining revealed that sh-NC-MSCs infusion suppressed insulitis and preserved insulin-producing cells in the islets. However, sh-TGFBI-MSCs transplantation cannot effectively protect the destructive islet tissue and insulin-producing cells. Flow cytometry results showed that silencing TGFBI significantly weakened the ability of hUC-MSCs to inhibit the secretion of pro-inflammatory cytokines IFN-γ and IL-17A in the spleen of T1DM model mice. Additionally, according to immunofluorescence analysis we found that downregulating TGFBI markedly mitigated the suppressive effects of hUC-MSCs on suppressing the infiltration of T cells labeled with green fluorescent CD3 antibody in the pancreas in STZ-induced T1DM model. In vitro we constructed a co-culture system to culture MSCs and CD3+T cells sorted by CD3 MicroBeads. Consistent with in vivo, we further proved that TGFBI derived from hUC-MSCs could repress the activated T cells proliferation. Mechanistically, TGFBI secreted by hUC-MSCs could be able to repress activated T cells proliferation by interfering with the T cells expression of G1/S checkpoint CyclinD2 and arrests T cells in G0G1 phase.

In conclusion, we have demonstrated that TGFBI secreted by hUC-MSCs can suppress the proliferation of activated T cells and the precise mechanism of this phenomenon remains to be determined, our analysis suggests CyclinD2 downregulation and T cell cycle arrest may be involved. Our study provides new sight into immunoregulatory mechanism of the hUC-MSCs mediated by TGFBI, which might be therapeutic target for the treatment of T1DM.

P1-37

The role of insulin resistance and pancreatic β-cell dysfunction in the development of prediabetes in obese adolescents

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Background: The pathophysiology of type 2 diabetes mellitus (T2DM) is based on defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond appropriately to insulin. Young people have a more aggressive course of the disease. However, the impact and sequence of pathological mechanisms involved in the development of T2DM in adolescents hasn't been established. Diagnosis of the prediabetes in time can be useful in prevention T2DM progression.

Aims: to study the role of pancreatic β-cell dysfunction and insulin resistance in the development of prediabetes in obese adolescents.

Materials: The Study included 95 obese adolescents. Inclusion criteria: SDS BMI≥2.0, Tanner stage ≥II, age <18.0 years, exclusion criteria: diabetes mellitus. The sample was divided into prediabetics (n=40, mean age 14,0±1,53 years; SDS BMI 3,1±0,54, boys n=23) and nonprediabetics (n=55, mean age 14,6±1,67 years; SDS BMI 3,1±0,54; boys n=32). Both groups were matched on age, SDS BMI, sex (p=0.082, p=0.975, p=0.947, respectively). Prediabetes in adolescents was diagnosed using American Diabetes Association criteria. The research included the estimate levels of insulin and c-peptide as well as the calculations of the HOMA-IR, HOMA-B and disposition index (DI). Data was analyzed by using SPSS Statistics for Windows, Version 26.0.

Results: There were statistically significant differences between indices of groups with prediabetes and nonprediabetics: HOMA-B (median 116.56; IQR [88.55-197.44] vs 217.85; [144.44-301.20] %, respectively; p<0.001), DI (median 35.68; IQR [30.35-47.57] vs 51.13; [44.04-88.56] %, respectively; p<0.001).

The indices of fasting insulin (median 13.26; IQR [9.54-17.67] vs 15.19; [10.57-22.23] μIU/ml, respectively; p=0.263); c-peptide (median 1.87; IQR [1.46-2.27] vs 1.91; [1.41-2.49] ng/ml, respectively; p=0.582) and HOMA-IR (median 3.48; IQR [2.20-4.56] vs 3.16; [2.16-5.12], respectively; p=0.892) between the groups didn't differ.

Statistically significant logistic regression model was obtained for evaluating the dependence of the development of prediabetes on the HOMA-B, HOMA-IR, DI (p<0.001). The increase of HOMA-IR is a risk factor for developing prediabetes (odds ratio (OR) =1.7; 95% confidence interval (CI): 1.16-2.51). The decrease HOMA-B and DI by 1%, increased the chances of developing prediabetes in 1.01 times (odds ratio (OR) = 0.99; 95% (CI): 0.98-0.99) and 1.06 times (OR=0.94; 95% CI: 0.91-0.97), respectively.

Conclusions: Despite the fact that both groups had the equal level of insulin resistance, the impairment of β-cell function in prediabetics and nonprediabetics was too dissimilar. Hence, β-cell defect can be the main driving mechanism in youth-onset prediabetes and an unfavorable prognostic factor.

P1-38

Severe clinical presentation of congenital hyperinsulinism due to newly discovered mutation of HK1: case report

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Introduction: Congenital hyperinsulinism (CHI) is a disorder of pancreatic beta-cells characterized by inappropriate secretion of insulin leading to hyperinsulinemic hypoglycemia. Insulin secretion is a complex, genetically regulated process. Mutations in several genes known to regulate insulin secretion result in CHI. Recently, non-coding mutations in HK1, which cause the aberrant expression of hexokinase 1 (HK1) in beta cells, have been reported as a novel cause of CHI in 17 individuals. In the initial publication the median birthweight was 0.61SDS [IQR: 0.10-1.84] and 5/17 cases required pancreatic surgery.

Case Report: A 5-month-old girl [FS1] was referred to pediatric endocrinology department with diagnosis of severe hypoglycemia (0.8mmol/l) following an epileptic episode. She underwent an EEG, brain MRI and started with anti-epileptic therapy. Further investigations confirmed that the seizures were due to severe hypoglycemic episodes. A diagnosis of CHI was confirmed based on inappropriately high[FS2] insulin level (7.74mlU/ml) during <2.8mmol/l hypoglycemia (1.1mmol/l), and treatment with diazoxide was initiated.

Genetic analysis of the KCNJ11, ABCC8, GLUD1, GCK, HADH, HNF4A, INSR, KDM6A, KMT2D, SLC16A1, CACNA1D, PMM2, TRMT10A and HNF1A genes by targeted next generation sequencing did not identify a disease-causing variant. The patient's sample was subsequently screened for HK1 mutations and a novel heterozygous variant (g.71,108,654A>C) was identified within the critical regulatory region. The variant was not present in the sample from the unaffected mother, a sample from the unaffected father was not available for testing. This case shows an early onset of severe, symptomatic, diazoxide-sensitive hypoglycemia and seizure episodes in a girl with a novel HK1 mutation.

Conclusion: The present case represents one of the first reports of CHI due to a HK1 mutation and provides new insights into the clinical manifestations associated with this genetic subtype. Further research is needed to investigate the clinical presentation and the natural course of HK1-CHI in comparison with other known molecular-genetic basis of CHI.

P1-39

Case report: Suppression of gonadotropins with contraceptives in type A insulin resistance ameliorates virilizing insulin-induced hyperandrogenism

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Insulin-induced ovarian hyperstimulation and hyperandrogenization can cause virilization in children and adults. It rarely occurs in children and adolescents but when it does, it is usually caused by congenital adrenal hyperplasia or virilizing tumors. In very rare cases severe hyperandrogenism is caused by severe insulin resistance, either due to germline mutations in genes encoding the insulin receptor or proteins in downstream insulin signaling or due to insulin receptor antibodies

Case Description: A 13-year-old adolescent girl with monogenic severe insulin resistance due to an INSR mutation encoding

a substitution in the tyrosine kinase-encoding domain (p. Leu1150Arg) developed severe hyperandrogenism with virilization. Testosterone levels were elevated into the adult male range. Treatment with a gonadotropin-releasing hormone (GnRH) analog led to normalization of testosterone (and insulin C-peptide) and remission of the clinical findings, which persisted with the subsequent switch of treatment with an anti-androgenic contraceptive.

Conclusion: Suppression of gonadotropins with anti-androgenic contraceptives may be a feasible therapeutic modality in insulin-induced severe ovarian hyperstimulation and hyperandrogenism.

P1-40

Pancreatic Shear Wave Elastography in Children with T1D; Relation to Functional B cell mass Pancreatic Reserve

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Background: Little is known about the pancreatic changes during type 1diabetes (T1D) progression. Recently shear wave elastography (SWE) has emerged as a tool of pancreatic stiffness assessment in chronic pancreatitis and pancreatic cancer with few studies assessing it in diabetes.

Objective: to compare the pancreatic SWE in children with recent-onset and long standing T1D to healthy controls and to correlate it to diabetes-duration, glycemic control (HbA1C), functional B-cell reserve (fasting C-peptide) and diabetic complications.

Methods: Fifty children with T1D (25 with recent-onset and 25 with long standing T1D) and 50 controls were enrolled. Diabetes-duration, insulin therapy, fundoscopic examination of the eyes and the neuropathy disability score were assessed. Fasting C-peptide, lipids, HbA1C and urinary albumin-creatinine ratio were measured. Pancreatic SWE was measured using logic-P9GE ultrasound-system.

Results: The mean SWE of the studied children with recent-onset T1D is 4.81 ± 0.62 KPa, those with long standing T1D is 7.10 ± 1.56KPa, while that of the controls is 5.57 ± 0.27 KPa ($p<0.001$). SWE was positively correlated to diabetes duration ($p<0.001$) among children with T1D. Moreover, it was negatively correlated to fasting c-peptide ($p<0.001$). Regarding diabetes complications, SWE was positively correlated to severe hypoglycemia frequency ($p=0.005$), HbA1C ($p=0.034$), low-density lipoproteins ($p<0.001$) and cholesterol ($p<0.001$) and significantly related to diabetic neuropathy ($p= 0.036$) and nephropathy ($p=0.049$). Diabetes-duration, fasting C-peptide, HbA1C and severe hypoglycemia frequency were the significant independent variables related to SWE increase by multivariable regression analysis.

Conclusion: Pancreatic SWE changes significantly during the course of T1D being lowest during recent onset T1D and highest in those with longstanding T1D; particularly those with diabetic nephropathy and neuropathy.

P1-41

A rare cause in childhood: MODY 11

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MODY (Maturity Onset Diabetes of Youth), mitochondrial diabetes, Wolfram syndrome, neonatal diabetes and the group of special syndromes seen due to gene defects that cause insulin resistance are called monogenic diabetes. MODY is an autosomal dominant form of diabetes with a relatively young onset. It constitutes 2-5% of all diabetes cases. The presence of more than one affected family member in extended families has facilitated studies of this type of diabetes. In monogenic diabetes, where patients are often misdiagnosed as type 1 and type 2 DM, the fact that the treatment varies according to the underlying genetic etiology increases the clinical importance of the rare disease. Mutations in the B lymphocyte tyrosine kinase (BLK) locus are in the very rare group. Here, we present a case who presented with hyperglycemia and diagnosed as BLK mutation in the follow-up.

A 17-year-old female patient applied to the dermatology department due to psoriasis and was referred to our outpatient clinic due to polyuria, polydipsia and weight loss in the last 2 months. Since the patient had a diagnosis of diabetes in first-degree family members and insulin value was not low at the time of hyperglycemia, a genetic study was performed considering the preliminary diagnosis of MODY and heterozygous mutation of BLK (NM_001330465.2):C.1081G>T(p. Gly361Trp) was detected. Afterwards, the insulin dose was decreased and oral sulfonylurea therapy was started gradually.

This type, also called MODY type 11 or BLK mutation, is a very rare type of MODY that has not been studied much. The 8p23, B-lymphocyte kinase (BLK) gene encodes a nonreceptor tyrosine kinase (nrTk) from the protooncogene Src family. The BLK gene is expressed in beta cells and is responsible for insulin synthesis and secretion through the transcription factors Pdx1 and Nkx6.1. nrTk is responsible for cell growth and differentiation. BLK mutation reduces insulin secretion by reducing BLK expression and/or activity. Compared to other MODY types, cases are usually obese phenotype. 60% of cases are treated with insulin. However, sulfonylurea can be tried. There is no publication in terms of diabetes complications. It is noteworthy that the case has a rare mutation and that blood sugar regulation was achieved with oral sulfonylurea therapy, and MODY should be a diagnosis that must be kept in mind in patients with diabetes mellitus in close family members, who do not present with severe ketoacidosis despite hyperglycemia, and who have relatively low insulin levels.

P1-42

Symptoms and Glycemic Control in Young People with Type 1 Diabetes following SARS-CoV-2 Infection: an Observational Study

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Objective: To describe clinical manifestations of SARS-CoV-2 infection in children, adolescents, and young adults with established type 1 diabetes and explore the effects of COVID-19 on glycemic control and disease course.

Methods: Observational study conducted at three pediatric diabetes clinics in Israel between mid-March-2020 and mid-March-2021. Included were young people with established type 1 diabetes, <30years, who tested positive for SARS-CoV-2 (qRT-PCR). Data was collected from medical files, diabetes devices, and COVID-19 questionnaire. Outcome measures were analyzed by presence/absence of clinical symptoms (symptomatic/asymptomatic) and by age group (pediatric, <19years/young adults, 19-30years).

Results: Of 132 patients, mean age 16.9±5.3years, with COVID-19 confirmed infection, 103 (78%) had related symptoms; the most common were headaches, fatigue, fever and loss of sense of smell. All had mild disease course, but four required hospitalization and two cases were directly related to COVID-19 infection (pleuropneumonia in a patient with immunodeficiency syndrome, one case of diabetic-ketoacidosis). Logistic regression analysis showed that age (OR=1.11, 95%CI, 1.01, 1.23; P=0.033), elevated glucose levels (OR=5.23, 95%CI, 1.12, 24.41; P=0.035) and comorbidities (OR=8.21, 95%CI, 1.00, 67.51; P=0.050) were positively associated with symptomatic infection. Persistent symptoms occurred in 16.5% of the cohort over a median of 6.7 months; age (OR=1.14, 95%CI, 1.01, 1.29; P=0.030) and elevated glucose levels (OR=3.42, 95%CI, 1.12, 10.40; P=0.031) were positively associated with persistent symptoms. Usually, no change was reported in glucose levels (64%) except for a temporary deterioration in glycemic control during the short infection period.

Conclusions: Young people with established type 1 diabetes experience mild COVID-19 infection. Elevated glucose levels during COVID-19 infection and older age were associated with prolonged disease course.

P1-43

The spectrum of paediatric diabetes subtypes from a single center in a highly consanguineous region

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Introduction: Monogenic diabetes has been estimated to be 1 - 6% of all diabetic cases in European countries which are primarily non consanguineous populations, while the incidence in highly consanguineous areas is insufficiently defined. However, the genetic aetiology of monogenic diabetes has been shown to be widely different in areas with prevalent consanguinity compared to areas with lower rates.

In this single-centre study, we aimed to evaluate the prevalence of monogenic forms of diabetes in comparison with the other types of diabetes, obtain consanguinity rate, and study the genetic background of syndromic and neonatal diabetes.

Methods: Data collection was done retrospectively at the diabetic clinic at the Dr. Jamal Ahmad Rashid Hospital in Sulaimani in the Kurdistan region of Iraq. In November 2021, there were 753 diabetic patients (376 males) up to 16 years of age registered. The age at diagnosis, type of diabetes (clinically defined), syndromic features (if any) and insulin dosage were documented from patient files. Consanguinity status was known in 734 patients. Furthermore, 11 patients with neonatal and syndromic diabetes consented to genetic testing by Next Generation Sequencing methods when offered.

Selected variants were evaluated by American College of Medical Genetics standards.

Results: 268/734 patients (36%) were offspring of consanguineous families. An overwhelming majority of 716/753 (95%) patients had Type 1 diabetes (35% of them were from consanguinity) whereas only 7/753 (0.9%) had Type 2 diabetes (42% consanguineous). 13/753 (1.7%) had neonatal diabetes (54% consanguineous), 6/753 (0.8%) syndromic diabetes (100% consanguineous), and 11/753 (1.5%) clinically defined MODY (10% consanguineous).

The genetic cause was elucidated thus far in 4/6 syndromic diabetes patients (homozygous variants in *INSR*, *SLC29A3*, *WFS1* [2x]) and in 5/11 neonatal diabetes patients (de novo heterozygous variants in *ABCC8*, *INS* and homozygous variants in *GLIS3* [2x], *PTF1A*). 5 variants are novel.

Conclusion: This single center study confirms that even in a highly consanguineous population, type 1 diabetes represents the prevailing paediatric diabetes subtype, and that syndromic diabetes arises predominantly from consanguinity. More extensive studies would be required to calculate a precise incidence of diabetes subtypes in this population.

P1-44

Characterisation of Type 2 Diabetes mellitus in children and young people across 2 large tertiary Paediatric Diabetes centres

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Introduction: The prevalence of paediatric Type 2 diabetes (T2DM) is increasing, contributed by rising incidence of obesity worldwide. Paediatric T2DM is a progressive disease with increased risk of complications and morbidities. Despite recent research, many aspects such as its pathophysiology and optimal management remain unknown.

Aim: To characterise the cohort of T2DM patients across 2 large tertiary paediatric diabetes centres and evaluate current management practices.

Method: Retrospective data was collected from medical notes of all paediatric T2DM patients in Bristol and Cardiff.

Results: Out of 20 T2DM patients, 60% were female. Mean age at diagnosis was 13.3 (± 1.9) years and mean duration of diagnosis was 2.98 (± 2.3) years. 75% were Caucasian. Positive family history in a first-degree relative was reported in 85%.

Commonest clinical feature at diagnosis were obesity (65%).

Median fasting glucose and C-peptide level at diagnosis were 8 mmol/L and 1870 pmol/L respectively. Pancreatic antibodies were measured in 90% of whom 10% had GAD antibodies. Current mean HbA1C (60.3±19.1 mmol/mmol) was not significantly different from that at diagnosis(65.6±17.5 mmol/mmol).

Improvement of latest mean BMI SDS (1.89±0.6) from that at presentation (2.14±0.4) was 0.25.

80% had at least one comorbidity (dyslipidaemia, hypertension, microalbuminuria, fatty liver, PCOS, OSA), commonest being dyslipidaemia and hepatic steatosis (55%).

All patients had lifestyle counselling including dietetic appointments (median=3.5 per year) and weight management advice. 25% were on low-calorie diet (<1400 Kcal/day).

45% children were on monotherapy (metformin in 30%, insulin in 5% and GLP-1 analogue in 5%). Double therapy included: metformin/GLP-1 analogue in 25%, metformin/insulin in 10% and metformin/SGLT-2 inhibitor in 10%. 15% were on a combination of 3 drug therapies.

Conclusions: Interestingly, the majority of our cohort is Caucasian, whereas other studies report a preponderance of non-Caucasian ethnicity in T2DM. Similar to other studies, obesity and positive family history are the most important risk factors. BMI SDS improvement was 0.25, an encouraging finding as it is known that an improvement of >0.25 can improve insulin sensitivity. Similar to that in literature, 10% of cohort had positive GAD antibodies. Dyslipidaemia and hepatic steatosis were the commonest co-morbidities. There is a clear shift from insulin therapy to newer therapies (GLP1 agonists and SGLT-2 inhibitors). Medical and dietetic management varied considerably similar to other studies, highlighting need for clinical trials, especially with the newer medications and low calorie diet to identify optimal treatment strategies.

P1-45

Non-insulin-dependent diabetes mellitus due to a variant in MAPK8IP1: a case report

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Introduction: non-insulin-dependent diabetes mellitus (type II) is an increasing problem in childhood. With the advancement of genetic testing and genome-wide association studies, mutations in genes causing loss or dysfunction of the pancreatic cell have been associated with type II diabetes. A heterozygous mutation of the MAPK8IP1 (Mitogen-activated protein kinase 8 interacting protein 1) gene is associated with a rare form of diabetes with few cases reported.

Objective: to increase awareness of type II diabetes due to a variant in the MAPK8IP1 gene.

Case: 14-year-old boy with insulin resistance developed type II diabetes due to a missense heterozygous variant in MAPK8IP1: (NM_005456.3): c.1895G>A (p.Gly632Glu), maternally inherited and responded to the administration of glucagon-like peptide 1(GLP-1) receptor agonist.

Discussion: MAPK8IP1 encodes IB1, a regulator of the pancreatic beta-cell function, that is a DNA binding transactivator of the glucose transporter GLUT2, and a homologous of JIP (regulator of the c-Jun amino-terminal kinase), which plays an important role in cellular apoptosis and increased inflammatory response that causes type II diabetes. Administration of glucagon-like peptide 1 (GLP-1) receptor agonist improved glucose levels due to the positive effect on the pathogenic mechanisms.

Conclusion: Upon an uncommon presentation of type II diabetes, a molecular genetic test should be performed allowing early assessment and management of this condition.

Table 1. Laboratories and anthropometric measurements, 2019-2022

	Dates								
Measurements	**Apr-19**	**Jul-19**	**Oct-19**	**May-20**	**Jun-20**	**Jul-20**	**Oct-20**	**May-21**	**Jan-22**
Fasting glucose (mg/dl)	98	74	88	87	83	75	85	90.8	81.8
Oral glucose tolerance test (mg/dl)	122	152	124	104	228	80	119	101	104.7
Fasting insulin (uUl/ml)	91	41.8	28.8	43.3	18.9	43.5	25.7	22.1	20
Insulin levels 2 hours after glucose load (uUl/ml)	501	697	255	132	412	295	222	200	90
HbA1c test (%)			5.5		5.2	5.3	4.9	4.9	5.2
ALT (U/L)		40							
AST (U/L)		21							
HOMA	150.9	261.5	78.1	33.8	231.9	58.2	65.2	44.4	18
Weight kg		48.6	52.2	55.2		54.2	57.0	56.8	58.1
Height cm		156.5	159.5	164		164.4	165.0	168	169
BMI (kg/m2) (Percentile, p%)		19.7; p75	20.5; p80	20.5; p76		20.1; p71	20.9; p61	20.1;p52	20.1;p50
Medications	Metformin 500 mg BID	Metformin 850 mg TID	Metformin 850 mg TID	Metformin 850 mg tid	Metformin changed for Liraglutide 1.8 mg per day	Liraglutide 1.8 mg per day	Liraglutide 1.8 mg per day	Liraglutide 1.8 mg per day	Liraglutide 1.8 mg per day

P1-46

The incidence of Type 1 diabetes mellitus has stopped falling and is rising again in Ireland – a preliminary report from the Irish Childhood Diabetes National Register

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Introduction and Aim: The Incidence of Type 1 diabetes mellitus (T1DM) varies markedly between populations and over time. Recently a number of high incidence countries, including Ireland, have reported a stabilisation and/or reduction in their T1DM incidence rate (IR) in childhood. Ireland, a high incidence country for T1DM, experienced a dramatic increase in T1DM incidence between 1997 and 2008, a stabilisation in incidence between 2014 and 2018 followed by a minor reduction in incidence in the period 2014 to 2018. This study sought to determine IRs for 2019 to 2021 to clarify if this reduction in IR had continued.

Methods: Using the established mechanism of the Irish Childhood Diabetes National Register (ICDNR), incident cases of T1DM in those aged under 15 years were prospectively recorded in all 19 centres nationally providing care to children and young people with diabetes. Following verification of cases, IRs were calculated. Capture-recapture methodology was employed to provide a measure of ascertainment. Population data derived from census data from the Central Statistics Office was used.

Results: A total of 1,030 cases were reported in the period 2019 to 2021 (age range 0.51 – 14.96 years), with significantly more males (542, 53%) and male to female ratio of 1.11. Standardised IRs for T1DM in the period increased overall, and were: 31.1; 32.4; and 37.8/100,000/year respectively.The incidence increased in both males and females. As in previous years the highest IR was in the 10-14-year-old age category (approximately 50 % of total cases) in 2019 and 2020. However, in 2021 the highest incidence was in the 5-9 year old age category (accounting for 40% of total cases).

Conclusions: The incidence of T1DM in Ireland, a high incidence country has started to rise again. In 2021 the highest incidence has been noted in the 5-9 year old age category for the first time since epidemiological monitoring commenced in this population. This increase in incidence and move to an earlier age at diagnosis may reflect increased environmental pressure, such as viral infection, in this population or the previously recognised periodicity in T1DM incidence. Ongoing epidemiological monitoring of T1DM through national registers is vital to support appropriate healthcare planning, paediatric diabetes management, clinical audit and, research relating to T1DM aetiology.

P1-47

Congenital hyperinsulinism: a case with a missense monoallelic heterozygous *ABCC8* mutation responsive partially to diazoxide therapy

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Congenital hyperinsulinism (CHI) is a rare hereditary condition that causes excessive insulin production in the clinical picture of severe hypoglycemia. Patients with CHI frequently have mutations in the *ABCC8* and *KCNJ11* genes, which code for K_{ATP} channels in pancreatic beta cells. We present a case of partial diazoxide responsiveness caused by a heterozygous *ABCC8* mutation in a child with moderate CHI. A four-month-old term baby with a birth weight of 4.8 kg came with seizures and hypoglycemia. A hypoglycemia panel test verified CHI. Diazoxide was started due to persistently high glucose needs (10 mg/kg/min), but after escalation to a high dose (14 mg/kg/day), divided every 6 hours, titrated timing; glucose-enriched formula meals, glucose levels remained below safe range in the late afternoon. Diazoxide medication was thus continued, and a once-daily subcutaneous octreotide infusion was started. Both intravenous glucose and glucagon were terminated as normoglycemia was established throughout the day at a dosage of 8mg/kg/day of diazoxide and 2 mcg/kg/dose once a day of octreotide. Later genetic testing revealed a heterozygous *ABCC8* missense mutation [NM 001287174.1c:89>T,p.Ala30Val]. The mutation is a paternally inherited monoallelic variant previously linked to a focused type of CHI. This patient was previously assumed to be diazoxide non-responsive, but after a timed low dosage of octreotide and a lower dose of diazoxide, he achieved a near-optimal glycemic response. We emphasize the clinical manifestation of this missense heterozygous variant in a patient with CHI in our report to contribute to the strengthening of the data on this likely-pathogenic variant.

P1-48

Maternal Hepatic HKDC1 Expression Impacts Offspring Glucose Metabolism

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Gestational Diabetes (GDM) increases risk of developing type 2 diabetes in the mother and child later in life however, despite the increasing prevalence of GDM, its molecular mechanism remains unknown. A recent Genome-Wide Association Study (GWAS) identified a unique genetic association of the novel 5th hexokinase, hexokinase domain component-1 (HKDC1) to gestational glucose tolerance at 28 weeks of gestation linking it to GDM. We have previously shown that liver-specific overexpression of HKDC1 modulates maternal glucose tolerance, insulin sensitivity and nutrient mobilization during late gestation in pregnant mice. Since nutrient metabolism and mobilization is essential for offspring health, we hypothesized that maternal hepatic HKDC1 plays dictates offspring health. The aim of this study was to determine the role of hepatic HKDC1 on maternal and offspring glucose metabolism using our novel liver specific in utero HKDC1 knockout (HKDC1-LKO) mice to study glucose metabolism and nutrient mobilization at different gestational stages in offspring. Our results show that offspring born to HKDC1-LKO mice were lighter and had impaired glucose tolerance compared to offspring born to HKDC1 floxed mice (which served as controls) at 4 weeks. Further this difference seen at 4 weeks were lost at 21 weeks indicating that HKDC1 might be essential in the early development process. To assess this, we measured hepatic HKDC1 expression at different gestational ages and after birth and our exciting data shows that HKDC1 is highly expressed during gestation and shortly after birth. Taken together our data suggests that maternal hepatic HKDC1 expression plays important role in offspring development.

P1-49

Impact of Metabolic-associated fatty liver disease (MAFLD) on the Cholesterol efflux capacity of High-density lipoproteins in adolescents with type 2 Diabetes

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Background: Type 2 diabetes (T2D) is an emerging disease in the pediatric population. T2D is associated with metabolic-associated fatty liver disease (MAFLD). High-density lipoproteins (HDLs) are lipoproteins that are believed to have atheroprotective properties that reduce the risk of cardiovascular disease (CVD). Current evidence suggests that the physicochemical and functional features of HDLs may play a key role in the pathogenesis of atherosclerosis.

Objective: To assess the impact of MAFLD on cholesterol efflux capacity (CEC) in in T2D youths.

Materials and Methods: This Cross-sectional study included a total of 70 adolescents, 47 of which had T2D and 23 were healthy individuals. The protocol was approved by the local Ethics and Research Committees. The presence of MAFLD was determined by MR spectroscopy with proton density fat fraction. We compared the distribution of HDL subtypes (HDL2b, HDL2a, HDL3a, HDL3b, and HDL3c) and the chemical composition of HDLs (total protein, triglycerides, phospholipids, cholesteryl esters, and free cholesterol). HDL functionality was determined by the CEC, measuring the fluorescent cholesterol efflux from J774 macrophage cells.

Results: In Our study, we observed a prevalence of MAFLD in 66% of adolescents with T2D, similar to the reported in other international studies (60-80%). In the T2D and MAFLD population, we didn't observe a decrease on CEC. Initially, we found an elevation of CEC in adolescents with T2D, however, with the increase in liver fat, a decrease is observed, which could explain a probable metabolic phenomenon, since the physicochemical composition and distribution of the particles is associated with the percentage of liver fat. We observed a correlation between the percentage of liver fat and the HDL2b concentration (p=0.011), HDL2a (p=0.014) and average particle size (p=0.011 and the proportion of triglycerides inside the particles (p=0.007). Likewise, a negative correlation was found with the percentage of liver fat, the cholesterol esters (p=0.010) and the free cholesterol of the particles (p<0.001).

Conclusions: In adolescents with T2D, the presence of MAFLD is associated with abnormalities in the distribution and the lipid composition of HDL particles. Building on the momentum generated by the original MAFLD proposal and adapting the recommendations for pediatric MAFLD would be a step forward that could help to study the impact of MAFLD in the atheroprotective properties of HDL particles.

P1-50

An Evaluation of MiniMed™ 780G System Performance in Childhood: A Single Center Experience from Turkey

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Introduction: Automated insulin delivery systems provide significant improvement in the time in range (TIR) centered diabetes care. This study analyzes the real-word performance of Minimed 780G™system-Advanced Hybrid Closed Loop (AHCL) in children from a single center.

Methods: Of the 93 children started to use AHCL between January 2021 and April 2022, 64 whose data could be accessed were included. 3,6,9 and 12 month-data were analyzed in terms of the proportion of users achieving recommended glucose management indicator (GMI<7.0%), TIR (70-180 mg/dL >70%) and time below range (TBR<5%) goals. In a second analysis, data of the children previously treated with multiple daily injections (MDI) (group-1,n:23) and with insulin pumps (group-2,n:39) were analyzed regarding glycemic profile before and after AHCL.

Results: At the baseline mean TIR, TBR<70 and HbA1c were 72.7±11.7%, 4±4.5% and 7.3±0.9% while they were 80.1±8.7%, 3.4±3% and 6.8±0.8% respectively at 3-month.TIR increased by 7.4% at 3-month, compared to baseline (p:0.001). At 3-month, 88% of the participants achieved TIR>70% goal, 80.4% achieved TIR >70% and GMI<7% and TBR<5% goals. No significant difference was noted between 3-6-9 and 12th month TIR percentages (80%, 79%, 81%, 82%, p:0.122). In group-1 and group-2, the increase in TIR from baseline to 3-month were 13%, 6%, respectively (p1:0.01; p2:0.017). The increase in TIR at 3-month in Group-1 was significantly higher than in Group-2 (p 0.014).

Conclusion: AHCL is a reliable system for achieving and maintaining glycemic goals, mainly TIR >70%goal in children. The improvement is more prominent in the children previously treated with MDI.

Table 1. Glycemic metric values at 1-year follow-up before and after AHCL use

	Baseline(n:33)	3-month(n:58)	6-month(n: 41)	9-month(n:34)	12-month(n:24)
Automode(%)	N/A	96.3±8.1	95.6±6.9	97±4	95.2±7.7
TIR(%)	72.7±11.7	80.1±8.7	79.1±9.2	81.4±7.8	82.1±7
TAR>180(%)	18.8±8.4	13.8±6.5	15±6.6	13.5±5.3	13.3±5.3
TAR >250(%)	4.2±4.6	2.6±2.8	2.8±2.7	2.5±2.8	2±2.2
TBR<70(%)	4±4.5	3.4±3	2.4±2.2	2.2±1.7	2.5±1.8
CV(%)	33.7±6.1	33.7±5.1	33±4.2	32.7±6	31.8±7.3
GMI(%)	N/A	7±3.8	6.6±0.2	6.5±0.2	6.5±0.28
HbA1c (%)	7.3±0.9	6.8±0.8	6.8±0.4	7.1±0.8	6.8±0.5
TIR of>%70	60	87.7	82.9	94.1	95.8
3 goals (TIR>70%+GMI<7%+TBR<5)	N/A	80.4	77.5	85.3	87

*Linear regression model was used in the analysis of the data

P1-51

Health-related quality of life and metabolic control in children and young patients with type 1 diabetes and in their parents before and after the COVID-19 lockdown

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Introduction: Italy was the first EU country to be affected by COVID-19 outbreak. The sudden change in everyday life was challenging for children and young people (CYP) who rely heavily on peer connections for emotional and social support. Concerns for consequences in CYP with type 1 diabetes (T1D) rose.

Objectives: To compare the diabetes-specific health-related quality of life (D-HRQOL) of CYP with T1D and their parents and the glycemic control before and after COVID-19-related lockdown.

Methods: The Pediatric Quality of Life Inventory™ 3.0 Diabetes Module (PedsQL™ 3.0 DM) was used to evaluate the D-HRQOL. Patients who filled the D-HRQOL before lockdown (December 2019–February 2020; T0) were recruited in the study and filled the same survey immediately after the lockdown was stopped (June 2020; T1) during a routine outpatient or telemedicine visit. Data on diabetic ketoacidosis (DKA), severe hypoglycemic events, insulin therapy [dose and delivery method (MDI/CSII)], glucose monitoring method (SBGM/isCGM/rtCGM), glycosylate hemoglobin (HbA1c), physical activity (h/week), and SARS-CoV-2 infection were also collected. Continuous and categorical data are reported as median and percentage, respectively.

Results: Sixty-two CYP (males 48.4%; age: 12.6 [5.25-17.8] years; T1D duration 4.23 [0.45- 16.4] years; MDI 71%; rtCGM 52%, SBGM 29%, and isCGM 19%; telemedicine visit 56.5%) with T1D and their parents (60 mothers, 10 fathers) were enrolled. Patients' and fathers' scales scores did not significantly change from T0 to T1. Mothers' "*Diabetes symptoms*" scale score increased (67.0 vs. 70.4; p=0.007). According to visit type (outpatient vs. telemedicine), glucose monitoring (SBGM vs. isCGM vs. rtCGM), and insulin therapy (MDI vs. CSII), D-HRQOL data were longitudinally comparable and no differences was found between groups. During lockdown no DKA, severe hypoglycemic events, and SARS-CoV-2 were recorded in patients. Despite the significant decrease of exercise from T0 to T1 (3.25 vs. 0.50 h/week; p<0.0001), glycemic control (HbA1c 58.5 vs. 57.9 mmol/mol) and total daily insulin dose (0.86 vs. 0.82 IU/kg/day) were unchanged. At T1, the lower the HbA1c, the better patients' "*Diabetes symptoms*" (R=-0.41, p<0.001), "*Worry*" (R=-0.27, p=0.032) scales, and total scores (R=-0.33, p=0.009). Similar results were found in parents.

Conclusions: During COVID-19 pandemic-related lockdown the D-HRQOL did not change in CYP with T1D and their parents. During visits we stressed the importance to keep a balanced nutritional program, according to new time spent on exercise, making diabetes managements easier and allowing the maintenance of good glycemic control without acute complications.

P1-52

Relationship between the quantification of physical activity according to the PAQ-c survey and the metabolic control of pediatric patients with type 1 diabetes

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Introduction: To achieve glycemic control goals in patients with type 1 diabetes (T1D), they are instructed in three fundamental principles: diet, insulin therapy and physical activity. Physical activity recommendations for children and adolescents with T1D are the same as for the general population. Following the physical activity recommendations helps mitigate the increased cardiovascular risk inherent to DM. We set out to explore the degree of glycemic control in relation to physical exercise performed by our patients with T1D.

Methods: We carried out an observational, descriptive and cross-sectional study in which we included pediatric patients with T1D from two University Hospitals. The participants answered the questionnaire on physical activity in children (PAQ-c) after signing the informed consent. We also recorded their demographic, anthropometric and metabolic control data on the same day they answered the survey. A PAQ-c score > 2.5 was considered as adequate physical activity. We follow the ISPAD and ADA criteria for the objective of metabolic control in capillary HbA1<7.0.

Results: We recruited 93 patients (45 girls; 48.4%), age average 12.2 (2.81) years old and T1D evolution of 5.77 (3.48) years. The mean BMI z-score was 0.45 (1). 6 children were obese, 30 (32.3%) were prepuberal, 38 (41.3%) had tanner 5 and 38 (40.1%) were on hybrid closed-loop insulin pumps. The average Hb1Ac(%) was 7.2 (0.71). 39 (42.4) had Hb1Ac<7.0%. 29 patients (33.9%) had Time in rage >70%. The mean PAQ-c score was 2.52(0.54); 49 patients (54.8%), had a PAQ-c Score > 2.5.

In the contingency study, the groups with c-PAQ >2.5 had higher proportion of patients with Hb1<7.0% (31/39 (64.6%) vs 8/44 (18.2%); p <0.001) and in Time in range > 70% (20/39 (41.2%) vs 9/44 (22%); p= 0.180) with no differences in average time in hypoglycemia (3.2(0.4) vs. 3.7(0.6); p-value= 0.323)

Conclusion: Patients performing sufficient physical activity are more likely to meet HbA1 and TIR goals than those who do not, without increased odds of hypoglycaemia.

P1-53

One Case Report of MODY5 with MCPH3

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Objective: Maturity onset diabetes of the young (MODY)5 is a type of monogenic diabetes. Primary autosomal recessive microcephaly (MCPH)3 is a rare microcephaly caused by depletion of neuronal progenitor cells characterized by mostly normal brain structure, mental retardation, and premature closure of the frontal cranial suture. To report a case of MODY5 combined with MCPH3, in order to increase the clinical attention to this disease.

Methods: The clinical data and genetic testing of the children were analyzed to confirm the diagnosis.

Results: The proband, a 13 years and 5 months girl, admitted to our hospital with "diabetic ketosis". The physical examination was central obesity, microcephaly (48cm, -4.1SD), and acanthosis nigricans could be seen under the neck and armpit, nervous system examination revealed no abnormality. The child was born naturally at 38 weeks, with normal birth length and weight, and a head circumference of 29 cm (-4.1SD) at birth. There was no history of birth trauma or asphyxia. At the age of 7, it was found that the intellectual development was low, the number was insensitive, and the fine motor was poor. The intellectual evaluation showed the passing level of intellectual development. At present, the fine motor is still poor, and he is studying in the first year of junior high school, and his academic performance is not good. There was no family history of diabetes and microcephaly. Auxiliary examination: Diabetic antibodies were negative, OGTT test showed hyperinsulinemia, dyslipidemia, glycosylated hemoglobin 12.3%. Abdominal CT showed fatty liver and small right kidney. Cranial MRI showed that bilateral cerebral hemispheres, cerebellum, and brainstem were small in size, and the front of the falx was widened. Whole-exon gene detection revealed 2 novel heterozygous mutations in CDK5RAP2 gene: c.4270G>T (p.E1424X), c.1594C>T (p.Q532X), and 1 novel splicing mutation in HNF1B: c.1534+10C>T. The three mutations in this case were all novel mutations.

Conclusion: This patient with MODY5 and MCPH type 3, the connection between the two has not been reported. What's more, we found 3 novel mutations, which expands the database of HNF1B and CDK5RAP2 gene mutations.

P1-54

Relation between body weight and bone mineral density in type 1 diabetic patients

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Objective(s): Type 1 Diabetes Mellitus (T1DM) is associated with poor bone health. It is shown that the increased fracture risk in T1DM is multifactorial. The aim of current study is to determine the body weight correlation with bone mineral density (BMD) in type 1 diabetic non-obese patients.

Materials and Methods: To evaluate the factors associated with bone mineral density in type 1 diabetic patients a total of 45 patients with T1DM, aged 20-35 years, with a duration of diabetes >5 years were investigated. The serum levels of 25-hydroxyvitamin D3 (25OHD3), glucose, thyroid hormones, and glycosylated hemoglobin (HbA1c) were evaluated. Anthropometric measurements were carried out, the Body Mass Index (BMI) was calculated. BMD was evaluated using dual energy X-ray absorptiometry (DXA). Statistical analyses were performed with SPSS Version21.0 to determine the significance of findings. In all cases null hypothesis was rejected if $p<0.05$.

Results: Significantly positive correlations were found between body weight and forearm BMD ($P<0.01$), body weight and foramen nek BMD ($P<0.01$). The mean levels of 25OHD3 concentration found to be higher in male than in female patients, 19.5ng/mL and 16,7ng/mL, respectively, without statistical significance ($P>0.05$). No any significant connection was revealed between duration of diabetes, HbA1c and BMDs.

Conclusion: Body weight modification in young T1DM patients can be considered as a correlative measure of BMD to predict the further risk of possible low BMD and osteoporosis development. Current results indicate the need of new larger studies to investigate the direct and indirect effects of T1DM on the bone health in early young age.

P1-55

Screening for disordered eating behaviours and associated factors in children and adolescents with type 1 diabetes

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Introduction and Purpose: Patients with type 1 diabetes mellitus must be extremely concerned with what they eat and their insulin dose as part of their treatment. Therefore, the risk of eating disorders increases in this patient group. This study, it was aimed to determine the disordered eating behaviors of patients with Type 1 DM and to evaluate the results of the general demographic characteristics, diabetes care behaviors, and quality of life scale that which these behaviors may be related to.

Material – Method: Sociodemographic characteristics and diabetes management of 191 patients aged 9-18 years with type 1 DM were analyzed. Quality of Life for Children Scale (PedsQL), Quality of Life for Children with Diabetes Scale (PedsQL 3.0 Diabetes Module), and Eating Problems in Diabetes Questionnaire-Revised (DEPS-R) were applied.

Results: In this study, the median DEPS-R score of the patients was 18 (19.00), and the DEPS-R score of 44.5% was above 20. A significant correlation was found between age, duration of diabetes, frequency of blood glucose measurement, HbA1c, BMI-SDS, and DEPS-R score. There was no significant difference between girls and boys. The proportion of patients with a high DEPS-R score was higher in patients with HbA1c levels >9 and patients aged >12 years. Patients with a high DEPS-R score had significantly lower Children's Quality of Life Scale (PedsQL), and Children's Quality of Life with Diabetes (PedsQL 3.0 Diabetes Module) scores. There was no significant relationship between long-term complications of diabetes and DEPS-R score.

Conclusion: The DEPS-R scale is a diabetes-specific, easily applicable, and effective method for screening patients with type 1 DM for impaired eating behaviors. It will prevent the progression of impaired eating behaviors to clinical eating disorders in patients with type 1 DM. It would be beneficial to use it as routine screening, especially in clinics where access to a psychologist is not possible.

P1-56

Curative effect contributors of exercise in type one diabetes: Irisin and Sestrin

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Type 1 Diabetes (T1DM) is a chronic metabolic disease characterized by hyperglycemia due to absolute insulin deficiency as a result of autoimmune damage of pancreatic β cells. In its treatment, insulin, medical nutrition therapy and exercise is recommended. Although it is known that exercise contributes to disease control, the mechanism of these effects has not been fully clarified. It is thought that myokines such as irisin and sestrin, can be effective by secreting with exercise, turning white fat tissue into brown.

Aim: This study aimed to compare serum irisin and sestrin levels between patients with T1DM and healthy controls, determine the changes in the clinical and laboratory findings of the patients with T1DM before and after exercise program and evaluate relationships of these changes with the levels of irisin and sestrin.

Materials and Methods: 33 patients with T1DM diagnosis and 36 control groups were involved. Firstly, exercise capacities ($MaxVO_2$) and Physical Activity Status (PAS) were determined in T1DM and control groups and serum Irisin and sestrin levels measured in both groups. Secondly T1DM patients attended to the online exercise program 3 days a week for 3 months due to COVID19 restictions. At the end of the exercise program, 10 of the T1DM patients (exercised group) participated in at least 50% of the program. $MaxVO_2$, PAS, serum irisin and sestrin levels were reevaluated and compared with the previous results in exercised and non-exercised groups. Their examinations were obtained from file data and computer records. Changes in laboratory and clinical findings were compared.

Results: Sestrin level was higher in the T1DM group than in the control group (p=0.003). This is the first data on sestrin and type one diabetes. There was no significant difference in irisin levels between T1DM and control groups (p=0.511). Both groups were sedentary due to the Covid19 lockdown. There was positive correlation between Irisin and maxVO2 in the patients with T1DM and control groups (r=0,34, p=0,02). In the second part of the study, irisin levels increased in the exercised group (p=0.012) and sestrin levels decreased in the non-exercised group (p<0.001). Physical activity score improved in the exercised group (p=0,028) and exercise capacity increased in both groups (<0,001). HbA1c levels decreased (p=0,032) and basal insulin requirement decreased (p=0,038) in the exercised group, unlike the non-exercised group.

Conclusion: Our findings suggest that the irisin and sestrin could contribute to the curative effects of exercise in type one diabetic children.

P1-57

Implications of parental anxiety, and fear of Hypoglycemia in glucose control of their Children with Type 1 Diabetes

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Introduction: Hypoglycemia is the most common acute complication in T1D. It has ominous symptoms and it is potentially fatal. Parents of infants with T1D are instructed in how to avoid, detect and manage these episodes. However, it is well known that

R value of correlation study

	1	2	3	4	5	6	7
1. STAI total	-	0.750*	0.854*	0.334*	0.229*	0.311*	-0.145
2. STAI-S		-	0.328*	0.329*	0.22	0.306*	-0.039
3. STAI-T			-	0.236*	0.152	0.226*	- 0.121
4. HFS-P total				-	0.718*	0.911*	-0.152
5. HFS-P W					-	0.399*	-0.112
6. HFS-P B						-	-0.115
7. Hb1Ac							-

* is asigned when p-value <0.05

many parents develop fear of hypoglycemia (FoH) which may lead to phobic avoidance behaviors such as permanent hyperglycemia and anxiety, losing optimal metabolic control. We aimed to explore how parenting stress and FoH impacts their children's glucose performance towards the goals.

Methods: To assess both dimension we used two questoinaires: the spanish verison of Parent's fear of hypoglycaemia scale (HFS-P) whit Behviors (B) and worries (W) caractherist and the spanish version Spielberger State-Trait Anxiety Inventory (STAI) whit both validated in spanish population. STAI-total score >45 has been classified as important clinical anxiety. Main caregivers were recruited from three pediatrics T1DM units (Jerez, Puerto Real and Puerta del Mar Universitary Hospital) who accepted, signed informed consent and completed both questionaires during their routine physician's appointment. Clinical, antropometric and metabolic data were colected from clinical history and analyzed. Descriptive and correlation study was performed using p-value<0.05 to determine stadistical significance

Results: 77 main caregivers were recruited, mostly mothers (mean age 44.9 +/- 6.8 years). Their children had a mean age 11.67 (3.7), mean diabetes duration 5.5 (3.4) years, 46 (59.7%) females, 51 (68%) patients had closed-loop insulin pumps. HbA1c mean levels of 7.2 (0.77) and mean time in range of 66.3 (15.4). 18 (23.3%) had STAI total>45 and HFS-P mean was 66.7 (15.5). Correlation study (table 1), showed a positive correlation between both scores, but none between any of the scores items and Hb1Ac or any other glucose control parameter.

Conclusions: Our study observe a high prevalence of important clinical anxiety in main caregivers. Correlation study shown higher FoH is asociated to elevated Ansiety. No association on metabolic control with anxiety or FoH were observed.

P1-58

Developing a digital Southeast Asia Type 1 diabetes healthcare educational platform in local languages during the pandemic

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Introduction: Action4Diabetes (A4D) is a non-profit UK organisation formed in 2016 that is making sustainable and scalable progress to provide quality Type 1 diabetes (T1D) healthcare in Southeast Asia (SEA). A4D provides comprehensive partnership programmes through a Memorandum of Understanding (MOU) signed with the governments in SEA that guarantees ongoing supplies of free insulin, blood glucose testing, HbA1c tests and hospital emergency funds in low-middle-income countries (LMICs)-Laos, Malaysia, Vietnam, Cambodia, Thailand and Myanmar. During the pandemic, in 2020-2021 in collaboration with SEA local healthcare professionals, A4D developed HelloType1 an innovative digital healthcare educational resource platform of T1D in SEA local languages for healthcare professionals, families and people with T1D.

Objective: To educate, engage and empower healthcare professionals, families and people with T1D by creating a digital platform that is free-to-access and provides accurate up-to-date information, patient-oriented education and best practice care about T1D care in SEA local languages.

Methods: HelloType1 content has been designed for 2 core audiences. A user option of choosing either 'healthcare professional' or 'people living with T1D and caregivers' on entry to the website. It covers 8 core topics and content is curated using information from accredited sources such as International Diabetes Foundation (IDF) and International Society for Paediatric and Adolescent Diabetes (ISPAD).

All content was reviewed and translated to local languages by a panel T1D healthcare experts and lay people with T1D to ensure that the information was appropriate in the local context. HelloType1 was launched in English, Khmer and Vietnamese languages in 2021-March 2022. Adaptation in Thai, Bahasa, Burmese and Laotian languages will be launched in August-October 2022. A Facebook page was created for each country in their local languages for signposting to the HelloType1 websites.

Results: There was an 80% increase in the number of users and 113% increase in the number of pages visited (pageviews) between Q3 and Q4 2021 in English and Khmer languages. 53% of pageviews were coming from healthcare professionals and 47% from families

and people with T1D. The HelloType1 Cambodia Facebook analytics showed approximately 1000 followers and had a 4% increase each month. On average, 3 posts were published weekly which generated a monthly average reach of 4000.

Conclusion: Strengthening health systems and developing sustainable and locally owned solutions are vital to improve health and quality of life of people with T1D. This requires universal coverage, upskilling and education to close the T1D gaps in SEA.

P1-59

Type 1 diabetes glycated haemoglobin outcomes did not differ by insulin regimen in two large Cambodian tertiary hospitals

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Introduction: Action 4 Diabetes (A4D) is a UK non-profit organisation which has been providing free insulin and self-monitoring blood glucose test kits for children and young people (CYP) with type 1 diabetes (T1D) in Cambodia's 2 large tertiary hospitals-Kantha Bopha II Hospital based in Phnom Penh (KB2H) and Jayavarman VII Hospital based in Siem Reap (J7H), since July 2018 and January 2020, respectively.

Objective: To report the glycated haemoglobin outcomes of T1D patients in the two hospitals stratified by insulin treatment regimen, namely, twice daily injections using self-mixed short- and long-acting insulin (BD); and basal-bolus multiple daily insulin injections (MDI).

Methods: Data on gender, current age, HbA1c at enrolment and during follow up in A4D clinical support programme, were reviewed.

Results: A total of 263 patients (109 male; 41%) were supported by A4D by December 2021. Mean age of patients in KBH2 on self mixed BD regimen was 16.6 years vs 17.4 years for MDI regimen. Mean age of patients in J7H on self mixed BD regimen was 14.5 years vs 18.1 years for MDI regimen. On average, the patients in KB2H were 1.4 years older than those in J7H In both hospitals, the patients on MDI were older than those on BD treatment. Overall glycaemic control did not differ by insulin regimen, and was sub-optimal with mean HbA1c >10% (>86 mmol/mol) between 2019 to 2021, except for those on MDI in KB2H during 2020. In KB2H, mean HbA1c did improve marginally during follow-up, but not in J7H where the mean HbA1c during follow-up was similar to the mean HbA1c at enrolment.

Conclusion: The glycated haemoglobin outcomes in the patients with T1D in these two hospitals in Cambodia were sub-optimal regardless of the insulin treatment regimen. The findings in this study suggest that in addition to providing insulin and blood glucose test kits, there is urgent need to further provide support and education to families and people with T1D and upskill the local healthcare professionals in T1D management so that they can empower the patients and their caregivers to optimise self-management effectively on a daily basis.

P1-60

Prevalence of autoimmunity in relatives of patients with type 1 diabetes: Time to the clinical onset of diabetes and associated risk factors

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Introduction: Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by the presence of pancreatic-autoantibodies, which are diagnostic biomarkers. The detection of autoantibodies in first-degree relatives of patients with T1D is considered a risk factor for developing the disease; however, there is little information on how long it takes from the detection of autoimmunity to the clinical onset of T1D.

Objectives: To assess the autoimmunity in first-degree relatives of patients with T1D, as well as the time to the clinical onset of diabetes and the associated risk factors.

Methods: Multicenter study of 3,430 first-degree relatives of patients with T1D collected between 1992-2018 (parents and siblings). Pancreatic-autoantibodies (IAA, GADA, IA2A and ZnT8A) were determined by radioimmunoassay, starting the analyses at diagnosis of the proband. Qualitative variables were described as percentages and non-parametric quantitative variables as median and interquartile range (RIQ: P25-P75). Statistical analysis was carried out using univariate and multivariate logistic regression models.

Results: The prevalence of autoimmunity among relatives was 1.75% (60/3430). GADA was the most prevalent autoantibody present in 78% of the relatives, followed by IAA, ZnT8A and IA2A (42%, 23% and 13%, respectively). In particular, 65% had one autoantibody, 20% two, 8% three and 7% four. The age of autoimmunity onset was 36 years (RIQ: 11.4-44.9) for those with one autoantibody and 10 years (RIQ: 4.2-20.6) for those with multiple autoantibodies ($p<0.01$, Mann-Whitney-U test). Duration of follow-up 22 years (RIQ: 9.6-24.3) without differences between those who developed T1D and those who did not. Diabetes onset occurred in 40% (24/60) of cases at age 20 (RIQ: 9.7-36.7) within 5 years (RIQ: 3.8-8.4). Regarding the risk factors, the univariate analysis showed that 83% (20/24) were siblings of the proband (OR=10.0; 95%CI 2.79-35.9), 62.5% (15/24) had multiple autoantibodies (OR=8.3; 95%CI 2.50-27.80) and 75.0% (18/24) developed

autoimmunity before adult age (OR=6.3; 95%CI 1.94-20.22). No significant differences were found in either the sex or the type of detected autoantibody. Multivariate analysis showed that having a sibling with T1D along with the presence of multiple autoantibodies has a high predictive value for the development of T1D (AUC-ROC=0.82; 95%CI 0.71-0.93; p=0.7, Hosmer–Lemeshow test).

Conclusion:

1. The development of autoimmunity in first-degree relatives of patients with T1D is uncommon and is associated with the clinical onset of the disease.
2. After detection of multiple autoantibodies, the siblings of patients with T1D are at high risk of developing diabetes within the first 5 years.

P1-61

Increased incidence of childhood type 1 diabetes during COVID-19 pandemic. Figures from an Italian tertiary care center

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Background: CDC (Centers for Disease Control and Prevention) reported an increased risk of newly diagnosed diabetes over 30 days after SARS-CoV-2 infection among persons aged < 18 years.

Similarly, the results from the DPV Registry demonstrated a significant increase in the incidence of pediatric Type 1 Diabetes during COVID-19 pandemic. The underlying mechanisms are not yet elucidated.

Aim: To investigate the incidence of type 1 diabetes in children and adolescents during COVID-19 pandemic compared with previous 5 years

Methods and Results: We conducted a retrospective study in a cohort of new onset type 1 diabetes at Bambino Gesù Children's Hospital. In 2021 as a whole we report an increase in incidence of Type 1 Diabetes compared to the years 2017 to 2020: in particular the newly diagnosed cases from 2017 to 2021 were 89 (2017), 102 (2018), 99 (2019), 99 (2020) and 121 (2021) with an increase in 2021 compared to 2017 and 2018-2020 respectively of 35% and 22%. We observed the peak of incidence in the last four months of 2021, when the "fourth wave" of COVID-19 peaked in Italy. Between September and December 2021 we recorded 50 new diagnoses of diabetes, which represent 41% of all new diagnoses of the year.Stratification of the newly diagnosed population by age groups showed that in the last quarter of 2021 there was a significant increased Type 1 Diabetes incidence in the age group under 12 years: in particular we observed that 88% of the new diagnosed children were younger than 12 (44 patients out of 50), that is significantly different from what we observed during the first 8 months of the year (43 patients out of 71, equal to 60 % of the sample). None of the patients reported previous symptoms of COVID-19 or contact with infected people. Finally, 25 newly diagnosed subjects in the last quarter of 2021 underwent serological tests for the presence of anti-SARS-CoV-2 antibodies and 8 patients (32% of tested cases) were positive, suggesting a previous asymptomatic SARS-CoV-2 infection.

Conclusion: We speculate that Sars-CoV-2 infection may have had an impact on Type 1 Diabetes incidence in children, especially in age groups not protected by vaccination. Prospective and targeted population studies are needed to consolidate this hypothesis and to verify if vaccination to Sars-CoV-2 can be considered protective in the pathogenesis of childhood Type 1 Diabetes.

P1-62

A rare case of concomitant inflammatory polyneuropathy and type 1 diabetes with COVID 19 in a teenager

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Introduction: Reduced consciousness during diabetic ketoacidosis (DKA) is an acute medical emergency which necessitates rapid escalation of care. Rarely it can point towards unusual comorbidities too. We report a case of new- onset type 1 diabetes (T1D) presenting with severe DKA in a teenager, complicated by an evolving neuropathy.

Case Report: A previously healthy 17-year-old girl presented in severe DKA following a 4-day history of vomiting, lethargy and recent history of polydipsia. She recently returned from a holiday when all family members had COVID (initial history was taken from family via telemedicine). She also intentionally lost weight by physical exercise during covid lockdown. On presentation she needed intubation and ventilation in intensive care unit. Due to profound encephalopathy she underwent CT and MRI head which were normal.

Despite resolution of DKA with standard treatment protocol, she had fluctuating level of consciousness and increasing oxygen requirements. She was started on antibiotics and antiviral for chest consolidation and presumed viral meningitis respectively. She was also treated with antifungal medication for positive candida on blood culture. Due to confusion, evolving bulbar palsy with aspiration pneumoniae and seizure activity further head CT and MRIs were done which were normal. Subsequently an EEG showed features of encephalopathy but no epileptiform waves. She eventually underwent nerve conduction studies and electromyography which was suggestive of widespread demyelinating radiculoneuropathy and the cerebrospinal fluid protein was high on lumbar puncture, both consistent with the clinical diagnosis of Guillain- Barre syndrome (GBS). She was commenced on a course of plasma exchanges which improved her neurological status. Due to persistent neuropathic pain, she received extensive input from neuropsychology, speech and language, physiotherapy and occupational therapy teams. Before discharge she was started on continuous glucose monitoring in view of impaired hypoglycaemia awareness. Her GAD antibodies were positive, but her extensive autoimmune polyneuropathy screen was negative.

Conclusion: The case shows a rare combination of GBS, T1D with DKA and COVID-19 infection in our patient. It also highlights the challenges associated with neurological manifestations during DKA. A short prodrome and severe DKA may have been precipitated by the concomitant COVID-19 infection. Persistent neurological symptoms presented a conundrum and eventually led to the diagnosis of GBS in a newly diagnosed T1D patient. It's very plausible that COVID-19 infection played part in GBS too. This underpins the importance of thinking broadly on differential diagnoses when a patient presents in severe DKA and evolving abnormal neurology.

P1-233

Effects of cystic fibrosis transmembrane conductance regulator (CFTR)-modulating therapy on glucose metabolism in cystic fibrosis patients

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Introduction: CFTR-modulating therapy aims to restore CFTR function. It improves lung function and quality of life in CF patients however, its effects on glucose metabolism are not yet well defined.

Methodology: Retrospective and longitudinal study.

Inclusion criteria: patients with CF genetic diagnosis ≥10 years old on modulator therapy (ivacaftor + lumacaftor or ivacaftor + tezacaftor or triple therapy: elexacaftor + tezacaftor + ivacaftor) and who had OGTT ± Continuous-glucose-monitoring (CGM) performed before and after therapy onset.

Tests were performed without underlying disease exacerbations or corticosteroid at the time of test or 4 weeks prior.

OGTT classifies patients into normal tolerance (NGT), impaired tolerance (AGT) or diabetes (CFRD). CGM (IproTM2-Medtronic) performed for 6 days with regular exercise and diet; patients were classified as NGT: <4.5% of monitoring time >140mg/dl, AGT: ≥4.5% of monitoring time >140mg/dl or one glucose peak ≥200mg/dl and CFRD: ≥2glucose peaks ≥200mg/dl on different days.

Results:

HbA1c was <6% before and at therapy control, except for patient Nº6 who started with HbA1c7.9%.

Five patients (62.5%) were homozygous and 3 heterozygous for F508del mutation.

Patients with pre-therapy glucose abnormalities improved and one patient without glucose abnormalities worsened.

Patient nº8 required nasogastric tube feeding, insulin (CFRD) and was a lung transplant candidate before beginning triple therapy; nowadays he doesn`t need nasogastric tube feeding, stopped insulin after 16 months on therapy and he is no longer a transplant candidate.

Patient nº6 had 11 peaks of postprandial glucose >200mg/dl on control CGM while OGTT showed normal glucose values (maximum 138mg/dl).

Conclusions:

- CFTR-modulating therapy appears to improve glucose metabolism in patients who had glucose abnormalities.
- The effects of CFTR-modulating therapy on glucose metabolism seem to take longer than the rapid improvement observed in lung function and nutritional status.
- CGM is more sensible than OGTT to changes of glucose metabolism in CF patients.

Patients and glucose metabolism

				Pre-therapy			Control	
NO	Therapy	F/M	Age (years)	OGTT	CGM	Time to control study (months)	OGTT	CGM
1.	A	F	10,25	**AGT** (INDET)	--	17	**NGT**	--
2.		M	14,58	NGT	**AGT**	13	NGT	**NTG**
3.		M	15,50	NGT	NGT	7	NGT	--
4.	B	M	15,60	NGT	NGT	17	NGT	NTG
5.		M	17,25	NGT	NGT	13	NGT	--
6.		F	17,33	NGT	**NGT**	18	NGT	**CFRD**
7		F	20,50	**AGT**	**AGT**	19	**NGT**	**NGT**
8	C	M	17,50	**CFRD**	--	21	**AGT**	--

A:lumacaftor and ivacaftor. B: tezacafor and ivacaftor. C: ivacaftor, tezacaftor and elexacaftor

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P1-234

Paediatric Post-Prandial Hyperinsulinaemic Hypoglycaemia

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Objective: Postprandial hyperinsulinaemic hypoglycaemia (PPHH) or "late dumping syndrome" is a well-recognised complication following gastrointestinal surgery and has been less commonly identified idiopathically in paediatric patients. This study describes and compares the characteristics, diagnosis, management and outcomes of paediatric idiopathic and surgical PPHH.

Design: Retrospective chart review of children (≤ 18-year-old) at a single tertiary paediatric hospital diagnosed with PPHH between 2003 and 2018.

Method: Cases of PPHH were identified from the Endocrinology unit database. Demographics, method of diagnosis, management and outcomes were evaluated. Diagnostic tests included standard/prolonged oral glucose tolerance test (OGTT/POGTT), mixed meal test (MMT) and feed test (FT). Demographic data were summarised using standard descriptive statistics. Continuous and discrete variables were analysed using unpaired t-tests. Statistical significance was defined as P value <0.05.

Results: 34 children, 18 idiopathic and 16 surgical (post-gastrointestinal surgery), were diagnosed and managed for PPHH. 41% of cases had a family history of diabetes mellitus or hypoglycaemia and 24% had a history of resolved perinatal hypoglycaemia. Idiopathic patients had a significantly longer duration of symptoms prior to diagnosis (2.54 vs 0.18 years, p=0.0009). 71% of PPHH were diagnosed on OGTT/POGTT and 18% of cases required repeat testing. Change in feed regimen was the most common intervention, utilised in 88%. 79% of cases required management with corn-starch or other medications. 8 patients (24%) required >1 medication and the mean number of medications was higher in surgical PPHH (1.4 vs 0.83, p=0.04). Acarbose was the most common medication, used in 20 of patients, and improved glycaemic control in 80%. Diazoxide was used in 10 and improved control in 50%. Patients were followed up for an average of 4.0 years (±3.4). 18 (53%) had improved glycaemic control and nine (26%) had no hypoglycaemic episodes on treatment. Resolution occurred in 12% taking from 1.54-5.54 years.

Conclusion: This study is the first and largest to describe and compare paediatric surgical and idiopathic PPHH. Diagnosis of PPHH was often delayed, particularly in idiopathic PPHH, and prolonged or repeated testing may be required in patients with a consistent history. PPHH tended to be more aggressively managed in surgical PPHH, with more medications trialled and stricter feeding regimens, but had better outcomes. Acarbose and diazoxode can be considered as medical agents in those with refractory hypoglycaemia, although use of both were limited by side-effects. PPHH improved in the majority of children but resolution was uncommon in our population.

P1-235

Etiology-based diagnosis of pediatric patients with atypical diabetes using routine and omic-based phenotyping and genotyping: results from the GENEPEDIAB study

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Objective: To provide etiology-based diagnostics to pediatric patients with diabetes in Belgium using routine clinical phenotyping and thorough genotyping.

Methods: A Belgian GENEPEDIAB study consortium was created to screen, using routine diagnostic tools, for monogenic forms of diabetes in pediatric patients followed in convention centers for type 1 or type 2 diabetes, while presenting atypical biological and clinical features of the disease (e.g. lack of anti-islet antibodies, persistence of C-peptide secretion and low glycemic variability; features not considered by the MODY calculator). We compiled the most representative clinical features of monogenic diabetes into a new diagnostic tool, the DIAMODIA score. Patients enrolled in GENEPEDIAB were phenotyped (e.g. glycemic variability, glucose tolerance, multiplex serum protein assays) and genotyped for "type 1 diabetes risk" (HLA typing and SNP-based diabetes risk score determination as established by the team of Prof A Hattersley (Exeter, UK). Patients fulfilling sufficient criteria were genotyped (restricted gene panel [University of Antwerp] then whole-exome sequencing using NGS). Gene-phenotype correlations were performed using bioinformatics (Prof. N. Limaye, de Duve Institute). Phenotyping analyses were compared to a control cohort of 295 patients with classical type 1 diabetes.

Results: A cohort of 750 patients diagnosed with type 1 and type 2 diabetes was evaluated. Our DIAMODIA score identified a subgroup of 107 patients (the "ADia cohort") likely to present atypical diabetes. Data derived from the ADia cohort confirmed the following characteristics: absence of anti-islet antibodies (44%), presence of residual C-peptide secretion (median random C-peptide levels of 0.5±0.7 nM), diabetes control within recommended targets (median HbA1C: 6.6%). In ADia patients, routine MODY gene panel analysis identified 23 class 5 variants and 5 class 3 variants (10 HNF1A, 11 GCK, 4 HNF4A, 2 HNF1B, 2 ABCC8, 2 KCNJ11). In-depth WES analysis retrieved class 3 variants in 19 patients, providing our DIAMODIA score a yield of 21.9% for class 5 and 18.1% for class 3 gene variant positivity. Familial clustering analysis of variants is ongoing. Also, low levels of glycemic variability were key in identifying ADia patients with monogenic gene variants: a delta GTAA1C and delta IDAA1C score of >2 helped discriminate monogenic vs type 1 diabetes patient cohorts.

Conclusion: In our GENEPEDIAB cohort, phenotyping and genotyping helped us decipher new molecular elements in patients with atypical diabetes. Our consortium will now evaluate how etiology-based diagnosis of atypical forms of diabetes in children and adolescents might impact patient education and treatment individualization.

P1-236

A novel homozygous mutation in the Glycerol-3-Phosphate Dehydrogenase 1 gene combined with a heterozygous mutation in the Glucokinase Regulator gene associated with hyperglycaemia, hypertriglyceridaemia and non-alcoholic fatty liver in a 17 year old woman

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Background: Hyperglycaemia combined with hypertriglyceridaemia and non-alcoholic fatty liver, not directly related to Type 1 diabetes mellitus (T1DM,) is a rather uncommon metabolic disorder in children, which often evades early and accurate diagnosis. Even though considerable progress has been made in identifying some of the genes involved, the molecular basis of conditions presenting with hypertriglyceridaemia, deranged liver function and insulin resistance remains undefined.

Case Presentation: We present a case report of a 17-year-old female with initial findings of hyperglycaemia, hypertriglycaemia and non-alcoholic fatty liver. An elevated glycosylated haemoglobin (HbA1c) was documented. Due to the absence of T1DM autoantibodies in repeated blood assays, the diagnosis of maturity-onset diabetes of the young (MODY) was suspected. Nevertheless, all relevant genetic tests conducted to verify this assumption remained inconclusive. The patient was subsequently placed on metformin without sufficient improvement. Aiming to at least achieve normalization of blood glucose, adjuvant diet and lifestyle changes were advised. Further testing using next-generation sequencing analysis (NGS) for familiar hypertriglyceridemia and hypercholesterolemia revealed the presence of the missense variant c.895G>A in the Glycerol-3-Phosphate Dehydrogenase 1 gene (GPD1), resulting in the amino acid substitution p.(Gly299Arg). Furthermore, the heterozygous variant c.307G>A in the Glucokinase Regulator gene (GCKR) was detected, resulting in the amino acid substitution p.(Val103Met). To the best of our knowledge and following extensive research of online databases, this constitutes the first case of an adolescent patient with a homozygous c895G>A mutation in the GPD1 gene presenting with hypertriglyceridaemia, hyperglycaemia and insulin resistance. The heterozygous mutation c.307G>A in the GCKR gene represents the second such reported case.

Discussion: The presence of hyperglycaemia and hypertriglyceridaemia combined with non-alcoholic fatty liver in paediatric patients, in the absence of T1DM antibodies, should raise suspicion of GPD1 and GCKR mutations. Early detection of such patients through genetic screening allows prompt disease recognition and specific treatment, whilst minimizing disease progression.

Keywords: Type 1 diabetes mellitus, hyperglycaemia, hypertriglyceridaemia, non-alcoholic fatty liver, MODY, GPD1, GCKR.

P1-237

Neurodevelopmental outcomes in children with congenital hyperinsulinism

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Background: Congenital hyperinsulinism (CHI) is a rare group of genetic disorders resulting in persistent hypoglycemia which can lead to a considerable risk of neurological damage and developmental delay.

Aim: To assess the neurodevelopmental outcome in children with CHI.

Methods: Thirty-three patients with CHI aged from 7 to 58 months were included. All subjects underwent clinical examination including physical and neurological assessment as well as 18F-DOPA PET/CT. Twenty two patients undergone genetic testing (66%). Developmental screening was performed in 6 months after treatment using "Ages and Stages" questionnaires. Such areas as communication, social skills, motor skills (fine and gross), and problem-solving skills were evaluated. Possible risk factors for neurodevelopmental sequelae due to hypoglycemia were analyzed (form, age of onset and confirmation of CHI, lowest recorded blood glucose level, highest rate of glucose consumption). Statistical analysis was performed using Jamovi 2.3.2. Univariate and multivariate binary logistic regression models were applied to determine variables that significantly affected the outcome. A p-value <0.05 was considered statistically significant.

Results: Out of 33 patients 42% (14) had focal form of CHI, 34% (11) had diffuse form and 24% (8) had atypical form of CHI. All patient with focal form undergone surgical treatment and had recovery as a result. Causative variants in KATP-channel were identified in 19 patients (86%). Causative variants in GLUD1 gene were identified in 1 patient, in GCK gene – in two patients. Normal neurodevelopment in general was observed in 23 subjects (69%), 10 patients had developmental delay. Neurodevelopmental outcome in general (p=0,01) and such individual skills as communication (p=0,03), fine (p=0,04) and gross motor (p=0,01), problem solving (p=0,02) in children with a focal form of CHI were significantly better developed than in those with nonfocal forms. Age of onset and confirmation of the disease, the lowest recorded level of glycemia and the highest level of glucose consumption did not significantly affect the formation of either individual skills (with the exception of gross motor skills) or neurodevelopment in general (p>0,05). Gross motor skills in children with a lower level of glucose consumption turned out to be significantly better (p=0.026).

Conclusion: Focal form of CHI has the greatest modifying effect on positive neurodevelopmental outcome. Risk factors associated with disease did not significantly affect the neurodevelopmental outcome other than gross motor skills which were better formed in children with a lower level of glucose consumption.

P1-238

Faster-acting insulin Fiasp versus insulin Novorapid in type 1 diabetes children and adolescents with sensor-augmented pump therapy

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Introduction: Rapid-acting insulin analogues have been developed to mimic more closely the physiological action of endogenous insulin. However, they still have a delayed onset of action and a longer duration compares to endogenous insulin. Therefore, newer insulin analogues have been developed with a faster onset and a shorter duration of action.

Aim: To evaluate the efficacy of rapid-acting insulin analogues (Novorapid) vs a faster acting insulin (Fiasp) in children and adolescents with type 1 diabetes (TIDM) treated with sensor-augmented pump (SAP).

Materials and Methods: This was a randomized cross-over study conducted in 33 children and adolescents (60,6% males, median age 12 years) with TIDM using SAP. Most of the participants were receiving Novorapid before the initiation of the study (51.5%), while 3 out of 10 (30.3%) were receiving lispro (Humalog). After randomization, 21 participants (52,4% males) received Fiasp and 12 NovoRapid and crossed over after 3 months. Height, weight, BMI, daily total insulin dose, HbA1c, percentage of time spent in euglycemic range (TIR), time above range (TAR), time below range (TBR) and time of sensor use were reported at the study onset, 3 and 6 months afterwards.

Results: There was a significant difference in the total daily insulin dose per kg at three and six months in the group of Fiasp (p=0.034 and 0.028 respectively) compared to base line which was not observed in those receiving Novo Rapid. Furthermore, there was no difference between the two groups regarding daily insulin dose per Kg at 6 months. No difference was observed regarding HbA1C, TIR, TAR, TBR, BMI, BMI-Zscore and duration of sensor use at 3 and 6 months between the two groups. However, 70% of participants decided to continue with Fiasp after the end of the study.

Conclusion: Fiasp and NovoRapid are equally efficient in children and adolescents with TIDM treated with SAP with no difference in glycemic control.

P1-239

Why understanding hemoglobin glycated measurement can be important: Santa Juana hemoglobin variant and falsely elevated HbA1c

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Diabetes mellitus is a chronic disease. The risk of microvascular complications is correlated with hemoglobin A1c (HbA1c) level [1] Educating the diabetic patient to keep an HbA1c below 7% reduce the risk of long-term complications.

We report the case of a 15 years old teenager, with chronical headache, referred for diabetes mellitus with a fasting glycemia of 83 mg/dl (normal < 100) and an HbA1C of 8.3% using an Ion-exchange High Performance Liquid Chromatography (HPLC, Adams A1C HA-8180V, normal 4-6%) and negative anti-islet and anti-insulin antibodies. She has no medical history and is of Bosnian descent. Her father due to persistently high HbA1c around 8.9% was diagnosed type II diabetic, is under Gliclazide, Semaglutide and Metformin. His diabetologist would like to add insulin to his treatment. He told us never had hyperglycemia on his glycemic profile. Our patient has no symptoms of diabetes. Her clinical examination is normal. Her body mass index is 22.6 kg/m2 (+0.8 sds). We controlled the HbA1c who was again 8.2%, using the same automaton (HPLC Adams A1C HA-8180V). We suspected a MODY diabetes or an interference with the HbA1c measurement. We asked the patient to perform glycemic profile which was normal during waiting for additional results who were all negative: fructosamine 261µmol/l (normal 205-285), capillary electrophoresis of hemoglobin and MODY Panel. Due to discrepancy between the results and high HbA1c level, we controlled the HbA1c with another HPLC automaton (TOSOH G8 normal 4-6%). The results were 6% for our patient and 6.13% for her father. This difference of HbA1c value between the two automata has led us to suspect an interference in the HbA1c measurement caused by an unusual hemoglobin variant. Genetic assessment of patient's hemoglobin gene shows indeed a mutation coding for hemoglobin of Santa Juana and a deletion coding for the alpha thalassemia minor. The Santa Juana hemoglobin migrate in HPLC at the HbA1c level and interfere with his measurement. The interferences of Santa Juana hemoglobin seem less with TOSOH automaton than the Adams automaton. Because of intrinsic characteristics of automata, different degrees of interference can be observed and explaining why the HbA1c control of our patient is 6.0% and of her father still 6.12%. Existing enzymatic and immunohistochemical methods that are totally not influenced by any hemoglobin variants. The literature described only one similar adult case with T2DM. Finally, our patient has no diabetic and his father most likely not either.

P1-240

Successful inpatient use of a fully closed-loop (FCL) insulin delivery system in an adolescent with diabetes secondary to pancreatitis

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Background: Variable rate intravenous insulin infusion (VRIII) is commonly used in unwell patients with diabetes and complex nutritional needs. However, frequent blood glucose monitoring with infusion rate adjustment gives rise to significant safety concerns and is extremely resource intensive.

Fully closed-loop (FCL) systems are promising technological advancements in diabetes management. It comprises of continuous glucose monitoring and a control algorithm to automatically modulate insulin delivery via an insulin pump in response to glucose concentration.

CamAPS HX is one such system that has shown to improve glycaemic control in adult inpatients receiving nutritional support, although there are no data for children. The CamAPS HX algorithm is an Android 'app' initialised by input of body weight and total daily insulin dose, and has an adjustable nominal glucose target of 5.8mmol/l and options for bolusing for carbohydrate intake.

Objective: We present a case of a hospitalised adolescent with diabetes secondary to acute pancreatitis managed with a FCL system.

Case Report: A 14 years-old boy (weight=63kg) was admitted to the paediatric intensive care unit with acute necrotizing pancreatitis and oesophageal perforation. Persistent hyperglycaemia with low c-peptide levels (12pmol/L with glucose level of 14.4mmol/L), suggested diabetes secondary to pancreatic beta-cell failure. He was started on VRIII from Day-2 of admission and required daily insulin doses of 0.9-1.2unit/kg while on total parental nutrition (TPN). The clinical course was complicated by near complete necrosis of pancreas and peripancreatic collections. Undulating clinical course, frequent titration of TPN and variable tolerance to nasogastric feeds resulting in frequent unscheduled changes posed significant challenges to conventional insulin pump therapy. Therefore, CamAPS HX FCL was started off-licence on Day-20 following institutional governance approval. The system allowed stable glucose levels with no adverse effects during time on and off TPN and while reintroducing enteral feeds (Table 1). The patient was switched to CamAPS FX (hybrid closed-loop system) on day 25 prior discharge home.

Conclusion: This case supports the safe and effective use of FCL systems for inpatient management of paediatric patients with complex nutritional needs. To our knowledge, this is the first reported paediatric inpatient case to use this system.

P1-241

3 Screen ICA TM ELISA - A new tool for identify pre-clinical diabetes in first-degree relatives of patients with type 1 diabetes (Pre-diabetes study)

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System	Days admitted	Insulin Total Daily dose (units/kg)	Basal (%)	Time in Range 3.9-10mol/(%)	Time below range below 3.9mmol/l (%)	Average glucose (mmol/l)	Glucose variability (SD)mmol/l
VRIII	18	0.91	-	75.6	1.2	7.8	2.6
CamAPS HX	20	0.45	46	89	1	7.5	1.7
CamAPS FX	25	0.50	23	94	1	7.2	1.5

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Background and Aims: A pre-clinical stage of type 1 diabetes (T1D) often precedes by many years the overt clinical symptoms. Diagnosis during this period is often difficult and is based on the presence of specific islet autoantibodies in the subject's blood. First-degree relatives of patients with T1D were tested using the 3 Screen ICA TM ELISA (RSR Ltd) for combined testing for autoantibodies to GAD65 (glutamic acid decarboxylase, 65kDa isoform), ZnT8 (zinc transporter 8), and the islet antigen IA-2. 3 Screen positives were subsequently tested for individual antibodies. Potentially, approximately 70% of individuals with two or more types of autoantibodies (including IAA, anti-insulin) will need insulin treatment over the next 10 years.

Methods: Clinical Centers from Białystok (n=237), Rzeszów (n=80), Poznań (n=74), Warsaw IP-CZD (n=109), Warsaw (n=42), Opole (n=85), Wrocław (n=90), Gdańsk (n=55), Łódź (n=118), Katowice (n=46), Kraków (n=14), Szczecin (n=20), Bydgoszcz (n=44), Lublin (n=42) participated in the study, a total of 1056 patients (age 1-18). Blood was sent to the coordinating clinic and forwarded to FIRS Laboratories, RSR Ltd (Cardiff, UK) for testing. 3 Screen positive serum samples were assayed in the GAD65 Ab ELISA, IA-2 Ab ELISA, ZnT8 Ab ELISA and the Insulin Ab RIA (www.rsrltd.com).

Results: Out of 1056 samples n=85 (8,04%) were 3 Screen positive, 59 children with multiple autoantibodies were identified as pre-clinical diabetes (5,58%). As follow-up oral glucose tolerance test and glycated hemoglobin were performed.

Conclusions: Early detection of islet autoantibodies by 3 Screen identifies pre-clinical T1D preceding carbohydrate abnormalities and give the possibility of therapeutic interventions in innovative clinical programs. Patients covered by early education and multidirectional diabetes care will avoid the severe clinical condition associated with ketoacidosis.

P1-242

The lncOb rs10487505 polymorphism impairs insulin sensitivity and glucose tolerance in children and adolescents with obesity

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Purpose: Leptin plays a key role in the regulation of body weight and other endocrine systems. Recently, impairment of leptin gene transcription due to genetic variations in a long-noncoding RNA, also referred as lncOb, has been described in mice. In humans, a correspondent polymorphism (rs10487505) has been associated with relatively low plasmatic leptin levels compared to obesity severity and with early obesity onset.

Objectives: To characterize the clinical and metabolic phenotype of children and adolescents with obesity homozygous for lncOb rs10487505 leptin lowering allele.

Methods: children and adolescents attending the pediatric obesity clinic underwent an anthropometrical evaluation, standard 2-hour oral glucose tolerance test, and genotyping for lncOb rs10487505. Fasting and dynamic index of insulin-resistance and secretion were calculated. Plasma leptin levels were assessed in 75 children and adolescents.

Results: 434 subjects (210 girls) were enrolled, of whom 320 were G-allele carriers and 114 were homozygous for the C (leptin lowering) allele. Subjects were divided in two groups according to rs10487505 recessive inheritance (CC versus GG/GC). We did not observed differences in anthropometric parameters and obesity age of onset between groups. CC group showed significantly higher fasting insulin levels (p=0.01), higher HOMA-IR (homeostasis model assessment of insulin-resistance, p=0.01), lower WBISI (whole-body insulin sensitivity index, p=0.02), and lower DI (disposition index, p=0.03). Moreover, CC patients showed higher prevalence of prediabetes (9.3% versus 3.4%, p=0.04) and a 2.9-fold (95% CI 1.1-7.9, p=0.04) higher risk of prediabetes compared to G-carriers independently from confounders. Leptin plasma levels were significantly lower in CC group (p=0.03). Hormone levels correlated with Z-score BMI (r=0.25, p=0.04), fasting insulin (r=-0.30, p=0.01), HOMA-IR (r=-0.34, p=0.005), WBISI (r=0.35, p=0.004), and DI (r=0.34, p=0.007).

Main Conclusion: the lncOb rs10487505 variant affects leptin circulating levels and appears to worsen insulin-resistance and heighten the risk of prediabetes in children and adolescents with obesity.

P1-243

Did Covid-19 pandemic restrictions impact on diabetic care of children and adolescents in Armenia?

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Background: Type 1 diabetes mellitus (T1DM) is an autoimmune disorder, which occurs mostly among children and adolescents. Armenia is a middle-low income country, where pediatric diabetic care is given centralized in three main centers. The 85-90% of diabetic children and adolescents are followed in the university hospital. During Covid-19 pandemic Armenia was under either lockdown or strict restrictions. The purpose of the current study is to assess the dynamics of mean glycosylated hemoglobin (HbA1c) levels in T1DM children and adolescents before, during and after the Covid-19 restriction period.

Materials and Methods: HbA1c levels; sex and age of 250 randomly chosen T1DM patients were evaluated from 2018 until 2021 years. The patients were divided into 4 age groups: I (0-4years); II (5-8years); III (9-13years) and IV (14-18years). All the patients were on multiple daily injections (MDI) regimen. Statistical analyses were performed with SPSS Version 21.0 to determine the significance of findings. In all cases null hypothesis was rejected if $p<0.05$.

Results: A total of 250 patients of were included in the study; about 48.8% were females. It is shown in the Table 1, that there is a connection between age and HbA1c levels, HbA1c is higher in older patients without statistical significance ($p>0.05$). Mean HbA1c is higher in female comparing with male not significantly ($p>0.05$). Based on the results, there is an increase in HbA1c mean level during 2020, when the pandemic restrictions in the country were lounged ($p<0.05$), particularly the tremendous increase was observed in the age groups II-IV.

Conclusion: T1DM children and adolescents had higher mean HbA1c levels in 2020, when Covid-19 pandemic restrictions were implemented. Tele-medicine improvement and implementation in Armenia could be an option to improve the follow-up of T1DM children in lockdown or restriction periods leading to normalization of HbA1c levels as a goal.

P1-244

Glycemic Outcomes and Safety During the MiniMed™ 780G Advanced Hybrid Closed-Loop System in Egyptian Patients with Type 1 Diabetes

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Background: Advanced Hybrid Closed Loop (AHCL) system includes an algorithm that provides both automated basal rate and correction boluses to keep glycemic values in a target range. Patients are only required to estimate carbohydrate consumption for meal boluses.

Table 1. Dynamics of mean HbA1C (%) in different age groups of type 1 diabetic children and adolescents in Armenia during 2018-2021 years.

Years	Age groups			
2018	**I (0-4years)**	**II (5-8years)**	**III (9-13years)**	**IV (14-18years)**
Male	6,40	7,58	8,24	6,10
Female	7,07	7,85	8,29	8,15
Average	6,65	7,71	8,27	8,04
2019				
Male	6,87	7,12	7,86	8,16
Female	7,32	7,65	7,76	8,63
Average	7,03	7,35	7,80	8,33
2020				
Male	7,46	8,23	8,99	8,57
Female	7,34	8,45	7,96	9,16
Average	7,41	8,32	8,46	8,80
2021				
Male	7,35	7,36	7,63	7,99
Female	8,54	7,67	7,93	8,27
Average	7,68	7,49	7,79	8,13

Objectives: To evaluate the real-world performance of the MiniMed TM 780G system in Egyptian patients with type 1 diabetes.

Methods: Data uploaded from October 2021 to March 2022 were aggregated and retrospectively analyzed. Percentage of time spent within (TIR= 70–180 mg/dl), below (TBR) and above (TAR) glycemic ranges, the mean glucose management indicator (GMI), system use, and insulin consumed in users with 14 or more days of sensor glucose data after initial auto mode start were determined. Baseline and follow-up visits at days 7 and 180 were carried out; data were downloaded at each visit. 34.3% (n = 22) of patients previously used sensor augmented pump-predictive low glucose management (SAP-PLGM), with baseline HbA1c 7.8% ± 1% were included. The paired student t-test was used and a value<0.05 was considered statistically significant.

Results: Users (n = 64, aged 8–24 years, males represents 54 % of participants) spent a mean of 88.4% of the time in auto mode (SmartGuard). When compared with pre-auto mode initiation, time in range significantly increased from 64.6% at baseline to 75.1 %, and 79.6 % at days 7 and days 180 respectively($p<0.001$). Time above range (for both >180 mg/dL and time >250 mg/dL) significantly decreased from 28.2% to 17.9% ($P < 0.001$), while time below range (for both <70 mg/dL and time <54mg/dL) significantly decreased from 7.2% to 2.5% ($P < 0.001$). Mean glucose levels were reduced from 167.5 mg/dL at baseline to 131.4 mg/dL ($P < 0.001$) at last visit. Coefficient of variation (%) decreased from 38.4% to 30.5%. Significantly improved glycemic control was observed as GMI was reduced by 0.8% ± 0.3% while the total daily dose of insulin increased mostly due to increased basal insulin delivery (auto-basal). Average set and reservoir change was 3.2±0.4 days and mean blood glucose calibration per day was 3.6 times. No episodes of severe hypoglycemia or DKA were reported.

Conclusions: Most MiniMed TM 780G system users in Egypt achieved TIR more than 70% and GMI less than 7% while minimizing hypoglycemia, in a real-world environment with no serious adverse effects. The international consensus outcomes were enabled by automated insulin delivery; meeting real-time insulin requirements adapted to each individual user.

P1-245

Analysis of peripheral nerve conduction function and its influencing factors in children and adolescents with type 1 diabetes mellitus

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Objective: To explore the status and the main influencing factors of peripheral nerve conduction dysfunction in Chinese children and adolescents with type 1 diabetes mellitus (T1DM).

Methods: Nerve electrophysiological indicators including amplitude, latency and conduction velocity of median nerve, ulnar nerve, superficial peroneal nerve, sural nerve, common peroneal nerve and tibial nerve were collected, and the results of the last follow-up examination were included in statistical analysis.

Results: The median age of 69 T1DM patients was 10.75 years. The rate of abnormal nerve conduction examination was 43.48% (30/69), and the rate of chief complaint of paresthesia was 37.68% (26/69). A total of 621 peripheral nerves were detected, and 12.24% was abnormal in all, 11.23% in motor nerve, 13.04% in sensory nerve, 10.87% in the upper limb and 13.33% in the lower limb. The abnormal rates of common peroneal nerve, median nerve, sural nerve, superficial peroneal nerve, tibial nerve and ulnar nerve were 18.84%, 17.39%, 14.49%, 7.25%, 5.80% and 5.07% respectively. The abnormal nerve conduction examination group had higher HbA1c, triglyceride, low density lipoprotein cholesterol, CD4+/CD8+T cells, neutrophil to lymphocyte ratio (NLR), longer course of disease and lower C-peptide and 25-hydroxyvitamin D levels. The course of disease and NLR were risk factors for abnormal peripheral nerve conduction in T1DM.

Conclusion: The abnormal nerve conduction function of T1DM is very common in children and adolescents. Selective NCS examination is helpful to improve the sensitivity of nerve conduction examination in diagnosing DPN.

P1-246

Developmental surveillance in children with Congenital Hyperinsulinism (CHI) - Personalising care

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Background: CHI is a rare condition which can be related to neurological damage due to hypoglycaemic brain injury. Long hospital admissions maybe necessary which can impact babies' experience of posture and movement, translating to a motor delay. A physiotherapy developmental assessment is a vital part of a multidisciplinary team approach to personalising care. Assessment during admission is essential to provide appropriate developmental support, particularly as repeated hypoglycaemic episodes can lead to lethargy, further impacting opportunities to explore and engage with their environment.

Aim: To assess initial physiotherapy developmental status and progress of CHI infants.

Methodology: Retrospective data collection of infants (0-12 months old) diagnosed with CHI between April 2020 to April 2022 and admitted in our tertiary CHI centre, excluding those with syndromes. All patients assessed for: 1) neurological impairment using standardised assessment Hammersmith Neonatal Neurological Examination (HNNE) and 2) motor development by using the Alberta Motor Infant Score. Both methods used as it can be difficult to get discerning data from a motor assessment tool for newborns, as postural development is the main parameter of motor skills, which may not offer sufficient information. The HNNE looks at quality and quantity of spontaneous movement which can give us some further insight into motor skills.

Results: Eleven infants with genetic defect in one of the known genes (ABCC8, KCNJ11, HNF4A) implemented in CHI included in our study. Four patients have longitudinal assessment data. All had uncomplicated deliveries, one (KCNJ11) at 34 weeks and 3 (ABCC8) at 37 weeks+, with mean birth weight 3.94kg, presented day one of life. Mean length of initial hospital admission was 115.5

days. All the infants had initial newborn developmental assessment and follow-up assessment completed between ages of 6-12 months. At newborn assessment, the data showed postural developmental within age-appropriate norms, but with a reduction in quality and quantity of movement. In all cases, follow up assessment showed a drop in percentiles, some with delay well below normative. In these patients we use an equivalent 50th percentile age match to describe extent of delay.

Conclusion: These findings prompted further questions about the incidence of developmental delay in CHI and potential influencing factors. Results highlight the need for ongoing support of infants to ensure their developmental needs are met. Personalised care with developmental surveillance of CHI patients could improve long term outcomes. Prospective studies data are essential to formally assess the developmental needs of CHI patients.

P1-247

Monogenic diabetes clinic: 3-year experience

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Background: In Italy monogenic forms of hyperglycemia account for more than 6% of cases referred to pediatric diabetes clinics. In January 2019 we started a Monogenic Diabetes Clinic (MDC) with the three main aims: a) implementing a standardized pathway towards genetic testing, 2) ease the revision of complex cases, 3) implement standardized therapies for monogenic diabetes mellitus (MDM) subtypes.

Methods: Type 1 diabetes-related autoantibodies were tested by ELISA. DNA analysis was performed by NovaSeq6000 platform. Forty-two MDM genes were analyzed, including rare recessive subtypes. Chromosome 6 aberrations were analysed by MLPA. Genetic variants were classified into 5 categories; only variants classified as likely pathogenic (LP), pathogenic (P) or variant of uncertain significance (VUS) were considered.

Results: A total of 102 incident, T1DM autoantibodies negative patients with hyperglycemia were referred during the Jan 2019-Dec 2021 period. No genetic analysis was requested for 12 patients and DNA was not available for 9 patients at the time of writing.

We analyzed reports of genetic testing obtained in 60 patients until June 2021.

Forty-seven patients were referred to investigate the origin of impaired fasting glucose or diabetes with onset beyond 1 year of age (Group 1). Eight incident cases were diagnosed with Neonatal Diabetes Mellitus (NDM; Group 2). Two lean female patients with fasting hyperinsulinism and post-load hyperglycemia were diagnosed as type A severe insulin resistance (Type A SIR).

A pathogenic or likely pathogenic variant of GCK, HNF1A and HNF1B were identified in 10, 4 and 1 patients of Group 1, respectively. A large deletion of chromosome 17q12 encompassing HNF1B was also identified. Biallelic SLC2A2 gene (Fanconi-Bickels.) variants were detected in 1 patient. VUS in KCNJ11, ABCC8, and PDX1 (two) were identified in 4 patients, while 26 were negative to the genetic testing.

In Group 2 a pathogenic or likely pathogenic variant was identified in KCNJ11 (3 variants), ABCC8 (1 variant) and PDX1 (biallelic variants); a VUS in ABCC8 was detected. In one patient a 6q24 methylation defect was found. Heterozygous pathogenic variants in the INSR were identified in patients with Type A SIR.

If we consider also VUS, pick-up rate was 44.6% and 87% for Group 1 and Group 2, respectively. When 14 patients with normoglycemic parents were excluded, pick-up rate for Group 1 increased to 63.6% (21/33).

We conclude that including patients with no parental history of hyperglycemia decreases the pick-up rate of "common" autosomal dominant forms of MDM.

P1-248

Carbohydrate counting efficacy in glycaemic control among children and adolescents with type 1 diabetes mellitus: a systematic review and meta-analysis

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Background: Carbohydrate counting is an essential part of comprehensive diabetes management and is required for children and adolescents with type 1 diabetes mellitus (T1DM), according to available guidelines. However, there is no specific evidence-grading for carbohydrate counting. This review was done to determine the effectiveness of carbohydrate counting in improving glycaemic control among children and adolescents with T1DM as measured by glycated haemoglobin (HbA1c).

Methods: We screened and reviewed randomised controlled trials conducted with at-least twelve months follow-up period that compared carbohydrate counting to assess prandial insulin dose with usual diabetes care. Quality assessment was guided by the Cochrane Collaboration's Risk of Bias tool. HbA1c was extracted and compared at baseline, 12 months, and 24 months. Chi-squared test and I^2 statistics were done to assess heterogeneity. Homogenous results were pooled using the random-effects model.

Results: We identified six eligible studies of 493 potential records, comprising 1,043 children with T1DM. One of five studies showed strong evidence of HbA1c decrease after the 12 months of

intervention compared to the baseline. There was no evidence of HbA1c reduction between baseline and 24 months among both the intervention and control groups. The mean difference of HbA1c between baseline, 12 months, and 24 months was too heterogeneous to pool. After 12 months of the follow-up period, there was strong evidence of lower HbA1c levels among participants who received education about carbohydrate counting and practising insulin dose adjustment throughout the trials than the control group who did not receive both interventions (mean difference=-0.24; 95%CI=-0.42 to -0.07; p=0.005) with no evidence of heterogeneity (p=0.72; I^2=0%). The pooled estimate of HbA1c after 24 months suggested strong evidence of lower HbA1c among the carbohydrate counting group than control (mean difference=-0.46; 95%CI=-0.90 to -0.02; p=0.04), with weak evidence of heterogeneity (I^2=58%; p=0.09).

Conclusion: Meta-analysis showed that education about carbohydrate counting and adjusting insulin dose based on carbohydrate quantification improved glycaemic control among children and adolescents with T1DM. More further higher-quality studies are necessary to evaluate the effectiveness of carbohydrate counting in improving glycaemic control.

P1-249

Glycemic control and complications of type 2 diabetes mellitus in children and adolescents during the COVID-19 outbreak

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Introduction: Obesity has been on the rise in children, adolescents and young adults during the Corona virus disesase-2019 (COVID-19) outbreak. Obesity is known as the main risk factor for a number of diseases including type 2 diabetes mellitus (T2DM) and more than 90 percent of T2DM patients are overweight or obese. Along with the rise in obesity during the COVID-19 pandemic, we investigated the impact of COVD-19 pandemic on type 2 diabetes in children and adolescents.

Materials and Methods: A retrospective case analysis of children and adolescents diagnosed with T2DM who visited Korea University Hospital in both 2019 and 2020. We investigated changes in weight and body mass index (BMI)-standard deviation scores (SDS), glycated hemoglobin (HbA1c), diabetic complications, and management from 2019 to 2020.

Results: The Mean age of patients at study was 15.48 ± 2.15 years old and the mean disease duration was 2.56 ± 1.51 years. 70.6 % of patients were obese and the mean BMI-SDS was higher in 2020 than before the COVID-19 pandemic (2.21 ± 1.25 vs 2.35 ± 1.43, P=0.044). From 2019 to 2020, HbA1c level has also increased (6.5±2.72 mg/dL vs 7.3±3.70 mg/dL, P<0.001) and blood pressure (BP), total cholesterol, non-high density lipoprotein (HDL) cholesterol have also significantly increased. Obesity was found to be independent predictor of increased HbA1c in multivariable analysis (95% confidence interval 1.071-50.384, P=0.042). In non-obese subjects, HbA1c level has not significantly increased during the COVID-19 outbreak. In obese subjects, HbA1c and BMI-SDS have increased during the COVID-19 outbreak (6.45±2.30 mg/dL vs 7.20±3.05 mg/dL, P<0.001, 2.88 ± 0.75 vs 3.08±0.98, P=0.045, respectively). Diastolic BP, total cholesterol were also higher in 2020 compared to 2019 (P=0.037, 0.019 repectively).

Conclusion: During the COVID-19 outbreak, glycemic control and complications of type 2 DM have deteriorated in children and adolescents. This tendency was prominent in obese patients. Obese type 2 DM patients should be more closely monitored in glycemic control and complications.

P1-250

The Metabolic Syndrome is frequent in Children and Adolescents with Type 1 Diabetes Compared to Healthy Controls

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Background: There is a rise in overweight and obesity among children and adolescents with type 1 diabetes (T1D) in parallel with a rise in the metabolic syndrome (MS) among children and adolescents in general.

Objective: The aim of the study was to describe the prevalence and characteristics of the MS in children and adolescents with T1D compared to their healthy counterparts.

Design and Setting: The study includes two Danish cohorts; (i) the Copenhagen T1D cross sectional cohort 2016 of

277 children and adolescents with T1D that attend the pediatric outpatient clinic at a large hospital in greater Copenhagen and (ii) the a control cohort from the CHAMPS-study DK which is a population-based cohort study of Danish children and adolescents. Participants were categorized to have MS if at least two of the following criteria were met: (i) systolic and/or diastolic blood pressure ≥ 90th percentile, (ii) waist circumference ≥ 90th percentile, and (iii) triglyceride ≥ 90th percentile and/or HDL ≤ 10th percentile. In according to consensus in studies with participants with T1D, the definition does not include blood glucose levels.

Results: The prevalence of children with MS in the T1D cohort was higher than in the control cohort (13% vs. 7%; p=0.002). In addition, participants with T1D had MS at a lower BMI z- score (z-score=0.90) compared to the control cohort (z-score: 1.43; p<0.001) and lower waist circumference z-score (z-score=1.51) than participants with MS from the control cohort (z-score=2.02; p<0.001). Participants with MS were younger than the other T1D participants (median 12.8 [9.9,14.8] vs median 14.6 [11.2,16.9] years, p=0.006) and had a higher HbA1c adjusted for sex and age (p=0.003).

Conclusion: Children and adolescents with T1D have an increased risk of MS compared to healthy controls; hence clinicians and caretakers should consider early prevention and health promotion strategies.

P1-251

Does the Diagnosis of Type 1 Diabetes Affect Only Diabetics? What About Family?

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Introduction and Aim: Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases of childhood. After being diagnosed with diabetes, the lives of both children and parents change dramatically. Managing the disease brings great responsibilities to the family and all family members need to change their daily routines. In this study, it was aimed to evaluate the effects of Type 1 diabetes on the family and the relationship between these effects and glycemic control.

Cases and Methods: The socio-demographic data form and the Family Impact of Type 1 Diabetes Scale were filled in online by the caregivers (single parent) of children and adolescents aged 6-18 years who were being followed up in the Pediatric Endocrinology outpatient clinic with the diagnosis of Type 1 diabetes mellitus. The relationship between scale scores and metabolic control was evaluated. In addition, it was investigated in which areas diabetes has more negative effects and the relationship of this effect with variables such as the patient's age, duration of diabetes, parent education, and the number of siblings.

Results: 62 patients with a mean age of 11.03±3.15 (6.08-17.50) were included. The mean age at diagnosis was 7.06±3.24 (1.58-14.25), and the mean duration of diabetes was 3.9±2.7 (0.5-14.25). The mean Hba1c value was 7.5% ±1.2 (5.6-11.6). While the rate of those who stated that a person in their family could not work due to diabetes was 55%, the rate of those who said that a person was prevented from doing their job due to diabetes was 65%. While the rate of those who stated that their sleep quality decreased due to diabetes was 87.4%, the rate of parents who stated that their children's activities and holidays were affected due to diabetes was 63.5%. In addition, 60% of the parents who filled out the questionnaire stated that they could not spare enough time for their spouses, and 43.4% stated that they could not spare enough time for their other children. Discussion: Although the effect of diabetes on the family has not been found on glycemic control, it is clear that families with diabetes are particularly affected by this economic situation. In addition, it was determined that when there is a person with diabetes in the family, the relationship between parents is negatively affected and the interest in other children decreases.

P1-252

Novel insights on the associations between specific brain tract segmental alterations, glucose levels, and cognitive performance among adolescents with type 1 diabetes

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Objective: The overarching hypothesis explored in this research was discerning the relations between the neuro-cognitive accomplishments of adolescents with T1D patients and healthy siblings of similar age, according to the transient glucose excursions, and the quantitative parameters of white matter in specific pathways according to glycaemic control.

Research Design and Methods: A case-control study included 12-18 years old patients with T1D (N=17, 8 males, diabetes duration of 6.53±4.1 year) and their healthy siblings (N=13). Participants underwent brain imaging, including diffusion tension imaging (DTI) and baseline neurocognitive tests. All were hospitalized for 30 hours for continuous glucose monitoring and multiple repeated neurocognitive tests as a function of controlled manipulation of food intake and pre-meal insulin administration to enable capillary glucose of above 240 mg/dl versus lower than 180 mg/dl.

Results: T1D patients' mean HbA1c was 8.61±1.26, 8 of them having HbA1c≤8.3. Significant associations were detected between glucose level, HbA1c, and executive function (EF), inhibition ability, and semantic and episodic memory. White matter analysis demonstrated opposite effects of diffusion coefficients in various

regions according to glycaemic control, indicating specific associations between anatomical pathways and cognitive performance as a function of the group, with novel association to food stimuli.

Conclusions: Worse glycaemic control and transient high glucose levels are associated with lower executive function performance and variability in brain architecture in related areas.

P1-253

Incidence and risk factors for paediatric diabetic retinopathy: case control for a tertiary hospital in Leeds, United Kingdom

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Introduction: Diabetic retinopathy is a leading microvascular complication and preventable cause of vision loss. NHS diabetes eye screening program (DESP) assesses for early signs, with population prevalence between 3.5% and 24.2%. Understanding the factors involved is important to reduce morbidity.

Aims and Objectives: Establish clinical characteristics and modifiable risk factors for patients with retinopathy identified by DESP under the care of Leeds Children's Hospital.

Material and Methods: Retrospective case control, comparing patients with evidence of diabetic retinopathy versus age-matched control. Patients identified by DESP, mild non-proliferative diabetic retinopathy (NPDR) (R1/M1) or more severe. Review data collected as part of routine care from the diabetes management system (DMS) and electronic records.

Results: Retinopathy was apparent in 9.7% of those eligible for eye screening (n=37/380). There was a female predominance at 59.4% (n=22/37) compared to the control group 47.2% (n=27/36). On average, the retinopathy group had 2.6 years longer duration of diabetes and lower clinic attendance.

The mean last two HbA1C measurements were higher in the retinopathy group (n=69.9mmol/mol and 71.4mmol/mol) compared to control (n=60.6mmol/l and 58.7mmol/mol). Similarly time in range (TIR) was lower (n=43% versus n=52%). More of those in the retinopathy group had an HbA1C >80mmol/l 29.7% (n=11/37) versus 13.8% n=5/36).

There was more technology uptake in the control group; pump use 63.8% (n=23/36) versus 54.0% (n=20/37), hybrid closed-loop (HCL) (n=5 versus n=1) and 86.1% (n=31/36) using sensors versus 75.6% (n=28/37).

The retinopathy group had more evidence of other microvascular disease, urine albumin-creatinine ratio (uACR) 1.35mg/mmol versus 0.7mg/mmol, with 5 patients in retinopathy group having uACR >2.5mg/mmol compared to 0.0mg/mmol.

Importantly both groups mean body mass index (BMI) standard deviation score (SDS) were in the overweight category (SDS>+1) and mean total lipids and triglycerides exceeded recommended cut offs of >4mmol/l and >1mmol/l respectively. More patients had high triglycerides (>1.5mmol/l) in the retinopathy group 27.0% (n=10/37) versus 8.3% (n=3/36). Systolic blood pressure (SBP) was comparable.

Conclusion: Rates of retinopathy are comparable to previous studies. Observationally, those with retinopathy were mostly female, had slightly higher mean HbA1C, lower mean TIR and longer mean duration of diabetes. Those with retinopathy were twice as likely to have a meanHbA1C >80mmol/l. Technology uptake was 10% greater in those without retinopathy, with additional five times greater HCL use.

Engaging the teenagers with poor control remains a key challenge, notably those with retinopathy had poorer clinic attendance. Additionally the importance of lifestyle intervention has been highlighted.

P1-254

Auxological parameters and metabolic control in children and young patients with type 1 diabetes 1-year after COVID-19 pandemic

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Introduction: COVID-19 pandemic, by restricting outside activities, encouraged a sedentary lifestyle due to social distancing and, alongside, an increase in the consumption of canned food and industrialized foods, resulting in a negative impact on the growth of children and young people (CYP). Concerns for consequences in CYP with type 1 diabetes (T1D) rose.

Objectives: To investigate 1-year effects of the COVID-19 pandemic on auxological parameters and metabolic control in CYP with T1D.

Methods: Anthropometric [BMI (SDS), waist circumference/height (WHt) ratio] and glycemic control data of CYP with T1D were collected during the annual routine outpatient visit between December 2020-February 2021 (T1, 1-year after the pandemic) and were compared with the ones of the same period in 2019-20 (T0, before lockdown). Data on number of visit (outpatient and telemedicine), diabetic ketoacidosis (DKA) and severe hypoglycemic events, insulin dose (IU/kg/day), glucose monitoring (SBGM/isCGM/rtCGM), glycosylate hemoglobin (HbA1c), physical activity (h/week), and SARS-CoV-2 infection were collected.

Results: Seventy-eight CYP with T1D (males 61.5%; age 13.7 [5.7-17.8] years; T1D duration 5.96 [2.1-15.4] years) were enrolled. The interval between visits was 1.06 years. Clinical and average annual HbA1c data at T1 were comparable to T0 (see Table). Physical activity decreased, while insulin TDD increased. The prevalence of patients with last HbA1c value ≤53 mmol/mol increased (24 vs 28%, p<0.0001). The SARS-CoV-2 infection was recorded in 12 patients (15.4%).

Characteristics/Period	T0	T1	p
Ht (SDS)	0.04±1.02 (0.04)	0.04±0.97 (0.02)	0.860
BMI z-score (SDS)	0.06±0.95 (0.08)	0.10±0.95 (0.04)	0.220
WHt Ratio	0.45±0.04 (0.44)	0.45±0.06 (0.45)	0.077
Exercize (h/week)	2.24±2.75 (2.00)	1.11±2.61 (0.00)	<0.001
TDD insulin (IU/kg/day)	0.87±0.22 (0.84)	0.90±0.20 (0.94)	0.029
HbA1c (mmol/mol)	62.2±12.6 (62.0)	61.3±13.9 (60.3)	0.066

At T1, CGM use increased (67.9 vs 71.8%, p<0.001). The telemedicine visits increased because 56.4% of patients had at least one telemedicine. Rate of secondary DKA remained comparable and no severe hypoglycemic event was recorder.

Conclusions: In our patients with T1D, both the BMI z-score and the glycemic control were maintained during the 1-year COVID-19 pandemic period, despite the decrease of regular physical activity. Our data may be possibly related to the increase of telemedicine visits that allowed us to adjust patients' insulin TDD, to avoid acute complications, and also to continue educational training to start CGM, complying with safety rules to avoid COVID-19 spread.

P1-255

Initial results in the initiation of the hybrid closed-loop system in Spanish children with type 1 diabetes mellitus

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Introduction: Tandem Control-IQ and Minimed 780G are advanced hybrid closed-loop pumps (HCL) that began to use in adults and children in our hospital in 2021. These systems are made up of a continuous interstitial glucose monitoring (CGM) system, the insulin infuser, and the algorithm that automatically adjusts insulin delivery based on real-time glucose levels. Patients only require carbohydrate counting to calculate boluses.

The aim of our study was to compare glycemic control before and three months after the start of HCL therapy.

Materials and Methods: In the Paediatric Endocrinology Department, Joan XXIII University Hospital of Tarragona we have a total of 100 patients with diabetes mellitus type 1 (DM1) between 0 and 18 years of which 26 use HCL pumps.

A retrospective observational study was conducted comparing clinical and CGM data from the month prior to starting HCL therapy (T0) with data from the first three months (T1, T2, and T3).

Results: We studied a total of 26 patients with a median age of 12 years (8.6-14.8). Six (37.5%) were male. They were diagnosed of diabetes mellitus type 1 (DM1) at the age of 7.1 years (5-9.9) and currently have 4.4 years (2.3-5.7) of disease evolution. They have a BMI of 0.6 SD (-0.4-1). Nine (35%) patients previously received treatment with multiple doses of insulin (MDI) and seventeen (65%) pumps with suspension in prediction of hypoglycemia (PLGS).

The results three months after the start are shown in the following table:

	T0	T3	T3-T0	p
Insuline dose (UI/kg/d)	0,8	0,9	0,1	
basal (%)	41,9	46,5	4,6	
HbA1c (%)	7,0	6,7	-0,3	0,031
Time in range, TIR (%)	61,5	72,0	10,5	<0,001
Time above range, TAR (%)	25,0	20,5	-4,5	<0,001
Time above range, TAR > 250mg/dl (%)	8,5	4,5	-4,0	0,006
Time below range, TBR (%)	1,0	2,0	1,0	0,317
Time below range, TBR < 54mg/dl (%)	0,0	0,0	0,0	0,081
Average glucose (mg/dl)	161,0	153,0	-8,0	0,005
Coefficient variation, CV (%)	34,0	37,0	3,0	0,066

Expressed values in median

Conclusions: HCL pumps significantly improve glycemic control both at the HbA1c and TIR levels, reducing TAR at the expense of slightly increasing the time in TBR without presenting severe hypoglycemia. These results are already observed in the first month and improve both the patients with previous treatment with MDI and with PLGS.

Despite the short experience with this technology in our area, the results are positive and promising for improving the quality of life of patients with DM1.

P1-256

Analysis of NGS panel examination in patients suspected of MODY in a single tertiary hospital

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Introduction: Maturity-onset diabetes of the young (MODY) is a genetically heterogeneous group of monogenic endocrine disorders which is inherited as autosomal dominant pattern and characterized pancreatic β-cell dysfunction. It has been estimated to represent around 1% to 6% of all diabetes. The hallmark of MODY is that the onset is before 25 years of age and inherited in an

autosomal dominant manner. Generally, there are several known genes that cause MODY: HNF-4α, GCK, HNF-1α, PDX1, HNF-1β, NEUROD1, KLF11, CEL, PAX4, INS, BLK, ABCC8, APLL1 and KCNJ11. Since MODY is relatively rare in Korea, there have been few studies about its genetic findings and clinical characteristics. Thus, we analyzed genetic findings of MODY in a single tertiary university hospital.

Methods: We reviewed retrospectively 24 patients' medical records and genetic analysis using Next-Generation Sequencing (NGS) panels from June, 2019 to May, 2021 in Inha university hospital.

Results: Mean age of the subjects was 13.9 years old. The number of male was 10 and female was 14. Of the 24 subjects, 8 (33.3%) patients had sequence variants in at least one gene. Variants in NEUROD1, WFS1, HNF1A, GATA4, CEL, ABCC8, SLC2A2, CP and HADH gene were detected as pathogenic, likely pathogenic or variants of uncertain significance type. Among them, a NEUROD1 variant which is rare in MODY was first detected in Korea. Additionally, heterozygous variants in both HNF1A and CEL gene in one of the subjects were found.

Conclusions: Since studies related to MODY have not been actively or on a large scale in Korea, there has been lack of knowledge about prevalent genes associated with MODY in Korean populations. So, we report the results of NGS panels analysis in MODY patients in our hospital. To identify more candidate genes and inheritance patterns, further large studies are needed.

P1-257

A novel mutation in INS gene in an infant with neonatal diabetes mellitus: A case report and functional study

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Neonatal diabetes mellitus (NDM) is a hyperglycemic status usually diagnosed before first 6 months of life, which is caused by monogenic mutations. INS gene mutation is the second most common cause of permanent NDM, causing misfolding of proinsulin and accumulation in the endoplasmic reticulum, leading to apoptosis of the pancreatic beta cells. We report a case of NDM in a 2-month-old girl with a novel heterozygous mutation of the INS gene, and functional studies to confirm the pathogenesis of the mutation.

A 2-month-old girl presented with mild fever, cough, and dyspnea for 2 days. The serum blood glucose was 702 mg/dL, pH 7.01, and serum and urine ketones were positive. She was diagnosed with NDM and diabetic ketoacidosis (DKA), and intravenous hydration and insulin infusion therapy were started. After resolution of DKA, she applied continuous glucose monitoring system and insulin pump. Next-generation sequencing revealed a novel heterozygous mutation in the INS gene. The newly discovered variant is c.64G>C (p.Ala22Pro). Further functional studies were performed to identify its clinical implications. Western blot analysis and RT-PCR showed decreased expression of protein and RNA in A22P mutant compared to wild-type, respectively. Insulin levels were lower in the mutant than in the wild type by ELISA. Confocal microscopy showed accumulation of human proinsulin proteins in the endoplasmic reticulum in A22P mutant.

In conclusion, a novel mutation of the INS gene, c.64G>C (p.Ala22Pro), was discovered in a 2-month-old girl diagnosed with NDM, and decreased insulin secretion from pancreatic beta cells is confirmed based on various functional studies.

P1-258

Effect of Multidisciplinary Intervention on Emotional and Behavioral profile in Children with Type 1 Diabetes Mellitus: An Interventional Longitudinal study

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Introduction: Mental health comorbidities are getting more recognized in children with chronic illness like Type 1 Diabetes Mellitus (T1DM). Increased rates of depressive symptoms and anxiety disorders in pediatric patients with TIDM have been found in many previous studies. However, not much literature is available regarding impact of multidisciplinary intervention in pediatric patients with T1DM in developing countries where there is increased patient load with lack of time for counselling. Hence, we have planned this study to see the impact of an interventional tool on emotional and behavioral profile of children with T1DM.

Material and Methods: A prospective interventional study was conducted in the department of Pediatrics, Pt. B.D.S. PGIMS, Rohtak from April 2021 to March 2022. Children in the age group of 6-14 years with Type 1 DM diagnosed within last 1 year were enrolled from Pediatric outpatient department, endocrinology clinic and wards. Sick Children with Diabetic Keto acidosis/ Hyperosmolar Coma, neurological illness, IQ less than 80 and on anti-epileptic drugs were excluded. After undergoing a baseline assessment, they were subjected to emotional and behavioral assessment as per Strength and difficulties questionnaire (SDQ) and Self-perception profile for children. They were later subjected to an interventional tool which included one to one counselling of the mother and child, showing them a brief video film regarding insulin administration, providing them booklet regarding knowledge about T1DM, sessions with dietician, psycho- behavioral session with child psychologist to address their psychological issues once in a month for 3 months and incorporating telemedicine in their management. Same scores were applied to these children after 6 months and the data was analyzed using appropriate statistical methods.

Results: Forty-eight patients were enrolled during the study period. Average mean age was 9.2 years and M:F ratio was 1:1.7. HbA1c significantly declined from a mean of 11.8(1.6SD) to 8.9(1.1SD) ($p<0.05$). Initially, patients had higher scores in SDQ specially in emotional problem scale, hyperactivity and peer problem scale and lower scores for prosocial behavior. Post

intervention there was significant decline in Total difficulties score in SDQ; specially in Emotional symptoms and Hyperactivity subscale ($p < 0.001$). Self-perception profile scoring also showed significant improvement in scholastic competence and global self-worth scores after the intervention ($p<0.05$).

Conclusion: This study has highlighted role of multidisciplinary intervention programme in the management of T1DM. Improvement in emotional and behavioral profile should also be considered as a goal in the management of TIDM.

P1-259

Tear Proteomics in Children and Adolescents with Type 1 Diabetes Mellitus and Correlation with Cognitive Function Levels

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Background: Several studies have shown that type 1 diabetes mellitus (T1DM) may contribute to the early onset or acceleration of cognitive impairment (intelligence, psychomotor efficiency, information management speed, visual attention, visual perception and cognitive flexibility). Tear proteomics seems to provide useful information for understanding the molecular mechanisms of various ocular and systemic diseases.

Objective and Hypotheses: The purpose of this prospective study was to identify the proteomic profile in tear samples in children and adolescents with T1DM that are followed at the Diabetes Center of the First Department of Pediatrics of the National and Kapodistrian University of Athens, at "Aghia Sophia" Children's Hospital, and to correlate with the level of cognitive functions of these patients.

Methods and Results: Seventy children and adolescents, aged 6-17 years, with T1DM and seventy healthy age- and gender-matched children and adolescents were recruited by recording clinical and laboratory data (glycosylated hemoglobin, high sensitivity CRP, IL-6, TNF-α, BDNF, salivary amylase and lipidogram). The assessment of the level of cognitive functions were performed using the Wechsler Intelligence Scale for Children (WISC-V), Achenbach and Stroop. Tear sampling was performed with Schirmer strips. The tear proteins were isolated and trypsinised, and then peptides were separated by high performance liquid chromatography. The identification and quantification of the peptides and therefore the corresponding proteins were achieved using a Q Exactive HF mass spectrometer. The results of the bioinformatics analysis of the differentially expressed proteins and the results of the psychometric tools were combined with the clinical and laboratory parameters of the patients in order to identify and use biomarkers in tears that will show an increased risk in a first-diagnosed child or adolescent with T1DM. Preliminary data showed that children and adolescents with T1DM had higher concentrations of cystatin S, extracellular glycoprotein lacritin, beta-2-microglobulin and mesothelin, and lower concentrations of galectin-3, alpha-1-antitrypsin, neutrophil gelatinase-associated lipocalin and leukocyte elastase inhibitor, compared with the control group.

Conclusions: These preliminary data showed differential expression of tear proteins in children and adolescents with T1DM. Further bioinformatics analysis will identify tear biomarkers that might be used in assessing the risk of cognitive dysfunction early in diagnosis of T1DM.

P1-260

The association between Epilepsy and Diabetes mellitus diagnosed before 2 years of age

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Introduction: Epilepsy or seizures are often observed in patients with diabetes mellitus (DM). Different types of seizures occur in approximately 25% of patients with DM. The exact cause remains undetermined. Moreover, a possible association between T1DM and epilepsy exists. Risk factors for epilepsy in T1DM include younger age at onset, recurrent hypoglycemia or DKA, and poor glycemic control.

Aim of the Work: The aim of this work was to detect the relationship between DM diagnosed before 2 years of age and epilepsy.

Methods and Patients: This study was an observational retrospective study conducted on 62 patients diagnosed with DM before 2 years of age attending the Pediatric Diabetes clinic in Alexandria University Children's Hospital. Their mean age at onset was 11.21 ± 5.06 months, with almost 1:1 male to female ratio. Patients were divided into 3 groups according to age of onset: Group 1 (≤6 months), Group 2 (6-12 months), and Group 3 (>12-24 months). Detailed history taking and thorough clinical examination were done to all patients with emphasis on duration of diabetes, initial presentation (DKA or non-DKA), cerebral edema, convulsions at diagnosis, and history of hypoglycemia. In addition, laboratory investigations were performed such as blood glucose level, HbA1c at follow up, antiGAD-65 Ab levels, and all these parameters were compared in epileptic and non-epileptic diabetic patients. EEG was done to all patients, and brain imaging was done in patients with associated neurological manifestations.

Results: Nine patients (14.5%) diagnosed with DM before 2 years had associated epilepsy; which was commonly observed in patients aged 6-12 months at onset (66.7%). Six of these patients were on anticonvulsants. 77.8% of the patients with epilepsy had DKA at initial presentation, and most of them had severe forms. Eight patients (88.9%) had EEG findings. Generalized epileptiform

activity was the most frequently encountered (62.5%). Five patients had T1DM (55.6%), 3 patients had monogenic DM (33.3%), and one patient had an unidentified cause of DM. No significant difference could be demonstrated between epileptic and non-epileptic patients as regards duration of DM, DKA, cerebral edema, hypoglycemic attacks, or glycemic control, while T1DM patients experiencing convulsions at diagnosis were more likely to have epilepsy (^{FE}p=0.036*). There was no statistically significant relation between epilepsy in T1DM and antiGAD-65 Ab level.

Conclusions: DM diagnosed before 2 years of age can be associated with epilepsy, especially type 1 DM. However, risk factors causing this association still need to be further investigated.

P1-261

Parental stress in children with type 1 diabetes from different socioeconomic backgrounds

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Background: Type 1 diabetes is one of the most common chronic diseases in childhood. Parents of children with type 1 diabetes are significantly involved in the treatment, rendering them vulnerable to parental stress. Psychological difficulties experienced by the parents may have adverse effects on disease management and the child's psychological and somatic health.

Objectives: To assess parental stress and factors influencing it in a cohort of parents of children with type 1 diabetes.

Design: This is a cross-sectional study. The parents of children attending the diabetes clinic were asked to fill PIP- Pediatric Inventory for Parents and a sociodemographic questionnaire during a routine visit. Background information was withdrawn from the patients' files. Higher PIP scores indicate more parental distress.

Results: The cohort included 86 parents, with a mean age of 42.3 years, 74.4% mothers, 95.4% married, and 52.5 % with academic education. The diabetic children's mean age was 11.7 years with a mean diabetes duration of 3 years. Children treated with insulin pumps had lower scores on all PIP subclasses with statistical significance in some of the subclasses. Some PIP subclass scores were significantly higher in younger patients and patients diagnosed at a younger age. Parents from the Orthodox Jewish community and parents with academic education had lower scores in some of the PIP subclasses.

Conclusion: In this study, we found that younger age and young age at the diagnosis of diabetes are associated with increased parental stress while insulin pump therapy and certain sociodemographic background lessen the parental stress in parents of children with type 1 diabetes.

P1-434

Role of glucose variability on linear growth in children with Type 1 Diabetes

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Objective: Linear growth is impaired in children with type 1 diabetes (T1D) and poor metabolic control. A good metabolic control is a key therapeutic goal to prevent vascular complications but also for ensuring an appropriate anthropometric development during childhood. In this study, we aimed to identify and characterize the effects of glycemic variability on linear growth in children with T1D.

Methods: Data from 144 prepubertal children with T1D were evaluated. Anthropometric measurements (weight, weight-SDS, height, height-SDS, BMI, BMI-SDS) were collected and glycosylated hemoglobin (HbA1c) was measured at admission and every four months over a 2-year period. Glycemic variability indexes (glycemic coefficient of variation [CV], glycemic CV percentage [CV%] and the product between HbA1c-mean and HbA1c-SDS/100 [M*SDS-HbA1c/100]) were calculated. According to height-SDS changes after 2-years of follow up, the study population was divided into three tertiles groups and differences across groups were investigated for variables of interest.

Results: The three groups were similar in terms of age, gender and follow up period. After 2 years, all prepubertal children showed a significant positive trend of anthropometric data. Across the three tertiles groups, HbA1c-SDS, CV, CV% and M*SDS-HbA1c significantly decreased from the first to the third tertiles of height-SDS. During follow-up children with lower Δheight-SDS values, reported higher values of HbA1c-SDS, CV, CV% and M*SDS-HbA1c than subjects with higher linear growth.

Conclusions: Glycemic variability correlates with the linear growth in children with T1D. Low glycemic variability indexes were reported in higher height-SDS tertile. Δheight-SDS is inversely correlated with glycemic CV, CV% and M*SDS-HbA1c.

P1-435

Are we sure that the prevalence of SARS-CoV-2 infection is not underestimated? Usefulness of serological antibodies assays in children and adolescents with type 1 diabetes

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Introduction: The true incidence of SARS-CoV-2 infection in children and young people (CYP) is unclear and data are influenced by testing strategies. CYP have so far accounted for 17.5-22% of diagnosed infections. In adults, diabetes was identified as risk factor for severe symptoms and hospitalization with the COVID-19. Eighteen months into the pandemic, studies in CYP with type 1 diabetes (T1D) reported only an increased prevalence of diabetic ketoacidosis (DKA) at T1D onset.

Objectives: To investigate the prevalence and clinical characteristics of SARS-CoV-2 infection in CYP with T1D.

Methods: SARS-CoV-2 infection was defined according to self-reported previous SARS-CoV-2 nasal swab PCR results in 210 CYP followed during 18 months of the pandemic and seroprevalence of antibodies against the SARS-CoV-2 spike protein assessed in 85 CYP (previous negative nasal swab PCR or never performed) from January to June 2021, before COVID-19 vaccination era. SARS-CoV-2 IgG were assessed using a chemiluminescent immunoassay (CLIA). Data on clinical characteristics as well as glycemic control were collected before (T0) and 3-months after (T1) infection.

Results: SARS-CoV-2 infection was detected in 39 patients (males 61.5%; median age 13.5 and T1D duration 5.49 yrs.) during second and third wave: 26 (66.6%) based on the self-reported nasal swab PCR results and 13 (33.4%) on the SARS-CoV-2 IgG assay. All patients detected by CLIA were asymptomatic. Four patients detected by nasal swab PCR were asymptomatic (15.4%). Other patients reported ≥1 symptoms lasting a median of 5 days and including: fever (46.1%), headache (28.2%), anosmia and/or ageusia (25.6%), nasal congestion (15.4%), and fatigue/myalgia (10.2%). Dry cough, pharyngeal erythema, nausea and/or vomiting, diarrhea, abdominal pain, and arthralgia were less reported (2.56%). None had dyspnea, skin lesion, and MIS-C. Hospitalizations, DKA, and severe hypoglycemic events were not recorded. Glycemic control was not impaired from T0 to T1 (see Table).

Characteristics/ Period	T0	T1	p
HbA1c (mmol/mol)	62.4±16.4 (58.5)	60.2±13.6 (57.4)	0.332
TIR (%)	52.3±17.0 (58.5)	55.5±15.4 (56.5)	0.186
TAR (%)	42.1±16.2 (39.0)	40.2±15.1 (40.5)	0.518
TBR (%)	4.64±4.41 (3.00)	4.33±3.48 (3.00)	0.632

Conclusions: We found evidence for increased prevalence of SARS-CoV-2 infection among CYP with T1D using antibodies against the SARS-CoV-2 spike protein assessment. Asymptomatic subjects were 43%. COVID-19 pandemic had no impact on glycemic control and acute complications. Our data suggest that serological assay is useful to diagnose previous SARS-CoV-2 infection in not vaccinated CYP and to reconstruct the disease prevalence.

P1-436

Association of the apoptotic markers Apo1/Fas and cCK-18 and the adhesion molecule ICAM-1 with Type 1 diabetes mellitus in children and adolescents

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Introduction: Type 1 diabetes mellitus (T1DM) is characterized by insulin-producing pancreatic β-cells loss. Apo1/Fas, a glycosylated surface protein, is implicated in maintaining homeostasis of the immune system. Cytokeratin-18 (cCK-18) is a predictive marker of liver disorders in T2DM. Intercellular adhesion molecule-1 (ICAM-1) is considered a candidate gene for susceptibility to diabetes mellitus.

Aim: To investigate the possible role of Apo1/Fas, cCK-18 and ICAM-1, in children and adolescents with T1DM. Materials and

Methods: 49 children and adolescents with T1DM and 49 controls were included into the study. Somatometric measurements were obtained and the Body Mass Index (BMI) of the participants was calculated. White cell count and biochemical parameters were measured. Apo1/Fas, cCK-18 and ICAM-1 were measured using ELISA. The statistical analysis was performed using IBM SPSS Statistics 23.

Results: Apo1/Fas ($p=0.001$), cCK-18 ($p<0.001$) and ICAM-1 ($p<0.001$) were higher in children and adolescents with T1DM compared to the controls. Apo1Fas was negatively correlated with glucose ($p=0.042$), uric acid ($p=0.026$), creatinine ($p=0.022$), total cholesterol ($p=0.023$) and LDL ($p=0.005$) in the controls. In children and adolescents with T1DM, Apo1/Fas was positively

correlated with total cholesterol (p=0.013) and LDL (p=0.003). ICAM-1 was negatively correlated with creatinine (p=0.019) and positively with SGPT (p=0.014) in the controls, whereas in children and adolescents with T1DM it was negatively correlated with HbA1c (p=0.05).

Conclusions: Apo1/Fas, ICAM-1 and cCK-18 may be useful as serological markers for monitoring for potential complications and long-term morbidity or mortality in children and adolescents with T1DM. Also, Apo1/Fas may have a protective role against metabolic complications in healthy children.

P1-437

The relationship between visceral adipose index and metabolic syndrome in children with type 1 diabetes mellitus

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Background/Aim: Prediction of metabolic syndrome (Mets) plays important role in cardiovascular disease risk prevention. Although Mets is relatively common in children with T1DM, diagnosis and prediction are ignored. Visceral Adiposity Index (VAI) has been defined as a new cardiometabolic risk marker reflecting abdominal fat distribution and dyslipidemia. The aim of the study is to reveal the relationship between Mets and components of VAI in patients with T1DM.

Materials and Methods: This is a single-center prospective study. 168 patients aged 7-17 years with a diagnosis of T1DM were included. All patiens were performed following parameters: body mass index (BMI) z-score, waist-circumference, waist-to-height ratio (WHR), VAI, neck circumference, blood pressure, blood lipids, transaminase levels, heaptic ultrasound. The following criteria were used for obesity; high BMI (>95percentile) high neck and waist circumference (>90percentile), and high HHR (≥0.5) For VAI, the previously known formulation was used, and VAI cut-off:1.77 was accepted as a marker for Mets. Elevated ALT (≥45IU/l) unexplained for other reasons were considered to be risky for hepatosteatosis (HS). Patients who met WHO's child-adapted criteria were considered Mets positive.

Results: Eighty-four (50%) were female. The mean age of the patients was 12.54±2.85 years. According to BMI-SDS, 25 patients were overweight, while 2 were obese. The number of patients with high-waist and neck-circumferences as follows: 22 (13.09%), 68 (42.5%). The mean values of these anthropometric measurements were as follows: 69.59±8.33cm, 30.75±3.17cm. Of the patients, 32 (19%) had HS. Of the patients, 33 (19.6%) made diagnosed with Mets, while the VAI was found to be high in 109 (64.8%) cases. A significant relationship was found between the presence of Mets and high VAI (p<0.001).

The mean waist-neck circumferences and WHR were found to be higher in patients with high VAI (p=0.023, p=0.006 and p=0.004, respectively). Waist circumference was found to be associated with both the presence of Mets (p=0.03) and the high VAI (p=0.02). The high neck circumference was found to be associated only with the high VAI (p=0.006), not with the Mets (p=0.418).

While the relationship in terms of HS or its risk was significant with the presence of Mets, it was not found with high VAI (p=0.02, p=0.356)

Conclusion: This study showed that high VAI is common in children with T1DM and is associated with Mets. It suggests that the use of VAI may be an appropriate approach in terms of its potential to predict the development of Mets early, which is overlooked in non-obese children with T1DM.

P1-438

Abstract Withdrawn

P1-439

Deciphering monogenic diabetes mellitus in spanish pediatric patients: A cross-sectional study

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Background and Aims: The introduction of next-generation sequencing (NGS) as an essential tool for the routine molecular diagnosis of DM has highlighted the under-diagnosis of monogenic diabetes mellitus (MonDM). Accurate molecular diagnosis of the MonDM subtype has important implications for prognosis and choice of treatment, family counseling and health management, enabling precision medicine. The main objective was to clinically and molecularly characterize the different forms of MonDM in pediatric patients referred by pediatric endocrinologist in Spanish tertiary hospitals during the period from January 2009 to December 2021.

Materials and Methods: Multicenter cross-sectional study that included 131 pediatric patients with suspected MonDM analyzed by targeted NGS with a custom panel including up to 482 genes implicated in or associated with dysglycemia. The variants detected were classified according to ACMG rules and prioritized using criteria of confidence and quality, coverage (20x/pb >95%), allele frequency in control population (<1%, gnomAD) and predicted deleteriousness (CADD>15). Quantitative data were expressed as mean±standard deviation and qualitative data as absolute frequencies and percentages

Results: Variants in known MODY genes were identified in 95/121 patients (78.5%). We identified variants in 13/14 MODY genes, excepting the APPL1-MODY subtype. The most prevalent form was GCK-MODY (43.8%) followed by HNF1a-MODY (9%)

and HNF4a-MODY (5%). There were 4 digenic MODY forms, 5 novel variants, 3 de novo, and two patients with positive pancreatic autoimmunity. 17.3% (n=21) of the cases presented with predicted deleterious variants in candidate genes (MODY-X), suggesting a potential role for NR4A3, RFX6, PCK1, PCK2, SERPINB3, SERPINB4, GLUD1, FOXA1, FOXA2 and PPARG in the etiology of MonDM; 28% (n=34) presented >1 deleterious variant in dysglycemia-related genes; 6.6% (n=8) had neonatal DM (NMD) with variants in ABCC8, KCNJ11, RFX6 or HNF1b, and 1 case transient NDM (disomy of chromosome 6). Lastly, 5.7% (n=7) presented syndromic forms of diabetes: four cases compatible with Wolfram Syndrome 1 (WFS1, AR), two with Wolfram-like Syndrome (WFS1, AD) and four cases with Martínez-Frías/ Mitchell-Riley syndrome (RFX6, AR).

Conclusions: The study of MonDM by NGS reveals a greater genetic complexity than initially expected. The clinical heterogeneity classically described for MonDM may be due to the oligogenic combination of variants in different relevant genes. The identification of new genes involved in its etiology will make it possible to establish genotype-phenotype correlations to guide diagnostic suspicion, predict the evolution, prognosis and transmission of MonDM and optimize/personalize treatment.

P1-440

Abstract Withdrawn

P1-441

NEUROD1 mutation as a cause of neonatal diabetes: The rarest of the rare!

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Background: *NEUROD1* encoding neurogenic differentiation 1 is known to play an important role in the development of the pancreas and central nervous system. Heterozygous mutations have been rarely identified as a cause of maturity-onset diabetes of the young (MODY6). Biallelic *NEUROD1* mutations have been reported to cause neonatal diabetes mellitus (NDM) as well. However, only 3 cases have been reported worldwide so far.

Case Summary: We report a 4-month-old girl with NDM who presented only with abdominal distension to Alexandria University Children's Hospital. She was born to consanguineous parents at 37 weeks of gestation, and was small for gestational age with a birth weight of 1.250 Kg (-4.41 SD). On examination, her weight was 4.200 Kg (-2.8 SD), length was 64 cm (+0.5 SD), and head circumference was 38 cm (-2.1 SD). She had hepatosplenomegaly, no lymphadenopathy, no jaundice or pallor. In addition, she had bilateral lower limb hypotonia, and head lag on pulling to sit. Her routine laboratory investigations revealed hyperglycemia (500 mg/dl) with normal venous blood gases. A diagnosis of NDM was confirmed with glycated haemoglobin of 13.4%, and low C-peptide level (0.197 ng/ml), and she was started on NPH insulin (requirements 1 U/Kg/day). Otherwise, her complete blood count, serum chemistry, and virology were normal. Audiometry showed bilateral sensori-neural hearing loss in the frequency range 2-4 KHz. She was suspected to have a mitochondrial cause of diabetes, so serum lactate was done and was mildly elevated. Her brain imaging showed hypoplasia of cerebellar vermis, enlarged posterior fossa, and cystic dilatation of 4th ventricle. She had normal pancreatic size on abdominal sonography. Her electroencephalogram, nerve conduction velocity, echocardiography, and fundus examination were normal. Her genetic analysis revealed a novel homozygous likely pathogenic *NEUROD1* missense variant [c.374G>C, p.(Arg125Pro)]. This variant has not been reported in the gnomAD database and affects a highly conserved residue within the DNA-binding domain. On follow-up, she developed generalized tonic convulsions in the absence of hypoglycemia and was diagnosed with epilepsy, so oral levetiracetam was added to her therapy with good control.

Conclusion: NDM patients with associated neurological abnormalities (especially cerebellar hypoplasia), and sensori-neural hearing loss should undergo genetic testing for *NEUROD1*. To our knowledge, this is the 4th reported NDM case with *NEUROD1* mutation worldwide and the first reported in Africa.

P1-442

A continuous quality improvement effort implemented by the Italian network of pediatric diabetes clinics

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Pediatric diabetes management extends beyond glycemic control. A gap between guidelines and actual care exists. Standardized performance measures represent a key strategy to improve quality of care. In Italy, a non-profit initiative of continuous monitoring and quality improvement of diabetes care is in place since 2018, promoted by the ISPEDCARD association and involving the

			Age classes (years)		
			0-6	6.1-12	12,1-18
	N (%)		311 (8.5)	1354 (37.2)	1973
	Males (%)		54.3	54.4	53.1
	Mean visits/yr		3.4±1.7	3.1±1.4	2.8±1.2
Descriptive	First accessed (%)		10.9	6.4	1.9
	New diagnosis (%)		26.7	12.7	6.0
	Insulin Regimen (%)	CSII	48.6	39.2	34.8
		MDI	48.9	57.5	61.7
		Other	2.5	3.2	3.6
	Patients monitored during the year for: HbA1c	1 test	13.8	10	11
		>= 2 tests	80.7	87.2	87.1
	Obesity (%)	BMI	75.2	65.4	64.9
Process		BMI and waist c	21.2	32.8	33.0
	Lipid profile (%)		47.3	46.2	44.6
	Blood Pressure (%)		49.5	66.8	74.5
	Albuminuria (%)		21.9	37.0	40.8
	Eye examination (>=11yr)		-	8.3	13.4
	HbA1c % (mean±SD)		7.7±1.4	7.5±1.2	7.7±1.4
Outcome	LDL-cholesterol > 100 mg/dl (%)		27.2	28.3	27.4
	Blood pressure > 140/70 mmHg (%)		4.5	9.0	23.8
	BMI/SDS > 1.5 (%)		22.0	26.9	21.8

Society for Pediatric Endocrinology and diabetology (ISPED). Aim of the present work is to report the state-of-art of the initiative.

Materials and Methods: A predefined set of descriptive, process and outcome indicators was identified to assess strengths and weaknesses of the current care. All participating centres share the same electronic medical records system (EMR) and a software for the standardized data extraction. Participation is voluntary, anonymous, and free.

Results: Data on 3,638 patients with type 1 diabetes seen during 2019 were obtained from 18 pediatric diabetes clinics (representing 1/3 of all Italian clinics). Table shows ISPEDCARD indicators by age class.

Conclusions: Data show that process indicators regarding HbA1c and obesity indices are satisfactory, while other process indicators require additional attention in the execution and/or in data recording on EMRs. Outcome indicators show satisfactory mean HbA1c levels and need of reducing BMI, LDL-cholesterol, and, in age 12-18 years, blood pressure. Direct measurement, feedback, and regular reporting and discussion of indicators are expected to further enhance the effectiveness of care in the years to come.

P1-443

Co-segregation analysis and functional trial *in vivo* of candidate genes for monogenic diabetes

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The aim of this study was to perform familial co-segregation analysis and functional trial *in vivo* during mixed meal tolerance test (MMTT) of novel variants in diabetes candidate genes.

Methods: This study is a continuation of collaborative research project "Genetic diabetes in Lithuania" with the cohort of 1209 young diabetes patients. Prior screening for GADA, IA-2, IAA, ZnT8A confirmed type 1 diabetes (T1D) diagnosis in 88.1% (n=1065) of patients, and targeted next-generation sequencing (NGS) identified 3.5% (n=42) pathogenic variants in MODY genes. After screening for autoimmune markers, and genetic analysis, 102 patients were classified as having diabetes of unknown etiology. 12/102 were found to have novel variants in potential diabetes genes (*RFX2, RREB1, SLC5A1* (three patients with variants in this gene: 2 were brothers with c.1415T>C variant, and one unrelated - c.932A>T), *GCKR*, *MC4R, CASP10, TMPRSS6,*

HGFAC, DACH1, ZBED3). Co-segregation analysis and MMTT were carried out in order to study pancreatic beta-cell function in subjects with specific variants.

Results: MMTT analysis showed that probands with novel variants in *MC4R, CASP10, TMPRSS6, HGFAC, SLC5A1* (c.1415T>C) had sufficient residual beta-cell function with stimulated C-peptide (CP) >200 pmol/L. Seven individuals with variants in *RFX2, RREB1, GCKR, DACH1, ZBED3* and *SLC5A1* (one of brothers c.1415T>C, and proband with c.932A>T) presented with complete beta-cell failure during MMTT. No statistical differences were found between patients with sufficient CP production and those with complete beta-cell failure when comparing age at the onset and duration of diabetes. Nineteen family members were included in co-segregation analysis, no diabetes cases were reported among them. Only in patient with the variant c.1894G>A in *RFX2* gene, none of the family members were affected by proband's variant.

Conclusion: Functional beta-cell study *in vivo* allowed to select five most probable genes for monogenic diabetes. Familial co-segregation analysis showed that novel variant in *RFX2* gene could be a possible cause of diabetes in the proband. Future functional analysis of these genes in vitro could support or rule out the genetic background as a cause of diabetes.

P1-444

Influence of Family Status and Living Circumstances on Metabolic Control in Patients with Type 1 Diabetes

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Object and Aim: The quality of metabolism in type 1 diabetes depends on different external factors, e.g. the circumstances of living of a patient. We investigated how far the family status, living situation or own children have influence on metabolic control in patients who were transferred to adult care after long-term care in pediatric diabetology.

Patients and Methods: From 1998 until 2019 we annually sent a questionnaire to all patients with type 1 diabetes who left our pediatric diabetes specific care. We asked for current metabolic control (HbA1c), circumstances of living (alone, with parents, with own family), and family situation (single, married, with children). Participation was voluntary. We analyzed the data mixed longitudinal and cross-sectional.

Results: Age at transfer was 21.2 years (mean), diabetes duration 11.3 years. The mean age when answering the questionnaire was 26.5 years. 84.8% of patients (190 of 224) answered at least once during the study period. 48% of patients were female. 24.2% of patients were married. HbA1c of married vs. single patients 7.01% vs. 7.30%; p<0.05. HbA1c before transfer of patients married vs. single 7.47% vs. 7.62%; n.s. HbA1c of patients who live alone vs. patients who still live at their parents 7.23% vs. 7.22%, n.s.. Thirty of the patients (15.8%) became parents. HbA1c of patients with children vs. without children 6.93% vs. 7.28%; p<0.01. HbA1c before transfer vs. after in patients with children 7.46% vs. 6.93% p<0.05. HbA1c in women in the year of pregnancy vs. in years without pregnancy 6.38% vs. 7.33%; p<0.01.

Conclusion: Married patients with type 1 diabetes and patients with children show better metabolic control. Changes like a marriage or becoming parents could have favorable effects on metabolic control in patients with type 1 diabetes.

P1-445

Glucagon response to hypoglycemia during extended oral glucose tolerance test in children with cystic fibrosis and comparing with healthy peers

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Post-OGTT hypoglycemia is common in Cystic Fibrosis (CF). The aim of the study is to determine of the role of glucagon in the pathogenesis of hypoglycemia in CF patients.

A 3-hour-OGTT was performed fifty-three subjects (44CF,9 age-matched controls).

Sixteen (36.4%) subjects had normal glucose tolerance (NGT), 13 (29.5%) had isolated hypoglycemia (IsoHypo), 8 (18.2%) had hypoglycemia with abnormal glucose intolerance (Hypo+AGT), 5 (11.4%) had AGT and 2 (4.5%) had CFRD. After AGT and CFRD were excluded, there was no statistical significance between 4 groups in terms of age,sex,BMI and FEV1.In Hypo+AGT, the peak insulin was delayed compared to IsoHypo.Glucagon response to glycemic fluctuations in OGTT was nearly absent in Hypo+AGT and NGT compared to controls.Whereas it was relatively preserved in IsoHypo though not as robust as the controls.IsoHypo was further divided into two groups according to the presence of pancreatic insufficiency(PI).Insulin and glucagon response to glucose loading in IsoHypoPI(+) were very similar with Hypo+AGT, whereas relatively preserved but not as robust glucagon response and higher insulin response at 30-60.min were persisted in IsoHypoPI(-).

In conclusion, impaired glucagon response appears to contribute to hypoglycemia in CF. Decreased robustness of glucagon response detected even in IsoHypoPI(-) supports an intrinsic effect of CFTR gene on glucagon secretion.

	IsoHypo (n=13)	Hypo+AGT (n=8)	NGT (n=16)	Control (n=9)
Glucose(mg/dL)				
0.min*	85±5	92±13	87±5	83±4
30.min**	169±28	178±27	140±25	133±16
60.min***	152±43	229±21	125±30	126±26
90.min**	120±37	177±40	104±18	120±27
120.min*	100±23	133±35	105±13	101±21
150.min*	77±20	91±23	102±18	90±17
180.min***	64±9	60±10	93±18	87±14
Insulin(mIU/mL)				
0.min	8±6	6±5	8±4	11±7
30.min*	72±76	20±16	66±29	38±30
60.min	93±91	64±71	59±35	52±25
90.min	60±55	72±45	43±27	55±49
120.min	40±22	35±14	42±19	49±36
150.min*	17±7	18±11	35±18	32±35
180.min**	8±5	8±6	29±25	23±18
Glucagon(pmol/L)				
0.min	6,1±5,6	5,7±2,9	4,9±2,4	7,2±3,7
60.min*	3,4±1,5	5,8±5,1	2,8±2,4	1,7±1,2
120.min*	3,8±2,1	4,2±3,3	3,0±2,2	1,3±1,1
150.min*	4,1±3,0	4,0±2,5	2,6±1,7	2,0±2,3
180.min	6,7±6,2	5,1±4,0	2,7±1,7	5,4±6,6

P1-446

CASE REPORT: LRBA deficiency related Monogenic Neonatal Diabetes Mellites

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Introduction: NDM is a monogenic form of diabetes that occurs in the first 6 months of life. NDM is a rare condition accounting for up to 1 in 400,000 infants in the United States.

Recent molecular analysis of NDM identified at least 12 genetic abnormalities: chromosome 6q24, KCNJ11, ABCC8, INS, FOXP3, GCK, IPF1, PTF1A, EIF2AK3, GLUT2, HNF1β, and GLIS3. Of these, imprinting defects on chromosome 6q24 and the KCNJ11 mutation have been recognized as the major causes of TNDM and PNDM, respectively, in Caucasian subjects.

Only seven cases of LRBA related neonatal diabetes are reported in literature so far.

Case Report: We report a case of a baby boy who was born at 36 weeks to non-consanguineous parents following IVF. He presented with severe diabetic ketoacidosis at the age of three months. He later on experienced recurrent bacterial chest infections and was diagnosed with autoimmune enteropathy causing profuse diarrhoea.

GAD and IA2 antibody were negative. Genetic testing showed LRBA deficiency (Homozygous mutation c.3678_3679insTATT p.Asp1227Tyrfs*2). In accordance with LRBA deficiency, he had absent CD3 stimulation and slightly impaired T cell proliferation upon PHA stimulation.

Parents were found to be carriers of LRBA mutation on genetic testing.

Discussion: LRBA related neonatal diabetes is autosomal recessive condition. LRBA deficiency is also associated with common variable immune deficiency which manifests as hypogammaglobulinemia, autoimmunity, antibodies deficiency, lymphoproliferation and a high susceptibility to inflammatory bowel disease in early childhood. growth retardation and short stature have also been reported in some patients with LRBA deficiency

Diagnosing monogenic autoimmunity is crucial not only for patients' prognosis and clinical management but also to anticipate related other conditions and to provide genetic counselling to parents.

P1-447

Access and use of new technologies in diabetes care in patients that need an Interpreter compared to those that do not

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Young people with Type 1 Diabetes Mellitus encounter daily struggles with titrating insulin to achieve adequate glycemic control. Technology is improving with insulin pumps and continuous glucose monitoring (CGM) however access to it remains variable across the UK. Those from ethnic minorities and deprived areas are less likely to access technology and more susceptible to developing complications of diabetes with worsening HbA1c's. Understanding the reasons for health inequalities is essential to facilitate use of technology in this population.

Aim: To review the use of technology across our diverse population of young people with T1DM.

Method: We prospectively invited families over a 3 month period to participate in a voluntary questionnaire during clinics or by post to review the use of technology.

Analysis: Ninety Eight families responded and 88 questionnaires were included in the analysis (5- Type 2 DM, 1- duplicate,4- incomplete excluded). We found that 35%(31/88) used an Insulin Pump and 60% (53/88) CGM. Those receiving pump therapy and CGM achieved the best HbA1c (<8%) with 70.9%(22/31) and 76% (40/53) respectively. Data was divided into two groups; those who spoke English as a first language((EFL) n=65) and English as a second language ((ESL)n=23). Findings are summarised in Table 1. The difference between access to mobile phones was statistically significant ($p<0.005$) between the groups with 82% (18/23) in ESL compared with 97% (63/65) in EFL. Access to a home computer was similar (ESL- 78% and EFL- 88%) however a difference exists in downloading and reviewing blood glucose patterns with ESL achieving 26% (6/23) whilst EFL achieved 40% (26/65). CGM was accessed in only 48%(11/23) in ESL compared with 65%(42/65) in EFL. Time in Range(TIR) was reduced and statistically significant ($p<0.05$) with TIR< 50% in 58% (11/19) in ESL compared with 32% (18/57) in EFL.

Table 1.

	English 1st Language (n=65)	English 2nd Language (n=23)	P value
Home Computer	57 (88%)	18 (78%)	0.273
Phone	**63 (97%)**	**18 (82%)**	**<0.005**
Insulin Pump	21 (32%)	9 (39%)	0.553
CGM	42 (65%)	11 (48%)	0.157
Downloads	26 (40%)	6 (26%)	0.233
Time in range < 50%	**18 (32%)**	**11 (58%)**	**<0.05**
HbA1c<8% (64mmol/mol)	44 (68%)	16 (69%)	0.868

Conclusion: Our study demonstrates a clear reduction in access to technology including phones within our ESL population with significantly decreased TIR. Technology in T1DM improves HbA1c however families, especially in this ESL population need targeted support to achieve this.

P1-448

The effect of physical activity on leptin and adiponectin in youth with T1D

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Introduction: Exercise has pleiotropic positive effects for children and adolescents with Type 1 Diabetes (T1D). It improves glycemic control, daily insulin requirements, quality-of-life, morbidity and mortality rate. Leptin and adiponectin are adipocytokines produced by adipose tissue cells. Adiponectin is anti-atherogenic, anti-diabetic and anti-inflammatory, whereas leptin induces insulin resistance, has thermoregulatory properties and is pro-inflammatory.

Aim: To determine the role of physical activity in T1D young patients on leptin and adiponectin levels.

Methods: Eighty children with T1D [36 (45%) boys, age: mean ± SD, 14.8 ± 3.4 years] were recruited. Mean disease duration was 5.8 ± 4 years, mean annual HbA1c: 8.0 ± 1.41. Height, weight and waist-circumference were recorded, body-mass-index (BMI) and waist-circumference to height ratio were calculated. Seven-days physical activity was assessed with pedometers and questionnaires validated for the Greek population. Serum leptin, adiponectin, HDL-C, Lp(a) was obtained after overnight fasting.

Results: Twenty (25%), 40 (50%) and 20 (25%) children were above the 75th, between the 25th and 75th percentile and below the 25th percentile, respectively, regarding physical activity. In the upper quartile group of patients, the amount of exercise correlated positively with HDL-C (beta=0.014, p=0.048) and negatively with Lp (a) (beta=-0.004, p=0.035) concentrations. Main independent predictors of leptin concentrations were gender, chronological age, weight and body mass index while main independent predictors of adiponectin concentrations were chronological age and waist to height ratio. In multiple regression models leptin concentrations were associated negatively with physical activity as a categorical variable (beta=-0.43, p=0.015) and positively with adiponectin concentrations (beta=0.46, p=0.038). Adiponectin concentrations were associated negatively with muscle mass (beta=-0.0136, p=0.020).

Conclusion: In this study a considerable proportion of T1D young patients were physically active. The results of this study indicate that physical activity has a positive effect on the health of young people with T1D by decreasing leptin and lipid concentrations.

P1-449

Do-It-Yourself Artificial Pancreas Systems in a PediatricPopulation with Type 1 Diabetes in a Real-life Setting: The AWeSoMe Study Group Experience

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Aims: Do-It-Yourself Artificial Pancreas Systems (DIYAPS) represent a unique patient-initiated treatment in which commercially available and approved medical devices such as continuous glucose monitoring systems (CGMs) and insulin pumps are connected by an off-label algorithm, and are remotely controlled by open-source algorithms to automate insulin delivery. While these systems are co-created by the DIYAPS community, and access is open to everyone, users have to build their own individual system and use it at their own risk. Emerging data regarding the safety and efficacy of DIYAPS use in children and adolescents with type 1 diabetes (T1D), although reassuring, remains limited. We aimed to examine the impact of DIYAPS on glycemic parameters, characterize the socioeconomic position of individuals who switch to this mode of therapy, and identify factors affecting the successful use of the DIYAPS.

Methods: In this multi-center observational real-life study from the AWeSoMe Group, we compared glycemic parameters of 51 individuals with T1D (54.9% males, mean diabetes duration 4.2±4 years), who switched from therapy with various insulin pumps and CGMs to a DIYAPS. Data from the last clinic visit prior to DIYAPS utilization, was compared with data from the most recent clinic visit using DIYAPS. Socioeconomic position (SEP) index was retrieved from the Israel Central Bureau of Statistics (values ranging from -2.797 to 2.59).

Results: The mean age at DIYAPS initiation was 11.4±3.8 years, age range 3.4-20.7 years with a median usage duration of 13±9 months. Mean SEP Index was 1.051±0.956. Glycemic control improved following transition to DIYAPS: the mean percentage of time spent in glucose target range of 70 to 180 mg/dl (TIR) increased (from 69.1±12% to 75.1±11.6%, P<0.001), and HbA1c levels decreased (from 6.9±0.7% to 6.4±0.6%, P<0.001). Percentage of time spent in severe hypoglycemia (<54mg/dl), was significantly reduced (median before 1% and after 0.7%, P<0.001). No episodes of severe hypoglycemia or DKA were reported. Linear regression analysis revealed no associations between improvements in glycemic parameters, age at initiation of DIYAPS, duration of diabetes, or SEP index.

Conclusions: In our cohort of children and adolescents with above average socioeconomic position, the use of DIYAPS for diabetes management was beneficial, regardless of age, diabetes duration or socioeconomic position. Since our study population had excellent glycemic control at baseline, the improvement in TIR, with a simultaneous decrease in severe hypoglycemia, is all the more remarkable.

P1-450

Unstable glycaemia in rare, early-onset Shwachman-Diamond syndrome-associated diabetes mellitus

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Shwachman-Diamond syndrome (SDS) is a rare congenital disease, which is caused by SBDS gene mutations. The main characteristics of SDS are pancreatic exocrine deficiency, hematological dysfunction, and skeletal growth failure. Emerging data from case reports and patient registries suggest, that SDS could also be associated with an increased risk for diabetes mellitus. Additionally, a small number of case reports in the literature describe a susceptibility to hypoglycaemia as a rare symptom in young SDS patients. However, currently available data on SDS-associated diabetes and hypoglycaemia is limited and does not allow conclusions neither about prevalence and incidence rates, nor about clinical course and outcomes.

In the current work we report a case of a 5-year old girl with SDS, who underwent bone marrow transplantation at the age of 3 months, and developed a combination of recurrent severe non-symptomatic hypoglycaemias starting at the age of 1 year and auto-antibody-positive type 1 diabetes mellitus, diagnosed at the age of 1.8 years. Manifestation and course of diabetes development was complicated by concurrent spontaneous episodes of hypoglycaemia of unclear etiology. Mild hyperglycaemia allowed for postponing initiation of insulin therapy and an initial treatment trial with glibenclamide, which did not lead to any improvement of glycaemia. Six months after diabetes manifestation, good metabolic control is maintained by dietary intervention with a special high-fibre formula feeding only, under which hypoglycaemia also no longer occurred (time in range before and after dietary intervention were 62 and 81%, respectively).

Taking into account that SBDS protein regulates mitosis and ribosomal biosynthesis, and its suppression can cause immunological instability and chronic inflammation, the current case

provides valuable insight into the early clinical course of rare, Shwachman-Diamond syndrome associated dysglycaemia development.

P1-451

Maintaining insulin and medical supplies for disadvantaged people with Type 1 Diabetes in Southeast Asia during the COVID-19 pandemic

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Introduction: As COVID-19 spread across Southeast Asia (SEA) in 2020-2021, healthcare systems in Cambodia, Laos and Myanmar braced as public health officials closed many outpatient diabetes clinics and healthcare professionals (HCPS) were redeployed to COVID-treatment zones. Action 4 Diabetes (A4D) is a UK non-profit organisation that has been providing free insulin and medical supplies to LMICs in SEA since 2016. With historically limited healthcare coverage in Cambodia, Laos and Myanmar, patients enrolled on A4D's programme travel hundreds of miles to diabetes clinics to collect free insulin, blood glucose strips and other medication.

Due to COVID-19 lockdowns, insulin often arrived with short expiry dates due to delays in shipments caused by bottlenecks at international logistic hubs, and patients were known to ration insulin due to lack of supply. For disadvantaged people with Type 1 diabetes (T1D) in SEA low-middle-income countries (LMICs), this posed a serious threat due to inaccessible insulin and medical supplies.

Methods: A4D developed a strategic plan to maintain insulin and medical supplies to LMICs in collaboration with local HCPs on the ground to ensure that the T1D community regained access to insulin and essential medical supplies, as well as supporting the development of remote-consultation with patients.

Results:

Access to medical supplies

A4D initiated networks of couriers to rural parts of Myanmar, Laos and Cambodia to deliver medical supplies. In Cambodia, TukTuk drivers who ferried tourists around Angkor Wat were used to deliver insulin to the T1D in farming communities. In Myanmar, truck drivers that transported vegetable crops were used to transport medical supplies to remote areas. During COVID-19, A4D used local suppliers for insulin and had to purchase insulin and blood testing strips at a premium rate.

Access to education and consultation

Prior to COVID-19, clinic visits were a primary source of advice and management for the patient and family. With clinic closures, A4D initiated remote access consultation working with local HCPs to support disadvantaged families.

By end 2021, 3 deaths were reported of patients on the A4D programme as result of the pandemic, and incidence of diabetic ketoacidosis rose sharply among the 350 people with T1D on A4D's programme.

Conclusion: For many disadvantaged people with T1D in SEA, the COVID-19 pandemic reinforced the fragile nature of their T1D management. Through collaborating closely with HCP and partners on the ground, A4D has developed a more dynamic and resilient logistical system to maintain key life-saving medical supplies.

P1-452

Limited genotype-phenotype correlation in FOXP3 gene within same family member

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Introduction: FOXP3 protein is crucial in enabling T-regulatory cells to maintain tolerance to self-antigens. Mutations in human Foxp3 gene are associated with immune diseases, such as multi-organ autoimmune disorder, immune dysregulation, poly-endocrinopathy, enteropathy and X-linked syndrome (IPEX).

Case Presentation: A 15 months old male, presented initially at 2 weeks of age with failure to thrive hyperglycemia and severe DKA, and a consequent diagnosis of neonatal diabetes. Genetic testing identified p.(Pro75Leu)mutation in the foxp3. At 1.3yr along with his diabetes the patient was growing well with only mild asthmatic symptoms.

Family history revealed that: the mother is asymptomatic, a maternal cousin has IDDM since the age of 6 months, associated with a history of lymphadenopathy, and due to (autoimmune? Hemolytic?) anemia required recurrent blood transfusion. Another cousin had a history of neonatal DM, diagnosed at 6 months of age, and died at 6yrs after severe DKA complicated by cerebral edema. The patient`s 20y old uncle has rheumatoid arthritis and IDDM history since the age of 6 months. A grandmother in her 50s was diagnosed recently with DM and has rheumatoid arthritis. His aunt had a history of gestational diabetes. Genetic screening for affected family members indicated that all share the same p.(Pro75Leu) genetic mutation of foxp3.

Conclusion: The variability in organ involvement and in timing of clinical presentation within the same family in spite of caring an identical mutation is unique especially given the monoallelic expression of the FOXP3 gene in males. It does suggest modifying genes that are significantly involved in the pathogenesis of IPEX syndrome.FOXP3 sequences should be perform in males with a history of neonatal diabetes inspite of not having yet developed autoimmune associated conditions.

Further studies will delineate genetic and other modifier of FOXP3 gene that contribute to the variable clinical severity within the same family.

P1-453

Usability of CGM for hyperglycemia detection during systemic glucoriticoid treatment

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Glucocorticoids are widely used to treat autoimmune and inflammatory diseases. The side-effects of glucocorticoids are well known, but not routinely monitored in the pediatric population. Recommendations regarding the timing of blood glucose screening are lacking and understanding about the correlation between different glucocorticoid treatment regimens and glucose variability is insufficient.

Our objective was to test the usability of continuous glucose monitooring (CGM) to detect glucocorticoid-induced hyperglycaemia (GIH) and to alalyze the glucose profile in children receiving systemic glucocorticoid treatment.

Three pediatric patients with different underlying diseases receiving systemic glucocorticoid treatment in a dose of at least 1 mg/kg/day prednisolone-equivalent were started on CGM in a hospital or non-hospital setting. Patients receiving systemic glucocorticoids during the last 30 days were excluded from the study. Patients stuck to their regular meal times and kept a food diary. Medronic iPro2 CGM with an Enlite sensor was used in all the subjects. Data from CGM was uploaded and analyzed retrospectively at the end of the treatment course or CGM life-time. Time above range (TAR – the percentage of time, when sensor glucose is above 10 mmol/L) and average sensor glucose (ASG) was measured and diurnal glucose fluctuations were analyzed in each study subject.

The first study subject was a 14-year-old girl with newly diagnosed autoimmune hepatitis started on prednisolone 1mg/kg per mouth daily for seven days. Her TAR was 32% and ASG 9.1 mmol/L for the whole study period. Her glucose readings were above 10 mmol/L most frequently during the hours 16:00-24:00. The second study subject was a 10-year-old girl with treatment-resistant epilepsy, who received intravenous Solu-Medrol in a prednisolone-equivalent dose of 35.5 mg/kg/die on all four study days. Her TAR was 9% and ASG level 7.0 mmol/L. The typical time period for GIH episodes to occur was from 18:00-22:00 in the evening. The third study subject was a 4-year-old girl with focal epilepsy, who received intravenous Solu-Medrol in a prednisolone-equivalent dose of 39 mg/kg/die. Her TAR was 8% and ASG 6.8 mmol/L. The highest glucose values were measured during 16:00-20:00 in the evening.

All the study subjects had GIH episodes regardless of their age or glucocorticoid dose. GIH episodes occurred most frequently in the evening regardless of glucocorticoid administration time and this should be taken into account, when screening for glucocorticoid-induced-hyperglycemia. Further subjects are expected to be studied and presented for the meeting.

P1-454

Clinical and genetic evaluation of patients with maturity onset diabetes of the young (MODY): Single center experience

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Purpose: MODY is a monogenic diabetes with autosomal dominant inheritance that usually occurs in adolescence or young adulthood. It constitutes 1% of diabetes cases in childhood. The diagnosis of MODY is very difficult due to genetic heterogeneity, rarity, and clinical overlap with other diabetes types. In recent years, the diagnosis of MODY has become easier with genetic developments. On the other hand, misinterpretation of results can cause confusion. In this study, it was aimed to retrospectively evaluate the clinical, laboratory and genetic data of our MODY patients.

Methods: Among the 583 diabetic patients followed up in our clinic,26 patients who met the diagnostic criteria of MODY were included in the study. The clinical and genetic characteristics of the cases were obtained retrospectively from the medical records.

Results: The mean age and duration of diabetes were 17.02±2.9 years and 6.8±2.7 years, respectively. Mean birth weight, body weight SDS and height SDS of the cases were 3.25 ± 0.39 kg, 0.04±1.4 and 0.1± 1.2, respectively. Two of the cases were obese (BMI>95 p), 2 of them were overweight (BMI 85-95 p), and 2 of them were underweight. The complaints at admission were coincidental high blood sugar (n=9), polyuria and polydipsia (n=6), incidental glucosuria (n=2), weight loss (n=1), diabetic ketosis (n=1), diabetic ketoacidosis (n=1). Diabetes history in at least 2 generations was present in 19 patients (14 with genetic diagnosis). Diabetes-associated autoantibodies were found to be negative in 24 of 26 cases. The mean C-peptide value and insulin value of the patients were 2.4±1.2ng/ml and 7.01±1.4mIU/ml, respectively. By next generation sequencing analysis, pathogenic (n=13) or possibly pathogenic (n=4) variants were detected in 17 (65%) of 26 cases. Variants were found in glucokinase (GCK) genes in 58.8% (n=10), hepatocyte nuclear factor 1A (HNF1A) in 29.4% (n=5), and in HNF4A and ABCC8 genes in 5.8% of 17 cases. Treatment consisted of diet alone in 15 (57%) patients, diet and oral antidiabetic (OAD) medication in 9 (34.2%) patients, diet and insulin and OAD treatment in 2.

Conclusion: In this study, GCK MODY was the most common MODY type. Recognition of MODY cases is essential for definite treatment and determination of prognosis. Studies in the field of molecular genetics facilitate the diagnosis of MODY, allow personalization of the treatment and the detection of other family members who may be ill. However, the detected variants should be interpreted together with the clinical follow-up of the cases.

P1-455

An adolescent with *HNF1B* deletion. A case report

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Introduction: Mutations in hepatocyte nuclear factor 1B (*HNF1B*) gene (chromosome 17q12), lead to monogenic diabetes (*HNF1B*-MODY or MODY5, OMIM 137920) accompanied by multisystem disorders. *HNF1B* gene encodes HNF1B protein, a member of the homeodomain-containing superfamily of transcription factors, expressed early in embryogenesis, contributing significantly to organogenesis and the function of many systems (kidneys, liver, pancreas, bile ducts, gut, urogenital tract, lung, and thymus).

Methods: A 14.3-year-old adolescent boy was referred to our Outpatient Obesity Clinic for investigation and management of impaired fasting glucose and unhealthy dietary habits. Elevated concentrations of fasting glucose (maximum 112mg/dL) and HbA1c (maximum 5.7%) alternating with normal values for 3 years were noted. The past medical history revealed unilateral nephrectomy due to polycystic kidney, a femoral fracture and hypertransaminasemia. Family history was unremarkable. At initial evaluation, our patient was pubertal (Tanner staging: G3, P4, A3, Testicular volume: 6-8mL) with normal weight (BMI z-score: - 0,07) and a right hydrocele. The OGTT was diagnostic of diabetes mellitus (plasma glucose 200 mg/dL at 120´), with maximum insulin concentration 96.94 ng/mL at 120´ (HbA1c: 5.5%, fasting c-peptide: 0,401 nmol/L, autoantibodies for Type I diabetes: negative). He also had hypomagnesemia, hypertransaminasemia, hyperparathyroidism with normal vitamin D levels, and hyperuricemia. Clinical genetic evaluation set a possible diagnosis of *HNF1B*-MODY. DNA from peripheral blood was obtained from the patient and his parents and MLPA methodology was implemented to evaluate the possibility of *HNF1B*, *GCK, HNF1A,* and *HNF4A* gene deletions or duplications.

Results: Genetic testing revealed a *de novo* heterozygous deletion of *HNF1B*, confirming the diagnosis of *HNF1B*-MODY. Further investigation with abdominal elastography, MRCP and MRI showed pancreatic hypoplasia and steatosis, liver fibrosis, a cystic formation in the epididymis and right hydrocele. A multidisciplinary management plan was introduced that included dietary consultation, a structured diabetes training program (glucose monitoring, carbohydrate counting, and insulin therapy), as well as monitoring of parathormone and magnesium concentrations and pediatric nephrological and gastroenterological care, to early detect and manage other multisystemic defects.

Conclusion: A child with impaired glucose metabolism or diabetes and multisystem (extrapancreatic or exocrine pancreas) involvement is of paramount importance to be investigated early towards monogenic forms of diabetes. *HNF1B* mutations lead to multisystemic manifestations, presenting with a heterogenous and broad phenotype. Such patients benefit from early diagnosis and require an integrated follow up by a multidisciplinary team, even in the absence of overt diabetes, to prevent and manage complications and comorbidities in time.

P1-456

Outmoded by MODY? A Case Report of HNF1A-MODY in Paediatric Stroke

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Background: The association between HNF1A-MODY and vascular complications including stroke has previously been identified in adults but to date there have been no reported paediatric cases published.

Description: We present the case of an Eritrean 13-year-old girl, who was admitted with an acute ischaemic stroke, on a background of Diabetes Mellitus (presumed Type 1) diagnosed the previous year. Aside from being on multiple dose injections (MDI) of basal-bolus insulin at 0.9Units/kg/day, she had no other regular medications. There was a history of vitiligo (longstanding, with negative adrenal antibodies) with no history of acanthosis nigricans or clinical features of insulin resistance. On acute presentation, she was normoglycaemic (7.2mmol/L), normotensive (122/90mmHg) with normal body habitus (weight 46kg) and no other known cardiovascular risk factors (non-smoker, normal lipid profile). She was confirmed to have an anterior spinal artery infarct and multiple small cerebellar infarcts on MRI and underwent extensive investigations to identify the cause. In view of her acute presentation on a background of negative islet cell autoantibodies at diagnosis and first degree family history of diabetes, a broader screen for mitochondrial and monogenic diabetes was performed. This identified a missense mutation in the HNF1A gene, (Ch12:g.121432011G>A). Of note, her father was mosaic for the mutation with 7% of his cells affected. She was diagnosed with Maturity Onset Diabetes of the Young (MODY) HNF1A, and her diabetes treatment was altered accordingly, enabling her to be switched from MDI insulin to sulphonylureas.

Discussion: Glycaemic control correlates poorly with cardiovascular risk in HNF1A-MODY, instead the increased risk may be related to wider metabolic dysfunction. HNF1A variants have been associated with changes to cholesterol homeostasis, lipid profile and endothelial factor dysfunction. Populations of Black African Heritage have an increased risk of stroke from a younger age, and a recent study identified the HNF1A variant (rd55931441) as a significant stroke-associated locus in this population. This clinical case supports the current evidence that single nucleotide polymorphisms at the HNF1A locus may be implicated in metabolic dysregulation and cerebrovascular injury, particularly in young black patients. Further genomic research is needed in this patient cohort. Aggressive cardiovascular risk reduction and primary prevention from adolescence may be implicated.

P1-457

Rabson mendenhall syndrome: A rare insulin resistance syndrome

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Introduction: Rabson-Mendenhall Syndrome (RMS) is an autosomal recessive, extremely rare, serious insulin resistance syndrome that occurs as a result of mutation in the insulin receptor (INSR) gene. Pathogenic variants in the INSR gene cause a broad spectrum of inherited insulin resistance syndromes. Here, a male case who presented with the complaint of diffuse acanthosis nigricans and was diagnosed with RMS is shared.

Case Report: A 12-year-old 4-month-old male patient, who had no known disease before, applied with the complaint of darkening on the body for the last 3 years. On physical examination, his general condition was good, his body weight was 32.6 kg (-1.05 SDS), his height was 140.1 cm (-1.71 SDS), and his body mass index was 16.61 (-1.05 SDS). Puberty examination was compatible with tanner stage 3. The patient had extensive acanthosis nigricans, hyperkeratosis and hypertrichosis, more prominently in the neck, axilla, umbilical region and genital region. He had a rough face and muscular body appearance. In her family history, the patient's mother and uncles had a heavy history of type 2 diabetes, who was born from a first-degree cousin marriage. In the laboratory tests, fasting blood glucose of 68mg/dl and simultaneous fasting insulin of 227μIU/ml were found in the patient, and insulin resistance syndromes were considered. HbA1c level was measured as 6.2%. In the oral glucose tolerance test, 0hr glucose was 50mg/dL, insulin was 386.4 μIU/ml, 2hr glucose was 182, and insulin was 1000 μIU/ml. Diabetic diet was started and blood glucose was monitored. Metformin treatment was started in the patient who had hyperglycemia-hypoglycemia attacks with diet. Genetic analysis with next-generation sequencing revealed a c.3529+5G>A homozygous mutation in the INSR gene. In the in slico analysis, the mutation was evaluated as pathogenic and Rabson-Mendenhall syndrome was diagnosed. The segregation analysis of the patient continues.

Conclusion: As a result, a 12-year-old male patient with only skin darkening was diagnosed with RMS, and he is being followed up with metformin treatment because he has postprandial hyperglycemia. However, RMS patients in need of recombinant IGF-1 and high-dose insulin therapy have been reported in the literature. This shows the variability of the clinic. In this syndrome, which has no definitive treatment, preimplantation genetic analysis, genetic counseling and close follow-up of the patients are required.

P1-458

BMI in Bulgarian children and adolescents with type 1 diabetes mellitus – data of two national cross-sectional studies

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Pediatric overweight and obesity are also an issue in children and adolescents with type 1 diabetes (T1D). Body Mass Index (BMI) is an accurate and widely used clinical method for assessing childhood obesity.

Objective: To analyze the BMI-standard deviation scores (SDS) in Bulgarian children and adolescents with T1D and its relationship with age, gender, type of insulin treatment, and HbAlc.

Materials and Methods: Two consecutive national multicenter cross-sectional studies of HbA1c in Bulgarian pediatric patients with T1D were done during 2012 and 2014 in 11 pediatric endocrine practices. 829 patients participated (422 boys, 407 girls) in the first study (mean age 11.9 ± 4.2 years), and 498 patients (261 boys, 237 girls) - in the second one (mean age 11.6 ± 4.1 years). BMI-SDS were calculated and compared to the WHO BMI charts (z-scores). Patients were divided into the following groups: underweight (UW) with BMI-SDS < −2SD, normal weight (NW): -2SD ≤ BMI-SDS ≤ +1SD, overweight (OW): +1SD < BMI-SDS ≤ +2SD, and obese (OB): BMI-SDS > +2SD.

Results: The mean BMI-SDS between different endocrine centers in the country varied considerably from 0.15±0.98 up to1.07±0.70.

We found significantly higher mean BMI-SDS for boys (0.50±1.07) compared to the girls (0.28 ± 0.99), (p <0.001). The average BMI-SDS in boys decreased with age, being highest in boys under 6 years of age (1.01±1.27).

In both studies, the percentage of overweight and obese boys, was significantly higher than for girls. The prevalence of UW, NW, OW and OB in the first study was: 0.5%, 70.9%, 22.0%, 6.6% for boys and 1.0%, 76.7%, 17.9%, 4.4% for girls. The prevalence of UW, NW, OW and OB in the second study was: 0.8%, 65.5%, 25.3%, 8.0% for boys and 1.0%, 78%, 16.5%, and 4.6% for girls.

We found a weak but significant negative correlation between BMI-SDS and HbA1c only for boys (p<0.009). The girls with T1D and HbA1c <7.5% had significantly lower mean BMI-SDS than girls with HbA1c >7.5% (p=0.006).

The boys treated with insulin analogs had a significantly lower mean BMI-SDS of 0.35±0.98 than those treated with human insulins: BMI SDS 0.49±1.16, (p=0.032). There was no such dependence for girls.

Conclusions: In our studies, significantly more girls with T1D had a normal BMI-SDS compared to boys. The established higher percentage of overweight and obesity in boys with T1D since early childhood requires measures to balance caloric intake, in order to prevent this unfavorable issue in pediatric diabetes.

P1-459

Usefulness of glycated albumin level as a glycemic index complementing glycosylated hemoglobin in children and adolescents

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Introduction: Serum glycated albumin (GA) is a glycemic marker reflecting the average serum glucose values for the previous 2 weeks. The purpose of this study was to evaluate the usefulness of serum GA as a glycemic index complementing glycosylated hemoglobin (HbA1c) in children and adolescents.

Methods: Fifty-four children and adolescents with diabetes mellitus (DM) and 98 children and adolescents without DM (Non-DM) were enrolled. The correlation between fasting glucose concentration (FG) and GA compared to HbA1c was investigated in Non-DM subjects. And, the correlation between mean glucose concentrations (MG) and GA compared to HbA1c were investigated in DM subjects. Factors affecting the relationship between GA and HbA1c (GA/HbA1c ratio) were analyzed.

Results: In DM subjects, strong positive correlations were observed between MG and GA (r=0.636, p=0.003), between MG and HbA1c (r=0.716, p=0.001), and between GA and HbA1c (r=0.860, p<0.0001). The correlation coefficient between MG and GA did not differ from the correlation coefficient between MG and HbA1c in DM subjects (p=0.811). DM subjects whose BMI SDS is ≥2 had lower GA/HbA1c ratio in comparison with DM subjects whose BMI SDS is <2 (2.21±0.39 vs 2.66±0.37, p=0.001). In Non-DM subjects, there were no significant correlations between FG and GA (r=0.110, p=0.284), between FG and HbA1c (r=0.089, p=0.385), and between GA and HbA1c (r=-0.040, p=0.700). Non-DM subjects whose BMI SDS is ≥2 had lower GA/HbA1c ratio in comparison with DM subjects whose BMI SDS is <2 (2.23±0.22 vs 2.38±0.22, p=0.003).

Conclusion: The usefulness of GA is comparable with HbA1c in reflecting glycemic control in children and adolescents with DM. GA is affected by obesity in children and adolescents with or without DM.

P1-460

Assessing the clinical effectiveness of advanced hybrid closed loop insulin pump therapy and calibration-free glucose sensor - experience of a single centre, Arendal, Norway

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Introduction: Automated insulin delivery has demonstrated improved glycemic control in children and adolescents with type 1 diabetes mellitus (T1DM). The present analysis investigates real-world glycemic outcomes in children and adolescent on the MiniMed™ 780G advanced hybrid closed loop (AHCL) system after switching from MiniMed™ 640G predictive low glucose suspend system (PLGS) or MiniMed 670G hybrid closed loop (HCL) system and calibration-free glucose sensor Guardian 4 (G4) after switching from Guardian 3 (G3) glucose sensor within the single centre in Arendal, Norway

Methods: Retrospective analysis enrolled 29 children and adolescent (11 males and 18 females, mean age 12.7, range 7-17 years) with T1DM duration for >1 year and AHCL system >6 months. Pre-AHCL therapy included PLGS in 27 and HCL in 2 patients. Analysis included HbA1c (mmol/mol; immunoassay method in Siemens A1c Vantage Analyzer, Siemens Healthcare GmbH, Erlangen, Germany) and body mass index standard deviation score (BMI SDS) pre-AHCL, 3 and 6 months post-AHCL. Secondary analysis included 20 of those patients (9 males, 11 females, mean age 12.1, range 7-16 years) switched from G3 to G4. Analyses included HbA1c, percentage of time with sensor, percentage of time in target range (4-10 mmol/l), percentage of time in hypoglycaemia (≤3.9 mmol/l), the insulin dose (U/kg) and BMI SDS prior and 3 months post-G4.

Results: AHCL system showed a significant improvement in HbA1c compared to previous insulin therapy both after 3 and 6 months post-AHCL (53.0 mmol/mol, 95%CI 49.0-55.6 vs 50.5 mmol/mol, 95%CI 47.4-53.0; p=0.013; and 49.0 mmol/mol; 95%CI 44.7-51.0, p=0.0002, respectively). No statistically significant difference was found in HbA1c with AHCL and G4 compared to G3 glucose sensor, but significantly increase in TIR was achieved with G4 (54.5%, 95%CI 51.0-61.0 vs 67.5%, 95%CI 56.0-71.0, p=0.006). No statistically significant differences in percentage of time with sensor use, percentage of time spent in hypoglycaemia and insulin dose were found between the two sensors. BMI SDS increased but not significantly with the introduction of AHCL (pre-AHCL: 0.49, 95%CI -0.12-1.11; post-AHCL 0.57, 95%CI 0.03-1.02; p=0.058), but reached statistical significance with use of G4 (pre-G4: 0.53, 95%CI -0.08-1.69; post-G4 0.53, 95%CI 0.002-1.83; p=0.032).

Conclusion: The use of ACHL systems led to a significant improvement of glycemic control. Calibration-free glucose sensor G4 appears to be more effective in increasing TIR despite time of sensor use. During education in new technologies, an additional effort should be made for weight gain prevention.

P1-461

Risks and Metabolic Consequences of Ramadan Fasting on Egyptian Adolescents With Type 1 Diabetes Mellitus

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Background: Although Ramadan fasting is one of the five pillars of Islam and is compulsory for all healthy Muslims from puberty onwards, religious exemptions exist for patients with type 1Diabetes. The risks of fasting include: hyperglycemia, hypoglycemia, ketoacidosis, thrombotic episodes, and dehydration. Many adolescents still insist to fast due to religious or social motives.

Objectives: To study the risks and metabolic consequences of Ramadan fasting among Egyptian adolescents with Type I diabetes mellitus (T1DM) who insisted to fast

Methodology: This was an observational case-control study (retrospective clinical and laboratory data from files and hospital records before Ramadan as well as prospective follow up clinical and laboratory data of patients after Ramadan). This study was conducted on a total of 109 adolescents with type 1 diabetes patients; the fasting group included 76 patients while, the non-fasting group included 33 patients. Serum HBA1c and Fructosamine were assessed before and after fasting.

Results: Hyperglycemia was the most common complication as it was experienced in 66(86.8%) patients in the fasting group and in 24(72.7%) patients in the non-fasting group. Hypoglycemia occurred in 60(78.9%) patients in the fasting group compared to 24(72.7%) patients in the non-fasting group. DKA developed in 15(19.7%) patients during Ramadan and 17(22.3%) patients during Shawal in the fasting group while none of the non- fasting group developed DKA and dehydration during Ramadan or Shawal (P=0.003 and 0.009 respectively). Serum fructosamine was significantly higher in the non-fasting group compared to the fasting group after Ramadan (P= 0.002). Fasting had adverse changes also on lipid profile.

Conclusion: Type 1 Diabetic children and adolescents should be considered high risk or very high risk for fasting. Those who insist to fast during Ramadan should seek medical advice concerning the risks involved and should be warned against fasting. Fasting was associated with significant increase in frequency of acute complication; hyperglycemia, hypoglycemia, DKA and dehydration. Fasting also had negative impact on glycemic control represented by HbA1c and on lipid profile as both were significantly deteriorated after Ramadan fasting. These effects were mostly due to wrong dietary habits during Ramadan, improper administration of insulin and lack of commitment to different advices given during the pre -Ramadan education sessions. Moderate or low risk are well controlled type 1 DM patient, using insulin pump and or CGM with compliance and strict follow up and time in range: 70% or more.

Fat, Metabolism and Obesity

P1-63

Association of transient elastography and ultrasonographic fatty liver indicator in pediatric non-alcoholic steatohepatitis

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Background: Transient elastography (TE) uses pulsed echo ultrasound to measure the hardness of the liver, showing excellent accuracy in the assessment of fibrosis, and is considered a useful test in nonalcoholic fatty liver disease (NAFLD). Ultrasound fatty liver indicator (US-FLI) is proposed as a non-invasive, semi-quantitative method for predicting hepatitis in children with NAFLD and may reflect the severity of liver histological changes. US-FLI ≥4 or 6 has been suggested as a predictive finding for NASH. These non-invasive imaging tests have been proposed to predict the diagnosis of NASH as an alternative to liver biopsy.

Objects: This study aimed to investigate the relationship between US-FLI and TE, which indicate the severity of NAFLD.

Methods: We enrolled 87 participants aged 11.42±2.19 years who were diagnosed with fatty liver on ultrasound. US-FLI is a scoring system ranging from 2-8, assessing the following items: liver/kidney contrast, posterior attenuation of ultrasound beam, difficulty visualizing the gallbladder wall, vessel blurring, difficult visualization of the diaphragm and areas of focal sparing. NAFLD is diagnosed with a minimum score of ≥2. TE was used to evaluate liver fibrosis in terms of liver stiffness measurement (LSM). The association between US-FLI and TE was analyzed by dividing into two groups using US-FLI ≥4 and ≥6 as predictive findings for NASH.

Results: The TE was significantly correlated in both NASH groups by US-FLI ≥4($r=0.251$, $p<0.019$) and ≥6($r=0.376$, $p<0.001$). As a result of univariate logistic regression analysis, TE was significantly associated with NASH diagnosed by US-FLI ≥4(OR 1.927; $p=0.028$) and ≥6(OR 3.277; $p=0.003$). In the receiver operating characteristic analysis, the TE showed good performance in detecting NASH diagnosed by US-FLI, with area under the curve [AUC] of 0.674($p=0.015$) in NASH by US-FLI ≥4 and AUC of 0.794($p=0.004$) in NASH by US-FLI ≥6.

Conclusions: TE is significantly associated with US-FLI in pediatric NASH. TE and US-FLI are expected to complement each other in the evaluation of the severity of NAFLD, and further studies are needed.

P1-64

microRNA-27a - a strand specific regulator of adipogenesis and adipocyte function

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MicroRNAs (miRNAs) are small non-coding RNA molecules and play an important role in the post-transcriptional regulation of gene expression and thereby influence important cellular functions. In adipocytes, miRNAs regulate key processes such as differentiation, inflammation, metabolism, and adipokine secretion. Recently, we found that miR-27a is upregulated under proinflammatory conditions in human adipocytes. Thus, our goal was to better understand the function of miR-27a in adipocytes.

The expression of the 3p and 5p strand of miR-27a was measured in Simpson-Golabi-Behmel-Syndrom cells (SGBS), human multipotent adipose-derived stem cells (hMADS) and human primary adipose-derived stromal cells. Gain-of-function and loss-of-function studies were performed by transfection of miRNA mimics and inhibitors. Adipogenesis was analysed by measuring the mRNA and protein expression of adipogenic marker genes as well as triglyceride content. Cellular respiration was studied using the Seahorse XFe96 extracellular flux analyser. Potential target genes of miR-27a-5p were identified by mRNA sequencing and in silico target gene prediction, and their role in human adipogenesis was assessed by siRNA-mediated knockdown.

The expression of both, miR-27a-3p and -5p levels decreased during adipogenic differentiation in all model systems. We confirmed that miR-27a-3p is an important negative regulator of adipogenesis by targeting the transcription factor PPARγ. Interestingly, modulation of miR-27a-5p did not alter the adipogenic differentiation capacity but led to an 85% decrease of uncoupling protein 1 (UCP1), the major marker of brown, thermogenic adipocytes. The change in gene expression was paralleled by a significant impairment in cellular respiration after miR-27a-5p transfection. mRNA sequencing followed by gene set enrichment analysis revealed crucial change in gene ontologies like 'mitochondrial gene expression', 'respiratory electron transport chain', and 'oxidative phosphorylation'. Subsequent in silico analyses identified several potential miR-27a-5p target genes, among them chemerin (RARRES2). SiRNA-mediated knockdown of chemerin resulted in decreased UCP1 protein expression and significant alterations of cellular respiration.

Taken together, we conclude that miR-27a is an important regulator of human adipogenesis and adipocyte function. While miR-27a-3p inhibits the adipogenic program per se by targeting PPARγ, miR-27a-5p acts as a strong inhibitor of UCP1 expression and function. Tackling either the miRNA or its downstream targets might provide a useful strategy to induce browning or UCP1 expression in white adipocytes.

P1-65

Congenital Leptin Receptor deficiency: An Indian family with novel Homozygous LEPR gene mutation (LEPR): c.1752G>A (p.Lys584=) presenting with severe early onset obesity

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Introduction: Congenital deficiency of the leptin receptor is an extremely rare cause of early-onset monogenic obesity with rapid weight gain and compulsive overeating. LEPR mutations is responsible for extreme form of obesity associated with other endocrine abnormalities and respiratory tract infection. Till date, approximately 50 families have been reported to have mutations in the leptin receptor gene.

Case: 9-year-old girl and her 15-month-old brother born of third-degree consanguineous marriage with Asian ethnicity came for obesity assessment. Their elder sibling with morbid obesity succumbed at 1.5 years. Both children had normal birth weight with rapid weight gain during early infancy. Girl started to put on weight after 3 months of age (weight 10.3 kg; Z score -4.77) rapidly increasing to 19 kg (Z score -6.66) at 11 months. She had undergone bariatric surgery twice first at 11 months of age and later at 7years due to rapid weight gain [weight-49 kg and Z score -3.02] and type 2 DM. Boy also started to put on weight after 4 months with current weight of 18 kgs (Z score: 5.78) and length 80cms (Z score –0.77) with weight for height more than 99th percentile (Z score -6.82). Both had dyslipidaemia and high serum leptin levels.

WES reported novel homozygous mutation synonymous variant NM_002303.6 (LEPR):c.1752G>A (p.Lys584=) on chromosome 1p31, which had not been reported previously. The nucleotide c.1752 in LEPR is predicted conserved by GERP++ and PhyloP across 100 vertebrates. The variant is segregating in two affected siblings whose serum leptin levels were also elevated, parents and an unaffected sibling were heterozygous carriers, whereas another unaffected sibling does not harbour the variant. For these reasons, this variant was classified as Pathogenic variant in our case. This is only second family in India with LEPR gene mutation and first with novel mutation.

Setmelanotide is a selective melanocortin-4 receptor agonist which has been approved by US FDA in November 2020 for genetically proven obesity with LEPR mutation in children older than 6 years. Currently Setmelanotide is not available in India but could be used in future.

Conclusion: Our case illustrates the importance of early molecular genetic diagnostics in patients with severe, early-onset obesity to avoid lengthy diagnostic and unsuccessful and frustrating therapeutic procedures especially where consanguinity is more common. Improving overall awareness and availability of genetic testing will help these patients with monogenic obesity to gain access to treatment with recently developed newer drugs.

P1-66

Effect of gender and age on the mental well-being and self-esteem of adolescents living with obesity: subanalysis from the ACTION Teens global study

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Background: The ACTION Teens study aimed to identify attitudes, behaviours and perceptions among adolescents living with obesity (ALwO), caregivers of ALwO (CGs) and healthcare professionals (HCPs) who treat ALwO. This subanalysis assessed the mental well-being and self-esteem of ALwO.

Methods: ACTION Teens was a global, cross-sectional study (NCT05013359) that surveyed 5275 ALwO (aged 12–<18 years), 5389 CGs and 2323 HCPs. The mental well-being and self-esteem of ALwO were assessed using the World Health Organization–Five Well-Being Index (WHO-5; score range 0–100: score <50 indicates poor well-being) and Rosenberg Self-Esteem Scale (RSES; score range 0–30: score <15 suggests low self-esteem), respectively. Results were stratified by gender and age. Proportions were compared with a Z-test; # indicates significant difference ($p<0.05$).

Results: ALwO had a mean age of 14.8 years, and most were classified as obesity class I (65%), followed by class II (21%) and class III (14%). A total of 2971 (56%) ALwO were male and 2304 (44%) were female. The mean WHO-5 score for all ALwO was 56.3. More female than male ALwO had a WHO-5 score <50 (46 vs 34%[#]), and the percentage with a WHO-5 score <50 was greater among older age groups for both males and females (Table). The mean RSES score for all ALwO was 17.1, and the proportion of ALwO with an RSES score <15 was greater for females than males (34 vs 24%[#]). Among females, the proportion with an RSES score <15 was greatest in the oldest age group (Table). In contrast, the percentage of males with an RSES score <15 plateaued after age 14–15 years (Table).

Conclusions: A substantial proportion of ALwO had poor mental well-being and low self-esteem, particularly females and older adolescents. HCP awareness of the need for active screening for depression in a substantial proportion of ALwO may improve the obesity care they provide.

Table. WHO-5 and RSES scores among ALwO by gender/age subgroups

	Male ALwO age, years			Female ALwO age, years		
	12–13 (n=938)	14–15 (n=829)	16–17 (n=1204)	12–13 (n=549)	14–15 (n=650)	16–17 (n=1105)
WHO-5 score <50, %	22	34*	43*,†	35	41*	54*,†
RSES score <15, %	15	28*	27*	29	32	37*

*$p<0.05$ vs 12–13 years within gender; †$p<0.05$ vs 14–15 years within gender. ALwO, adolescents living with obesity; RSES, Rosenberg Self-Esteem Scale; WHO-5, World Health Organization–Five Well-Being Index.

P1-67

Effect of unawareness of obesity on perceptions of obesity and food/diet among adolescents living with obesity and their caregivers: subanalysis from the ACTION Teens global study

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Background: This subanalysis of the ACTION Teens study aimed to explore perceptions of obesity and food/diet among adolescents living with obesity (ALwO) and caregivers of ALwO (CGs) who were unaware of their/their child's obesity.

Methods: The global, cross-sectional ACTION Teens survey study (NCT05013359) assessed perceptions, attitudes and behaviours among 5275 ALwO (aged 12–<18 years), 5389 CGs and 2323 healthcare professionals who treat ALwO. ALwO and CGs were categorised based on their perception of their/their child's weight: believes weight is normal/below normal = 'obesity-unaware'; believes weight is slightly/a lot/extremely above normal = 'obesity-aware'. Proportions were compared with a Z-test; # indicates significant difference ($p<0.05$).

Results: In total, 24% of ALwO were obesity-unaware; among ALwO with obesity class I, II or III, 26%, 14% and 27% were obesity-unaware, respectively (obesity class I vs class II$^{\#}$; obesity class II vs class III$^{\#}$). Only 12% of ALwO who were obesity-unaware received an obesity diagnosis from their doctor, compared with 54%$^{\#}$ of obesity-aware ALwO. Fewer ALwO who were obesity-unaware were highly motivated to lose weight than those who were obesity-aware (29 vs 50%$^{\#}$). Obesity-unaware ALwO more often agreed that they have a healthy relationship with food (60 vs 29%$^{\#}$) and less often agreed that they eat food for comfort (41 vs 61%$^{\#}$) than obesity-aware ALwO. Overall, 34% of CGs were unaware that their ALwO had obesity; among CGs with ALwO with obesity class I, II or III, 39%, 20% and 36% were obesity-unaware, respectively (obesity class I vs class II$^{\#}$; obesity class II vs class III$^{\#}$). More CGs who were obesity-unaware thought that their child would slim down naturally as they age than those who were obesity-aware (54 vs 41%$^{\#}$). Conversely, compared with obesity-unaware CGs, those who were aware of their ALwO's obesity more often agreed that their child could lose weight if they set their mind to it (57 vs 73%$^{\#}$) and that their child is highly motivated to lose weight (25 vs 44%$^{\#}$). Obesity-unaware CGs more often agreed that they themselves have a healthy relationship with food than obesity-aware CGs (63 vs 49%$^{\#}$).

Conclusions: A subset of both ALwO and CGs were obesity-unaware. ALwO who were obesity-aware appeared more motivated to lose weight but had a poorer relationship with food than obesity-unaware ALwO. Among CGs, the perception that ALwO will lose weight naturally over time was more common when CGs were obesity-unaware.

P1-68

Gender variability and associations of blood dopamine, leptin and insulin in overweight children

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Background: Some neuropeptides and hormones, for instance dopamine, leptin and insulin can affect the food consumption, eating behavior and can lead to obesity.

Research goal was to discover the gender differences, associations and joint influence on body weight of blood dopamine (DA), leptin (LP) and insulin (Ins) concentrations in obese children.

Material and Methods: We discovered cross-sectional retrospective data of 216 11–17.9 y.old children (II–V Tanner stages), involved in the national obesity study. According to BMI SDS for age and sex, participants were split up into: normal weight healthy children (NW, ±1 SDS, n=30); I–II WHO obesity classes (I–II-OC, ≥2&≤4 SDS; n=84): III WHO OC (III-OC, SDS >4; n=102). Girls/boys (B/G) ratio was 112/104. DA, LP and fasting Ins concentrations, fasting blood glucose (FBG) and HOMA-IR indexes were analyzed using non-parametric methods, and binary logistic regression ($p<0.05$).

Results: Blood DA was higher in III-OC children than NW ($p=0,003$) and I-II-OC peers ($p=0,01$). The same pattern of DA changes was in III-OC B, compared to NW ($p=0,008$) and I-II-OC peers ($p=0,001$). LP concentrations raised from NW children (p1-2<0.001); through I-II-OC (p2-3=0.02) to III-OC peers (p1-3<0.001). The same serum LP changes had NW G (p1-2<0.001), I-II-OC (p2-3=0.001) and III-OC peers (p1-3<0.001). Ins and HOMA-IR were higher in I-II-OC ($p<0.001$ and $p<0.001$ prop.) and III-OC children ($p<0.001$ and $p<0.001$ prop.) in contrast to NW both gender peers. HOMA-IR values were elevated in III-OC than the I–II-OC children ($p=0.023$).

Blood DA were associated with BMI ($\rho=0.3$; $p<0,001$), SDS BMI ($\rho=0.3$; $p=0.002$), Ins ($\rho=0.3$; $p=0.005$) and HOMA-IR ($\rho=0.4$;

p<0.001) in both sexes. LP values were correlated with BMI (ρ=0.5; p<0.001), SDS BMI (ρ=0.5; p<0.001), Ins (ρ=0.3; p=0.039), and HOMA-IR (ρ=0.3; p=0.046), in G. We created math models with a high percentage of correct predicted values (86.6–90.4%) that allowed us to determine separate and joint influence on body weight of DA and LP concentrations in I-II-OC and III-OC children.

Conclusions: DA concentrations were associated with BMI, its SDS, Ins and HOMA-IR values in obese children particularly in boys (p<0.05). LP values were related to anthropometric and metabolic indexes mostly in girls (p<0.05). DA and LP combination seem to be significant predictors of childhood obesity, particularly the IIIrd WHO OC.

P1-69

Clinical evolution after a 24 month nutritional intervention based on carbohydrate restriction in adolescents with obesity

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Introduction: Carbohydrate restriction (CH-R) in adolescents with obesity results in faster BMI reduction and glucose metabolism improvement than diets with normal carbohydrate proportion, without a higher weight regain in the short term. However, data on weight and metabolic trajectories of these patients after a more prolonged follow-up are sparse.

Objectives: To evaluate metabolic and body composition evolution during the second year of follow-up in adolescents with obesity who underwent a nutritional intervention with carbohydrate restriction for 12 months compared with patients without carbohydrate restriction (CH-N).

Patients and Methods: Prospective study of 111 Caucasian adolescents (14.5±1.8 years; 64% females), with non-syndromic obesity (+4.58±1.84 BMI-SDS).

At baseline, patients were randomized into two different nutritional interventions (both 1500 kcal/day): CH-R (CH supplying 10% of daily caloric intake during months 1 to 4; 30% during months 5 to 8 and 52% during months 9 to 12) vs. CH-N diet (no carbohydrate restriction [52% of total daily caloric intake]). During months 12 to 24 both groups received CH-N diet. BMI, body composition (bioimpedanciometry), glucose, insulin, lipid profile, leptin and HMW-adiponectin levels at baseline, 12 and 24 months were recorded.

Results: Both groups had similar age, BMI, body composition, metabolic features and sex distribution at baseline. At 12 months, both groups significantly reduced BMI, body fat mass, glycemia, insulinemia and leptin levels and increased HMW-adiponectin levels to a similar extent.

Between 12 and 24 months, BMI-SDS (+2.94±1.71 to +3.86±2.31 SDS, p<0.001) and body fat percentage (30.9±8.9 to 33.8±9.7 %; p<0.001) increased in the CH-R group but not in CH-N group (+3.47±1.82 to +3.47±1.83 SDS and 32.8±8.5 to 32.5±7.6%, respectively). Leptin and leptin/HMW-adiponectin ratio increased only in the CH-R group (40.8±21.3 to 49.0±23.8 ng/ml and 12.0±7.9 to 16.1±11.7; p<0.01 and p< 0.001, respectively). A significant increase in fasting glucose (p<0.05) but not in insulinemia or HOMA index was observed in both groups. No significant changes in the lipid profile were observed except for LDL cholesterol levels, increasing in the CH-R (89.8±26.2 a 99.8±23. 1 mg/dl, p<0.05) but not in the CH-N group. No significant intergroup differences at 24 months were observed in any of the studied parameters.

Conclusion: Nutritional interventions base on CH-R in adolescents with obesity may be associated to a higher rate of weight regain in the middle-term, once carbohydrate restriction is stopped.

P1-70

Abstract Withdrawn

P1-71

Circulating mRNA and miRNA Signatures as Predictive Markers of Lifestyle Modification Outcomes in Pediatric Obesity Treatment

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Context: The response to lifestyle modification (LSM) in children with obesity is variable and difficult to predict.

Aim: A systematic search for molecular markers to predict outcomes of LSM in pediatric obesity management.

Patients/Methods: Out of 240 children with obesity (BMI>97%) recruited to a prospective 'multi-OMICS' study granted by ESPE Research Unit, 159 subjects (age 8-17 yrs, median 12.8 yrs; 45% females) finished twelve-months (V12) of LSM obesity management at three centers in Poland, Turkey and Italy. Four of >180 baseline clinical/laboratory (V0) features (sex/age/severity of obesity at V0/delta z-score BMI V12-V0) were used to select 50 representatives for RNA-seq analysis. We searched for circulating mRNA & miRNA capable of predicting the response to LSM defined by a decrease in z-score BMI (Responders/RS). First, the candidate gene approach with previously documented *STAT3, CORO1C, SERPINH1, MVP, ITGB5* (upregulated in obesity), *PCM1, SIRT1, EEF1G, PTEN* and *RPS2* (down-regulated in obesity) hub genes was applied. The pairwise ratios of transcripts per million (TPM)s of these genes were tested for statistical significance between RS (n=31) and non-RS (n=19) groups. Secondly, the TPM expression values of 2,129 miRNAs and 33,246 *RPL13A*-normalized mRNAs were compared between RS and non-RS to get a list of putative significant genes ($p < 0.05$; the Welch t-test). Enrichr, a web-based tool (http://amp.pharm.mssm.edu/Enrichr), was used for analysing gene sets.

Results: Expression values for 909 mRNA and 24 miRNA genes were significantly different between RS vs non-RS. For example, *STAT3/PTEN, CORO1C/PTEN, MVP/PTEN*; *miRNA-10a, miRNA-122, miRNA-127, miRNA-502, miRNA-210* were significantly higher and *SIRT1/PTEN, EEF1G/PTEN, RPS2/PTEN, miRNA-27a* were lower comparing RS vs. non-RS ($p= 0.009, 0.022, 0.030, 0.048, 0.029, 0.045, 0.035, 0.020, 0.047, 0.04, 0.039, 0.029$, respectively). Several pathways, including *"Vitamin B6 metabolism"* and *"Insulin receptor signaling"*, were enriched in our differentially expressed mRNA ($p<0.001$): *PNPO, PHOSPHO2, PDXP, PSAT1* were up-regulated in RS vs. non-RS. *"Leptin signaling pathway WP2034"* were enriched in *STAT3* and *PTEN* ($p<0.0001$).

Conclusions: The role of the balance between *STAT3* and *PTEN* in LSM was discovered. The importance of previously described miRNA markers (*miRNA-122, miRNA-127, miRNA-27a*) related to adipogenesis risk, insulin resistance, hepatic fat reduction, *PPAR-γ* expression were confirmed. A combination of the previously reported V0 Leptin feature together with *STAT3/PTEN* and *miRNA-27a* levels showed promising predictive results. Our findings not only showed the predictive molecular markers but also pointed to their role in personalization of therapeutic management.

P1-72

Energy Drinks: Acute Effects on Central Hemodynamics in Healthy Children and Teenagers. A Randomized Trial

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Introduction: Adolescents are considered the main consumer group of Energy Drinks (EDs). EDs are associated with adverse cardiovascular events, such as severe cardiac arrhythmia or arterial hypertension. Recent studies of our department revealed a significantly increased brachial blood pressure and arterial stiffness after the acute ED consumption in healthy adolescents. Increased central blood pressure is linked with the onset of end-organ damages such as left ventricular (LV) hypertrophy. The aim of this study was to investigate the acute effects of ED consumption on central hemodynamics in healthy children and teenagers.

Methods: This study was a prospective, randomized, single-blind, placebo-controlled, crossover clinical trial. Study participants received a bodyweight-adjusted amount of an ED (3mg caffeine per kg of bodyweight) or a placebo-beverage with similar sugar content but without conventional ED ingredients on two consecutive days. Ambulatory pulse wave analysis was executed using an oscillometric blood pressure device (Mobil-O-Graph®), which assessed the following parameters automatically: central systolic blood pressure (cSBP, mmHg), central diastolic blood pressure (cDBP, mmHg), central pulse pressure (cPP, mmHg) and pulse wave velocity (PWV, m/s). Cardiovascular measurements between one and four hours after beverage consumption were averaged. The absolute change to baseline was calculated. A paired t-test was applied to compare the absolute changes of the cardiovascular parameters studied between both groups. A p-value <0.05 was considered statistically significant.

Results: In total, 20 adolescents were included in the present study (mean age: 14.49 years, 55% male). Cardiovascular parameters studied, did not show significant differences at baseline. The acute ED consumption led solely to a significantly higher absolute change of cDBP compared to the placebo-beverage (0.21±5.87

mmHg vs. -4.33±7.49 mmHg; p=0.023). In addition, the absolute change of PWV tended to be higher after the acute ED consumption (0.16±0.36 m/s vs. -0.07±0.45 m/s; p=0.056).

Conclusions: The results of this study suggest an increase of central blood pressure after the consumption of a single, body-weight-adjusted ED amount. The increased central blood pressure can lead to a higher LV afterload, subtle impairment of cardiac function and hence an elevated cardiovascular risk. Therefore, the chronic ED consumption might cause the onset of LV hypertrophy. Adolescents with chronic cardiovascular conditions (e.g., arterial hypertension) should be discouraged from the ED consumption. Further research is required investigating the effects of chronic ED consumption on central hemodynamics and end-organ damages in minors.

P1-73

Glucose alterations, insulin resistance, hypertension, and activation of the renin-aldosterone system are strictly associated in pediatric obesity

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Background: The increase of global childhood obesity has led to an increase of associated co-morbidities also at a young age. The pro-inflammatory state and insulin resistance are two master regulators of several complications, including hypertension and prediabetes frequently connected in a complex crosstalk.

Aim: To evaluate the relationship between glucose alterations and blood pressure and the pathogenetic involvement of the renin-aldosterone system (RAAS) in pediatric obesity.

Methods: We retrospectively evaluated 800 paediatric subjects (11.4 ± 3.1 years) with overweight or obesity at the first visit with a complete clinical and metabolic screening (BMI, BMI-SDS, blood pressure, glucose, and insulin levels during an OGTT). Aldosterone and renin were measured with chemiluminescence, and their ratio (ARR) was calculated.

Results: 774 patients had all the parameters. 11.5% of patients were with overweight and 88.5% with obesity. Blood pressure has been characterized following the last American Academy of Pediatrics guidelines: 679 patients (87,6% 88.0%) had hypertension (HTN). Of them, 38 (5%) had elevated blood pressure, 226 (29.2%) were classified as HTN stage 1, and 414 (53.4%) stage 2. Regarding glucose levels, 41 subjects had impaired glucose levels, (IFG), 52 impaired glucose tolerance (IGT), 3 type 2 diabetes (T2DM), and a totally 80 subjects had one or more glucose alterations (IFG/IGT/T2DM).

Patients with IFG ($p<0.01$), IGT ($p<0.02$), or T2DM/glucose alterations ($p<0.02$) were more frequently with HTN. Blood pressure levels were higher in subjects with glucose alterations ($p<0.04$) than those with normal glucose levels (NGT). OGTT glucose levels and HOMA-IR ($p<0.002$) were higher in subjects with the three HTN stages than those with normal levels. Subjects with glucose levels > 155 mg/dl after 60' at OGTT had more frequent HTN ($p<0.001$) and higher diastolic blood pressure levels ($p<0.002$) than NGT. We also found increased activation of the renin-angiotensin-aldosterone system (RAAS), positively correlated with BMI and female gender, that mainly characterized subjects in HTN stage 2. Aldosterone levels were higher in subjects with glucose levels > 155 mg/dl after 60' at OGTT than those without it ($p<0.003$).

Conclusions: Already in childhood obesity, there is a close relationship between insulin resistance, glucose alterations, hypertension, and RAAS. The identification of specific risk categories, such as the presence of altered blood glucose or hypertension, could provide risk indicators to close clinical surveillance for the prevention and identification of complications and follow-up of organ damage.

P1-74

Metabolic risk assessment in children and adolescents using the tri-ponderal mass index

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We assessed the risk of metabolic syndrome in children and adolescents who were classified using the tri-ponderal mass index (TMI) with data from the Korea National Health and Nutrition Examination Survey (KNHANES). Data from 10-18-year-old subjects that were overweight or obese (n=1,362) were extracted from the KNHANES 2007-2018. Weight classifications were determined by TMI and included overweight and Class I, Class II, and Class III obesity. The standard deviation scores (SDS) of weight, waist circumference, and body mass index (BMI) as well as cardiometabolic risk factors, including blood pressure, serum glucose levels, total cholesterol (T-C), triglycerides, HDL-c, and low-density lipoprotein cholesterol (LDL-c), worsened with the severity of obesity. Most risk factors showed a linear association with the severity increase, except for fasting glucose levels, T-C, and LDL-c. The prevalence of cardiometabolic risks also increased with the severity of obesity, which developed earlier in boys than in girls. The risk of metabolic syndrome significantly increased with the severity of obesity in both unadjusted and adjusted analyses. TMI reflected the severity of obesity and predicted the risk of metabolic syndrome and its components. Therefore, clinical applications of TMI could be a useful to identify the incidence of childhood obesity and metabolic syndromes.

P1-75

The association between C-reactive protein, metabolic syndrome, and prediabetes in Korean children and adolescents

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Purpose: Metabolic syndrome (MetS) is a state of chronic inflammation, and high-sensitivity C-reactive protein (hsCRP) indicates inflammation. This paper evaluates the association between hsCRP and MetS and its components in Korean children and adolescents.

Methods: We analyzed the data of 1,247 subjects (633 males, 14.2 ± 2.7 years) from the Korea National Health and Nutrition Examination Survey (KNHANES) 2016-2017. This study defined MetS and its components using the modified National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria.

Results: The mean hsCRP level was 0.86 ± 1.57 mg/dL (median and interquartile range: 0.37 and 0.43 mg/dL). Subjects with MetS had higher hsCRP levels than subjects without MetS (geometric mean: 1.08 vs. 0.46 mg/dL, P<0.001). With the higher quartile value of hsCRP, the prevalence of MetS increased. Compared to the lowest quartile, the odds ratio (ORs) for having MetS in the highest quartile was 7.34 (3.07-17.55), adjusting for age and sex. In the top quartile of hsCRP, the risk of having abdominal obesity and low HDL was high after adjusting for age, sex, and other components of the MetS. Additionally, the ORs for having prediabetes (HbA1c ≥5.7%) in the highest quartile was 2.70.

Conclusions: Serum hsCRP level is positively associated with MetS and prediabetes even using NCEP-ATP III criteria. Among the MetS components, abdominal obesity and low HDL were highly correlated with hsCRP in Korean children and adolescents.

P1-76

Omentin-1, vaspin, peptide YY and oxyntomodulin levels in cord blood newborns and correlation with anthropometric parameters

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Background: The gastrointestinal (GI) tract plays a central role in maintaining energy balance and body weight regulation. These functions are mediated by the secretion of gut hormones, including ghrelin, cholecystokinin (CCK), peptide YY(PYY), oxyntomodulin (OXM) and many other hormones. Some of them are orexigenic hormones that promote food intake, while others act as satiety signals and enhance insulin secretion from the pancreatic beta cells. Current evidence suggests that dysregulation in gut hormone secretion may be associated with metabolic disturbances, such as obesity, insulin resistance, and Type 2 Diabetes Mellitus (T2DM).

Objective: Evaluate the level in cord blood of omentin-1, vaspin, OXM and PYY in a population of newborns.

Methods: We studied 79 newborns born at term in the Paediatric Department of Novara. For each newborn we evaluated gestational age, birth weight, length, head circumference and collected a venous cord blood sample for determination of levels.

Results: Males were 41 (52%) and females 38 (48%); mean gestational age was 38 weeks. Medium birth weight was 3264 gr, lenght was 49 cm and head circumference 33 cm. In our population, newborn weight was influenced by mother's height (r=0.294; p<0.01), weight before pregnancy (r=0.369; p<0.01) and mother's weight at childbirth (r=0.471; p<0.01). Mother's weight at childbirth is also related with child length (r=0.329; p<0.01) and head circumference (r=0.290; p<0.01). Regarding hormones production, mean omentin-1 levels in cord blood were 1.92 ng/ml (range 0.15-7.73 ng/ml), mean vaspin levels 2.84 ng/ml (range 0.53-14.53 ng/ml), mean OXM levels 0.21 ng/ml (range 0.050-6.78 ng/ml) and mean PYY levels 0.065 ng/ml (range 0.007-0.278 ng/ml). OXM levels had significant correlation with gestational age (r= 0.281; p<0.05) and AGA newborn (r= 0.373, p<0.01). Its function is confirmed by the negative correlation with newborn LGA for the weight (r= -0.281; p<0.05). No other associations between the other hormone levels and newborns auxological data were found.

Conclusion: The negative correlation found in our study between cord OXM levels and birth weight in LGA neonates could suggest that this hormone plays the same metabolic activities exerted in adulthood, where it reduces the food intake and increases energy expenditure. Our preliminary data are the first described in a population of newborns and should be validated in a wide cohort.

P1-77

Abstract Withdrawn

P1-78

Obstructive sleep apnea (OSA) is associated with the impairment of beta-cell response to glucose in children and adolescents with obesity

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Purpose: The main purpose of the study is to assess the association between obstructive sleep apnea (OSA) and insulin secretion in children with obesity.

Objectives: To achieve our aim we have assessed OSA and measured insulin secretion by the using the oral minimal model (OMM) in a cohort of 77 obese children and adolescents.

Methods: We retrospectively enrolled children and adolescents who have attended our pediatric outpatient obesity clinic because of obesity and suspected OSA. Glucose homeostasis, insulin-sensitivity, and insulin secretion were assessed through standard 2-hour OGTT. Nocturnal cardio-respiratory polygraphy was performed for OSA diagnosis. A subgroup of 22 patients underwent a 3-hour OGTT test to investigate insulin secretion and sensitivity though the oral-minimal model.

Results: seventy-seven children and adolescents (11.3± 2.9 years, z-score BMI 3.53±0.76) were included in the study. All of them presented with OSA (29 had mild, 29 moderate, and 19 severe OSA). Based on OSA severity, the cohort was divided into three groups. The group with mild OSA showed lower 30-minutes glucose (p=0.01), 60-minutes glucose (p=0.03), and prevalence of elevated 1-hour glucose (10.4% versus 44.8% in moderate and 31.6% in severe OSA, p=0.01). The odds of showing elevated 1-hour plasma glucose was 6.2 fold (95% CI 1.6-23.4) higher in children with moderate and severe OSA compared to mild OSA (p=0.007) independent of confounders. Spearman correlation analyses revealed a positive correlation between 30-minutes plasma glucose and AHI (r=0.31, p=0.01), ODI (r=0.31, p=0.009), and mean desaturation (r=0.25, p=0.04). The exploratory study included 22 children and adolescents, 7 presented mild and 6 had severe OSA. The group with mild OSA showed a higher dynamic, static, and total insulin secretion compared to those with moderate and severe OSA (p<0.0001, p=0.007, p=0.007, respectively). OSA severity index (AHI) was significantly correlated to dynamic insulin secretion (r=-0.48, p=0.02).

Main Conclusion: OSA might impair beta-cell function reducing insulin secretion in obese children and adolescents, in the absence of an effect on insulin sensitivity.

P1-79

Severe early-onset obesity and diabetic ketoacidosis due to a novel homozygous c.169C>T p.Arg57* mutation in CEP19 gene

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Background and Objective: Homozygous mutations in the "Centrosomal Protein-19 (CEP19)" gene are extremely rare causes of early-onset severe monogenic obesity. We, herein, report three siblings with CEP19 mutation.

Case Presentation and Method: The index case was a 12-years-old female who presented with severe obesity (BMI:62.7kg/m2), metabolic syndrome and diabetic ketoacidosis. Her non-identical twin female siblings (Case-2&3) also had early-onset severe obesity, metabolic syndrome and diabetes. Besides, Case-2 had situs inversus abdominalis, polysplenia, lumbar vertebral fusion and right-left disorientation. Whole-exome sequencing and subsequent Sanger sequencing was performed. A homozygous nonsense (c.169C>T, p.Arg57*) mutation was detected in exon-3 of CEP19 in the index case and her affected twin sisters. One unaffected sister and unaffected parents were heterozygous for the variant. This variant is predicted to cause a stop codon at the amino acid sequence 61, leading to a truncated CEP19 protein.

Conclusion: Our study expands the phenotypical manifestations and mutation database of CEP19 variants. Findings in one of our patients reaffirm its role in the assembly and function of both motile and immotile cilia.

P1-80

Obesity and overweight increased in pre-school Swedish children during the COVID-19 pandemic

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Background: The COVID-19 pandemic has had wide effects on child health globally. Increased prevalence of childhood obesity has been observed during the pandemic. The absence of a formal societal lockdown during the pandemic, made Sweden stand out compared to other countries. Several studies have shown increases in obesity in children during the COVID-19 pandemic. These studies mainly focused on school age children and adolescents in countries that underwent periods of societal lockdown. Child health nurses in socioeconomically deprived areas in Sweden have signalled a rise in childhood obesity during the pandemic, however not yet analysed scientifically. This study hence aimed to examine changes in BMI among pre-school children in Sweden before and during the COVID-19 pandemic.

Methods: Retrospective population based cross-sectional study, with longitudinal follow-up for a portion of the children, data was obtained from the national quality register for child health care, BHVQ. The study included 25049 children from three Swedish regions, with growth measures at three- (n=16237), four- (n=14437) and five-years of age (n=11 711). Care Need Index was used as a socioeconomic parameter at health centre level. BMI was calculated and categorized based on sex-specific BMI-for-age in months (IOTF body mass index cut-offs for thinness, overweight and obesity).

Results: There was an increase in BMI in children aged three (p=0.028), and four (p <.001) during the COVID-19 pandemic. Obesity in three-year-old girls increased from 2.8% to 3.9%. Four-year-olds increased in obesity (both sexes), overweight (girls) and the prevalence of underweight decreased in boys. A lower proportion of girls had a normal weight status during (80.9 %), compared to before the COVID-19 pandemic (82.6 %) (p=0.049), while no difference in normal weight status was found in boys the same age (p = 0.977). No change in BMI was observed in five-year-olds. Children in areas with the lowest socioeconomic status had higher risk of obesity, increasing from 2.4% to 4.4% during the pandemic, overweight increased in these areas from 9.5% to 12.4%.

Conclusions: Overweight and obesity increased among three-four year old Swedish children, especially for children attending child health centres in areas with lower socioeconomic status. The COVID-19 pandemic is likely to have affected health behaviours negatively in Swedish pre-school children. Our results expose the need for extended efforts directed to prevent childhood obesity, especially targeting lower socioeconomic areas.

P1-81

The relationship between body mass index, adipose indices measured by whole-body DXA and markers of cardio-metabolic risk in survivors of childhood medulloblastoma

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Background: Endocrine disturbances are the most prevalent complications in childhood cancer survivors (CSS), especially in those treated with cranial and cervical radiation for brain tumours, such as medulloblastoma. Recent data have shown frequent delays in the diagnosis and treatment of these complications that may lead to potential side-effects on general health. Apart from the well-known hypothalamic–pituitary and growth disorders observed in CSS, these patients are predisposed to the development of obesity and metabolic syndrome (MS) which increase the risk of cardiovascular disease (CVD) and type 2 diabetes mellitus.

In this study we aimed to determine adiposity by dual-energy x-ray absorptiometry (DXA) and compare it with conventional anthropometry and identify their association with markers of cardio-metabolic risk in a cohort of childhood medulloblastoma survivors.

Material and Method: Anthropometric measurements and metabolic/hormonal profile were obtained from 16 survivors of childhood meduloblastoma that were evaluated in our clinic for long-term endocrine complications. Total body fat mass and android/gynoid (A/G) ratio were measured by whole-body DXA in 15 subjects.

Results: Our study showed a statistically significant correlation between FMI z-score and anthropometric parameters, such as BMI z-score (r=0.882, p<0.001), waist/height ratio (r=0.786, p=0.004) and waist/hip ratio (r=0.786, p=036) and HOMA index (r=0.773, p=0.002), respectively. Furthermore, we found a strong positive correlation between A/G ratio and HOMA index (r=0.744, p=0.006) in our cohort.

Conclusion: Our study demonstrated a strong relationship between conventional anthropometric measurements and adipose indices measured by DXA and HOMA index. Therefore, we suggest that these parameters can be used in this population to predict the metabolic risk.

P1-82

Cardiometabolic Health in Adolescents Conceived by Assisted Reproductive Technologies: Preliminary Results from the Munich heARTerY-Study

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Background: Since its introduction in 1978, assisted reproductive technologies (ART) have been widely used to treat infertility. Worldwide, over 8 million children have been conceived by ART. Literature suggests that ART-adolescents potentially display altered vascular function. However, data concerning the cardiometabolic impact on the vascular function in ART-adolescents is limited. This study aimed to investigate the effects of blood lipids and HbA1c-levels on the vascular function in ART-adolescents compared to spontaneously conceived peers.

Methods: For the present study, ART-adolescents and spontaneously conceived peers between the ages of 10 to 17 years were recruited. Systolic (SBP) and diastolic (DBP) blood pressure were recorded by an ambulatory blood pressure measuring device. In addition, the body mass index (BMI) was assessed. Total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), lipoprotein a (Lp(a)) and HbA1c were evaluated after a fasting period of ≥4 hours. To compare continuous and normally distributed values between both groups, the unpaired t-test was applied. The Mann-Whitney-U-test was utilized to compare non-normally distributed values. The Pearson correlation was used for normally distributed and the Spearman correlation for non-normally distributed variables. A p-value <0.05 was considered as statistically significant.

Results: 20 ART-adolescents (female: 35.00%) and 30 spontaneously conceived controls (female: 40.00%) were included in the present study. Both groups did not differ significantly in age (12.50 (10.00-17.00) years vs. 12.00 (10.00-17.00) years, p=0.824). No significant differences in SBP, DBP, BMI, blood lipids and HbA1c were detected between the ART and control group. A LDL ≥130 mg/dL was present in 15% of ART-adolescents but in none of the control subjects. A Lp(a) ≥30 mg/dL was detected in 15% of ART-individuals and in 13.3% of spontaneously conceived peers. An HbA1c ≥5.7 mg/dL was shown in 20% of ART-adolescents and in 10% of controls. No significant correlation between blood pressure, BMI, blood lipids and HbA1c was observed.

Conclusion: The results of this study suggest that LDL-hypercholesterinemia and pathological HbA1c-levels might be more present in ART-adolescents compared to spontaneously conceived peers. Vascular function, visualized by brachial blood pressure, did not differ significantly between both groups and did not correlate with cardiometabolic risk factors. As the examined ART-subjects of this study were relatively young, further research is required evaluating the cardiometabolic health and its potential impact on vascular function in larger adult ART-cohorts.

P1-83

Association between thyroid hormones and cardiometabolic risk factors in euthyroid overweight and obese children and adolescents following the implementation of a lifestyle intervention program

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Background: Thyroid hormones regulate metabolism and play a significant role in cardiovascular homeostasis. However, the association between thyrotropin (TSH), thyroid hormones and cardiometabolic risk factors has not been elucidated in euthyroid children and adolescents with overweight and obesity.

Aim: To evaluate the relation of TSH and thyroid hormones with cardiometabolic parameters in euthyroid obese, overweight and normal-weight children and adolescents before and after the implementation of a comprehensive, multidisciplinary, personalized lifestyle intervention program for 1 year.

Methodology: One thousand and four hundred twenty-eight (n = 1.428) children and adolescents aged 2–18 years (mean age ± SD: 9.923 ± 3.018 years; 742 females, 686 males) with normal thyroid function were studied prospectively. Subjects were classified as obese (n = 766, 53.6%), overweight (n = 408, 28.6%) or with normal body mass index (BMI) (n = 254, 17,8%) according to the International Obesity Task Force cutoff points. All participants were evaluated by a multidisciplinary team at frequent intervals, received personalized guidance on diet and physical exercise and were studied prospectively for 1 year. Detailed clinical evaluation and laboratory investigations were performed at the beginning and at the end of the study.

Results: Subjects with obesity had significantly higher systolic (SBP) and diastolic (DBP) blood pressure, waist circumference, hip circumference and waist-to-hip ratio than overweight and normal-BMI subjects on both assessments. In addition, they had significantly higher concentrations of fasting plasma glucose and serum insulin, HbA1C, triglycerides, LDL-cholesterol, uric acid and ApoB, and significantly lower concentrations of HDL-cholesterol, ApoA1 and Vitamin D than their overweight and normal-BMI counterparts. Baseline total T3 concentrations were positively associated with uric acid and negatively associated with HDL and creatinin, while Free T4 concentrations were inversely associated with baseline glucose and insulin concentrations. No associations were found between baseline TSH concentrations and cardiometabolic risk parameters. Following the 1-year of multidisciplinary management interventions, all cardiometabolic indices improved significantly in all subjects. In overweight and obese children changes in Free T4 concentrations were significantly associated with changes in cholesterol, LDL, glucose and creatinine concentrations. T3 changes were significantly associated with

changes in uric acid, glucose, creatinine and WHratio. Finally, TSH was significantly associated with changes in cholesterol concentrations.

Conclusions: In euthyroid overweight and obese children and adolescents thyroid hormones are associated with indices conferring cardiometabolic risk. Changes in Free T4, T3 and TSH concentrations are also associated with changes in various cardiometabolic parameters, such as cholesterol, glucose and creatinine.

P1-84

Osteocalcin in Infancy and Early Childhood Related to Covariates and Growth: A Longitudinal Birth Cohort Study

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Context: Osteocalcin is a bone formation marker that has recently sparked interest for its endocrine involvement in glucose homeostasis and obesity. Nevertheless, its natural pattern during infancy and early childhood remains unknown.

Objectives: We established reference values for total serum osteocalcin during specific timepoints from birth until five years of age, and presented these in the context of covariates.

Methods: Blood samples from the umbilical cord, and 4, 12, 36 and 60 months of age together with information about the mother, birth, anthropometrics, and a food diary were retrieved for a longitudinal birth cohort in Sweden.

Results: Gender- and age-specific reference values were established for the specified timepoints. Osteocalcin displayed a wave-like pattern over time, with low levels in the umbilical cord, a postnatal peak during the first year, and a decline thereafter that rose again by the age of five. Median osteocalcin levels were 43.7 - 91.0 - 68.9 - 61.6 - 79.7ng/mL for boys and 37.6 – 100.0 – 81.7 – 70.5 - 93.1ng/mL for girls. Gestational age, size for gestational age, breastfeeding practices, and growth influenced early osteocalcin values.

Conclusion: We suggest that osteocalcin follows a specific pattern, with high levels preceding the infancy BMI peak. Since covariates (e.g. sex, breastfeeding and size for gestational age) may impact the amplitude and/or the tempo along this pattern, osteocalcin levels should be interpreted with regards to these factors.

P1-85

The validation of Obesity interpreter, a mobile application-based tool, in evaluation of children and adolescents with obesity

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Background: The assessment of childhood obesity involves rational use of diagnostic tests in individuals with physiological causes while not missing pathologies. We have developed obesity interpreter, a mobile application that provides individualized guidance regarding the workup of children and adolescents.

Aim: To validate the diagnostic accuracy of mobile application in the evaluation of children and adolescents with obesity.

Methods: Retrospective records of 515 obese children and adolescents (318 boys, age 11.7 ± 3.17 years, BMI SDS 2.32 ± 0.6) were analyzed using the application. The application directed towards a specific diagnosis after the input of clinical parameters (age, height, weight, pubertal status, development, vision and dysmorphism).

Results: The diagnostic guidance provided by the application was compared to clinical diagnosis of 515 children with obesity (475 nutritional, 34 endocrine, 6 genetic and syndromic). The application guidance was concordant with clinical diagnosis in all cases.

Conclusions: Mobile application obesity interpreter provide a point of care, simplistic, and evidence-based evaluation of childhood and adolescent obesity.

P1-86

Detailed cardiac phenotyping of obese patients with mutations in the genes POMC and MC4R

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Pro-opiomelanocortin (POMC) and the melanocortin-4-receptor (MC4R) are playing a key role within the leptin-melanocortin-pathway and thereby for satiety regulation. Mutations within these genes are leading to hyperphagia and early-onset obesity. However, observations of cardiac abnormalities including left ventricular dilatation and reduced contractibility in the MC4R knockout mouse model and reports about a reduced blood pressure in human MC4R variant carriers, led us to investigate in detail the cardiac function of patients with mutations in the genes POMC and MC4R.

We characterized the cardiac phenotype of patients with homozygous or compound homozygous POMC mutations and patients with heterozygous MC4R mutations using cardiovascular MRI and 23Na-MRI and compared the results to non-monogenic obese

and normal weight controls. Additionally, we analyzed the blood pressure in a cohort of obese patients with heterozygous MC4Rmutations.

We observed a significant lower left ventricular mass/body surface area (LV mass/BSA) as well as reduced absolute LV mass. Moreover, the LV end-diastolic volume/BSA was significantly decreased and the skin Na+ content and skin water content were increased in MC4R- and POMC-variant carriers. We observed no altered blood pressure values in patients with heterozygous MC4R mutations compared to age- and weight-matched controls.

In conclusion, we identified cardiac abnormalities in this group of patients with mutations in the genes POMC and MC4R. In combination with the results of related animal models, this might point towards a complex connection between these genes of the leptin melanocortin pathway and heart function. Additionally, the results demonstrate the relevance to include cardiologic assessments into the diagnostic work-up of these group of patients.

P1-87

Thyroid disfunctions during pediatric obesity: Possible role in obese children with insulin resistance

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Introduction: Pediatric obesity (PO) is associated with hormonal dysfunctions contributing to an increased risk of cardiovascular disease and diabetes. Among these risks, thyroid disfunctions (TD) are the most common. The ethio-pathogenetic mechanisms underlying TD are not well known and include an adaptive response to a higher energy intake, hyperleptinemia, peripheral resistance to thyroid hormones, increased pro-inflammatory cytokines. Pediatric prevalence of TD in obesity is about 14%. In this study we correlated thyroid function with clinical and laboratory data of a group of obese Italian children living in the province of Salerno, Campania.

Materials and Methods: A retrospective study was conducted on 85 children (40M, 45F, age 5-16 years) with obesity (BMI z-score 2.59 ± 0.41) assessed at the pediatric endocrinology service of the Pediatric Unit - PO di Battipaglia - ASL Salerno from January 2016 to January 2020. All of them practiced: weight, height, BMI z score and blood pressure measurement; glucose, insulin (for calculating HOMA index), c-peptide, ALT, AST, gammaGT, total cholesterol, HDL, LDL, triglycerides, ESR, PCR blood dosages. They also followed the oral glucose tolerance test (OGTT). The correlation coefficient was calculated between TSH, FT3, FT4, antibodies antithyroperoxidase antibodies (AbTPO), antiantithyroglobulin antibodies (AbTG) and clinical/laboratory values identified.

Results: TSH significantly correlates with weight (r = 0.29495 p = 0.02593) and BMI z-score (r = 0.28157 p = 0.04760); ALT (r = 0.33858 p = 0.00153), gamma GT (r = 0.32337 p = 0.00286), HOMA index (r = 0.3268 p = 0.00309) increase with TSH levels as well baseline (r = 0.38185 p = 0.00037) and OGTT insulinemia (r = 0.67393 p = 0.00420) after 120 minutes. C-peptide levels increments when FT4 (r = -0.41053 p = 0.00415) and FT3 (r = -0.29266 p = 0.04590) are decreased. Finally, there is a positive relationship between Ab TG and HbA1c (r = 0.30759 p = 0.02506).

Conclusion: This study confirms the close relationship between TD and PO and demonstrates a possible role of TD also on hepatic metabolism and insulin secretion during OP. Autoantibodies can also be involved in glycemic homeostasis alterations but further studies are needed to confirm this hypothesis.

P1-262

Altered inflammatory parameters and chemokine network in obese children

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Background: Childhood obesity has increased in epidemic proportions worldwide. Growing evidence confirms persistent low-grade systemic inflammation in obese individuals. It eventually leads to insulin resistance and endothelial damage, thus setting the ground for the development of metabolic and vascular complications.

Aim: To investigate metabolic and inflammatory parameters and their relationship in obese children, by analyzing laboratory data and peripheral blood chemokine/chemokine receptor profile.

Materials and Methods: Mononuclear cells were isolated from peripheral blood of healthy controls (n=29, 14 M, age 15.46 +/- 1.51 years) and obese children (n=34, 19 M, age 14,69 +/- 1.60 years). B-cell (CD19+), T-cell (CD3+), and monocyte (CD14+) phenotypes were determined using flow cytometry for the chemokine receptors CCR2, CCR4, CXCR3, and CXCR4. Chemokines CCL2, CCL5, CXCL10 were determined using a bead-based immunoassay (LEGENDplex™, BioLegend) and CXCL12 was analyzed by ELISA. Chemokine levels and chemokine expressing cell populations were correlated with clinical parameters (age, body mass index, blood pressure), parameters of metabolic complications (HOMA-IR, ALT, lipid profile), and inflammation (CRP and fibrinogen).

Results: Obese children had higher concentrations of inflammatory markers (CRP and fibrinogen), as well as parameters of metabolic complications (higher ALT, LDL-cholesterol, triglycerides, diastolic blood pressure (DBP) and HOMA IR, lower HDL-cholesterol). In this group, we found a decrease of CCR4 and CXCR3 expressing monocyte subpopulation and a lower concentration of CXCL12. CRP and fibrinogen showed a strong positive correlation with metabolic parameters. CXCR3 expressing monocytes showed a negative correlation with CRP, fibrinogen, ALT, LDL-cholesterol, and HOMA-IR, while CCR4 expressing monocytes positively correlated with HDL-cholesterol, DBP and negatively with HOMA-IR and triglycerides. We also found a positive

correlation between CCR2 expressing B-cells and HDL-cholesterol and CCR4 expressing B cells and DBP. CCL2 positively correlated with ALT and triglycerides.

Conclusion: Obesity is associated with alterations in systemic inflammatory parameters and metabolic complications even at a young age. Identifying and targeting inflammatory molecules might be a potent therapeutic option for preventing obesity-related morbidity and mortality.

P1-263

Small integral membrane protein 10 like 1 (SMIM10L1) affects adipogenesis and apoptosis in adipose progenitor cells

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Background: Pediatric patients with germline pathogenic variants in the tumor suppressor gene PTEN frequently develop cancer and adipose tissue overgrowth in the form of lipomas. While the canonical function of the phosphatase PTEN is to antagonize the growth promoting PI3K pathway, non-canonical PTEN functions e.g. in the nucleus are less well described. To uncover the mechanisms leading to lipoma formation related to PTEN mutations, we previously performed RNA-sequencing of adipose progenitor cells (APCs) with PTEN knockdown (KD). The so far uncharacterized small integral membrane protein 10 like 1 (SMIM10L1) was the most significantly downregulated gene. We aimed to uncover the role of SMIM10L1 downregulation in APCs in relation to adipose tissue overgrowth and cancer formation.

Methods: SMIM10L1 was downregulated via siRNA or overexpressed via expression vectors in APCs and effects on gene expression, adipogenesis, and cell death were assessed.

Results: We observed a downregulation of SMIM10L1 mRNA to 35.5 ± 2 % ($p = 0.001$) after PTEN KD. This was independent of PI3K pathway activation, as stimulation with insulin-like growth factor 1 (IGF-1) or inhibition with wortmannin did not result in a SMIM10L1 regulation. Moreover SMIM10L1 KD itself led to a downregulation of PTEN on protein level (by 18.9 ± 7 %, $p = 0.023$) and mRNA level (by 12.7 ± 3 %, $p = 0.0018$) and a subsequent activation of the downstream signaling molecule AKT (1.9 ± 0.2 fold, $p = 0.11$). SMIM10L1 KD led to an increase in the lipogenic transcription factor SREBP1 protein expression (1.4 ± 0.2 fold, $p = 0.096$) and enhanced adipogenesis in APCs (1.6 ± 0.2 fold, $p = 0.032$) similar to PTEN KD APCs. Overexpression of GFP tagged SMIM10L1 led to detachment of cells and PARP cleavage, indicating apoptosis, while transfection of a mutant SMIM10L1 version with a stop instead of a start codon or GFP alone did not.

Conclusion: SMIM10L1 and PTEN mutually affect their expression, while activation or inhibition of the PI3K pathway did not alter SMIM10L1 expression, suggesting regulation via non-canonical functions of PTEN. The increased adipogenesis in conditions of SMIM10L1 downregulation observed in adipose progenitors potentially contributes to the adipose tissue overgrowth in patients with PTEN germline mutations. The induction of apoptosis through SMIM10L1 overexpression points to a regulatory mechanism that might be overcome by downregulation in conditions of PTEN insufficiency.

P1-264

Triglyceride–glucose–alanine aminotransferase index as a novel and superior predictor for non-alcoholic fatty liver disease in children and adolescents

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Background: Insulin resistance, non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome (MetS) are strongly correlated with each other. Triglyceride and glucose (TyG) index, a simple and useful insulin resistance surrogate marker, has recently been reported to be superior in predicting NAFLD in adults.

Objects: We evaluated the usefulness of TyG–alanine aminotransferase (ALT) for detecting NAFLD and compared to it to that of the TyG index and homeostatic model assessment for insulin resistance (HOMA-IR).

Methods: We enrolled 4,055 participants aged 10–18 years from the Korea National Health and Nutrition Examination Survey. Multivariable linear regression analysis was used to analyze the association between liver enzymes and insulin resistance surrogate markers. The TyG index and TyG-ALT were calculated as ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2] and [fasting triglycerides (mg/dL) × fasting glucose (mg/dL) x ALT/2], respectively.

Results: Multiple linear regression analysis revealed that ALT levels were significantly associated with HOMA-IR ($\beta=0.111$, $p<0.001$), the TyG index ($\beta=0.111$, $p<0.001$), the TyG–body mass index (BMI) standard deviation score (SDS) index ($\beta=0.310$, $p<0.001$), and the TyG–ALT index ($\beta=0.551$, $p<0.001$) after controlling for sex, age, and BMI SDS. In the receiver operating characteristic analysis, the TyG–ALT index (area under the curve [AUC]=0.939) showed a better performance than HOMA-IR (AUC=0.707), the TyG index (AUC=0.667), and the TyG–BMI SDS index (AUC=0.786) for NAFLD detection ($p<0.001$).

Conclusions: The TyG–ALT index is a more useful marker for NAFLD detection than HOMA-IR, the TyG index, and the TyG–BMI SDS index in children and adolescents. Further studies are needed to determine its potential role as a noninvasive method for NAFLD screening.

P1-265

A point mutation of SH2B1: a new cause of monogenic obesity?

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Early identification of monogenic obesity, a rare condition, is quite challenging for pediatricians.

Src-homology-2 (SH2) B adapter protein 1 (SH2B1) is an important component in the leptin-melanocortin pathway and it is found to play an important role in leptin and insulin signaling. In humans a rare deletion of a 220-kb region on chromosome 16p11.2 encompassing approximately 9 genes, including the SH2B1 gene, is associated with a highly penetrant form of isolated severe early-onset obesity, as well as obesity with developmental delay. We present the case of a young girl with an eterozigous mutation in SH2B1 gene (c.2039G>A; p.Arg680Gln) that could also be associated to obesity and insulin resistance according to clinical features. The same genetic studies are ongoing on the younger sister who presents the same clinical features.

A twelve-year-old girl presented to our hospital with a progressive obesity that began during breastfeeding (weight: 64.7 kg, +1,59 SD; height: 148 cm, -0,54 SD; BMI: 29,5 kg/m2, +2,14 SD; waist circumference: 99 cm). The patient had been followed by a nutritionist since the age of four and although she followed calorie restriction and physical activity programs, she had a constant and progressive weight gain. The physical exam showed excess weight with central distribution, adipomastia and I stage of pubarche. We excluded the most frequent causes of secondary obesity: thyroid hormones were normal and Cushing disease was excluded. In the suspicion of genetic obesity, we searched for mutations in the LEP, LEPR, PCSK1, MC4R, SIM1, POMC, NCOA1, SH2B1 genes with NGS sequencing on the NovaSeq6000 platform (Illumina). A mutation of SH2B1 gene (c.2039G>A; p.Arg680Gln) in heterozygosity was found. During the last hospitalization, at 13 years and 6 months (weight: 66 kg, +1,25 SD; height: 151 cm, -1,11 SD; BMI: 28,9 kg/m2, +2,0 SD), she underwent an oral glucose tolerant test (OGTT) which highlighted severe hyperinsulinism (basal insulin level of 17,1 mU/L and insulin peak of 358 mU/L at 120') and a glycemic level diagnostic for type 2 diabetes (glycaemia at 120 ' of 219 mg/dl). Based on these results, the patient started treatment with metformin at a dosage of 1000 mg three times a day.

In our case, we are strongly oriented to identify the Arg680Gln mutation of SH2B1 as a cause of obesity and sequentially type 2 mellitus diabetes. The presence of the same mutation in the younger sister with the same clinical features could confirm our hypothesis.

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Changes in hypothalamic functional connectivity in the brain following childhood-onset craniopharyngioma

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Background: Craniopharyngioma is a non-malignant, embryological brain tumour in the sellar and parasellar region. Hypothalamic damage is common and accompanied by development of obesity in at least 50% of cases. Mechanisms underlying hypothalamic obesity in craniopharyngioma patients however remain unclear and treatment options are invasive and limited. This feasibility study included a novel application of functional neuroimaging, an established method in obesity research, to childhood-onset craniopharyngioma.

Method: Young people with craniopharyngioma were recruited to the feasibility study. Full clinical characterisation was conducted using medical notes. Historical control participants were matched on sex and the closest BMI-SDS match to each patient with craniopharyngioma from a previous study with identical fMRI acquisition. Resting state functional magnetic resonance imaging (rs-fMRI) data (5 minutes) and a T1-weighted structural MPRAGE scan was acquired. Seed-based rs-fMRI analysis was conducted with hypothalamus as the seed region using FSL analysis software.

Results: Two of the eleven patients were unable to undergo MRI at 3T due to a 'bioplate' and suspected surgical clips. Neuroimaging data were acquired from nine patients (mean[s.d.] age=14.6[3.8]y; BMI-SDS=1.0[1.9]; 3F/6M) and nine controls (mean[s.d.] age=22.39[2.7]y; BMISDS=-0.6[0.9]; 3F/6M). In terms of surgery, three patients had debulking surgery, four had cyst aspiration and a ventricular access device inserted and three underwent transphenoidal resection. Paris grading of the tumours based on hypothalamic involvement post-surgery revealed six patients were grade 2, one patient was grade 1, and two were grade 0. In patients compared to controls, hypothalamic activity showed a stronger association with activity in occipital, parietal, cingulate cortices, and most notably, the insula which is a key region in the appetitive brain network. By contrast in controls, activity in the hypothalamus showed a stronger association with activity in the right cerebellum, bilateral brain stem, frontal and occipital cortices, and left thalamus.

Conclusion: These preliminary results suggest that craniopharyngioma or its treatment has widespread effects beyond the hypothalamus. Connectivity of the hypothalamus to other brain regions may be disrupted, including visual and appetitive areas. Disruptions within the appetitive brain network to regions such as the insula, frontal cortex, and cerebellum may contribute to the development

of obesity in patients with craniopharyngioma. These findings demonstrate the utility of these measures in understanding hypothalamic obesity in craniopharyngioma. Further research in larger samples is warranted to understand the relationship between these functional brain changes with the extent of hypothalamic damage and development of obesity.

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Feasibility of integrating an mHealth intervention to increase exercise and physical activity adherence into a weight management service for adolescents with severe obesity: MOTIVATE-WMA

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Introduction: The Royal College of Paediatrics and Child Health state that adolescents with significant obesity require access to evidence-based weight management services (WMS). Due to the known benefits of exercise and physical activity (PA) on physiological and psychological outcomes increasing exercise and PA should form a cornerstone of any WMS for adolescents living with obesity. However, supervised exercise interventions face challenges within a clinical setting, due to the need for dedicated space and qualified staff. Additionally, supervised exercise programs have high attrition rates and low adherence among adolescents with obesity. A promising method to encourage engagement in exercise and PA is the use of mobile health (mHealth) technologies. However, the feasibility of incorporating an mHealth supported exercise and PA intervention into a paediatric WMS has not been investigated. The aim of this trial was to assess the feasibility of a 12-week mHealth exercise and PA intervention in adolescents with severe obesity receiving treatment from a tertiary WMS.

Methods: Eleven adolescents with severe obesity (16±1yrs, BMI 41±7) supported by a tertiary WMS were randomised to receive routine care (n=4) or the MOTIVATE-WMA intervention (n=7). Routine care involved individualised management plans developed by a multidisciplinary team of healthcare professionals. The MOTIVATE-WMA intervention was a 12-week structured exercise and PA program which used mHealth biometrics to support a counselling intervention delivered by an exercise specialist. The program was supported by a smart watch and phone app, providing real-time feedback during exercise, and enabling improved communication between the exercise specialist and participant. The design of the MOTIVATE-WMA program was informed by social cognitive theory and used delivery of established behaviour change techniques and motivational interviewing to promote long-term adherence.

Results: We observed preliminary evidence of a large effect (d = 0.85, 95% CI = -2 to 7) in favour of the MOTIVATE-WMA (3±4 exercise sessions per week) intervention on exercise behaviour compared to routine care (0±1 exercise sessions per week). 57% (n=4) of MOTIVATE-WMA participants completed exercise sessions during the 12-week intervention compared to 25% (n=1) of participants receiving routine care.

Conclusion: This preliminary data from the MOTIVATE-WMA trial suggests incorporating an mHealth supported exercise and PA intervention to a multidisciplinary WMS increased exercise behaviour with participants completing more exercise than those receiving routine care. Future work needs to investigate the MOTIVATE-WMA intervention in a larger cohort, including clinical outcomes to evaluate how greater exercise adherence influences clinical outcomes.

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Preliminary evidence for a strong effect of leptin on mood and behaviour in patients with congenital leptin deficiency

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Purpose: States of starvation are characterized by reduced physical activity and social withdrawal. The reduction of leptin levels during starvation has been proposed to be a mediator of these changes, therefore we aimed to ascertain if leptin substitution in patients with congenital leptin deficiency (CLD) can increase physical activity and improve mood.

Methods: Seven CLD patients were filmed prior to and after short term (2-21 days, n=6) and long term (3-4 months, n=4) metreleptin substitution in a play situation. Each video was ranked by six independent and blinded investigators concerning the scales motor activity, social interaction, emotionality, and mood; ranking for all scales was such that high scores represent increments/improvements. Scale scores and a total score were calculated.

Results: Short term metreleptin substitution significantly increased the mean total score from 17.7 ± 4.1 to 22.6 ± 6.6 ($p = 0.039$). In 5 out of 6 patients, all four scales were ranked higher than at baseline. The mean scores for motor activity (4.1 ± 1.1 to 5.1 ± 1.5, $p = 0.023$) and social interaction (4.6 ± 1.1 to 6.2 ± 1.7, $p = 0.016$) also increased significantly. After long term substitution the means of all four scales and of the total score were even higher than at short-term follow-up.

Conclusions: Metreleptin substitution improved indices of physical activity and indices of psychological wellbeing in patients with CLD. These data suggest that reduced leptin levels in starvation might be in part responsible for emotional and behavioural changes seen during starvation.

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Characterization of glucose metabolism in obese and overweight children and adolescents during COVID-19 pandemic period

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Background: COVID-19 restriction measurements have enhanced the obesity status in the pediatric population which might further contribute to obesity related glucose-insulin metabolism alterations. Therefore, we retrospectively compared anthropometric and OGTT data on obese children during the 13 years before and during the COVID-19 pandemic period.

Subjects/Methods: Data from 741 obese/overweight children were retrieved and clustered into 7 groups starting from year 2008-2009 until 2020-2021. Differences in anthropometric measurements and glucose/insulin metabolism were evaluated between the different groups.

Results: Overweight/obese children in the COVID-19 restriction group did not present increased values of SDS-Body Mass Index (BMI). Significantly higher values for Waist Circumference (WC), SDS-WC, Waist/Height ratio (WHtR) and body mass fat were detected in these children (all $P<0.01$). Fasting glycaemia, glucose and insulin excursions during OGTT were significantly higher compared to pre-pandemic children (all $P<0.01$). Fasting and post-load insulin resistance indexes were higher while insulin secretion was lower (all $P<0.01$) during OGTT determining a significantly higher percentage of impaired glucose tolerance in the COVID-19 restriction group ($P<0.002$). Furthermore, High Density Lipoprotein (HDL) cholesterol was significantly lower ($P<0.01$) and SDS for systolic and diastolic blood pressure values were significantly higher ($P=0.03$ and $P=0.02$, respectively).

Conclusions: COVID-19 restriction measurements determined profound alterations in glucose and insulin metabolism in obese/overweight children. Urgent strategies are needed in order to reverse COVID-19 restriction measures effects on glucose and insulin metabolism.

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Homology modelling analysis provides insight into *ADCY3*, a candidate obesity gene

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Background: In an effort to better understand the molecular basis of obesity, studies focus on genetic loci mapping to the leptin–melanocortin pathway, one of the key mechanisms for controlling food intake and body weight. *Adenylate cyclase 3* (*ADCY3*) is a key genetic candidate as it seems to have an essential role at primary neuronal cilia in regulating body weight. We have previously reported the novel probably pathogenic *ADCY3* variant c.349T>A identified in young obese patients of Cypriot origin. In the present study we use molecular modelling to demonstrate that this variant causes a p.Leu117Met substitution in within one of the two pseudo-symmetric halves of the transmembrane part of the protein.

Methods: To investigate the possible effects of the novel p.Leu117Met variation on protein structure and function, the homology modelling of the ADCY3 model was carried out using Molecular Operating Environment. The electrostatic potential and available conformational space was calculated for both wild type and mutant models. Bonding interactions within the protein structure as well as with the surrounding lipid bilayer were studied.

Results: Molecular modelling data suggest a change in interactive forces and energy levels, probably affecting the pseudo-twofold symmetry of the transmembrane domain of the protein and its interaction with the surrounding lipid bilayer. This may be the result of stronger H-bonding interactions between the Met residue and adjacent residues, compared to the wild type Leu residue. The data suggest a change in the interaction of the two transmembrane halves of the enzyme which may possibly alter its catalytic function.

Conclusion: Our findings contribute to existing evidence linking *ADCY3* to obesity development. Further assessment of this variant using functional studies, should help elucidate its clinical significance and role in obesity development.

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Serum Osteopontin, NGAL and Sclerostin concentrations in children and adolescents with overweight and obesity

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Background: Obesity in childhood and adolescence represents a major health problem and is associated with significant morbidity and mortality in adult life. Osteopontin, NGAL and Sclerostin are bone biomarkers, however, little is known about their role in obesity.

Objective and Hypothesis: The aim of our study was to determine the concentrations of Osteopontin, NGAL and Sclerostin in children and adolescents with overweight and obesity.

Methods: The study sample consisted of 345 subjects aged 2-18 years (mean age ± SD: 10.36 ± 0.16 years; 172 males, 173 females; 181 prepubertal, 164 pubertal). Subjects were classified as obese (63.8%) and overweight (36.2%) and were enrolled in a personalized, life-style intervention program of diet and physical exercise for at least one year. Body composition and biochemical and endocrinologic parameters were determined at the beginning and at the end of the study. The study was approved by the Committee on the Ethics of Human Research, and written informed consent was obtained by all parents.

Results: Following one year of the intervention program, there was a significant decrease in BMI ($p<0.01$), BMI z-score ($p<0.01$), DBP ($p<0.01$), Waist-to-hip Ratio (WHR) ($p<0.01$), Waist-to-Height Ratio (WHtR) ($p<0.01$), AST ($p<0.01$), ALT ($p<0.01$), γGT ($p<0.01$), total cholesterol ($p<0.01$), LDL ($p<0.01$), Apo-B ($p<0.01$), Osteopontin ($p<0.01$) and NGAL ($p<0.01$) concentrations, and percentage of fat mass ($p<0.01$) and an increase in HDL ($p<0.01$), Vitamin D ($p<0.01$), PTH ($p<0.01$), Lp(a) ($p<0.01$) and Sclerostin ($p<0.01$) concentrations, as well as percentage of muscle mass ($p<0.01$), bone mass ($p<0.01$) and free-fat mass ($p<0.01$).

Osteopontin concentrations correlated positively with PTH ($b=0.26$, $p<0.05$) and vitamin D ($b=0.294$, $p<0.05$) concentrations in overweight subjects, with Ca concentrations ($b=0.275$, $p<0.05$) in obese subjects, and with glucose concentration ($b=0.366$, $p<0.05$) in all subjects. NGAL concentrations correlated positively with WHR ($b=0.439$, $p<0.05$) and HOMA-IR ($b=0.4$, $p<0.05$) in overweight subjects and with HbA1c in obese subjects ($b=0.326$, $p<0.05$).

The change of NGAL concentrations correlated negatively with the BMI z-score ($b=-0.494$, $p<0.05$) in overweight subjects, with cholesterol ($b=-0.271$, $p<0.05$) in obese subjects and with HbA1c ($b=-0.304$, $p<0.05$) in all subjects. The change of sclerostin concentration correlated positively with insulin concentrations ($b=0.46$, $p<0.05$) in overweight subjects, and glucose concentrations ($b=0.315$, $p<0.05$) and HOMA-IR ($b=0.3$, $p<0.05$) in all subjects.

Conclusion: These findings indicate an association of Osteopontin, NGAL and Sclerostin with overweight/obesity, cardiovascular risk factors and glucose metabolism. Further studies are required to determine the underlying mechanisms responsible for the above associations.

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High Triglyceride/HDL ratio suggests a higher risk of metabolic syndrome among children and adolescents with severe obesity

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Aim: Few data are currently available on the reliability of the different anthropometric, instrumental and biochemical indexes in recognizing the presence of the metabolic syndrome (MetS) in severe childhood obesity. The objective of our study was to find out a simple and accurate index to use in deciding whether to initiate a search for MetS in this at-risk population.

Patients and Methods: A retrospective study based on 1065 children and adolescents with severe obesity [563 females, aged 14.6±2.1 (range 10-17) years, and BMI-SDS 3.50±0.36 (range 3.00-5.17)], was performed. For each subject, all the components of MetS, defined according to the IDF criteria, were determined. The following indexes were calculated according to the following formulas: (a). BMI: weight (kg)/height (m2); (b). BMI-SDS: (BMI-mean BMI (for age and sex))/SD; (c) TMI: mass (kg)/height (m3): (d) WtHR: WC (cm)/height (cm); (e) TG/HDL-C ratio: TG (mmol/L)/HDL-C (mmol/L); (f) CMI: WtHR x TG/HDL-C ratio; (g) VAI: males: (WC/39.68+(1.88 x BMI)) x (TG/1.03) x (1.31/HDL): females: (WC/36.58+(1.89 x BMI)) x (TG/0.81) x (1.52/HDL). Median values were tested for statistical significance using 2-tailed Wilcoxon test and nonparametric one-way ANOVA. Spearman correlation coefficients were calculated to assess the relationship between indexes and metabolic characteristics. Adjusted receiver operating characteristic (ROC) analysis using clinical cut points for metabolic risks was performed to determinate the odds ratio of cardiometabolic risk factors across indexes. In addition, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), and negative predictive value (NPV) were examined.

Results: Overall, the presence of MetS was found in 324 patients (30.4%), 167 males (33.3%) and 157 females (27.9%). We found that three indexes (i.e. VAI, CMI and TG/HDL-C ratio), performed significantly better than the other ones in identifying MetS, with no difference among them. Consequently, we choose the TG/HDL-C ratio as the simplest index. TG/HDL-C ratio showed a strong correlation with the clinical and biochemical parameters of MetS, but not with glucose levels. The odds ratio showed a strong

association of TG/HDL-C ratio with the high triglycerides and low HDL-C, but not with glucose serum level, blood pressure and WC.

Conclusion: We have shown that a very simple index, which just need the evaluation of triglycerides and HDL-c serum levels, has the same accuracy of other more sophisticated indexes in recognizing MetS in children and adolescents with severe obesity.

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An adult-based genetic risk score for hepatic fat associates with liver and lipid traits in Danish children

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Background and Aim: Several genetic variants associating with hepatic fat content in adults have been identified in genome-wide association studies. Their effects in children remain unclear. This study aimed to test the effect of genetic variants known to associate with hepatic fat in adults, individually and combined as a genetic risk score (GRS), on cardiometabolic traits, and to investigate the predictive ability of the GRS for hepatic steatosis in children.

Methods: Children with overweight/obesity from an obesity clinic cohort (n = 1,843, median age 11.7 years, body mass index standard deviation score [BMI SDS] 2.85, 45.2% male) and a population-based cohort (n = 2,271, median age 11.6 years, BMI SDS 0.26, 40.1% male) were included. Anthropometrics and biochemical parameters were measured in both cohorts. Liver fat content (LFC) was measured by magnetic resonance spectroscopy in 539 individuals. We calculated a weighted GRS based on eight genetic variants known to associate with hepatic fat content in adults. Associations of individual genetic variants and the GRS with cardiometabolic traits were tested using multiple linear and logistic regression models. Receiver operating characteristic (ROC) curve analysis was performed on models based on risk factors for hepatic steatosis, defined as hepatic fat ≥ 5 %, and area under the curve (AUC) was calculated to evaluate model performance.

Results: Variants in *PNPLA3*, *TM6SF2*, *GPAM*, and *GCKR* were significantly associated with higher LFC ($p < 0.01$) and with distinct patterns of circulating lipids. The GRS was associated with higher LFC and alanine transaminase (ALT), as well as lower LDL-cholesterol and triglycerides in both cohorts. The GRS was not associated with adiposity or other metabolic traits. The GRS was associated with higher prevalence of hepatic steatosis (odds ratio [OR] per 1-unit GRS-increase: 2.18, p = 1E-8), and with lower prevalence of dyslipidaemia (OR 0.90, p = 0.02). A prediction model for hepatic steatosis including GRS alone, yielded cross-validated AUC of 0.76 (95% CI 0.69-0.83). The addition of the GRS to a model containing clinical risk factors for hepatic steatosis (BMI SDS, ALT, homeostatic model assessment of insulin resistance [HOMA-IR]) increased AUC slightly from 0.87 (95% CI 0.82-0.92) to 0.89 (95% CI 0.84-0.94).

Conclusion: The adult-based GRS for hepatic fat associated with LFC, liver enzymes, and lipid profiles, but was not associated with adiposity and other metabolic traits in children. The GRS could serve as a clinical risk predictor of hepatic steatosis and be used in early prevention.

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Thyroid function in overweight and obese children and adolescents

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Background: Obesity in childhood and adolescence represents one of the most challenging public health problems of our century. The prevalence of overweight and obesity in Greece is approximately 21% in children younger than 6 years and up to 40% in older children and adolescents. Mild elevations of TSH concentrations are often detected in obese children and adolescents.

Aim: To investigate the thyroid function in overweight and obese children and adolescents.

Methodology: We studied three thousand and ten (n=3,010) children and adolescents aged 2-18 years (mean age ± SD: 10.236 ± 3.011 years) attending our 'Out-patient Clinic for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence'. Subjects were classified as obese (n= 1,710; 56.8%), overweight (n=834, 27.7%) or as having normal body mass index (BMI) (n=466, 15.5%) according to the International Obesity Task Force cutoff points. All subjects were evaluated by a multidisciplinary team at frequent intervals, and received personalized guidance on diet and exercise. Detailed clinical evaluation and laboratory investigations were performed at each clinic visit.

Results: Obese subjects had significantly higher systolic and diastolic blood pressure, as well as significantly higher concentrations of fasting plasma glucose and serum insulin, HbA1C, triglycerides, LDL-cholesterol, uric acid and ApoB, and significantly lower concentrations of HDL-cholesterol, ApoA1 and Vitamin D than their overweight and normal-BMI counterparts. Furthermore, obese children and adolescents had significantly higher TSH (mean ± SD: 2.9 ± 1.4 mIU/L, p<0.005) and T3 (mean ± SD: 146,5 ± 31.4 ng/dL, p<0.001) concentrations compared with overweight and normal-BMI subjects. An increase in age by one year was associated with a decrease in FT4 concentrations by 0.007 ng/dL (95%CI, -0.007, -0.009, -0.003), in T3 concentrations by 3.847 ng/dL (95%CI, -3.847, -4.484, -3.210) and in TSH concentrations by 0.051 mUI/L (95%CI, -0.051, -0.083, -0.019) when all other variables remained constant. Compared with normal-BMI subjects, overweight subjects demonstrated an increase in T3 concentrations by 5.9 units (95%CI, 5.905, 1.986, 9.825), while obese subjects had an increase in T3 concentrations by 9.9 units (95%CI, 9.874, 6.007, 13.741) when all other variables remain constant.

Conclusions: Impaired thyroid function may be often seen in children and adolescents with overweight and obesity, and may change following weight loss. Further studies are required to investigate the possible association of thyroid hormones with cardiovascular risk factors in obese and overweight children and adolescents.

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Cardio-metabolic health in Danish children aged 7-10 years conceived after assisted reproductive technology

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Background: Children conceived after assisted reproductive technology (ART) with frozen embryo transfer (FET) are more often born large-for-gestational age (LGA) while children born after fresh embryo transfer (fresh-ET) are at risk of being small-for-gestational age (SGA).

LGA or SGA children are at increased risk of obesity, diabetes and cardiovascular disease later in life. The long-term cardiometabolic health of children born after ART is scarcely explored.

Materials and Method: The cross-sectional cohort study "Health in Childhood following Assisted Reproductive Technology" (HiCART) includes 606 singletons (292 boys): 200 conceived after FET; 203 conceived after fresh-ET; and 203 naturally conceived (NC) children matched for birth year and sex. They were examined at 7-10 years of age including anthropometric measurements, whole-body dual-energy x-ray absorptiometry (DXA), pubertal staging (Tanner), blood pressure (BP) and a fasting blood sample. Anthropometrics and BP were converted to standard deviation scores (SDS).

Results: In the following the three groups were compared pairwise and data shown in mean (SD). Children conceived after FET had significantly higher birth weight (SDS) (0.20 SDS (1.09)) and children conceived after fresh-ET had lower birth weight (SDS) (-0.22 SDS (1.00)) compared to NC children (-0.16 SDS (1.09)).

Pubertal onset in 54 girls (17%) and three boys (1%) was evenly distributed among the groups.

No differences in height (SDS), weight (SDS) or BMI (SDS) was found between the groups. A more thorough investigation of body composition showed no differences between the groups regarding waist-to-height ratio (FET: 0.44 (0.04), fresh-ET: 0.43 (0.03), NC 0.44 (0.04)) and fat percentage (DXA) (FET: 28.2% (6.77), fresh-ET: 28.1% (6.50), NC: 28.2% (6.24)).

Glucose metabolism was similar in the groups including fasting glucose, C-peptide, HbA1c and insulin resistance (HOMA-IR). Lipid profiles including cholesterol, low-density-lipoprotein and high-density-lipoprotein were also similar.

No differences were seen in diastolic BP (SDS) between the groups (FET: 0.46 SDS (0.56), fresh-ET: 0.39 SDS (0.58), NC: 0.49 SDS (0.57)) but surprisingly systolic BP (SDS) was slightly lower in the fresh-ET-group (0.53 SDS (0.67)) compared to both FET (0.70 SDS (0.86 SD)), p=0.03 and NC (0.71 SDS, (0.68)), p=0.01.

Conclusion: The differences in birth weight in children conceived after FET and fresh-ET was as expected but did not translate into differences in anthropometrics, glucose- or lipid profile in childhood. Systolic BP was not increased after FET nor fresh-ET. These findings are reassuring and may add to the knowledge about the safety and long-term consequences of FET and ART in general.

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Natural History of Pregnancy and Pregnancy Outcomes in Metreleptin-Treated vs Untreated Subjects with Lipodystrophy

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Metreleptin is a leptin analog used to treat metabolic complications of lipodystrophy, a set of rare disorders characterized by generalized (GL) or regional (PL) deficiency of adipose tissue, resulting in insulin resistance, diabetes, dyslipidemia, steatohepatitis, and reproductive dysfunction. Metreleptin increases fertility, particularly in GL; spontaneous pregnancy without metreleptin was reported in only 4 patients with GL. Risks of metreleptin suggested by rodent studies include prolonged gestation and dystocia, and there is theoretical concern that anti-drug antibodies could cross the placenta, causing adverse effects in offspring by binding to endogenous leptin. On the other hand, metabolic disease typically worsens during pregnancy, leading to known pregnancy complications in women with both GL and PL. By controlling metabolic disease, metreleptin might provide benefit during pregnancy. Thus, knowing pregnancy outcomes in patients with metreleptin exposed and unexposed pregnancies is important.

To obtain preliminary data on pregnancy outcomes in women with GL and PL who were, versus were not, exposed to metreleptin during pregnancy, we conducted a chart and literature review of pregnancy outcomes in these patients. There were 11 metreleptin treated patients (9 GL; 2 PL), and 50 untreated patients (4 GL; 46 PL).

In 9 patients with GL taking metreleptin during pregnancy, live birth occurred in 7 of 13 (54%) pregnancies (5 [71%] term; 2 [29%] preterm), with miscarriage in 6 (46%). 10 pregnancies occurred in 4 patients with GL without metreleptin. Of these, 8 (80%) were live births (7 [88%] term, 1 [12%] preterm; 1 unknown), with 2 (20%) miscarriages.

In patients with PL only 2 pregnancies in 2 patients occurred while patients were taking metreleptin, including 1 live term birth (50%) and 1 miscarriage (50%). In patients with PL taking metreleptin during pregnancy, live birth occurred in 71 of 99 (72%) pregnancies, with miscarriage in 27 (27%) and 1 termination. Among the 44 live births in which gestational age was reported, 39 (89%) were term, and 5 (11%) were preterm.

These data show higher percentages of miscarriage and preterm delivery in metreleptin-treated women with lipodystrophy. However, conclusions are limited by extremely low numbers of patients with GL with metreleptin unexposed pregnancies (N=4) and PL with metreleptin-exposed pregnancies (N=2). Furthermore, these data may be biased by differences in underlying disease severity in metreleptin treated vs. untreated patients, as well as underreporting of early-term miscarriages. We therefore plan a prospective study to collect pregnancy outcomes in women with metreleptin-treated and untreated pregnancies.

P1-277

The effect of obesity and nutritional intervention on depression levels and cognitive functions in adolescent girls, a randomized-controlled interventional study

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Background: Over the last thirty years, the incidence of adolescent obesity has quadrupled. While the physical risks of adolescent obesity have been well researched, there has been little research on its impact on mental health status and cognitive abilities. In the present study, we intend to examine whether nutritional intervention and weight loss affect executive functions and levels of depression of adolescent girls with overweight/obesity (OW/OB).

Methods: This prospective, interventional study included healthy adolescents aged 12-16 years. Girls with OW/OB (BMI percentage ≥ 85 CDC) were randomly assigned 1:1 to either nutritional intervention or no intervention. Participants in the intervention group received 12 weekly sessions with a dietitian, who gave evidence-based dietary recommendations aimed at lifestyle change. Control group members received no dietary intervention during the study period except for a single session at the end of the study. A second control group of healthy girls with normal weight (NW) was also enrolled. Demographics, anthropometric indices, and lab tests were collected at enrollment and at the end of the study after 12-24 weeks. At the beginning and at the end of the study, all participants took a test assessing psychological functions, and validated questionnaires regarding depression, state-trait anxiety, strengths and difficulties, self-esteem, body image, and quality of life.

Results: Seventy-two girls completed the study: 24 girls with OW/OB assigned to nutritional intervention (BMI-SDS 1.59±0.36), 24 with OW/OB assigned to no intervention (BMI-SDS 1.69±0.45), and 24 controls with NW (BMI-SDS 0.33±0.55). At baseline, NW girls had higher scores than OW/OB girls in recall memory ($p=0.039$), inhibition ($p=0.024$), and resilience ($p=0.027$). At the end of the study, BMI-SDS decreased only in the intervention group ($p<0.001$). The cognitive tests showed an improvement after intervention in the treatment group in flexibility ($p<0.001$), recall memory ($p=0.011$), executive functions ($p<0.001$), emotional bias ($p=0.045$), overall emotion ($p=0.025$) and overall self-regulation ($p=0.022$). Girls in the intervention group showed an improvement in self-esteem after intervention ($p=0.050$). There was a trend for improvement in the QL school sub-scale for the intervention group ($p=0.055$). No between-group differences were observed in baseline as well as the change depression questionnaire.

Conclusions: The results of the study indicate that normal-weight girls have higher cognitive abilities in several parameters compared to overweight/obese girls, and that intervention for weight loss may improve some of these measures in overweight/obese girls. Further research in this field is warranted.

P1-278

e-REC Capturing The Occurrence and Burden Of COVID-19 Infections In People With Rare Genetic Obesity Disorders

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Introduction: Following the onset of the COVID-19 pandemic in spring 2020, the European Registries For Rare Endocrine Conditions (EuRRECa), which is a collaboration between Endo-ERN, ESPE and ESE provided the possibility for registration of cases. Obesity is a risk factor for severe COVID-19 disease course in adults. In children and adolescents, COVID-19 disease course is much milder, but has also been identified as risk factor. As rare genetic obesity disorders often present with extreme obesity early in life, it might be postulated that they are at increased risk for severe course of COVID-19 infection. The aim was to study the clinical course of COVID-19 infection in these patients.

Methods: The RareEndoERN COVID-19 taskforce, formed in April 2020, set up the monthly e-REC reporting of new clinical encounters of confirmed or suspected COVID-19 cases in rare genetic obesity disorders. Thirteen centres committed to reporting. Case specific data were collected by an additional digital survey.

Results: Seventeen patients with rare genetic obesity disorders and COVID-19 infection were reported by two centers between April 2020 and December 2021. Median age was 16 years (range min 2 – max 22), 11/17 were female, median BMI was 28kg/m2 (min 17-max 73). Diagnosis was: rare genetic obesity- syndromal form in 13/17 cases (of which 8 Prader-Willi Syndrome (PWS) and 5 other forms of syndromal obesity); non-syndromal form in 2/17; and 'other' in 2/17 patients. The following co-morbidities were present: type2 DM in 3/17, dyslipidemia 2/17, NAFLD 2/17, sleep apnoea 1/17; COVID-19 was confirmed in all cases. Symptoms were Fever (5/17); Cough (3/17); Tiredness or exhaustion (2/17); Loss of appetite (1/17); Loss of taste or smell (0/17); Muscle pain (0/17); Runny nose (3/17); Headache (4/17); Sore throat (4/17); Stomach symptoms (1/17); Diarrhoea (0/17); None (/17)2; Other (3/17) like change of behavior or seizure. One patient with PWS was admitted to the emergency room due to a seizure and was dismissed after a few hours of observation. None of the patients needed admission to the hospital, IC unit care, or oxygen treatment; 18/17 patients fully recovered, 1 PWS patient had persistent complaints of tiredness.

Conclusion: In patients with rare genetic obesity disorders and confirmed COVID-19 infection reported number of cases are low, even in large centers of expertise. The clinical course seems mild for these patients, in the age range 2-22 years, even in the presence of extreme obesity and type 2 diabetes.

P1-279

Sex-specific POMC DNA methylation variability is associated with increased body weight

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The increasing prevalence of obesity and associated comorbidities worldwide is a major problem for national health care systems. For this reason, it is of importance to gain knew knowledge about the central regulation of body weight and to identify factors which are leading to an increased individual risk to gain weight. Despite large genome weight associations studies and related genetic risk scores, the regulation of inter-individual body weight variability remains elusive. Therefore, it has been hypothesized that epigenetic modification might be relevant for the regulation of body weight.

For this reason, we analyzed in a candidate approach DNA methylation of the POMC (pro-opiomelanocortin) gene, whose protein product is embedded in the leptin-melanocortin pathway and is pivotal for body weight regulation. In a cohort of the HNR (Heinz Nixdorf Recall) study (n=1383), we identified increased POMC methylation levels in DNA extracted from peripheral blood cells (PBC) of obese female participants. This epigenetic variant led to a 1.44 increased risk of the variant carrier to develop obesity. Further analysis reveals that this POMC methylation variant is non-genetically determined. Additionally, POMC methylation analysis of PBC DNA of monozygotic- and dizygotic twin pairs provide evidence for an early setting in utero of this POMC methylation variant. Therefore, POMC methylation fulfill the criteria for a so-called metastable epiallele. This are epigenetic regions where methylation is set early in embryonic development, is non-tissue specific and stable over time. Methylation variability at metastable epialleles have been already described to be associated with body weight and fur color in the Avy mouse model. The presented data are pointing towards a relevant role of hypermethylation at this POMC metastable epiallele in body weight regulation.

P1-280

A rare cause of monogenic obesity: Schaaf-Yang syndrome due to a novel *MAGEL2* gene variant

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Background: Paternally expressed mono-allelic pathogenic variants in the *MAGEL2* (melanoma antigen L2) gene cause Schaaf-Yang syndrome (SHFYNG), a multisystem disorder with psychomotor delay, intellectual disability, behavioral abnormalities, and obesity. Severity of the disease is highly variable, some patients may die in utero and some can live with moderate disabilities. *MAGEL2* gene is located in the 15q11.2– q13 region which includes the Prader Willi Syndrome (PWS) domain hence, some of the features of this syndrome overlap with PWS.

Case Report: A six-year-old girl was admitted for the evaluation of obesity. Prenatal history was uneventful. She was born at term with a birth weight of 3,300 g (0.5 SDS) to healthy second-degree cousin parents. She had no failure to thrive in infancy. She walked at 18 months and her first words were after 30 months old. She had behavioral problems and learning difficulties. The family noticed that she started to gain weight after 3 months of age. Her weight, length, and body mass index (BMI) at admission were, 38.7 kg (3.4 SDS), 116.4 cm (0.1 SDS), and 28.7 kg/m^2 (3.3 SDS), respectively. Coarse face, bitemporal narrowing, deep-set eyes, prominent nasal bridge, short neck, and tapering fingers were detected. She was prepubertal. Fasting blood glucose, insulin, HbA1c, transaminases and thyroid functions were normal. Her ophthalmologic, cardiac, and audiological evaluations were normal. Chromosome analysis was 46, XX, and methylation analysis for PWS was normal.

At 15 years of age, her weight, height, and BMI were 115.0 kg (5.8 SDS), 157.5 cm (-0.7 SDS), and 46.3 kg/m2 (4.5 SDS), respectively. She had severe acanthosis nigricans, striae, and hypertension (155-75 mmHg, >2.3 SDS). Menses were irregular. Metformin treatment was commenced due to severe insulin resistance; however, she was non-compliant with treatment and weight gain was progressive. New treatment options such as GLP-1 analogs were considered for weight management.

A novel heterozygous nonsense pathogenic variant (c.1732C>T; p. Gln578*) in *MAGEL2* (NM_019066) gene was detected using Clinical Exome Sequencing (CES). This variant was not reported in gnomAD, ESP5400, or G1000. Segregation analysis in the family revealed that this variant had arisen de novo.

Conclusion: SHFYNG is among the rare monogenic causes of obesity and should be included in the differential diagnosis of PWS. The advances in molecular genetic technologies help to determine the etiology of monogenic obesity promptly and the implementation of genetic diagnosis in clinical practice may enable a personalized medicine approach.

P1-281

Impact of Covid-19 pandemic on the efficacy of outpatient counseling in childhood obesity management

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Introduction: The Covid-19 pandemic drastically modified social life and lifestyle in particular among children and adolescents, promoting sedentary behaviors and unhealthy eating habits. In this scenario, the effectiveness of the outpatient approach for pediatric obesity may decrease.

Objectives: Aims of this study were to assess the rate and the factors associated with outpatient drop-out by comparing two groups of children and adolescents with obesity evaluated at the pediatric endocrinology outpatient clinic before and during the Covid-19 pandemic, respectively, and to evaluate how Covid-19 pandemic influenced the weight status and lifestyle of children and adolescents with obesity.

Results: One hundred and forty-five children and adolescents with obesity were evaluated, including 80 subjects (mean age 11.6 ± 2.3 years) evaluated before the Covid-19 pandemic (group A) and 65 subjects (mean age 11.8 ± 2.7 years) in the period straddling the Covid-19 pandemic (group B). Anamnestic (dietary habits, physical activity, screen time, family history of obesity), socio-cultural (economic status, employment and schooling of parents, household composition, place of living) and clinical (weight, height, BMI, waist circumference) data were analyzed at baseline (T0) and at 12-months (T1) in-person assessment. Glico-lipids biochemical profile was assessed at T0. The drop-out rate did not differ significantly between the two groups. BMI SDS at T0 (OR=2.52; p=0.004), female sex (OR=0.41; p=0.035) and incomplete household (OR=5.74; p=0.033) significantly influenced drop-out in both groups. BMI SDS, not significantly different between the two groups at T0, was significantly higher in group B than group A at T1. Consistently, weight loss between T0 and T1 was significantly greater among group A patients compared to group B (p=0.031). Hours spent in physical activity decreased significantly in group B from T0 to T1 and were significantly lower than group A at T1. Screen time increased significantly in group B from T0 to T1 and were significantly greater than group A subjects at T1. The consumption of sugary drinks and snacks was significantly greater in group B than group A at T1. Hours spent in physical activity (OR=2.27, p=0.038) and group A belonging (OR=0.16, p=0.028) significant influence weight loss.

Conclusions: Our study documented that the Covid-19 pandemic, although it has not affected the drop-out rate of obese children, negatively influenced lifestyle and reduced the effectiveness of outpatient counseling in childhood obesity treatment.

P1-282

Significant improvement in dietary behaviors and quality of life among adolescents with obesity in the COVID19 lockdown through telehealth

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Background: COVID19 Lockdown resulted in an extreme change in daily lifestyle with a significant increase in weight and loss of quality of life, as well as an increase in the risk of secondary health conditions even in young people. One reason for this is a fatal change in the nutritional situation, especially among adolescents. Convincing models to counter this problem are missing so far. Multiprofessional training programs could reveal an outstanding effect for secondary prevention of obesity in youth. Telehealth measures were successfully implemented several times during the COVID19 pandemic.

Methods: Adolescents (8-17 years) with severe obesity referred through a large obesity consultation were interviewed using standardized dietary behavior questionnaires (FEV-K, FFL-K, FFV-K) and quality of life questionnaires (WHO-5, KIND-L) and enrolled in a structured multimodal education program for adolescents with overweight. The program content (sports, nutrition, medicine, psychology) was tought exclusively video-based. After the end of the program (12 months), the patients were interviewed again regarding eating behavior and quality of life. In addition, a clinical examination including analysis of blood parameters was performed before and after the program. The results were analyzed and compared with results from the pre-pandemic period (2017 - 2019).

Results: 108 children and adolescents (mean age 12.1 yrs; male 46.2%, BMI SDS 2.21) were studied and telemedicated. Based on a significantly increased intake of fatty and sugary foods and an increased amount of meals per day (7.2 meals per day), a significantly increased intake of vegetables and fruits as well as a massive decrease of sweets, snacks and soft drinks was observed after program participation, which corresponds to a significant improvement in dietary behavior also compared to the pre-pandemic period. The amount of meals per day decreased to 4.1 meals per day. The quality of life of the adolescents increased significantly. The BMI SDS and the blood parameters (cholesterol, triglycerides, HOMA index) showed a decreasing trend, which roughly corresponds to the effect of the pre-pandemic period.

Discussion and Conclusion: This study demonstrated a beneficial effect on dietary behaviors and quality of life of adolescents with obesity during lockdown through video-based structured education. Future research needs to show the extent to which this effect is replicable with respect to new periods of contact restriction. It is possible that telemedicine obesity education components can reach a large number of patients and especially families in rural areas, and thus can be a supraregional support for adolescents with obesity.

P1-283

Single Nucleotide Polymorphisms (SNPs) Profile as Predictive Markers of Lifestyle Modification Outcomes in Pediatric Obesity Treatment

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Context: The response to lifestyle modification (LSM) in children with obesity is variable and difficult to predict.

Aim: A systematic search for identifying common single nucleotide polymorphisms (SNPs) to predict positive outcomes of LSM in pediatric obesity management, defined as decrease in BMI z-score (based on IOTF).

Patients/Methods: Out of 240 children with obesity (BMI>97%) recruited to a prospective 'multi-OMICS' study granted by ESPE Research Unit, 159 subjects (age 8-17 yrs, median 12.8 yrs; 45% females) finished twelve-months (V12) of LSM obesity management at three centers in Poland, Turkey and Italy. A genome wide association study was performed with Infinium Global Screenig Aarray+MultiDisease Early ACC Kit (Illumina). The filtered genotyping data was exported to gds format in R. Subsequently, kinship was estimated by means of the KING robust method via the snpgdsIBDKING function in package SNPRelate. The genetic relatedness matrix was used to estimate the principal components via the PCAiR method in package GENESIS. In what follows, the linear mixed model with one dependent variable (delta BMI z-score) and two independent variables: age and sex was used to estimate the fixed effects (via the function fitNullModel in package GENESIS). The random effect was associated with the individual participant of the study and the correlation matrix between random effects was set as the genetic relatedness matrix. The effect of individual SNPS was estimated by means of the Score test with the aid of the assocTestSingle function in package GENESIS. **The results** for SNP with MAF>0.05 and with Score p-value<1*10-5 were reported. The obtained result emerged one SNP **rs10425933** (chr 19, 9010208) with genome-wide significant threshold, which was

associated with reduction in BMI z-score (p<1.63*10-8). With suggestive significance, we observed SNPs which were also associated with BMI z-score reduction in tested group of children: **rs76751343** (chr 5, 166326168, p=2.95*10-6); **rs60674472** (*AP001122.1*, p=4.50*10-6); **rs339065** (*FAM71F1*, p=6.39*10-6); **rs78233922** (chr 17, 55738405, p= 6.49*10-6); **rs75642418** (*C16orf95*, p= 9.86*10-6).

Conclusion: Our findings suggests that weight reduction as response to LSM in childhood obesity may be modified by common genetic variants. We identified a novel loci presumably associated with the change in BMI z scores but it should be further investigated.

P1-284

Impact of bariatric surgery on newborn growth parameters

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Background: Maternal obesity is known to have many detrimental effects on pregnancy. Bariatric surgery represents the most efficient therapy for severe obesity. Although it is known to positively impact many pregnancy outcomes, bariatric surgery can disturb fetal growth due to nutritional deficiencies.

Objective: We aim to examine the repercussions of bariatric techniques on fetal growth, and to evaluate the risk of delivering a small for gestational age newborn while taking into consideration the type of bariatric surgery performed.

Methods: This is a single center retrospective study. Data were collected from the medical archive of Notre Dame Des Secours University Hospital-Jbeil, Lebanon between January 2013 and September 2021. In an effort to examine the effects of bariatric procedures on offspring growth, a study group(n=36) containing pregnant women who underwent bariatric surgeries, is compared with a control group of women who did not a bariatric procedure (n=98). Then the study group is divided into purely restrictive bariatric procedures and mixed procedures.

Results: Pregnancy after bariatric surgery was associated with a reduction in mean birthweight (2885.97 g vs 3244.69 g; P<0.001); mean birthlength (48.13 cm vs 48.93 cm; P=0.019), head circumference (33.91 cm vs 34.59 cm; P=0.017) and risk of large for gestational age (0% vs 7.1%; P<0.001). However it was linked with an increased risk of small for gestational age infants (13.9% vs 0%; P<0.001). When comparing bariatric surgery types, a higher mean birthlength was linked with purely restrictive surgeries compared with gastric bypass procedures with this association tending to significance (47.39 ± 2.03 cm vs 48.43 ± 1.30 cm; P=0.052).

Conclusion: Bariatric surgery was associated with an increased risk of small for gestational age. Women of childbearing age should do a nutritional follow-up after bariatric surgery and decide carefully whether benefits outweigh adverse outcomes.

Keywords: Bariatric surgery, Pregnancy, Maternal obesity, Small for gestational age, Fetal growth, Nutritional deficiencies.

P1-285

Nutritional disparities among Brazilian children: study of the temporal trend of the BMI from 2010 to 2021

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Introduction: The Body Mass Index (BMI) is an essential indicator for the nutritional assessment of children and reflects the exposure to health conditions that are harmful to the development of this population.

Objective: To analyze the temporal trend of the BMI of Brazilian children, 0 to < 10 years old from 2010 to 2021.

Methods: Descriptive ecological study. Data obtained from e-SUS Primary Care. The prevalence rate of the categories was obtained: severe thinness (ST), thinness (T), eutrophy (E), overweight (OW), obesity (OB), and severe obesity (SOB), and the trend was calculated by segmented linear regression, the variations annual percentages (APCs). In addition, time series analysis was performed in the Joinpoint Regression Program.

Results: In children under five years old, there was a decreasing character in "ST" and "OB" (APC: -3.9; p<0.001 and APC: -1.6; p=0.026, respectively), while "E" showed an increasing trend (APC: 0.4; p=0.007). "T" showed a decreasing trend in the South until 2018, changing its character to increasing from then on (APC: -1.3; p=0.012 and APC: 6.8; p=0.008).

When analyzing children aged 5 to 10 years, there was a decreasing trend for "ST" and "E" (APC: -5.0; p<0.001 and APC: -0.6; p=0.001, respectively). The "OW" (APC: 1.1; p=0.004), "OB" (APC:4.9; p<0.1), and "SOB" (APC:3.4; p<0.1) categories showed an increasing trend, except for the Northeast, where "SOB" showed a stationary trend.

Conclusion: Up to 5 years of age, a reduction in "ST" and "OB" and an increase in "E" denotes an improvement in the nutritional quality of this age group. In the age group of 5-10 years, there was also a reduction in "ST", but the increase in "OW", "OB" and "SOB" and concomitant reduction in "E" denote worsening of the nutritional diagnosis of this population. These data, associated with the increase in "T" in children under five years of age in the region, denounce the nutritional disparities between age groups and regions in Brazil and highlight the need to implement differentiated strategies to promote adequate nutrition for Brazilian children.

P1-462

Energy Trade-Off Score - a novel anthropometric polygenic trait, and related body types

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Background/Aim: The trade-off theory claims that a resource (calorie) stored in adipose tissue cannot be used for longitudinal growth, and a calorie used for growth will not be stored as fat.

Methods: Out of 2339 children with longitudinal heights and weights (birth to adulthood) from the GrowUp1990 Gothenburg cohort, 1993 (996 girls) were analyzed. For everyone we calculated Energy Trade-Off Score: ETOS = at early adulthood. Four extreme body types were defined based on ETOS and Height: 135 individuals (78 girls) were tall-slender and 137 (77 girls) were short-stout (trade-off body types), while 127 (59 girls) were tall-stout and 146 (72 girls) were short-slender (non-trade-off body types). Genome Wide Association Studies (GWAS) using 362K individuals from the UK BioBank were conducted to identify SNPs associated with height, BMI, and ETOS.

Results: and ETOS (unlike) trajectories in both trade-off groups showed a two-hit pattern with profound changes during early infancy and adolescent periods. In contrast, for the remaining groups their body type coalesced in childhood and changed little afterwards. Using GWAS, we identified 3258 SNPs out of ~11M gene variants in several loci (FTO, ADCY3, GDF5, among others) as being highly associated with ETOS. A subsequent pathway enrichment analysis discovered multiple pathways linked to 'extracellular matrix organization', 'signal transduction', 'chromatin organization', and 'energy metabolism'.

Conclusion: ETOS represents a novel anthropometric trait of body build that highlights the spectrum between slender and stout. Multiple genomic loci and pathways are involved in energy trade-off that measured by ETOS.

P1-463

Clinical characteristics of sitosterolemic children with xanthomas as the first manifestation

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Background: Sitosterolemia (STSL) is an extremely rare genetic disease. Xanthomas as the first symptom is frequently misinterpreted as familial hypercholesterolemia (FH) in children. Inappropriate treatment may deteriorate the condition.

Objectives: The goal of this study was to summarize the clinical characteristics of children with STSL who had xanthomas as their first symptom and to provide clues for early clinical diagnosis.

Methods: We summarized the clinical characteristics of STSL patients, and investigated the differences between the STSL and FH groups, as well as the diagnostic value of STSL.

Results: Two tertiary pediatric endocrinology departments contributed ten STSL cases. Five of the patients (50%) experienced mild anemia, whereas two (20%) had vascular complications. The xanthomas displayed comparable morphologies to the FH group. There were ten cases of homozygous FH with xanthomas as the predominant symptom, but no anemic patients. While serum cholesterol (Chol) and low density lipoprotein cholesterol (LDL-c) levels were significantly higher (p values of 0.002 and 0.003, respectively), MPV levels and anemia proportions were significantly lower (the p values were 0.009 and 0.033, respectively) than in the STSL group. The AUC values of Chol, LDL-c, MPV, and anemia for the diagnosis of STSL were 0.910, 0.890, 0.869, and 0.750, respectively. Chol15.41 mmol/L, LDL-c13.22 mmol/L, MPV9.05 fl, or anemia present were the best thresholds for diagnosing STSL.

Conclusions: The morphologies of STSL xanthomas vary. When xanthomas were the initial symptom of a child with Chol15.41 mmol/L, LDL-c13.22 mmol/L, MPV9.05 fl, or anemia, the clinical diagnosis of STSL was most likely made.

P1-464

Triglyceride glucose index is associated with the severity of ultrasonographic fatty liver indicator in pediatric non-alcoholic steatohepatitis

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Background: Triglyceride glucose (TyG) index is known as a reliable insulin resistance surrogate marker to identify non-alcoholic fatty liver disease (NAFLD). Ultrasound fatty liver indicator (US-FLI) is proposed as a non-invasive, semi-quantitative method for predicting hepatitis in children with NAFLD and may reflect the severity of liver histological changes. US-FLI ≥4 has been suggested as a predictive finding for severe NASH. US-FLI correlates significantly with metabolic disorders and can predict insulin resistance.

Objects: This study evaluated the relationship between US-FLI and TyG index in pediatric NAFLD and compare it with homeostatic model assessment for insulin resistance (HOMA-IR).

Methods: A cross sectional study was performed in 87 participants with mean age of 11.42±2.19 years diagnosed with fatty liver on ultrasound. US-FLI is a new scoring system ranging 2-8 based on the intensity of liver/kidney contrast, posterior attenuation of ultrasound beam, vessel blurring, difficult visualization of gallbladder wall, difficult visualization of the diaphragm and areas of focal sparing. NAFLD is diagnosed by the minimum score ≥2. Anthropometric and biochemical measurements were evaluated. TyG index was calculated as ln(fasting triglyceride (TG) [mg/dL] × fasting glucose [mg/dL]/2).

Results: The US-FLI was significantly correlated with BMI (r=0.288, p=0.007), BMI SDS (r=0.245, p=0.022), glucose (r=0.372, p=0.001), AST (r=0.255, p=0.017), ALT (r=0.301, p=0.005) and TyG index (r=0.311, p=0.006), and not with HOMA-IR (r=0.194, p=0.127). In multivariate logistic linear regression analysis, TyG index was an independent risk factor for severe NASH diagnosed by US-FLI (OR 4.032; P=0.009), but HOMA-IR was not statistically significant as a risk factor (OR 1.154; P=0.146).

Conclusions: The TyG index was significantly associated with US-FLI than HOMA-IR and may reflect the severity of NAFLD associated with insulin resistance. Therefore, the TyG index and US-FLI may be useful as non-invasive methods to monitor the severity of NAFLD in children and further studies are needed.

P1-465

Use of liraglutide for treatment of childhood obesity: early experiences from a tier 3 paediatric obesity service

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Background: Liraglutide is a glucagon-like peptide analogue which was approved for use in children and young people as an option for managing obesity in December 2020[1]. It is to be used in tier 3 services alongside a reduced-calorie diet and increased physical activity in children more than 12 years if they have a BMI SDS age-equivalent more than 30kg/m^2 for adults. We describe our initial experiences of using liraglutide in a tier 3 paediatric obesity service in a group of patients who have not previously lost weight despite multidisciplinary team input.

Methods: 10 patients were commenced on liraglutide in a tertiary paediatric obesity service who had previously failed to successfully lose weight with multidisciplinary input, including psychology and dietetics. 7 patients were female. They ranged in age from 13 years 1 months to 17 years 11 months. Initial starting BMI SDS scores ranged from 3.11 – 4.36 (mean 3.86). The patients all had comorbidities; 1 patient had autistic spectrum disorder, 2 attention-deficit hyperactivity disorder, 1 learning difficulties, 1 hypertension and 1 non-alcoholic fatty liver disease.

The initial starting dose of liraglutide used was 0.6mg and this was increased on a 2-weekly basis as tolerated up to a maximum dose of 3.0mg. All patients and their families were provided with training for administering liraglutide by a paediatric obesity clinical nurse specialist. Patients had BMI monitored regularly after commencing liraglutide and were reviewed for side effects.

Outcomes: 9 out of 10 patients who commenced liraglutide have continued on it but one patient stopped due to pre-existing mental health problems. Reports of gastro-intestinal side effects were frequent but felt to be tolerable and did not cause patients to discontinue treatment. The patients were taking between 1.8 – 3.0mg daily. 9 out of 10 patients had lost weight with mean BMI SDS decrease of 0.19 (range +0.07 to - 0.63) at between 3-6 months.

Discussion: These data represent early promising results for the effectiveness and tolerability of liraglutide in a clinical setting in adolescent patients who have not previously lost weight despite multidisciplinary team input. Therefore, liraglutide may be a useful weight loss intervention in paediatric clinical practice. Further follow-up is needed in order to assess longer term outcomes in these patients.

Reference

1. National Institute for Health and Clinical Excellence – Liraglutide for managing overweight and obesity technology appraisal guidance [TA664]. 9 December 2020.

P1-466

Lipidemic profile of adolescents with obesity after oral administration of krokos kozanis (Crocus Sativus): A pilot clinical study

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Introduction: Adolescent obesity is often characterized by comorbidities with cardiovascular effects in adulthood. Treatment options for these conditions are limited during adolescence. Basic research in animals and clinical data in adults have shown that Crocus Sativus (Krokos Kozanis) has a beneficial effect on dyslipidemia, obesity and type 2 diabetes.

Aim: The study of the lipidemic profile in fasting state, in adolescents with obesity, before and after oral administration of Krokos Kozanis, as a dietary supplement for a total period of 12 weeks.

Material and Method: Twenty-eight adolescents, aged 13.51±1.78 year old, with simple obesity without organic etiology, were studied in our Unit, for a period of 12 weeks. All patients, received nutritional consultation from a clinical dietitian and were thereafter randomized into two groups in order to receive (Study Group) or not (Control Group) intervention with oral suspension

Table.

	Control Group			Study Group		
	Before Intervention*^	After Intervention*~	*p	Before Intervention#^	After Intervention#~	#p
BMI(kg/m2)	28.35±4.9			27.59±4.3		
LDL(mg/dl)	86.89±36.5	87.73±31.7	0.80	96.00±24.7	90.21±25.6	0.10
HDL(mg/dl)	51.00±7.1	51.00±6.9	1	45.29±8.5	47.71±9.5	0.18
Cholesterol(mg/dl)	158.79±40.5	159.36±38.99	0.90	162.14±28.1	152.93±32.7	0.05
Triglycerides(mg/dl)	90.00±46.6	89.07±44.4	0.93	105.21±34.0	83.43±26.6	0.01
non-HDL Cholesterol(mg/dl)	104.61±39.4	107.84±39.3	0.39	116.85±28.5	105.21±30.7	0.008

of Krokos Kozanis (30 mg twice daily). Fasting lipidemic profile of all participants was assessed at the beginning and at the end of the study.

Results: After initial randomization, the two groups did not differ in terms of gender, age, Tanner stage and body mass index (BMI). At the beginning of the study, lipidemic profile of participants between the two groups did not differ in any lipid parameter (total cholesterol, triglycerides, HDL, LDL, non-HDL cholesterol) (Table). After 12 weeks of intervention, Study Group presented a declining trend in all lipidemic parameters with a statistically significant reduction in total cholesterol levels (p=0.05), triglycerides levels (p=0.012) and non-HDL cholesterol levels (p=0.008). Control Group did not significantly change lipidemic profile in any parameter after the study period. The change (delta) of non-HDL cholesterol levels within the same study group, during the study period, was significantly higher in the Study Group compared to the Control Group (p=0.009).

Conclusions: The use of Krokos Kozanis as a dietary supplement in combination with nutritional consultation, improves lipidemic profile of adolescents with obesity.

P1-467

The level of inflammatory markers and their relationship with fat tissue distribution in children with obesity and type 2 diabetes

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Introduction: Chronic inflammation is closely associated with metabolic disorders such as obesity, insulin resistance and Type 2 DM, and is dependent on abnormal cytokine production and activation of inflammatory signaling pathways. Adipose tissue is a metabolically active organ that can be a source of low-grade chronic inflammation in obese individuals. Our aim in this study; to determine whether there are changes in proinflammatory and antiinflammatory cytokine levels in obese/overweight and Type 2 diabetes mellitus children and to evaluate their relationship with clinical and laboratory findings and body fat distribution.

Materials and Methods: The study included 44 (50%) obese/overweight, 16 (18.2%) Type 2 Diabetes patients and 28 (31.8%) healthy children with normal body mass index (BMI), between the ages of 10-18 who applied to the Pediatric Endocrinology Clinic. TNF-α, IL-1β, IL-6, IL-18 and IFN-γ as proinflammatory markers; TGF-β and IL-10 levels as antiinflammatory markers were studied. Subcutaneous, preperitoneal and visceral fat tissue thickness was measured by abdominal ultrasonography in the obese/overweight group and Type 2 DM group, and the presence and degree of hepatosteatosis were evaluated.

Results: Age and gender distribution was similar between the groups. While all 16 patients in the Type 2 DM group had a family history of diabetes, 31 (70.5%) of 44 obese/overweight patients had a family history of diabetes (p=0.013). While hepatosteatosis was present in all cases in the Type 2 DM group, hepatosteatosis was detected in 36 cases (81.8%) in the obese/overweight group.

High density lipoprotein (HDL) cholesterol was lower in the Type 2 DM group than in the obese/overweight group (p=0.016). While visceral and preperitoneal adipose tissue thickness was similar to the obese/overweight group in the Type 2 DM group, subcutaneous adipose tissue thickness was higher than the obese/overweight group (p=0.021). Subcutaneous adipose tissue thickness and HDL cholesterol were significantly negatively correlated in the Type 2 DM group (p=0.003, r=-0.684). TGF-β level was significantly lower in the Type 2 DM group than the control group (p=0.039), and there was no difference between the groups in other cytokine levels. There was no significant correlation between TGF-β level and clinical findings and laboratory variables in the type 2 DM group.

Conclusion: TGF-β level was found to be lower than the control group in children with Type 2 DM. It was thought that the change in TGF-β level might have a role in the pathogenesis of Type 2 DM.

P1-468

Long term impact of a lifestyle intervention on anthropometry and biochemical parameters in patients with abdominal obesity

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Aim: to assess and follow-up anthropometric and biochemical parameters in patients with abdominal obesity after a lifestyle intervention.

Patients, Material and Methods: 122 children and adolescents with abdominal obesity, aged 7 to 16 years, were included in a control randomized intervention study (NCT031472). Abdominal obesity was diagnosed using the waist circumference. The intervention included an intensive phase during 2 months and follow-up at 12 and 24 months. Participants were divided in two groups: intervention and usual care. Intervention group was treated with hypocaloric Mediterranean diet and the usual care group with the standard recommendations from Community Nutrition Spanish Society, 2007. Both groups were advised to increase in 200 minutes per week their moderate-vigorous physical activity. Anthropometric parameters measured were: weight, height, body mass index (BMI), waist, and hip circumferences, fat mass and fat-free mass. Biochemical parameters determined were: glucose, insulin, leptin, cholesterol and triglycerides.

Results: at onset, most of anthropometric and biochemical parameters were similar in both groups, except for glucose and leptin. Usual care group (n=30) had higher both glucose and leptin levels, than intervention group (n=84).

The decrease in both BMI-SDS and waist to hip ratio (WHR) was statistically significant at 2, 12 and 24 months in both groups. In the intervention group, fat mass percentage significantly decreased, at 2, 12 and 24 months; and at 2 and 12 months in the usual care group. Lean mass (Kg) significantly increased at 12 months.

Glucose levels significantly decreased at 2 months in both groups. Insulin levels significantly decreased in the intervention group at 2 and 12 months. HOMA index significantly improved in the intervention group, at 2 and 12 months.

Leptin levels significantly decreased in both groups at 2 months. Later on, leptin levels significantly increased at 12 months, in the usual care group. There were not statistically significant differences in leptin level changes between groups. Total cholesterol, LDL/HDL-cholesterol, and triglycerides decreased significantly at 24 months follow-up.

Conclusions: in this intervention study, BMI-SDS, body composition improved significantly, likewise glucose, insulin, leptin and lipids levels. All these favourable metabolic changes persisted at 12 and 24 months follow-up, in both groups, without finding relevant differences between them. Therefore, a more intensive therapy does not seem to be more effective, than the usual intervention, in this group of patients.

P1-469

Triglyceride-glucose-alanine aminotransferase index is associated with the severity of transient elastography in pediatric non-alcoholic steatohepatitis

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Background: The triglyceride glucose (TyG) index is significantly associated with the presence of nonalcoholic fatty liver disease (NAFLD) and is a reliable insulin resistance (IR) surrogate marker. Alanine aminotransferase (ALT) has been commonly used to reflect liver inflammation and liver damage in patients with chronic liver diseases, including NAFLD. Transient elastography (TE) uses pulsed echo ultrasound to measure the hardness of the liver, showing excellent accuracy in the assessment of fibrosis, and is considered a useful test in NAFLD. Liver stiffness measurement (LSM)≥5.5 kPa has been suggested as a predictive finding liver fibrosis in Korean children and adolescents.

Objects: We hypothesized that the combination of TyG and ALT would also be useful in assessing the detection and severity of NAFLD. Therefore, this study evaluated the relationship between TyG-ALT index and TE in pediatric non-alcoholic steatohepatitis (NASH) and compare it with TyG index and homeostatic model assessment for IR (HOMA-IR).

Methods: In this cross-sectional study, elastography was performed on 87 participants with an average age of 11.42±2.19 years who were diagnosed with fatty liver on ultrasound. TE was used to evaluate liver fibrosis in terms of liver stiffness measurement (LSM). The TyG index, the TyG-ALT index, and HOMA-IR were calculated as follows: TyG index=ln(fasting TG [mg/dL]×fasting glucose [mg/dL]/2), TyG–ALT index=ln(fasting triglyceride [mg/dL]×fasting glucose [mg/dL]×ALT [IU/L]/2), and HOMA-IR=(fasting insulin [mIU/L]×fasting glucose [mg/dL]/405).

Results: The TyG-ALT index was significantly correlated with TE (r=0.268, p=0.022), TyG index (r=0.784, p<0.001), HOMA-IR (r=0.413, p=0.001), AST (r=0.664, p<0.001), and ALT (r=0.723, p<0.001). The TE was significantly correlated with BMI SDS (r=0.361, p=0.001), AST (r=0.432, p<0.001), and ALT (r=0.421, p<0.001), but not with TyG index (r=0.173, p=0.133) and HOMA-IR (r=0.074, p=0.454). According to the results of univariate logistic regression analysis, TyG-ALT index (OR 2.582; p=0.44) was significantly associated with NASH diagnosed by TE, but not with TyG index (OR 1.436; p=0.579) and HOMA-IR (OR 1.150, p=0.225). In the receiver operating characteristic analysis, the TyG–ALT index (area under the curve [AUC]=0.746, p=0.033) showed a better performance for detection of NASH than HOMA-IR (AUC=0.649, p=0.232) and the TyG index (AUC=0.537, p=0.750).

Conclusions: The TyG-ALT index was significantly associated with TE than TyG index and HOMA-IR, and further studies are needed as a useful non-invasive marker for NASH detection.

P1-470

High carbohydrate diet results in sex-specific differences in energy homeostasis in mice with PAPP-A2 deficiency

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The growth hormone (GH)-insulin-like growth factor (IGF-1) system is essential for optimal human growth and energy homeostasis. Deficiency of pregnancy-associated plasma protein-A2 (PAPP-A2), a protease involved in the liberation of free IGF-1, leads to problems in growth and bone density in humans and mice. Patients with PAPP-A2 deficiency also present lower body mass and mild glucose intolerance. The present study aimed to determine the influence of 1 month of high carbohydrate diet (HCHD) intake on metabolic parameters in homozygous Pappa2 knock-out (Pappa2ko/ko) mice of 8 months of age differentially affects males and females. Both male and female Pappa2ko/ko mice weighed less at baseline compared to their wild-type littermates. This was associated with a net increase in energy expenditure (EE) in both male and female Pappa2ko/ko as determined by employing metabolic cages. The higher metabolic rate accounted for weight loss despite the increase in cumulative food intake observed in Pappa2ko/ko males. Interestingly, Pappa2ko/ko males had lower locomotor activity, which suggests that the increased EE is associated with deregulation of thermogenic activity. Pappa2ko/ko females had a lower respiratory quotient (RQ, measured by vCO2/vO2 ratio), suggesting a shift towards lipid as the main source of energy utilization. HCHD consumption resulted in increased total caloric intake and body weight in males regardless of genotype, with no significant effect on RQ or locomotor activity. Female Pappa2ko/ko mice consuming the HCHD had an increase in total caloric intake. Female Pappa2ko/ko mice also had lower EE, which returned to that observed in wild-type females, and a higher RQ, indicating an increase in carbohydrate metabolism similar to that of their wild-type littermates. Glucose tolerance test (GTT) showed mild glucose intolerance in both Pappa2ko/ko males and females on a normal chow diet and glucose resistance in males and females regardless of their genotype. In summary, Pappa2ko/ko mice present a negative energy balance associated with disturbances in food intake, energy expenditure, and glucose tolerance that are sex dependent. The effects of HCHD, especially in females, opens a framework for dietary intervention in patients with PAPP-A2 deficiency.

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P1-471

Higher cognitive scores in 6-year-old children with healthier lifestyle: more physical activity and sleep time

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Background and Aims: Studies in adults and experimental animals suggest an inverse and bidirectional relationship between cognitive abilities and obesity. Clinical studies on cognition and obesity in children are scarce and methodologically heterogeneous. Indeed, various factors related to obesity including diet, physical activity, socioeconomic status and maternal obesity can affect neuropsychological development. We aimed to study the cognitive function in school-age children and assess its relationship to obesity, environmental factors and socioeconomic status.

Methodology: The study population consisted of 108 pregnant women-newborns pairs included in the Girona Prenatal Study cohort (Northeastern Spain). The newborns (50 girls and 58 boys) were followed up at 6 years of age, when a clinical assessment was performed, including clinical variables [weight, height, BMI, body composition (bioelectrical impedance)], environmental factors [dietary, physical activity and sleep habits (questionnaires)], laboratory variables [insulin, HOMA-IR and lipid profile], socioeconomic status [family income and parents' education level], and cognitive function [NEPSY II, neuropsychological battery - verbal fluency, recent and remote memory, attention, and abstract reasoning].

Results: The cognitive function (score) was negatively associated with children's endocrine-metabolic parameters (HOMA-IR and triglycerides) ($p<0.05$) and sedentary behavior ($p<0.01$) and was positively associated with hours of sleep ($p<0.01$). Significant associations were also observed with nutritional score ($p<0.01$); specifically, the consumption of wheat bread, fish, nuts, fruit and vegetables showed positive associations with cognitive function (all $p<0.05$) while the consumption of ice cream, fruit juice and sugary drinks showed negative associations (all $p<0.05$). Parents' education levels and family incomes were positively associated with children's cognitive function ($p<0.05$). Linear regression analysis including the most significant parameters from the bivariate analysis (HOMA-IR, sedentary behavior, sleep time, nutritional score, parents' education level and family income) and adjusting for age and sex, showed more hours of sleep were associated with higher cognitive function and that higher HOMA-IR and

sedentary behavior were associated with lower cognitive function (all p≤0.05, R2 model=30%).

Conclusions: Our results suggested that sleep time, the endocrine-metabolic profile and the physical activity were related to cognitive function in school-age children. Given the inverse and bidirectional relationship between cognitive abilities and obesity, the control of the parameters herein identified could be useful in the prevention and treatment of childhood obesity and in the improvement of cognitive function in these children.

P1-472

VENTURE: Design of a Phase 3 Multicenter, 1-Year, Open-Label Trial of Setmelanotide in Pediatric Patients Aged 2 to <6 Years With Rare Genetic Diseases of Obesity

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Background: Rare genetic diseases of obesity are often driven by gene variants in the melanocortin-4 receptor (MC4R) pathway. The MC4R agonist setmelanotide demonstrated significant reductions in body weight in patients ≥6 years old with various rare genetic diseases of obesity, including proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency and Bardet-Biedl syndrome (BBS). While these conditions are characterized by severe obesity and hyperphagia in the first years of life, few clinical trials have evaluated pharmacotherapies for patients aged <6 years with obesity. In addition, there are few safe and effective therapeutic options available for use in this population. The VENTURE trial will evaluate the safety, tolerability, and efficacy of setmelanotide in patients aged 2 to <6 years with POMC, PCSK1, or LEPR deficiency obesity or BBS (ClinicalTrials.gov identifier: NCT04966741).

Methods: This 1-year, open-label, Phase 3 trial will enroll ~15 pediatric patients (aged 2 to <6 years) with BBS or biallelic variants in POMC, PCSK1, or LEPR confirmed by genetic testing, obesity, and symptoms or behaviors of hyperphagia. Key exclusion criteria are significant hepatic, dermatologic, or metabolic conditions. Caregivers will administer setmelanotide via subcutaneous injection beginning at 0.5 mg daily. Doses will be increased by 0.5 mg every 2 weeks as tolerated, until the maximum target dose (based on weight bands to support similar exposure to adults receiving 2-3 mg) is reached. Patients will attend study visits every 4 weeks after achieving maximum dose level through Week 20 then every 8 weeks through Week 52. The primary endpoint is the proportion of patients demonstrating a >0.2-point decrease from baseline to Week 52 in BMI Z score. Key secondary endpoints are mean change from baseline to Week 52 in BMI Z score, mean change in the percent of the 95th BMI percentile, mean percent change in BMI, and mean change in vital signs, laboratory evaluations, bone age, and Ages & Stages Questionnaires®, Third Edition (ASQ®-3). Incidence and severity of treatment-emergent adverse events will also be reported. Exploratory endpoints include pharmacokinetics and changes in metabolic parameters, waist circumference, hunger, caregiver burden, and quality of life assessed by caregiver-reported outcome instruments. In conclusion, this trial will provide relevant safety and efficacy data for the potential early treatment of patients aged 2 to <6 years with POMC, PCSK1, or LEPR deficiency obesity, or patients with BBS.

P1-473

Prevalence and determinants of hyperuricemia in a Belgian multi-ethnic inner-city population of overweight/obese children and adolescents

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Background/ Aims: Hyperuricemia (HU) is a frequent finding in childhood obesity, ranging between 12 and 40%, and associates to a variable extent with different components of the metabolic syndrome (MS). In this study, the effect of gender, (a Belgian native vs a non-Belgian native) descent and degree of general and central adiposity on serum uric acid (SUA) and the prevalence of HU was investigated in a multi-ethnic population of overweight/obese children and adolescents living in/around Brussels, using an age and sex-specific SUA reference ranges.

Methods: Fasting morning serum concentrations of uric acid, glucose, insulin, total cholesterol, HDL cholesterol and triglycerides were measured in 388 overweight (BMI 1.3 – 2 SDS)/obese (BMI SDS > 2) children and adolescents, entering an ambulatory weight loss program. Routine anthropometry and blood pressure measurements were performed. SUA was measured by enzymatic colorimetry. HU was defined by a SUA above the assay specific and age and gender defined reference range. MS was defined by the IDF criteria. Insulin resistance was defined by a HOMA-IR >2.16 for prepubertal children and >3.6 for pubertal children.

Results: Their median age was 10.45 years (range 6-16). In total, 219/388 (56.4%) were females, 67/388 (17.2%) were pubertal or postpubertal, 65/388 (16.8%) subjects had MS, while insulin resistance was present in 258/388 (66.5%) subjects. Median SUA was 4.8 mg/dL and ranged between 0.5-9.5 mg/dL, with 80 (20.6 %) children and adolescents showing an elevated SUA. Degree of general obesity (BMI Z-score) and central adiposity (waist SDS),

pubertal status (prepubertal, pubertal and postpubertal), gender, descent (Belgian native and non-Belgian native origin), as well as the presence of MS and insulin resistance were not significantly different between those with and without hyperuricemia. Median waist-to-height ratio, serum triglycerides and insulin resistance were significantly (respectively P=0.011, P=0.006, P=0.008) higher in Turkish children/adolescents compared to Moroccan and children of other (mainly Belgian native) descent.

Conclusion: Hyperuricemia was present in one fifth of inner-city living overweight/obese children, irrespective of age ethnic background and severity of global or central obesity. No significant association between HU and metabolic syndrome or its different components was found. Future studies should focus on investigating the association with diet composition, obesity duration and degree of sedentary lifestyle and the eventual risk for cardiovascular complications.

P1-474

A National Multicenter Study of Leptin (LEP) and Leptin Receptor (LEPR) Deficiency and a Systematic Review of Patients with Pathogenic LEP/LEPR Variants

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Introduction: Homozygous leptin (*LEP*) and leptin receptor (*LEPR*) mutations lead to childhood-onset obesity due to deficient leptin signaling. The specific aims of this work are to explore genotype/phenotype correlations in a national multicenter cohort of 18 subjects with leptin (LEP) and leptin receptor (LEPR) deficiency, report on the long-term clinical follow-up of these rare cases, and systematically review all patients with pathogenic *LEP/LEPR* variants that have been reported so far.

Methods: Our cohort includes 11 patients with LEP and 7 patients with LEPR from 12 independent families. Of these patients, 8 have been previously reported. A systematic literature review in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was conducted in December 2021. 42/47 studies on LEP/LEPR were selected. Data are presented as the median (interquartile range).

Results: Childhood-onset obesity was caused by *LEP* mutations in 11 (current age:5-57 years, F/M:3/8) and *LEPR* mutations in 7 cases (current age:1.4-22, F/M:2/5). Two novel mutations were identified: one frameshift in *LEP* (*c.16delC*, p.Leu6CysfsTer65) and one splice site in *LEPR* (*c.40+5G>C*). The median follow-up was 5 (6) years. Eleven patients with LEP deficiency received metreleptin, four of whom had been receiving treatment for more than two decades. Among them, one patient developed loss of efficacy associated with neutralizing antibody development. Among 151 patients which includes 133 cases from the literature review in addition to our cases, frameshift mutations were the most common (48%) in 54 patients with LEP deficiency, whereas missense mutations (35%) were more common among 97 patients with LEPR variants. LEP deficient patients were diagnosed at a younger age (3 (9) vs. 7 (13) years, p = 0.02), and had a higher median BMI SD score (3.1 (2) vs. 2.8 (1) kg/m2, p = 0.02), which was more closely associated with frameshift mutations (p = 0.02). Both groups had similar incidences of hypogonadism, recurrent infections, hyperlipidemia, growth failure, and hypothyroidism. On the other hand, LEP deficient patients were more likely to have hyperinsulinemia (p = 0.02).

Conclusion: Our analysis revealed that frameshift mutations were more common in *LEP* whereas missense mutations were more common in *LEPR* genes. LEP deficient patients were identified at younger ages, had higher BMI SD scores, and had higher rates of hyperinsulinemia than LEPR deficient patients. In our experience, 11 patients took metreleptin treatment for long term with persistent benefit, with one patient developing loss of efficacy due to neutralizing antibody.

P1-475

The Impact of Acute Exercise on 12,13-Dihydroxy-9Z-Octadecenoic Acid (12,13-DiHOME) Levels in Male Adolescents with Obesity

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Aim: 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME) is a lipokine secreted from brown adipose tissue, and it is shown to have positive effects on dyslipidemia. Acute exercise have been shown to lead to an increase in its secretion.

It was aimed to investigate the relation of 12,13-diHOME with obesity, exercise and dyslipidemia for the first time in the adolescent age group.

Methods: This is a prospective study including a total of 28 male adolescents with obesity and the same number age-matched healthy normal-weight male controls. Fasting serum glucose, insulin, lipid and 12,13-diHOME levels were measured. Cardiopulmonary exercise testing was performed in all subjects stress test treadmill 3 days in a row. Peak oxygen consumption (peak VO2) and anaerobic threshold heart rate (ATHR) were measured.

Results: Adolescents with obesity had lower 12,13-diHOME levels than normal-weight adolescents both before and after acute exercise (p=0.025 and p=0,019, respectively), and after acute exercise, 12,13-diHOME levels increased significantly in both groups. 12,13-diHOME levels negatively correlated with triglyceride, total cholesterol, LDL-C, and positively correlated with HDL-C. Also, peakVO2 and ATHR levels showed positive correlation with 12,13-diHOME levels.

Conclusion: 12,13-diHOME levels were found to be lower in adolescents with obesity than normal-weight adolescents and increase with acute exercise regardless of body mass index. Also, the close relation of this molecule with dyslipidemia in addition to obesity suggests that it has an important role in the pathogenesis of these disorders and that 12,13-diHOME may be a promising therapeutic agent for dyslipidemia and obesity in the future.

P1-476

Do integrase inhibitors alter body composition in young patients living with HIV? The experience with a dolutegravir-based regimen

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Medical antiretroviral treatment changed dramatically the course of the infection and life expectancy of people living with HIV (PLWH). However, age-dependent morbidity and mortality remains high, mostly due to non-HIV related conditions. Among others, cardiovascular diseases is nowadays an important cause of morbidity in PLWH.

Integrase inhibitors are now part of the standard treatment scheme, because of their efficacy and tolerability. However, recent reports showed an important weight gain in adults treated with dolutegravir.

The aim of the present study was the assessment of weight and body composition changes in a cohort of young PLWH, after switching to a dolutegravir-containing antiretroviral regimen.

Vertically HIV infected young patients were enrolled at the time of switching (9 girls, 4 boys, aged 12-18 y). Body weight was evaluated by calculating the body mass index (BMI), and the triponderal mass index (TMI). Body composition was measured by dual energy X-ray absorptiometry (DXA) at the time of the switch to dolutegravir-containing regimen (T1) and after one year (T2). Quantification of abdominal adipose tissue was performed by means of a 1.5-T MRI system in a subset of 5 patients at T2. Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SCAT) were measured.

BMI values increased significantly (z=34,5, p=0,0134) between T1 (20.6±3.0 kg/m^2) and T2 (21.5±3.2 kg/m^2) while TMI did not change significantly over time (T1: 12.9±2.1; T2: 13.2±2.2 kg/m^3). Body composition measurements showed a marked (z=31,0 p=0,0276) increase in trunk fat (T1: 20.2±9.1; T2: 23.1±10.4 %), together with a significant decrease (z=-36,0, p=0,0085) in the limbs/trunk fat ratio (T1: 1.3±0.3; T2: 1.1±0.3). The mean VAT area of our patients at MRI was significantly greater than the one of healthy subjects (t=5,4, p=0,0056). Conversely, mean SCAT areas were not significantly different (t=2,3, p=0,0822).

Our results suggest a role of a dolutegravir-containing regimen in the increase of trunk fat at 12 months from the start of the new therapy. Additionally, the amount of VAT in our patients resulted significantly greater compared to healthy subjects, warranting the monitoring of these patients.

P1-477

Homozygous LEPR mutation as a cause of early onset childhood obesity in a Pakistani girl

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Background: Monogenic nonsyndromic obesity is severe, has early-onset with abnormal eating behaviour and endocrine disorders. Leptin (LEP), Leptin receptor (LEPR), and Melanocortin 4 receptor (MC4R) gene mutations are identidied as the cause of early-onset childhood obesity. These pathogenic mutations are rare and have been described in less than 50 obese individuals worldwide, from consanguinous families. A cohort of Pakistani obese children from consanguineous parents showed LEP gene mutation in up to17% cases. LEP mutations result in a complete lack of its protein, loss of function mutations in the LEPR renders the carrier insensitive to leptin, both leptin and leptin receptor deficiency result in identical early-onset severe hyperphagic obesity. This is the first case of LEPR mutation leading to early onset obesity in a girl from our center.

Objective: To describe a case of morbid early onset childhood obesity due to LEPR and MC4R mutations.

Case Summary: We report a 1 year old girl, weighing 23 KG (BMI:31.8kg/m2), with progressive and rapid weight gain since 1 month of life. Born at term with, no prenatal or postnatal concerns, parents were first cousins. Father, 2 paternal uncles and 5 maternal aunts had history of early onset obesity till 5-6 years of age after which their weights normalized. Her birth weight was 3 Kg, 11.7 kg at 4 months of age (BMI: 26.4kg/m2) and 16 kg at 5 and a half months of age (BMI: 30.4kg/m2) when she presented. She was on exclusive breast feeding. Weaning foods were very rarely taken. Her gross motor milestones were slightly delayed but intellectual development was normal with no other associated illness. Considering the possibility of a genetic form of obesity, a monogenic obesity panel was sent in which testing of 68 genes was done. Two homozygous Pathogenic variants were identified in LEPR,(Exon 4,c.133_136dup (p.Tyr46*). This sequence change creates loss of function in LEPR gene and leptin receptor deficiency with very early onset childhood obesity which is most likely the case in our patient giving the matching phenotype and clinical presentation. An additional heterozygous variant of uncertain significance identified in the MC4R gene,(Exon1,c.63_64del (p.Tyr21*) also creates a premature translational stop signal in the MC4R gene and is found in patients with early onset obesity. Parents genetic testing has been sent and is awaited.

Conclusions: Our case highlights the implication of rare LEPR mutations in severe early-onset obesity in a consanguineous family diagnosing which is important for understanding of satiety regulation. Genetic diagnosis can help devising strategies of lifestyle interventions to support the patient and parents in coping.

P1-478

The impact of the COVID-19 pandemic, lockdown and school closure on weight and body mass index in low-income children and adolescents with previous overweight in Southern Brazil

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Lockdown and school closure related to COVID-19 pandemic increased sedentary time and greater consumption of ultra-processed foods, an environment that may exacerbate the childhood obesity epidemic. In Brazil, public schools remained closed for more than 40 weeks. In Brazil, prior to the current pandemic, 15.9% of children under 5 yr.-old, 29.3% of those between 5 and 9 yr.-old and 30.8% of adolescents were overweight.

Aims: To verify the impact of school closure on the weight, body mass index (BMI), changing lifestyle habits and increasing the prevalence of obesity in children and adolescents at the pediatric obesity clinic of a public tertiary hospital in Southern Brazil.

Methods: Cross-sectional observational study of overweight/obese patients aged 6 to 15 years who attended a medical appointment from November 2019 to May 2021. Patients with an organic or endocrine cause of obesity, monogenic obesity and genetic syndromes were excluded. The study protocol was approved by the Ethics Committee. Data of the last pre-pandemic visit were extracted from the clinical records and anthropometric measurements were assessed in the first visit during the pandemic. A survey was aimed to assess whether nutritional and consumer habits have been affected under quarantine conditions.

Results: 50 patients (31 girls) aged 11.6±2.4 yr.-old were included. All of them were from low-income families and had not been returned to school. The interval between visits was 382.7±76.6 days. Over 58% reported snacking more, greater consumption of ultra-processed foods and increased sedentary time. Forty-five patients (88%) experienced weight gain [9 kg (-3.6 to 25.5)] and there was a gain of 19.6% compared to pre-pandemic weight. The median BMI and its z-score variation between visits were +1.9 kg/m2 (-2.9 to +7.7) and +0.07 (-0.93 to +1.47), respectively. The change in adjusted BMI to the median for sex and age was +1.65 kg/m2 (-3.60 to +6.90). There was an increase in the prevalence of obesity of 12% in this group.

Conclusion: Defining the longitudinal change in BMI in the pediatric age group is a challenge. This study showed an unhealthy weight gain in a group of previously overweight pediatric patients, increased sedentary time and some difficulties faced by children during quarantine in Brazil. The study highlights that lockdown imposed by SARS-CoV-2 affected eating behaviors, dietary and sedentary habits, and advocates for organized nutritional support during future epidemic-related quarantines, particularly for the most vulnerable groups, including children with overweight or obesity.

P1-479

4D-Blood+ Proteomic Profiling of Obesity and Metabolic Syndrome in Adolescents

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Objective: Obesity accounts for 8.9% of children and adolescents in China, and metabolic syndrome (MetS) accounts for 28.8% of obese children, rising year by year. There is no early prediction and screening index in the clinic, so it is urgent to develop early prediction of MetS in children and adolescents and screen pathogenic molecular markers. Therefore, we propose to establish and screen biomarkers for the prognosis of obesity in children and adolescents through serum 4D proteomics and metabolomics.

Methods:10 obese patients (OB),10 obese patients with metabolic syndrome (MetS), and 10 healthy controls (Con), all aged 10-14 years, were selected for serum 4D-BLOOD + high-throughput proteomics study to reveal the changes of serum proteome related to obesity and metabolic syndrome in adolescents.

Results: Serum proteomics showed that 15 KGEE enrichment signaling pathways were changed in the adolescent simple obesity group, including progesterone mediated oocyte maturation, Rap1 signaling pathway, platelet activation, insulin resistance, etc. Twenty-six signaling pathways were changed in the obesity combined with MetS group, of which seven pathways were changed in both OB and MetS. However, most of the changes in signaling pathways in the MetS group were related to the activation of neurodegenerative diseases and cancer pathways, and these pathways were normal in the OB group.

Conclusion: It is speculated that activation of neurodegenerative diseases and cancer pathways and down-regulation of inflammatory signaling pathway are closely related to numerous clinical manifestations and complications of MetS in children and adolescents, and that Rap1 signaling pathway, activation of platelets, and down-regulation of inflammatory signaling pathway are also speculated in the pathogenesis of MetS. Neurodegenerative diseases and activation of cancer pathways are important causes of blood proteome changes and related complications. This study provided a multiomics basis for the development of a prognostic test for adolescent obesity, so as to identify high-risk patients as early as possible and trigger early intensive surveillance and intervention.

Keywords: Proteomics; Obesity; Metabolic Syndrome.

P1-480

Clinical symptom and sequence variations in patients with sitosterolemia

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Backgrounds: Sitosterolemia is an inborn error of sterol metabolism caused by pathogenic variation of ABCG5 or ABCG8. It is characterized by increased plant sterol levels, xanthomas, and accelerated atherosclerosis; however, it is likely to be underdiagnosed in the clinical field. This study aims to describe the genetic variance of clinically confirmed patients with sitosterolemia and analyze the clinical spectrum according to genetic variance.

Methods: Nine children and adolescents including 2 previously reported siblings and 7 unrelated patients with sitosterolemia were enrolled. All patients were clinically diagnosed and confirmed with elevated plasma sitosterol levels (serum sitosterol measured by gas chromatography-mass spectrometry > 1.7 mg/dL). Whole-exome sequencing (WES) was performed to analyze the cholesterol-associated genes in 7 patients and their parents.

Results: The median age at diagnosis was 5.8 (1.2–13.0) years. All patients (N=9) showed hypercholesterolemia and seven patients (78%) showed xanthomas at initial diagnosis. Total cholesterol and sitosterol levels at diagnosis were 461.3 (203.0–811.3) mg/dL and 7.5 (2.2–16.5 mg/dL, reference range: 0.3-1.0 mg/dL). In WES analysis, variances in ABCG5 or ABCG8 were noted in all patients (2 patients with homozygous mutations and 5 with compound heterozygous variants). Eight sequence variances, including 4 pathogenic and 4 variants of unknown significance (VUS) were observed, and frequently observed pathogenic variances were c.1336C>T in ABCG5(N=4) and c.904+1G>A in ABCG5(N=4). In addition, c.694+5G>C, VUS in ABCG8 was observed in 2 unrelated patients. Most patients showed dramatic clinical responses to low cholesterol, low plant sterol diet, and cholestyramine or ezetimibe treatment, although their sitosterol levels are still elevated (2.7(1.8–5.8) mg/dL).

Conclusion: In this study, we described clinical characteristics and genetic variations in Korean patients with sitosterolemia. The earliest presentations were cutaneous xanthomas and/or hypercholesterolemia. Plant sterol assay should be considered in young children with severe hypercholesterolemia showing dramatic improvement to dietary modification and/or cholestyramine treatment. Genetic analysis also seems to be helpful for the diagnosis of sitosterolemia, especially in infants in whom the plant sterol levels are not high enough.

P1-481

Non-traditional cardiometabolic risk factors in obese children and adolescents with Metabolic Syndrome

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Background: The prevalence of obesity in childhood has increased dramatically during the last decades. Dyslipidemia, hypertension and insulin resistance – all components of the metabolic syndrome (MS) and well-known cardiometabolic risk factors – predispose to the development of inflammation and premature atherosclerotic cardiovascular disease in childhood.

Aim: To determine "non- traditional" cardiometabolic risk factors in obese children and adolescents with and without MS, before and after the implementation of a comprehensive, multidisciplinary, personalized life-style intervention program for 1 year.

Methods: One hundred and forty-nine (n=149) children and adolescents [91 males (61.07%), 58 females (38.93%), 32 prepubertal (21.48%), 117 pubertal (78.52%)] attending our 'Out-patient Clinic for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence' were studied prospectively. Subjects were classified as having MS (n=90; mean age±SE:13.19±0.2 years) or not (n= 59; mean age± SE: 12.05±0.28 years) according to the International Diabetes Federation criteria for MS. All participants underwent clinical examination, echocardiography, ultrasound of the carotid arteries to determine carotid intima-media thickness and blood sampling for biochemical, endocrinologic and "non-traditional" cardiometabolic risk factors (adiponectin, homocysteine, hs-CRP, leptin, IL-2, IL-4, IL-10, IL-17A, TNF, IFN-γ) at the beginning of the study and following 1-year of a personalized life-style intervention program.

Results: Systolic (SBP) and diastolic (DBP) blood pressure were significantly higher in children with MS (127.04±1.28 and 74.91±1.02mmHg, respectively) than those without MS (114.3±1.09 and 68.35±1.13mmHg, $p<0.05$) and improved significantly in children with MS after 12 months' intervention. Interventricular septal end systole (IVSs) was significantly higher in the MS group than the control group both at baseline (9.67±0.30 vs. 8.47±0.25mm, $p<0.05$) and after intervention (9.63±0.28 vs.8.58±0.24mm, $p<0.05$). Mean Right Common Carotid Artery (RCCA) was significantly higher in the MS group than the control group at baseline (0.65±0.02 vs.0.50±0.02mm, $p<0.05$), and decreased significantly in the MS group after 12 months' of intervention. Mean Left Common Carotid Artery (LCCA) did not differ significantly among groups. The proinflammatory cytokines IL-2, IL-6, TNF, IL-17A, IFN-γ were significantly higher at baseline in the MS group than the control group. Triglyceride concentrations at initial assessment were the best positive predictor of mean LCCA (β:0.37), while SBP followed by triglyceride concentrations at initial assessment were the best positive predictor of mean RCCA (β:0.25 and β:0.22, respectively).

Conclusion: Our findings indicate increased cardiometabolic risk in children with MS, as well as an improvement in cardiovascular parameters and cytokines following intervention.

P1-482

Liraglutide SC in the treatment of severe obesity in Pediatrics: a missed therapeutic opportunity?

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Liraglutide 3.0 mg has been shown to improve body mass index (BMI) and weight in obese adolescents. And it has done so in a randomized, double-blind, phase 3 clinical trial that has investigated the effect of liraglutide 3mg. compared with placebo for weight control in 251 obese minors, and as a complement to a healthy lifestyle. Adverse events associated with the use of liraglutide 3.0 in pediatric patients are not very different from those observed in adults. There may be cases of gastrointestinal discomfort such as a feeling of excessive gastric fullness, nausea on occasion and, more rarely, vomiting, all especially during the first weeks of administration.

Liraglutide 3.0 mg, although it requires a prescription for sale, is not funded by the SPS. Cost of a box of 5 pens is €283.05

The progressive increase in the prevalence of overweight and obesity in this age group. At Spain it can reach up to 40%. These have led to the appearance of new family models, eating habits and life models that facilitate the development of obesity in new generations. There are social and ethnic groups where the prevalence of childhood obesity is more prevalent.

Objective: To evaluate the clinical experience in the incorporation of SAXENDA in routine clinical practice.

Methods: severely obese patients over 12 years of age who are likely to use liraglutide under the indication of the technical data sheet. Presentation of the product and offer to the family. Socioeconomic study in direct interview, sex, age. Collection of impressions, in case of refusal the cause.

Results: 45 children older than 12 years (15♂), mean age 13.5 to [12-16]. Mean follow-up time in SCC of 3.5 years [2.8-5.2]. HbA1c (DCA): 5.7% [5-6.2], no DM 2, mean BMI 35.28 kg/m2 [29,42].

Ethnic origin 90% foreigners. Socioeconomic level manifested low (20/45), medium-low (12/45), medium (12/45), high (1/45), very high (0/45).

Rejection 40/45, value next visit 4/45, acceptance 1/45

Reasons for rejection: fear of needles 25/40, price 30/40, distrust 3/40, others 2/40.

Conclusion: We assume that this study may present some deficiencies due to the size of the sample, but our study demonstrates

the possibility of the limitation of a therapeutic tool associated with price, delving deeper into the poverty-disease-poverty circle. We believe that this drug should be financed even if its prescription in pediatrics is regulated or inspected.

P1-483

The ecology of the microbiome in children with congenital generalized lipodystrophy type 4 (CGL4) is quickly modified after metreleptin treatment

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Introduction: Lipodystrophy syndromes are characterized by a progressive metabolic impairment secondary to adipose tissue dysfunction and genetic background. The role of microbiota is still uninvestigated.

Objective: Evaluate the gut microbiome ecology in relation to dietary and clinical parameters in two infant siblings with congenital generalized lipodystrophy type 4 (CGL4) before and after treatment with recombinant leptin.

Methods: Two siblings (male, 5.5 years; female 2.5 years) with CGL4 caused by a new homozygous PTRF mutation (NM_012232 eson1:c T21A:p. Y7X) were identified and followed after the starting of leptin treatment. We collected auxological, metabolic, nutritional parameters, and stool samples at baseline and every 3 months. Two baseline stool samples were pooled. DNA was extracted directly from 0.25 g of stool using the QIAamp PowerFecal Pro DNA Kit. DNA was amplified with primers for the V3 and V6 regions of 16S rDNA tagged with Multiplex Identifier sequences using Microbiota Solution B Kit optimized for Illumina Miseq sequencing. Raw FastQ sequences were analyzed using MicrobAT Software. Statistical analyses were performed using MicrobiomeAnalyst and R software.

Results: At baseline, reduced subcutaneous fat, muscular hypertrophy, distinct facial features, myopathy, atlantoaxial instability were observed. Stature and BMI were normal. Blood tests showed elevated CK, mildly elevated levels of liver enzymes and triglycerides, low leptin and adiponectin levels. Fasting glucose and HbA1c were normal; HOMA-IR was mildly elevated in the female, and continuous glucose monitoring often detected glucose higher than 180 mg/dl after meals in male. They were hyperphagic, mainly for foods rich in fats and sugars. The 2 subjects showed a Bacteroides enterotype (F/M): 46%/44% Bacteroidetes, 49%/42% Firmicutes, 0.02%/0.04 other Bacteria, 3.2%/1.9% Actinobacteria, 0.7%/0.4% Proteobacteria; 0%/11%Verrucomicrobia. Treatment with metreleptin was started at standard dose according to age and weight. Metabolic parameters and hyperphagia improved, and they were more adherent to dietary indications. The male subject lost 0.8 Kg after 3 months, female weight was stable. We present microbiome ecology after 3-month treatment, before starting also medium-chain triglyceride oil formulas. Alfa-diversity increased in both children. Ecology was modified ($p<0.06$) with a reproducible signature with decreased and increased relative abundance of species linked to metabolic homeostasis.

Discussion: These preliminary results highlight as dietary adherence and leptin treatment were soon followed by improvements in metabolic alterations and changes in microbiome ecology. Whether microbiota composition and function have a role in the lipodystrophy phenotype needs further investigation. Our preliminary data should be validated in a wide cohort.

P1-484

Suboptimal adherence to statin therapy in children and adolescents with HeFH despite a high therapeutic efficacy: is the cardiovascular risk underestimated?

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Background: Heterozygous familial hypercholesterolemia (HeFH) is characterized by severely elevated low-density lipoprotein cholesterol (LDL-C) levels and premature cardiovascular disease. European guidelines currently support the initiation of statin therapy by age 8-10 years in patients with HeFH to slow the progression of endothelial disfunction and to reduce the risk of cardiovascular disease in adulthood. However, to date, there is lack of data on adherence to statin therapy in the paediatric population. Therefore, the aim of our study is to assess the efficacy and the adherence to statins among patients followed up at our Paediatric Dyslipidaemia Clinic.

Methods: This is an observational study recruiting a monocentric cohort of children and adolescents with genetically confirmed HeFH. Anthropometric measures, fasting lipid profile and therapeutic data were collected at diagnosis of HeFH [T0], on lipid-lowering diet before starting statin [T1], four weeks after starting therapy [T2] and yearly during the first two years on statin [T3 and T4].

Results: 24 HeFH children and adolescents (17/24 female) were started on statin at a mean age of 13.77±3.09 years (12 on atorvastatin, 10 on pravastatin and 2 on simvastatin). On lipid-lowering diet, lipid metabolism did not change significantly [T0 vs. T1: total cholesterol (TC) 314.80±59.83 vs. 313.39±62.82 mg/dl,

p 0.66; LDL-C 237.61±47.18 vs. 218.22±50.15 mg/dl, p 0.11], while on statin the improvement was quick and persistent [TC: T1 313.39±62.82, T2 237.84±28.19, T3 231.35±42.87, T4 227.66±33.42 mg/dl, p<0.05; LDL-C: T1 218.22±50.15, T2 163.85±27.64, T3 153.12±34.90, T4 156.37±34.11 mg/dl, p<0.05]. The mean reduction of LDL-C in comparison to baseline levels was: -34.68±12.99% at T2, -31.57±16.33% at T3 and -30.42±20.78% at T4 (p 0.03). Despite this efficacy and excluding one case of statin-intolerance, 9/23 patients (about 39%) dropped out after one year of statin therapy with a higher prevalence among families without an history of precocious cardio-vascular events (p <0.05).

Conclusions: We report an overall scarce adherence to statins in our paediatric HeFH population despite an efficacy in line with international data. Therefore, it seems imperative to reduce the therapeutic drop out in this category. GP involvement, a more effective communication with patients and their families to emphasize the high HeFH-related cardiovascular risk, and a periodic follow-up including telemedicine may be tools to achieve a better adherence to statins in HeFH paediatric patients.

P1-485

Thyroid hormones and food preferences in obese children and adolescents

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Background and Aims: Thyroid hormones profoundly affect energy metabolism but their interrelation with food preference, which might contribute to childhood obesity development, are much less understood. Here we investigated if age-related changes of thyroid hormone levels are paralleled by specific modulation of food preference and potentially linked to the level of obesity in children and adolescents.

Patients and Methods: Interrelations between food preference and peripheral thyroid activity were examined in a population of 99 non-obese and 101 obese children and adolescents (12.8±3.6 yrs. of age, 112/89 F/M) randomly selected from the patients of Obesity and Metabolic Disease Out-patient Research unit at NÚDCH in Bratislava in a period between 12/2017 and 3/2020.

Results: Obese children and adolescents had lower preference for the food rich in high sucrose, and high-complex carbohydrates, while the preference for protein and fat containing food and that for dietary fibers was identical in obese and non-obese. In obese adolescents positive correlations of FT4 with the preference for high protein, high fat rich diet was found irrespective of the fatty acid unsaturation level. Moreover, FT4 correlated negatively the preference for dietary fibers which was also exclusively found in obese adolescents. Obese individuals with higher FT4 levels (stratified by median value) had higher systemic levels of AST and ALT then the low FT4 group. Multiple regression analysis with age, sex, BMI-SDS and FT4 as co-variates revealed, that FT4 and gender are the major predictors of variability in the preference for diet high in protein, fat and monounsaturated fatty acids. FT4 was the sole predictor of the preference for diet containing saturated and polyunsaturated fatty acids as well as for diet low in fibers.

Conclusion: Serum levels of thyroid hormone FT4 were significantly associated with food preferences in obese children and adolescents. This may indicate that FT4 could contribute to development of childhood obesity and its complications by modulating food preference.

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Fetal, Neonatal Endocrinology and Metabolism

P1-88

An Ongoing Phase 2 Study of HM15136, a Novel Long-acting Glucagon Analogue, in Subjects with Congenital Hyperinsulinism (ACHIEVE, Outline Protocol)

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Congenital hyperinsulinism (CHI) is an ultra-rare disease characterized by excessive insulin secretion that results in persistent hypoglycemia. If left untreated, CHI-induced severe prolonged hypoglycemia may lead to permanent neurologic damage. Currently used pharmacologic agents fail to prevent hypoglycemia in a subset of patients with CHI. HM15136 is a novel long-acting glucagon analogue that have demonstrated good stability and extended half-life ranging from 77 to 167 hours, which is significantly greater than that of native glucagon (< 1 hour). The safety and tolerability of HM15136 along with dose dependent glucose escalation properties were demonstrated in Phase 1 studies. Based on its profile, we hypothesized that HM15136 can prevent hypoglycemia in subjects with CHI aged ≥2 years, who have persistent hypoglycemia while being on standard of care treatment.

We have planned a multicentered Phase 2 study at centers of United States, United Kingdom, and Germany including the

centers of excellence which provide the highest quality of care for CHI patients, which will be run from 2021 to 2024. In this study, 0.04 and 0.06 mg/Kg weekly doses of HM15136 will be tested for 8 weeks in children 2-11 years old (n=5 per dose) and in children and adults ≥12 years old (n=3 per dose). Because HM15136 was never evaluated among the subject with CHI and pediatric population before, step down approach is chosen for evaluating safety profile of HM15136 in subjects with CHI aged ≥12 years old first, though unmet needs are much higher among the children 2-11 years old. Dosing will be initiated in adolescents and adults at 0.04 mg/Kg. After review of safety/efficacy profile during 8-week treatment period, dose will be escalated to 0.06 mg/Kg in adolescents and adults, and younger children cohort will be initiated in parallel with dose of safety confirmed 0.04 mg/Kg. The dose escalation to 0.06 mg/Kg in children cohort will be decided by another safety/efficacy review.

The primary endpoints will be safety, tolerability, and pharmacokinetics of HM15136. The secondary endpoint, an efficacy outcome, will be reduction of weekly hypoglycemia events measured by 7-point self-monitored blood glucose compared to the baseline.

This Phase 2 study will provide important information about the safety, tolerability and efficacy of HM15136 for the development of a study design in neonates and infants and longer term Phase 3 studies in children with severe hypoglycemia due to CHI.

P1-89

A standard operating procedure for prevention, diagnosis, and management of hypoglycaemia in neonates ≥ 35 weeks of gestation

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Background: Hypoglycaemia is a common metabolic condition affecting up to 15% of all neonates and 50% of neonates with risk factors including diabetic mothers, large or small for gestational age, perinatal stress, or prematurity. It is well known that severe and prolonged hypoglycaemia, as commonly seen in congenital hyperinsulinism, can lead to brain injury. However, data on the effect of mild neonatal hypoglycaemia on neurodevelopment are limited. There is still no international consensus on glucose thresholds and management recommendations for neonatal hypoglycaemia differ worldwide. In Germany, there exists only one consensus guideline for management of infants of diabetic mothers.

Objective: Our aim was to create a standard operating procedure (SOP) for neonatal hypoglycaemia that provides a risk-adapted screening and a management strategy with appropriate and effective escalation steps, but also with minimal burden on the newborn.

Methods: A comparative analysis of published guidelines and current literature was performed. Based on the recommendations of different national guidelines, a flowchart was created, adapted from the 'Swedish national guideline for prevention and treatment of neonatal hypoglycaemia in newborn infants with gestational age ≥ 35 weeks' (Wackernagel et al., Acta paediatrica, 2019). The new SOP for neonatal hypoglycaemia was clinically tested for feasibility and finalized after repeated revisions by a multiprofessional team of nurses, midwives, neonatologists, paediatric endocrinologists and obstetricians. In March 2020, the final version of the SOP was introduced at the University Hospital Düsseldorf, Germany.

Results: Although neonatal hypoglycaemia is a common metabolic disorder, screening recommendations and treatment thresholds are inconsistent among guidelines. Most do not have specific recommendations for persistent hypoglycaemia. The new SOP includes preventive measures and a risk-dependent glucose screening. Detailed escalation steps for screening and treatment are provided for children with persistent hypoglycaemia.

Conclusion: We established a new SOP for neonatal hypoglycaemia that is practical for daily care and balances the aims of minimal neonatal distress and prevention of brain damage. Currently, this SOP is being systematically evaluated in a prospective longitudinal cohort study, both in terms of neurodevelopmental outcomes and its feasibility and potential to balance risks and benefits.

P1-90

Evaluation of the myokine irisin and adipocytokine leptin content in small for gestational age newborns and their mothers

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Objectives: The purpose of the study is to assess the levels of myokine irisin and adipocytokine leptin in SGA newborns, to analyze the relationship between the parameters of the hormonal status of children and their mothers.

Materials and Methods: 49 mother-newborn pairs were examined. Two groups of full-term newborns were distinguished. Group 1 (Gr1) - small for gestational age (body weight (BW) at birth 10th percentile and below), group 2 (Gr2) - appropriate for gestational age (BW above 10th percentile) according to the INTERGROWTH-21st scales. Body weight in Gr1 (n=24) was 2470 [2180; 2635] g, Gr2 (n=25) – 3380 [3260; 3620] g, U=7.5, p<0.001. MT percentiles – 8.4 [2.9; 9.7] and 66.8 [51.1; 79.9], respectively, U=13.0, p<0.001. The levels of irisin, leptin, IGF-1 were determined by enzyme immunoassay. Nonparametric methods were used for statistical processing.

Results: SGA newborns were found to have significantly lower cord blood leptin and IGF-1 levels than gestational age infants (2.43 [1.36; 3.52] versus 5.00 [4.00; 8.80] ng/mL, U=107.5, p<0.001 and 75.0 [63.5; 94.0] vs 97.0 [87.0; 109.0], U=62.5, p=0.022). In newborns Gr1 and Gr2, no significant differences were found in

the content of irisin in cord blood serum (325 [301; 470] ng/ml and 400 [290; 460] ng/ml, U=280.5, p=0.699). Significant (p<0.05) positive correlations were found between the level of cord blood irisin in SGA newborns and BW (r=0.39), BW percentile (r=0.46), z-score BW of children (r=0.46). Serum leptin levels in Gr1 mothers were 5.9 [1.8; 14.5] ng/ml, Gr2 – 14.1 [7.8; 18.2] ng/ml, p=0.021. We did not established statistically significant differences in the content of irisin in mothers of newborns of the surveyed groups (U=240.5, p=0.238). In Gr1, a positive relationship was found between the levels of irisin in mothers and newborns (r=0.52, p=0.028). The content of irisin in the cord blood serum in infants born per vias naturalis was statistically significantly higher than in patients with abdominal delivery (410 [350; 640] ng/ml vs. 305 [280; 410] ng/ml, U=155, 0, p=0.010).

Conclusion: Irisin levels in SGA newborns are associated with maternal serum irisin and birth weight of infants. Differences in the content of irisin in full-term newborns depend on the mode of delivery. The revealed statistically significant differences in the levels of the analyzed markers in mother-child pairs substantiate the importance of further research and may lead to an understanding of metabolic disorders that will occur at a older age.

P1-91

Global microRNA and protein expression in human term placenta may improve our understanding of fetal growth

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Introduction: The placenta is an endocrine organ vital to fetal growth. It has multiple functions: pregnancy maintenance, nutrient and oxygen transport to the fetus, and removal of waste products among other functions. MicroRNAs (miRNAs) and proteins are significant mediators of these functions. A description of their global expression in healthy placenta may increase our understanding of the molecular biological pathways that are important for normal fetal growth and development. The aims of this study were to explore the global expression of both miRNAs and proteins in the same samples of human term healthy placenta and to describe involved pathways.

Methods: Nineteen term placenta samples from healthy women with uncomplicated pregnancies were identified in a local sample collection. The samples were derived from uncomplicated vaginal deliveries with healthy normal weight new-borns (5 females). Next generation sequencing and nano-scale liquid chromatographic tandem mass spectrometry were used for the analyses of miRNA and protein expression, respectively. Ingenuity Pathway Analysis was used for functional bioinformatics analyses.

Results: A total of 895 mature miRNAs and 6,523 proteins were detected in the placenta samples, whereof 123 miRNAs and 346 proteins were highly abundant. The miRNAs were in high degree mapped to chromosomes 19, 14 and X. The most abundant proteins served as enzymes (23%), transporters (10%) or transcription regulators (8%). Of the 20 most significant downstream functions for the highly expressed miRNAs and proteins, respectively, eight shared functions were found, namely Cellular function and maintenance, Cell death and survival, Cell-to-cell signaling and interaction, Cellular assembly and organization, Organismal development, Digestive system development and function, Hepatic system development and function, and Inflammatory response.

Discussion: As far as we know, this is the first study presenting both global miRNA and protein expression in the same placenta sample set from healthy term pregnancies. Two of the chromosomes found to have high presence of miRNA genes in the present study are known to contain placenta-specific miRNA clusters (chromosomes 14 and 19), while chromosome X might have been identified here since it has a higher density of miRNA genes than autosomes. The biological functions for the miRNAs and proteins point at basic cellular actions and clearly illustrate that development is an important task during fetal life. Profound knowledge of miRNA and protein expression in healthy placenta can improve the management of aberrant fetal growth and development.

P1-92

Reference National Standards for Placental Weight in Infants born between the 37th and 43rd weeks of Gestation in Qatar. (A Population-Based Retrospective Data Analysis (n = 80722)

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Introduction: Because of the associations and links between abnormal placental weight and both fetal and maternal disorders, it is important to have the national normal standard for placental weight as a normality reference.

Aims: To find out the national placental weight standards for babies born between 37th and 43rd weeks of gestation in all groups of males and females babies born AGA, SGA, and LGA.

MALE NEWBORN PLACENTA Weight STANDARDS

Gestational age	mean	Sd	p5	p10	p25	p50	p75	p90	p95
37	632	114	440	482	565	640	700	755	810
38	652	109	470	510	600	650	700	780	830
39	664	101	490	530	610	680	710	780	820
40	682	96	520	565	626	680	725	800	850
41	693	101	515	575	640	700	750	810	860
42	677	100	520	550	620	680	720	800	850
Total	664	105	485	528	608	680	720	790	832

FEMALE NEWBORN PLACENTA Weight STANDARDS

Gestational age	mean	sd	p5	p10	p25	p50	p75	p90	p95
37	627	117	430	480	560	630	690	750	820
38	645	108	460	510	585	650	700	770	820
39	659	101	490	530	600	670	710	780	820
40	673	94	510	560	620	680	720	780	820
41	683	95	516	570	630	680	722	800	850
42	669	106	500	529	610	680	720	780	810
Total	658	103	480	522	600	665	710	780	820

Methods: This population-based analysis comprised of a 4-year cohort data (January 2016 to December 2019) for births conducted in all HMC hospitals (90% of all births in the country). The inclusion criterion for this analysis was term singleton live births, 37+0 to 42+6 weeks gestation. Furthermore, cases with missing placenta or placenta weight <100g or >2500g were excluded giving a final sample size of 80722 births.

Results: Infant and placental weight pairs were analyzed according to their gestational ages and growth categories (AGA, SGA, LGA). Mean placental weights continued to increase through 41 weeks' gestation in the SGA, AGA, and LGA groups and in both sexes and were heavier in boys. The mean placental weight at term was 682 +/- 96 g for boys and 673 +/- 94 g for girls.

Conclusions: Reference standards of our large national cohort were achieved. And demonstrated a consistent increase in placental size until 41 weeks of gestation with a mild but significant decrease in the 42nd week.

P1-93

Measurements of Growth Hormone in neonatal screening cards as a non-invasive and feasible tool: reference values in healthy term newborns

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Background: Severe congenital growth hormone deficiency (cGHD) is a rare but potentially life-threatening condition. Even though random growth hormone (GH) can confirm cGHD during the first week of life, the diagnosis remains extremely challenging in the absence of reliable reference values in healthy neonates and thus of a best diagnostic cut-off.

Aims: First, to provide solid reference values for GH concentrations in term newborns, by means of a non-invasive procedure (GH from screening cards), using a current ultrasensitive GH assay. Secondly, to investigate eventual maternal and neonatal predictors of GH concentrations.

Methods: Using Immulite 2000 assay, GH was measured simultaneously from 200 dried blood spots (DBS) and serum samples of controls, thus validating this method for DBS. With the same assay, GH concentrations were measured in 444 filter papers of term newborns after 48 hours of life. Maternal and neonatal anamnestic data were collected from clinical records.

Results: In our cohort (444 neonates, 212 males and 232 females), the auxological parameters were spread according with the reference neonatal anthropometric charts of Italian population (median length -0.05 SDS, median head circumference -0.07 SDS, median weight -0.12 SDS). Median GH value was 16.9 μg/L (IQR 11.2 - 23.1 μg/L), with no significant gender difference. We defined a lower limit of 6.5 μg/l as 5° centile through Harrell-Davis' method with a confidence interval at 90 % between 5.9 and 7 μg/l by bootstrap BCA method. Considering our lower limit of GH<6.5 μg/L, at logistic regression analysis, jaundice presented the greater association with GH concentrations (p<0.001). Indeed, neonates with jaundice had 5-fold increased risk of presenting a GH<6.5 μg/L. No other significant correlation was found between GH and maternal or neonatal characteristics. Yet, the association between neonatal hypoglycaemia and lower GH concentrations was suggestive, though not significant (p=0.077).

Conclusions: We defined the lower limit of reference values for GH in term healthy new-borns independently from sex, gestational age and auxological parameters using for the first time a widely available assay.

The relationship found between symptoms/signs suggestive for cGHD and lower GH concentrations, even in healthy subjects, confirmed the crucial role of clinical presentation in the diagnosis of cGHD.

Providing solid reference values in term newborns, we put the basis for further studies aiming at defining a reliable diagnostic cut-off of cGHD.

P1-94

Adipocytokine status and vitamin D level in large for gestational age newborns

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Objective: to study the features of the adipocytokine status and vitamin D status in large for gestational age (LGA) newborns.

Materials and Methods: 348 full-term newborns were examined. Three groups of LGA newborns were identified: taking into account the presence of mother's type 1 diabetes mellitus (DM) (Gr1, n=58, body weight (BW) – 4225 [4000; 4580] g), excess BW or obesity (Gr3, n=65, BW 4300 [4200; 4540] g), absence of carbohydrate and fat metabolism disorders (Gr2, n=66, BW 4185 [4100; 4320] g). Group 4 (Gr4, n=159, BW 3380 [3170; 3650] g) – appropriate for gestational age newborns from mothers without changes in carbohydrate and lipid metabolism.

Results: The mothers of the examined groups' newborns had statistically significant differences in the content of leptin (p=0.006), adiponectin (p<0.001). Serum leptin was higher in the group of women with overweight and obesity (32.0 [24.0; 48.0] vs 13.0 [6.0; 21.0] ng/ml in Gr1, 8.0 [4.0; 8.5] ng/ml in Gr2, 10.0 [6.0; 18.0] ng/ml in Gr4, p2-3=0.005, p3-4=0.027). The level of visfatin in Gr3 mothers was lower than that of Gr4 (8.6 [7.8; 10.0] and 12.0 [9.4; 27.0] ng/ml, p=0.020). Content of 25(OH)D in Gr1 was 13.1 [10.0; 17.7] ng/ml, Gr2 – 14.9 [11.6; 23.6], Gr3 – 10.9 [9.0; 16.8], Gr4 – 13.8 [9.3; 20.2] ng/ml, p=0.504. Significant differences in the content of leptin (p<0.001), adiponectin (p=0.006), IGF-1 (p=0.024), 25(OH)D (p=0.005) were found in newborns at birth. Adiponectin and IGF-1 concentrations in Gr1 were significantly lower than Gr2 (p=0.004, p=0.031). Vitamin D was in the lower normal range in all groups. The lowest level was 25(OH)D in newborns from mothers Gr3 (11.0 [8.0; 17.8] ng/ml, p3-4=0.003). Gr3 were divided into 2 subgroups: Gr3a – newborns from mothers with obesity and gestational DM (n=20), Gr3b –from mothers with overweight or obesity without DM (n=45). In Gr3a the levels of leptin and visfatin significantly exceeded those of Gr3b (19.8 [15.9; 37.4] vs 12.4 [7.2; 21.1] ng/ml, p=0.007 and 19.5 [14.5; 62.0] vs 10.3 [9.0; 13.0] ng/ml, p=0.034). The content of 25(OH)D in Gr3a was 17.4 [12.4; 28.7], Gr3b – 10.3 [7.9; 14.6] ng/ml, U=135.5, p=0.046.

Conclusion: The influence of women' metabolic disorders on the parameters of hormonal status and vitamin D status in LGA newborns was more intense if the mother has overweight or obesity.

P1-95

Relationship between placental PEG10 methylation and postnatal weight gain in 6 year-old children

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Introduction and Objectives: Imprinted genes have been broadly related to prenatal growth regulation. PEG10 is a maternally imprinted gene involved in cellular proliferation that is mainly expressed in the placenta and in some adult tissues. In mice, mutations in this gene have been related to growth restriction of both the embryo and the placenta. Nevertheless, its role in postnatal growth has not yet been established.

We aimed to study prospectively the relationship between PEG10 methylation in the placenta and postnatal growth in children at 6 years of age.

Subjects and Methods: The study population consisted of a cohort of pregnant women and their newborn infants who were followed from birth until 6 years of age. All mothers and newborns were healthy, with term pregnancies and infants' weights appropriate for gestational age. PEG10 methylation levels were analyzed by pyrosequencing in 104 placental samples. Associations between methylation percentage of PEG10 and offspring growth, anthropometric and metabolic parameters in the offspring from birth to 6 years of age were sought by correlation analyses, with adjustment for cofounding variables in multiple regression analyses.

Results: PEG10 methylation correlated with anthropometric parameters in the infants during the first year of life and at follow-up at 6 years of age. Specifically, PEG10 methylation correlated negatively with ponderal index (PI) at 2 and 4 months of age ($p=0.002$ to $p=0.005$). At follow-up at 6 years of age, PEG10 methylation correlated negatively with body mass index (BMI) and with weight and BMI SDS (z-score) changes from birth to 6 years of age ($p=0.04$ to $p=0.005$). After adjusting for cofounding variables, placental PEG10 methylation remained significantly associated with PI at 2 and 4 months, and with weight and BMI SDS (z-score) changes from birth to 6 years of age (β from -0.382 to -0.235, all $p<0.02$).

Conclusions: PEG10 methylation may have an important role in offspring development, by regulating postnatal growth during the first years of life. Specifically, PEG10 methylation may affect weight gain early in life, ultimately decreasing the risk of developing obesity in children.

P1-96

Optimizing Diazoxide dose for the treatment of newborns with hyperinsulinemic hypoglycaemia (HH)

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Introduction: Early initiation of diazoxide (DZX) treatment in neonates with HH can prevent permanent hypoglycaemic brain injury. The DZX standard therapeutic dose (STD) is 5 mg/kg/day, and rarely associated with adverse events. There are limited data for the effectiveness and safety of DZX low-dose (<5mg/kg/day) for the treatment of HH neonates.

Aim: To assess efficacy and safety of low-dose DZX in HH newborns.

Methods: Observational study with data collection on HH neonates (<28 days) referred to our tertiary HH Service between November 2016-April 2021. As per our experience, neonates commenced DZX based on their weight and divided into 3 cohorts: i) C1 <2kg, DZX 2mg/kg/day, ii) C2 2-3.5kg, DZX 3mg/kg/day, iii) C3> 3.5kg, DZX 5mg/kg/day. DZX responsiveness defined as tolerating a 6-hour fasting study. Efficacy assessed based on number of patients responding to the DZX starting dose. Safety measured based on the number of adverse events in each cohort. Age of HH resolution after passing a fasting study off DZX reviewed.

Results: 99 neonates with gestational age (GA) ranging 30-41 weeks (C1 24; C2 67; C3 8). A safety fast achieved on the starting dose of DZX in 46% of C1, 61% of C2, and 62.5% of C3 neonates. Majority of moderate to late preterm infants (GA 34-38 weeks, n=31/47) responded well to low-dose DZX. All of the very preterm (GA <34weeks, n=5/5) and most of the term (GA>38 weeks, n=16/33) small for gestational age (SGA) neonates required dose increment, with 1/3 achieving safety fast at a dose lower than the STD. Side-effects noticed in 20% of C1; 25% of C2; and 33% of C3. Oedema was the most common side-effect. There were no cases of pulmonary hypertension. The majority of patients (n=97) achieved HH resolution at a similar mean age in all cohorts (C1 5.6 months, C2 5.2 months, C3 5 months). Infants in C2 who responded to DZX low-dose came off treatment earlier (mean age 4.6 months).

Conclusion: Our study demonstrates that DZX low-dose can effectively treat preterm and SGA HH neonates. Close supervision is needed in case dose increments required, especially in the very preterm and term-SGA infants. Adverse events can still be observed with DZX low doses, but at a lower incidence compared to the STD. We recommend starting DZX 2-3mg/kg/day in preterm or SGA HH neonates and up-titrate as needed, to achieve euglycaemia with minimum effective dose, while reducing the risk of side-effects.

P1-97

Different types of gastrostomy device in paediatric patients with hyperinsulism

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Background: Hyperinsulinism (HI) is a major cause of hypoglycaemia during childhood and is related with neurological damage. Among the therapeutic options for HI patients with limited fasting tolerance are intensive feeding regimes, requiring continuous overnight and regular daytime feeds via gastrostomy.Two types of gastrostomy device are commonly used: Freka Percutaneous (FPEG) and Mic-key button (MB). MB is expected to have a higher rate of unintentional dislodgement than PEG.

Aim: To evaluate safety and efficacy of FPEG versus MB, in children with HI.

Method: We identified 33 HI patients with gastrostomy formation. We sent a survey and received responses from 16 patients. Parental consent was obtained. We measured the number of patients with FPEG which switched to MB when older. We also collected data retrospectively regarding complications before and after the device change. Also, parental anxiety about each device management was evaluated.

Results: All patients were informed regarding the gastrostomy device type before insertion. Fifteen patients (94%) had FPEG as initial device, and one patient had MB (6%). Complications related

to the gastrostomy were reported in 19% (3/16) including gastrostomy site infection (1/16), lump (1/16) and buried bumper (2/16). All patients had replacement of their original device at two years after insertion, with 50% (8/16) choosing to remain on FPEG (8/16), 44% (7/16) changing to MB and one 6% (1/16) some other device (Mic-Key transgastric jejunal tube). After the gastrostomy replacement, complications including infection and tube migration into bowel, reported in 19% of our cases (2 FPEG, 1 MB). These complications affected the glycaemic control in 13% (2/16, 1 FPEG, 1 MB) of our cohort. No cases with unintentional dislodgement were reported. There was no parental anxiety about the gastrostomy device in 94% of the cases, while 31% (5/16) of parents reported that gastrostomy has been reassuring for the management of their child's hypoglycaemia due to HI.

Conclusion: Among our HI patients, we noticed that gastrostomy could ensure euglycaemia and minimize parental anxiety. Complications were low for both FPEG and MB. However, observational studies with larger number of patients are needed to assess safety, efficacy and impact in quality of life of MB versus PEG in HI patients. Meanwhile, we recommend FPEG as first choice of gastrostomy in HI patients requiring overnight feeds. FPEG, due to its non-traction removable design is expected to have lower risk of unintentional dislodgement. A structured risk assessment should be considered to support decision for change to MB where appropriate.

P1-286

Sulphonylurea for Improving Neurological Features in Neonatal Diabetes: a systematic review and meta-analyses

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Background: In monogenic diabetes due to KCNJ11 and ABCC8 mutations that impair KATP- channel function, sulphonylureas improve long-term glycaemic control. Although KATP channels are extensively expressed in the brain, the effect of sulphonylureas on neurological function has varied widely. We evaluated published evidence about potential effects of sulphonylureas on neurological features, especially epilepsy, cognition, motor function and muscular tone, visuo-motor integration, and attention deficits in children and adults with KCNJ11 and ABCC8-related neonatal-onset diabetes mellitus.

Methods: We conducted a systematic review and meta-analyses of the literature (PROSPERO, CRD42021254782), including individual-patient data, according to PRISMA, using RevMan software. We also graded the level ofevidence.

Results: We selected 34 of 776 publications. The evaluation of global neurological function before and after sulphonylurea (glibenclamide) treatment in 114 patients yielded a risk difference (RD) of 58% (95%CI, 43%–74%; I2= 54%) overall and 73% (95%CI, 32%–113%; I2=0%) in the subgroup younger than 4 years; the level of evidence was moderate and high, respectively. EEG studies of epilepsy showed a RD of 56% (95%CI, 23%–89%; I2= 34%) in patients with KCNJ11 mutations, with a high quality of evidence. For hypotonia and motor function, the RDs were 90% (95%CI, 69%–111%; I2=0%) and 73% (95%CI, 35%–111%; I2=0%), respectively, with a high level of evidence. Visuomotor coordination seemed improved by sulphonylurea therapy, similarly to ADHD, which is extraordinarily prevalent in patients with KATP-channel mutations.

Conclusion: Glibenclamide significantly improved neurological abnormalities in patients with neonatal-onsetdiabetes due to KCNJ11 or ABCC8 mutations. Hypotonia was the symptom that responded best. Earlier treatment initiation was associated with greater benefits. Diagnosing neonatal diabetes and KATP- channel mutations early is therefore a major goal.

Keywords: Neurological disorders. Sulphonylurea. Neonatal diabetes. Epilepsy. Mental development. Motor development. Attention-deficit disorders.

P1-287

Hyperinsulinism secondary to *PMM2* gene variants: a case series from a quaternary centre reporting associated inflammatory bowel disease and aortopathy

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Introduction: A promoter mutation (c.167G>T) in the phosphomannomutase 2 (PMM2) gene, either homozygous or occurring in trans with a *PMM2* coding mutation, causes hyperinsulinism (HI) and polycystic kidney disease (PKD) – HIPKD. Organ-specific deficiency of *PMM2* leads to the restricted phenotype of HIPKD, without typical clinical features of the Congenital Disorder of Glycosylation Type 1a (CDG1a), which is caused by recessive coding variants in *PMM2*. To date, there are no reports of inflammatory bowel disease (IBD) and aortopathy in relation to HIPKD.

Objectives: To describe the phenotype of HIPKD due to *PMM2* gene variants.

Methods: Retrospective data collection of five patients with HIPKD due to compound heterozygosity for the c.167G>T promoter variant and a missense variant in *PMM2*, managed in a quaternary HI centre.

Results: HI was diagnosed in all cases by 3.5 years, with two presenting in the neonatal period. HI in all patients responded to diazoxide with or without nifedipine. Two are receiving dual therapy, with nifedipine (range 0.66– 1.66 mg/kg/day) allowing diazoxide dose reduction (range 4.16 – 7.39 mg/kg/day). All patients were diagnosed with PKD by the age of 4 years, with three patients diagnosed in the neonatal period. One patient had bilateral nephrectomies and a renal transplant. Four patients have hepatic cysts and two have hepatic fibrosis. Three patients have been diagnosed with Inflammatory Bowel Disease – Unclassified (IBDU), and demonstrate a distinctive pattern of gastric antral inflammatory involvement with foveolar hyperplasia. Dilatation of the aortic root and ascending aorta were found incidentally in two patients - they remain asymptomatic.

Discussion: In HIPKD, HI may present beyond the neonatal period and show variable severity. HI is responsive to diazoxide and nifedipine. The severity of individual organ involvement varies. Our case series suggests that atypical IBD and aortopathy may be additional features of this condition, although the underlying mechanisms are undefined, but presumably relate to abnormal glycosylation. Abdominal symptoms warrant specialist attention and faecal calprotectin may be considered as a non-invasive screening tool for intestinal inflammation if symptoms are suggestive. Monitoring for aortopathy via echocardiogram should be considered.

P1-288

Growth of very low birth weight infants: one year follow-up

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Background: Very low birth weight (VLBW) infants tend to have slower postnatal growth than the fetuses of the same gestational age (GA)[1]. Higher nutrient intake and better early growth are associated with better neurocognitive outcomes; excessive nutrient intakes may lead to metabolic consequences. Nutrient intakes for optimal growth, body composition and neurodevelopment are not known.

Objectives: To assess growth and neurodevelopment of VLBW infants during the first year of life and its relationship with early nutrition.

Methods: 120 VLBW infants were divided into 2 groups: extremely preterm (EP, <28 weeks) and very/moderately preterm (VP). 92 infants completed 12 months follow-up. Nutrient intake was calculated for the first 4 weeks. Growth (weight, length, and head circumference (HC)) was measured weekly until discharge, and at 3,6,9,12 months corrected GA (CGA) and related to healthy infants[2]. Body composition was assessed at discharge by dual X-ray absorptiometry (DXA). Neurodevelopment was assessed at 12 months using Bayley-II.

Results: At birth, $weight_{SDS}$ and $length_{SDS}$ were higher in EP than VP ($p<0.001$, and $p=0.019$, respectively), HC_{SDS} did not differ ($p=0.137$). There was no difference in $weight_{SDS}$, $length_{SDS}$ and HC_{SDS} at discharge or at 12 months CGA. EP infants had higher BMI and body fat at discharge ($p<0.001$), but BMI did not differ at 12 months ($p=0.545$). Acceleration of weight gain and HC growth occurred between 4 weeks and discharge in EP and between discharge and 3 months CGA in VP, while length growth accelerated most between discharge and 3 months in both groups. Nutrient intake during first 4 weeks and neurodevelopment scores at 12 months did not differ between groups. Higher nutrient intake was associated with better in-hospital growth and neurodevelopment scores in EP, but not in VP. In EP higher nutrient intake was not associated with higher BMI or DXA fat mass at discharge, but carbohydrates and fat intake was positively associated with BMI at 12 months CGA ($p=0.003$ and $p=0.013$, respectively). In VP group, protein intake correlated positively with BMI at discharge ($p=0.029$), fat intake - with DXA fat mass ($p=0.021$) but no correlation was found between nutrient intake and BMI at 12 months CGA.

Conclusion: Weight, length, and HC growth patterns are different in GA groups and should be considered when choosing feeding strategies. Nutrient intake should be balanced between improving neurodevelopmental outcomes and potential risk of metabolic syndromes.

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P1-289

Novel Mutations in GLIS3/TRMT10a as a Cause of Congenital Hyperinsulinism

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Introduction: Congenital hyperinsulinism (CHI) is a heterogeneous group of disorders characterized by hypoglycemia and inappropriate insulin secretion. Prompt identification of CHI and its genetic causes are essential to minimize the risk of permanent neurological damage as well as guide treatment options for these patients. Although, there are 15 known monogenic forms of CHI,

there remain 50% of patients without an identified genetic diagnosis, suggesting that there are genetic loci that remain yet to be discovered.

Case: We describe a 4 month old male presenting with new-onset seizures due to hypoglycemia. Lab evaluation was consistent with hyperinsulinism and a trial of diazoxide was pursued. He developed severe thrombocytopenia and was switched to octreotide and continuous feeds. A 98% pancreatectomy was performed and the resected pancreas was consistent with diffuse CHI.

Results: Targeted genetic evaluation was negative and whole exome sequencing of the patient and parents revealed a novel heterozygous mutation in GLIS3 (c.835G>A, p.Glu279Lys) and an extra copy of TRMT10a (entire coding sequence). Using the resected pancreas, we performed deep histological characterization to better understand changes in islet architecture and alterations in transcription factor expression profiles when compared to age matched islet controls. We observed a significant increase in insulin positive cells, along with an increase in polyhormonal cells expressing insulin/glucagon and insulin/somatostatin. Moreover, there was a reduction in pancreatic polypeptide expressing cells. Interestingly, we also observed an increase in ductal marker CK19 expression throughout all regions of the pancreas and increased co-expression of CK19 with single insulin positive cells consistent with nesidioblastosis. Proliferative index through Ki67 labelling was much higher in beta cells of the resected pancreas when compared to age matched controls. Finally, we observed a statistically significant increase in key beta cell transcription factors including FOXA2, PDX1 and NKX6.1.

Conclusion: For the first time, we demonstrate the connection between GLIS3/TRMT10a and CHI, expanding the list of known genetic causes. This case highlights the utility of whole exome sequencing in further identifying novel genetic causes for CHI and the benefits of deep histological characterization to better understand changes in islet architecture and gene expression.

P1-290

Impaired renal clearance among Swedish adolescents born preterm

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Aim: To determine whether adolescents born before 28 gestational weeks have an increased risk for renal impairment.

Methods: Swedish infants, born before 28 gestational weeks in 2001 and 2002, were identified from a local register. A total of 16 children, 12 females and 4 males, were examined at 16–17 years of age with 51Cr-EDTA clearance. A comparison group (n=26) was used.

Results: Most study participants (n = 13) had normal blood pressure; one individual had hypertension stage 1. All study participants had results within the reference interval for ionized calcium, parathyroid hormone, intact fibroblast growth factor-23, and for urinary albumin-to-creatinine ratio. Four out of 16 participants (25%) had a 51Cr-EDTA clearance less than 90 mL/min/1.73m2, indicating a reduced kidney function. However, 13 participants (81%) had an estimated glomerular filtration rate below 90 mL/min/1.73m2. Five study participants (31%) were referred for further investigations. We found a significant difference for the measured 51Cr-EDTA clearance values between the study and comparison groups, P=0.0012.

Conclusion: Swedish children born before 28 gestational weeks have an increased risk of renal impairment later in life, suggesting that the kidney function in these individuals should be assessed, at least once, during adolescence.

P1-291

Bronchopulmonary dysplasia is not related to neurofilament light chain for neuroaxonal damage in preterm infants

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Rationale: Bronchopulmonary dysplasia (BPD) is a common complication after preterm birth that is associated with neurodevelopmental impairment. Neurofilament light chain (NfL) has been identified as a biomarker for neuroaxonal damage in preterm infants, but its relation with BPD has not yet been established. We hypothesized that BPD is associated with increased NfL levels at an early stage, indicative of early neuroaxonal damage.

Table 1. Assocation between BPD diagnosis and NfL levels by time point

	No BPD (n=48)	BPD (n=19)	Crude results			Adjusted results		
	Median [IQR]	Median [IQR]	B	95%-CI	P-value	B	95%-CI	p-value
NFL CONCENTRATION (pg/mL)								
Day 1	19.9 [16.1, 25.5]	26.6 [20.3, 42.8]	1.52	1.03, 2.25	0.04	1.31	0.91, 1.88	0.14
Day 3	56.4 [39.0, 94.2]	106.6 [82.8, 184.1]	1.98	1.40, 2.81	<0.001	1.35	0.90, 2.04	0.15
Day 7	67.2 [53.5, 100.4]	95.9 [76.7, 136.7]	1.49	1.11, 1.99	0.01	1.04	0.75, 1.44	0.83
Day 14	32.2 [24.7, 51.5]	56.4 [30.2, 65.9]	1.57	1.07, 2.32	0.02	1.37	0.85, 2.20	0.20

Methods: In this prospective observational study we included preterm infants born <30 weeks of gestation, admitted to the Neonatal Intensive Care Units of Amsterdam UMC between October 2019 and March 2021. Serum NfL levels were determined using Simoa assay in cord blood and blood obtained at postnatal days 3, 7 and 14. Linear regression analysis was used to compare NfL levels between infants with moderate/severe BPD (BPD group) and infants with no/mild BPD (no BPD group), while linear mixed model analysis was performed to assess the effect of time on NfL levels between the two groups. Next, analyses were adjusted for gestational age (GA) and small for gestational age (SGA).

Results: Sixty-seven infants with a GA of 27±1.3 weeks were included for analysis, of whom 19 infants (28%) developed moderate/severe BPD. Although the NfL levels were significantly higher at every time point in the BPD group, statistical significance was lost after adjusting for GA and SGA (Table 1). No differences were found between the groups in NfL change over time.

Conclusion: We showed that the positive association between BPD and NfL among preterm infants in their first weeks of life could be explained by GA and SGA rather than by the development of BPD.

P1-292

Management and outcomes of congenital hyperinsulinism in infants and young children: a 5-year-experience from the tertiary referral hospital in Indonesia

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Background: Congenital hyperinsulinism (CHI) is a rare condition that becomes the most frequent cause of severe and persistent hypoglycemia in infants and young children. It may lead to debilitating morbidity and mortality if being diagnosed lately. Congenital hyperinsulinism can be caused by monogenic or syndromic disorders. The prevalence of CHI in Indonesia is still unknown. However, the increasing number of cases referred to the tertiary hospital recently may indicate that true prevalence of CHI in Indonesia is predicted to be higher due to underdiagnosis.

Objective: To demonstrate clinical manifestation, responses of medical and surgical intervention in infants and young children with congenital hyperinsulinism in a tertiary referral hospital in Indonesia.

Results: There were 14 cases of hyperinsulinism-induced hypoglycemia from January 2018 until March 2022 in Cipto Mangunkusumo General Hospital. Median age of diagnosis was 90 days with a range between 5 days until 7 years old. Subjects were 7 females (50%) and 7 males (50%). Median insulin level during critical sampling examination was 14.2 μU/mL (5.2-62.2 μU/mL). Majority of the patients (57%) were diazoxide-responsive. Genetic tests revealed that there were 4 patients with ABCC8 mutation (29%), 4 with KCNJ11 mutation (29%), 2 with unknown type (14%), 1 with GLUD1 mutation (7%), 1 associated with Beckwith-Wiedemann syndrome (7%). One patient with KCNJ11 mutation died due to complications of severe infection during hospitalisation. Pancreatic CT-scan or MRI was performed in the majority of the patients. Three patients received surgery management; 2 patients with near-total pancreatectomy and 1 patient with lesion resection surgery. All three patients showed normoglycemia after surgery and thus required no medication. Other 10 patients have been receiving subcutaneous octreotide with doses 5-15 mcg/kg/day without any significant hypoglycemic periods. Cornstarch was also given to 4 patients to keep their blood glucose above the target (> 70 mg/dL).

Conclusion: Congenital hyperinsulinism is a rare disease that needs comprehensive management, including medical treatment, frequent feeding, and pancreatic surgery. Octreotide and cornstarch added to the formula were given to the patients to maintain normoglycemia. Lack of access to diazoxide and PET-scan examination have become major challenges in managing CHI in Indonesia. Surgery management was taken into consideration to save the brain from long-term threatening impact of recurrent hypoglycemia.

P1-293

Placental methylation in the IRS1 gene is associated with obesity parameters in 6 year-old children born to mothers with pre-gestational obesity

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Background: Epigenetic alterations due to maternal obesity may contribute to an increased metabolic risk in the offspring. IRS1 has a critical role in insulin signalling and its methylation has been previously associated with body fat distribution and glucose metabolism in human adipose tissue. The relationship between IRS1 methylation in birth tissues and obesity parameters in the offspring is unknown.

Objective: To identify placental DNA methylation marks associated prospectively with obesity parameters in children at 6 years of age and to analyse whether maternal obesity could modulate these associations.

Methodology: Population-based cohort study of pregnant women and their newborns followed up to 6 years of age. A global methylation array (Infinium® Methylation EPIC BeadChip) was performed in 24 placental samples to identify DNA methylation marks associated with BMI-SDS in offspring at 6 years. Differentially methylated genes were validated by pyrosequencing in 145 additional placental samples from the same cohort. Associations between placental methylation and several offspring obesity parameters [anthropometric data, body composition (by bioelectric impedance), and fat distribution (by ultrasound)] were sought.

Results: The placental methylation array identified 546 CpGs significantly associated with offspring BMI-SDS at 6 years. Among them, a CpGs in the IRS1 gene (FDR = 3.1x10-34, $\beta = 0.793$ and OR = 2.2) was selected because of its high odds ratio (OR) and its role in metabolic regulation.

The validation analyses showed that IRS1 methylation associated positively with several obesity parameters in the offspring at 6 years: BMI-SDS, weight gain from birth-SDS, waist circumference, fat mass-SDS, subcutaneous and pre-peritoneal fat (r from 0.16 to 0.24; all $p < 0.05$) even after adjusting for confounding variables (β between 0.17 and 0.24; all $p<0.05$).

When the results were analysed by subgroups of maternal pre-gestational weight [88 women with normal weight (BMI <25) and 57 women with overweight or obesity (BMI ≥ 25)], associations between IRS1 methylation and obesity parameters in the offspring were more robust in the group of pre-gestational overweight/obese mothers [BMI-SDS, weight gain from birth-SDS, fat mass-SDS, subcutaneous, and pre-peritoneal fat (r between 0.26 and 0.35 all $p<0.05$)].

Conclusions: Placental methylation levels of IRS1 associate with obesity parameters in 6 year-old children, especially in those born to mothers with pre-gestational obesity. We suggest that IRS1 differential methylation is an epigenomic alteration caused by maternal obesity, which could explain, at least in part, the increased risk for obesity in the offspring.

P1-294

Foetal and Neonatal outcome of pregnant women with Thyroid Disorders

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Introduction: Thyroid disorders are the second commonest endocrine dysfunctions encounter in pregnancy after Diabetes. These include overt hypothyroidism, overt hyperthyroidism, subclinical hypothyroidism and subclinical hyperthyroidism. Pregnancy has profound impact on the thyroid gland and thyroid functions (TF). Failure to adapt to these physiological changes result in abnormal TF and cause adverse foetal and neonatal outcomes like miscarriages, placental abruption, preterm delivery, low birth weight <2500g (LBW), neonatal jaundice, respiratory distress and abnormal thyroid functions.

Objective: To compare foetal and neonatal outcome of pregnant women with TD and pregnant women with normal thyroid function test (TFT).

Method: Prospective analytical cohort study conducted in De Soysa maternity hospital in Sri Lanka from January 2018 to January 2021. Included pregnant women with newly diagnosed or existing hypothyroidism (n=186) and hyperthyroidism (n=38) on treatment. Foetal and neonatal outcomes compared with pregnant women with normal TFT (n=186). Trimester specific reference range for TFT as per American Thyroid Association. Occurrence of foetal and neonatal out comes recorded in antenatal and postnatal follow up.

Results: 82% (n=152/186) had overt hypothyroidism and 12% (n=34/186) had subclinical hypothyroidism. 79% (n=30/38) had overt hyperthyroidism and 21% (n=8/38) had subclinical hyperthyroidism.

In hypothyroidism group, pregnancy complicated with gestational diabetes 7.5% (n=14/186), pre-eclampsia 10% (n=19/186), maternal anaemia 6% (n=11/186). Hyperthyroidism group, gestational diabetes 2.5% (n=1/38), preeclampsia 15.7% (n=6/38), anaemia 2.5% (n=1/38). In control group, gestational diabetes 2.5% (n=5/186), preeclampsia 3% (n=6/186), anaemia 1.5% (n=3/186).

Among hypothyroid group pregnancy complicated with miscarriage 3.7% (n=7/186), placental abruption 1% (n=2/186), preterm delivery 5% (n=9/186). hyperthyroid group miscarriage 10.5% (n=4/38), preterm delivery 10.5% (n=4/38). In control

group, miscarriage 0.5% (n=1/186), preterm delivery 6% (n=11/186). Placental abruption not seen among hyperthyroidism and control groups.

Neonates born to hypothyroid women had LBW 11% (n=20/186), jaundice 18% (n=33/186), respiratory distress 7% (n=13/186). Neonates of hyperthyroid women, had LBW 16% (n=6/38), respiratory distress 5% (n=2/38), jaundice 16% (n=6/38). In control group, LBW 9% (n=17/186), Jaundice 15% (n=28/186), respiratory distress 4% (n=8/186). Two neonates (1%) in hypothyroidism group diagnosed with congenital hypothyroidism. Two neonates (5%) from hyperthyroidism group had abnormal TFT at birth which improved within 3 weeks without any interventions. Women with hypothyroidism had majority of maternal, foetal and neonatal complications. Women with hyperthyroidism had highest occurrence of miscarriage and LBW.

Conclusion: Our study concludes that occurrence of adverse outcomes comparatively higher among women with TD. It is important to create awareness and to implement TFT as routine antenatal screening.

P1-295

Continuous Glucose Monitoring for hypoglycaemia: the unheard patient voice

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Background and Aims: Hypoglycaemia is a constant threat for all patients with congenital hyperinsulinism (CHI) and, left untreated, can lead to neurological damage and impaired development. To improve glycaemic monitoring, self-monitoring-blood-glucose (SMBG) is increasingly being replaced by Continuous Glucose Monitoring (CGM) with potential to identify illness patterns and treatment responses although with unproven benefit for patients and families. Explorations of families' experiences have focused on those presently using CGM rather than those who have declined regular use. In contrast, our study eliminates positive bias to focus on families who have discontinued CGM and thus provides an essential alternative perspective of CGM use.

Methods: Families of patients with CHI treated in two specialist centres, who had used but discontinued CGM, were contacted for a semi-structured interview over a two month period. Families' experiences and narratives were transcribed in real time and analysed for themes.

Results: Of the 14 families eligible for inclusion, 10 were contactable and all agreed to take part. Mean age (range) of patients was 7 years (1 – 18 years). Known CHI-causing genetic mutations were present in 5 patients and all patients received disease modifying therapy for CHI. Dexcom G6 CGM had been used in all patients for a mean (range) duration of 91 (0-202) days (median 55). The primary themes identified were: pain; inaccuracy and device set up.

Pain was experienced by 4/10 (40%) participants and included siting and removal of the sensor as well as pain whilst in situ. Inaccuracy was a primary complaint for 9/10 (90%) participants, specifically around falsely low readings. All participants commented that device set up could be much improved upon: receiver device range; sensor changes; and usability by children were all cited as reasons for stopping CGM use.

Of this group, 7/10 (70%) believed that older patients might have better tolerance although, contrastingly, 2/10 (20%) believed tolerance would be better if the patients were younger. Importantly, 7/10 (70%) parents commented that they would like to use CGM for ongoing monitoring but devices were not sufficiently convenient to convince young patients.

Conclusions: Whilst many families with CHI continue to benefit from CGM, it is vital to understand perspectives from families who have discontinued use. The unheard patient voice has highlighted problems with CGM application that include pain, inaccuracy, range anxiety and non-adherence in younger children. These issues must be addressed if children with hypoglycaemia disorders are not to be left behind.

P1-486

Salivary Sex Steroid Levels in Infants During Minipuberty and Their Relationship with Infantile Colic

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Background: The etiology of infantile colic is unknown. Its timing overlaps with that of minipuberty. To the best of our knowledge, the relationship between these entities has not been investigated. In this study, we aimed to assess the relationship between minipuberty and infantile colic by measuring the levels of sex steroids in saliva among infants with and without infantile colic.

Methods: Saliva samples were collected from 15- to 60-day-old term infants (n=139) between 9 am and 5 pm. Group 1 included infants with infantile colic diagnosed according to the Rome IV criteria (n=68, male:31, female:37). Remaining healthy infants constituted Group 2 (n=71, male:37, female:34). The salivary levels of estradiol (E_{sal}) in females and testosterone (T_{sal}) in males were studied in duplicate by using the ELISA method. Demographic features and findings of physical examination and laboratory studies were compared between the two groups. Correlation analyses were performed while controlling for the effects of significant associations.

Results: The median (25^{th}-75^{th} centile) age and birth week for all infants were 33 (29-43) days and 39 (38.1-40) weeks, respectively. The demographic features of the groups were similar except for a median of 5 days earlier birth in the girls in Group 1 ($p<0.001$). T_{sal} in males showed a negative correlation with age (r_s=-0.622, $p<0.001$) while E_{sal} showed a similar tendency (r_s= -0.224, p=0.061). T_{sal} in males (Group 1, 73.35 pg/mL vs Group 2, 77.66 pg/mL, p=0.956) and E_{sal} (Group 1, 3.91 pg/mL vs Group 2, 4.03 pg/mL, p=0.683) in females did not differ between the groups. However, only in Group 1, E_{sal} and body mass index (BMI) standard deviation scores were positively correlated (r_s= 0.393, p=0.016) and there was a significant correlation between the sampling time and T_{sal} (r_s=0.469, p=0.009).

Conclusion: The levels of sex steroids in the saliva of subjects with infantile colic were not different from those of the control infants. On the other hand, only among subjects with infantile colic, salivary estradiol levels and BMI of females were significantly correlated. We also observed that the later the sampling was done in the day, the higher the salivary testosterone levels in males were. Therefore, our findings suggest the presence of a relationship between minipuberty and infantile colic.

P1-487

Early-life exposure to phthalates in a population of infants from the North of Italy: Characterization and time trends

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Background: Phthalates are ubiquitous environmental contaminants and endocrine-disrupting chemicals (EDCs). Nowadays, they are considered reproductive toxicants and in-utero exposure is well documented, although evidence of early life exposure is scarce, and needs to be described. Aim of this study is to assess phthalate exposure and its changes over the first months of life in a cohort of healthy full term infants and their mothers from a restricted area of the north of Italy.

Methods: Single-center, prospective birth-cohort study, assessing phthalate exposure in urine samples collected from mothers after the delivery and in their infants at birth(T0), 3(T3) and 6(T6) months. In infants, the collection was performed using phthalate-free bags. After solid-phase extraction, samples were analysed by triple Quad LC/MS Mass Spectrometry.

Results: 188 mother-infant pairs were enrolled. Data are summarised in the table. % represents the amount of positive detection (>LOD) for each sample. Significant associations between mother-infant pairs at birth were found for MMP, MEP, and MnBP. Significant relation in infant levels of phthalates at 3 and 6 months are represented by the 'p' column of the table, suggesting a continuative exposure to these chemicals during the indoor activities.

Conclusions: Phthalate exposure appears wide and extended over the first months of life. The exposure included phthalates more toxic and strictly regulated by the European Union that are still ubiquitous in unregulated consumers' products. A long term follow-up for at-risk categories, as infants who spend long time in indoor activities, is needed to detect endocrine and neurodevelopmental effects. Our results suggest the need for public health preventive actions to protect vulnerable subjects.

	MOTHER		NEWBORN/INFANT						
	T0		T0		T3		T6		
ng/ml	%	Mean (±SD)	%	Mean (±SD)	%	Mean (±SD)	%	Mean (±SD)	P
monomethyl phthalate(MMP)	66	0.504±0.61	66	0.469±1.01	85	0.500±0.86	95	0.992±2.58	0.004
monoethylphthalate(MEP)	100	45.789±148.21	100	31.572±40.72	100	56.442±178.86	100	86.649±263.11	0.037
mono(2-ethylhexyl)phthalate (MEHP)	32	1.547±1.89	24	1.233±0.99	18	2.186±2.36	41	1.230±1.26	<0.001
mono-(2-Ethyl-5-hydroxyhexyl) phthalate(MEHHP)	98	3.370±10.29	94	2.331±3.44	94	1.282±1.56	99	4.016±5.27	<0.001
mono-(2-Ethyl-5-oxohexyl) phthalate(MEOHP)	100	2.629±5.91	98	1.626±2.66	98	1.189±1.43	100	3.243±3.64	<0.001
mono-n-butylphthalate(MnBP)	94	12.093±27.31	93	14.471±17.47	100	5.496±10.75	100	6.809±10.46	<0.001
monobenzylphthalate(MBzP)	99	3.648±3.28	99	6.673±8.35	94	2.322±6.40	98	2.555±3.58	<0.001

P1-488

Very preterm infants developing BPD have increased levels of the cortisol precursors 17-OH progesterone and 11-deoxycortisol

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Rationale: Bronchopulmonary dysplasia (BPD) is a major complication of preterm birth, which pathophysiology involves systematic inflammation. Preterm infants commonly suffer from relative adrenal insufficiency (RAI) in their first week of life, resulting in an insufficient production of cortisol inappropriate for the degree of inflammation. One of the major causes of RAI is immaturity of adrenal cortex enzymes, leading to an accumulation of cortisol precursors relative to cortisol. A low cortisol concentration, in the presence of excess cortisol precursor levels, likely results in reduced glucocorticoid receptor signaling, and consequently an imbalance between inflammation and anti-inflammation. We hypothesize that this phenomenon could contribute to the development of BPD.

Methods: Preterm infants born <30 weeks of gestation and admitted to the Neonatal Intensive Care Units of the Amsterdam UMC between October 2019 and March 2021, were included in this prospective observational study. Serum cortisol, 17-OH progesterone (17-OHP) and 11-deoxycortisol levels were measured in cord blood and blood obtained at postnatal days 3, 7, 14 and 28 by liquid chromatography-tandem mass spectrometry. Hormone levels measured after administration of postnatal corticosteroids were excluded. Non-parametric tests were used to compare hormone levels between infants with and without BPD. BPD diagnosis was defined as the need for >21% oxygen for at least 28 cumulative days, and the need for oxygen or respiratory support at 36 weeks postmenstrual age.

Results: Sixty-eight infants with a gestational age of 27±1.3 weeks were included for the analysis, of whom 21 (31%) developed BPD. Cortisol levels did not differ between the two groups, but 17-OHP and 11-deoxycortisol levels were significantly higher in the BPD group compared to the no BPD group at day 3 (17-OHP 16.6 [10.8-25.4] versus 9.4 [5.7-15.0] nmol/L, p-value 0.007; 11-deoxycortisol 6.9 [5.6-10.2] versus 5.1 [3.8-7.5] nmol/L, p-value 0.009) and day 7 (17-OHP 14.3 [10.0-23.2] versus 9.4 [6.1-14.1] nmol/L, p-value 0.015, in the BPD group and the no BPD group, respectively).

Conclusion: Compared to preterm infants without the diagnosis BPD, preterm infants with BPD had higher levels of cortisol precursors in their first week of life, but similar cortisol levels. These findings suggest that the development of BPD is accompanied by excess levels of cortisol precursors relative to cortisol, suggestive of a more active hypothalamus-pituitary-adrenal axis that could not fulfill the high cortisol demands in tissues. This biological profile is likely to predispose to more inflammation and BPD.

P1-489

Longitudinal Growth Pattern in Children Born Large for Gestational Age

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Background: Abnormal birth weight, either small- or large for gestational age, has been influenced on long term heath. Previous data demonstrated small for gestational age infants have greater risk for developed obesity and metabolic diseases later in life but little was known in large for gestational age (LGA) babies.

Objective: To study the growth pattern of children born large for gestational age from birth until age of 8 years.

Methods: This study was a retrospective study. Data including weight, length/height, maternal history of gestational diabetes mellitus (GDM) of LGA infants who was born in Phramongkutklao hospital between January 1, 2007 and December 31, 2017 were reviewed.

Results: Two hundred and fifty-two LGA newborn were included. Of them, 159 (63%) were male. Gestational age at birth and birthweight were 39.3 weeks and 4,200 + 200 g, respectively. Sixty percent had birthweight 4,000-4,200 g and maternal GDM was found in 12.7% of subjects. Longitudinal growth pattern demonstrated mean BMI Z-score were decreased from birth to normal range during age 6 months to 1 year then re-increased after age of 2 years. Haft of LGA infants remained overweight/obesity until age of 8 years. The prevalence of overweight/obesity at age 6 months, 1, 2, 3, 4 and 6-8 years were 48.4, 47.4, 63, 48.8, 45.9 and 55.6%, respectively. Overweight/obesity at age 1 year were 4.2 greater risk of overweight/obesity after age of 4 years. LGA born from maternal diabetes have significant higher birthweight and BMI Z-score at birth, 2, 3 and 6-8 years compare to LGA born from maternal without diabetes.

Conclusion: LGA infant remain overweight and obesity until age of 8 years. Factor associated greater risk of overweight and obesity were maternal diabetes, BMI Z-score and overweight/ obesity at age 1 year.

P1-490

Delayed-onset Transient Hyperinsulinism in VLBW and ELBW Neonates

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Background: Transient hyperinsulinism (THI) is a hypoglycemia disorder manifesting during the first days of life and usually resolving within the first weeks or months of life. Neonates exposed to pre- or perinatal stress have a higher risk to develop THI. However, the exact pathomechanism has not been elucidated yet. The objective of this study was to analyze the clinical and biochemical data of neonates with THI and a birth weight <1500 g.

Methods: The electronic patient data base of the University Hospital Düsseldorf was searched for children born between 01/2013 and 12/2021 with a birth weight <1500 g and <1000 g (very low/extremely low birth weight; VLBW/ELBW) and a diagnosis of THI.

Results: Sixteen neonates (5 female) were identified. Median gestational age was 27+2 weeks (range: 24+0-33+6) and median birth weight was 970 g (range: 490-1470 g). 5/16 were small for gestational age (birth weight <10^{th} percentile). Median age at first registered hypoglycemia ≤45 mg/dl (age >3 hours of life) was 27 days (range: 6-52 days) and occurred in 13 neonates at a median of 16 days after cessation of regular parenteral nutrition. All neonates received carbohydrate-enriched meals to treat hypoglycemia. In addition, 6 neonates received intravenous (i.v.) glucose plus diazoxide, 3 received i.v. glucose plus subcutaneous (s.c.) glucagon, 4 were either treated with i.v. glucose, s.c. glucagon, diazoxide or octreotide. Two neonates were stabilized on carbohydrate-enriched meals. Mean maximum total glucose intake was 25 g/kg/d (range: 20.1-29.8 g/kg/d). In 14 infants THI resolved before first hospital discharge at a median age of 98 days (range: 29-147 days). Two infants were discharged home with diazoxide.

Conclusion: In comparison to term born or late preterm neonates, who usually have an onset of THI on the first day of life, VLBW and ELBW neonates show a distinctly delayed onset of THI. Severity varies widely ranging from mild forms requiring only carbohydrate-enriched meals to severe forms requiring intense medical treatment and high glucose intake. Interestingly, the manifestation of THI accompanies clinical stabilization and, in most cases, is not directly time-related to the cessation of parenteral nutrition. The pathomechanism of the delayed onset remains to be clarified. It might be possible that postnatal/extrauterine stress caused by prematurity and associated problems such as ventilation, infections, etc. lead to a predisposition to THI, as seen in term or late preterm born neonates in association with prenatal/intrauterine stress.

P1-491

Utilizing PES hypoglycemia guidelines to evaluate presence of known risk factors in HI Global Registry participants

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Congenital Hyperinsulinism (HI) causes severe hypoglycemia. In most countries, the estimated incidence of HI is approximately 1/25,000 to 1/50,000 births, classifying it as a rare disease. According to Pediatric Endocrine Society (PES) Guidelines, neonates should be screened for hypoglycemia if they have any of the following: symptoms of hypoglycemia, large for gestational age, perinatal stress, premature or postmature delivery, infant of diabetic mother, family history of a genetic form of hypoglycemia, or congenital syndromes or abnormal physical features. The aims of this study were to determine if Congenital Hyperinsulinism International HI Global Registry (HIGR) participants had documented hypoglycemia risk factors as defined by PES and if these neonates were screened for hypoglycemia prior to discharge from their birthing facility. This study utilized HIGR participant online survey data collected from individuals with HI or their parents between 2018-2022. All variables were categorical data analysis was conducted in Stata, and Chi-square analysis was completed. Of 169 participants, 76.9% (n=130) had an identified risk of hypoglycemia as defined by the PES guidelines. These included 26.3% who were premature, 16.1% who had mothers with diabetes, 26.2% were large birthweight babies, 48.6% were unable to maintain sugar above 50mg/dL (2,8 mmol/l or 0,5 g/L) before usual feed up to 48 hours of age, and 34.5% were unable to maintain sugar above 60 mg/dL (3,3 mmol/l or 0,6 g/L) before usual feed over 48 hours of age. Of those who had one or more of the identified risk factors, 64.6% (n=84, p<.001) reported that the individual with HI was identified as being at risk prior to leaving the birthing facility. This means that 27.2% (n=46) had a known risk as defined by PES guidelines but were not identified prior to leaving the birthing facility. Additionally, 32.9% (n=53) of individuals did not have an abnormal blood glucose test recorded before leaving the birthing facility or being released to parent care, of whom 47.17% (n=25, p<.001) had a known risk factor. Only 22.6% (n=38) of these neonates had a fasting study before leaving the birthing center, of which 94.7% (n=36) had an identified risk factor. Additionally, 66.7% (n=68) of individuals who had an abnormal blood glucose test did not have a fasting study before leaving the birthing study (p<.001). It is critical to identify the signs and symptoms of hypoglycemia and to manage hypoglycemia from HI in neonates to avert preventable brain damage.

P1-492

A Uniquely Mild Presentation of Hyperinsulinemic Hypoglycemia Due to a *HADH* Mutation (c.709+39C>G) Not Treated with Diazoxide: Long Term Clinical Course

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Short-chain L-3-hydroxyacyl-CoA (SCHAD, HADH) deficiency is characterized by diazoxide-responsive hyperinsulinemic hypoglycemia in the neonatal or infancy periods. These patients have severe protein (especially leucine) sensitivity. HADH mutations are recessively inherited with less than 50 patients reported so far. The mechanism behind unregulated insulin secretion in SCHAD deficiency is not understood but may involve changes in protein-protein interactions with glutamate dehydrogenase (GDH).

An 11.3 year-old-boy presented to the pediatric endocrinology clinic with a recent attack of weakness, sweating and pallor with glucose stick test of 44 mg/dl, treated by sweets intake. The event occurred after having his meal and following intense physical activity. His past medical history revealed recurrent unpredictable episodes of hypoglycemia since the age of 1.8 years. The first episode was the most severe manifesting with loss of consciousness and atonia, necessitating treatment by intravenous fluids infusion at hospital, but later episodes manifested only with lethargy and the desire for sweets intake. Fasting blood glucose was always normal. A starvation test was performed by his pediatrician at the age of 9 years after a second severe attack of pallor, sweating and sleepiness with blood glucose of 35 mg/dl. Blood glucose at the end of 12-hr starvation test was 99 mg/dl, insulin was elevated 43.6 mU/ml (normal <28.4), C-peptide 8 ng/ml (normal 0.9-7.1), Cortisol 45.8 mcg/dl (normal 5-25), GH 1.9 ng/ml, ammonia and lactate were both normal. Taking a detailed history revealed that his last two episodes of hypoglycemia at ages of 9 and 11 years occurred after having a high-protein meal (barbecue) followed by intense physical activity which raised the possibility of a HADH mutation, this differential diagnosis was also supported by the parents' consanguinity. Genetic testing identified a previously reported homozygous HADH splicing mutation, c.709+39C>G. Both parents were heterozygous. Parents were advised to start treatment with diazoxide, but as the hypoglycemic episodes became rare, they decided not to treat him. The patient is currently 18 years of age and in good health. He is in his final year at school with good performance. He only reports rare mild episodes of fatigue resolving spontaneously after sweets intake.

Finally, we report a mild case of hyperinsulinemic hypoglycemia due to a splicing HADH mutation that presented beyond infancy and ameliorated over long-term follow-up despite no treatment.

P1-493

Families' experiences of continuous glucose monitoring in the management of congenital hyperinsulinism: A thematic analysis

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Background and Aims: In patients with congenital hyperinsulinism (CHI), recurrent hypoglycaemia can lead to longstanding neurological impairments. At present, glycaemic monitoring is with infrequent fingerprick tests; a practice which can miss hypoglycaemic episodes between tests. Continuous glucose monitoring (CGM) is a promising alternative method which has the utility to identify risk and patterns of hypoglycaemia. Although CGM is well established in type 1 diabetes, its use has only been described in small studies in patients with CHI. In such studies, medical perspectives have been provided while ignoring the views of families using CGM. Within this qualitative study, we have aimed to explore families' personal experiences of using CGM in order to inform future clinical strategies for the management of CHI.

Methods: Ten patients with CHI in a specialist centre using CGM for sixteen weeks as a glucose monitoring tool were invited to participate. Audio-recorded semi-structured interviews were conducted with nine families in whom patient ages ranged between two and seventeen years. Transcripts of the audio recordings were coded and analysed using an inductive thematic analysis method.

Results: Analysis revealed five core themes: CGM's function as an educational tool; behavioural and routine changes; positive family experiences; negative family experiences and end users' design improvements. Parents reported that close monitoring and retrospective analysis of glucose trends allowed for enhanced understanding of factors that influenced glucose levels at various times of the day. They noted more hypoglycaemic episodes than previously encountered through fingerprick home glucose tests; this new knowledge prompted modification of daily living routines to prevent and improve the management of hypoglycaemia. CGM use was viewed favourably as offering parental reassurance, reduced fingerprick tests and predictive warnings. However, families also reported unfavourable aspects of alarms and questionable accuracy at low glucose levels. Adolescents were frustrated by the short proximity range for data transmission resulting in the need to always carry a separate receiver. Overall, families were positive about the use of CGM, but expected application to be tailored to their child's medical condition.

Conclusions: Patients and families with CHI using CGM noticed trends in glucose levels which motivated behavioural changes to reduce hypoglycaemia. Participants generally found that the advantages of CGM outweighed the disadvantages.

Families expressed that CHI-specific modifications and improved accuracy would enhance their experience. Future design of CGM should incorporate end users' opinions and experiences for optimal glycaemic monitoring of CHI.

P1-494

Postnatal growth pattern in (N=51) infants of non-diabetic mothers (INDM) who were born preterm or near term and had significant neonatal hypoglycemia

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Prematurity is a risk factor for significant hypoglycemia even in infants born to non-diabetic mothers (INDM) which could lead to postnatal growth abnormalities.

This study evaluated the growth pattern from birth until the age of 2 years of 51 INDM who were born preterm or near term and admitted with significant hypoglycemia.

Anthropometric measures (z scores) from birth, 2,4,6,12,18 and 2 years were measured in 51 INDM who admitted with neonatal hypoglycemia (plasma value less than 20-25 mg/dL (1.1-1.4 mmol/L)) that required proper therapy (IV glucose bolus followed by IV glucose infusion) for two days or more. Their anthropometric data were compared to standard growth for normal age and sex-matched infants (WHO growth standards). All preterm babies were started on preterm formula until their WAZ became >-1 SD. (average of 6 months)

Results: At delivery, gestational age (GA) was 36.7 +/-2.44 weeks. They had Weight Z score (WAZ) = -2.21 +/-2.02, length Z score (LAZ) = -1.9 +/-2.4 and Weight for length Z score (WLZ) =-2.47 +/-2.07.

At birth 28/51 (55%) had LAZ <-2, 35/51 (69%) had WAZ < -2 and 32/51 (63%) had WLZ <-2. They had a progressive gain in WAZ for the first 18 months (from -2.21 to 0.05). They had a progressive increase in the LAZ for the first 12 months (from -1.9 to -0.5) followed by stable LAZ (normal growth velocity) until 2 years of age. By the age of 12 months 6/51 (12%) had LAZ < -2, 4/51 (8%) had WAZ <-2 and only one had WLZ <-2. None of the infants had WLZ > 2. By the age of 2, none had LAZ, one infant had WAZ <-2, and only one infant had WLZ <-2. None of those infants had WLZ > 2 (overweight).

Age (mon)	Birth	2	4	6	12	18	24
WAZ	-2.21	-1.82	-1.21	-0.9	-0.12	0.05	-0.23
WLZ	-2.47	-0.05	-0.17	-0.19	0.14	0.28	-0.16
LAZ	-1.9	-2.02	-1.47	-1.13	-0.49	-0.39	-0.46

Conclusion: Preterm or near-term babies born for non-diabetic mothers with severe neonatal hypoglycemia had significant growth impairment when plotted on WHO growth charts. The use of the preterm formula results in a fast normalization of their growth in the first year of life with no apparent risk of being overweight at 2 years of age.

P1-495

A case report of hyperinsulinemic hypoglycemia caused by a heterozygous novel mutation in the insulin receptor gene

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Introduction: Mutations in the insulin receptor (INSR) gene usually progress with insulin resistance and hyperglycemia. However, rare heterozygous INSR gene mutations that cause hyperinsulinemic hypoglycemia (HH) have also been described. A case with hyperinsulinemic hypoglycemia due to a new variant mutation in the INSR gene, is presented.

Case: A 13-month-old male patient was referred to us with complaints of contractions in his entire body and low blood sugar in his history. He was born 3900 grams with spontaneous vaginal delivery as term birth. He had a similar seizure history 1 month ago. In family history; There was no consanguinity between father and mother. His father had a growth hormone treatment history and he had iris coloboma. Anthropometric measurements; Height: 78 cm (SDS: 0.24), weight: 12.1 kg (SDS: 1.08), head circumference: 45 cm (SDS: -0.37) was normal. In the physical examination of the patient, anterior fontanel was 0.5*0,5 cm open, elongated penis length was 3,5 cm, testicles were bilaterally palpable, other system examinations were normal. Laboratory values measured in hypoglycemic state (glucose: 35 mg/dL) are given in the table. In addition, the patient's metabolic tests (tandem, blood amino acid, urine organic acid, ammonia) were normal.

Hormonal Tests	Patient Results	Reference Ranges
İnsulin	7,6	(2,4-23,3)uU/mL
Cortisol	3,9	1,7-14,4ug/dL
C-peptide	1,68	(0,78-5,19) ng/mL
Growth hormone	4,1	(0,10-6,20) ng/mL
Lactic acid	11,8	(4,5-19,8) mg/dl
Adrenocorticotropic hormone	12,5	<46pg/mL
Thyroid stimulating hormone	0,69	0,66-4,75 uIU/mL
Thyroxine	12,1	15-20,4 pmol/L
Insulin like growth factor binding protein 3	3,04	0,8-3,9mg/L

Hydrocortisone and diazoxide treatment were started simultaneously because the cortisol levels measured at the time of hypoglycemic attack were 3.9 ug/dL (low) and insulin was 7.6 uU/mL. Abdominal ultrasound was requested for the examination of pancreatic anomaly and it was found to be normal. Genetic result showed in INSR NM_000208.2 Exon 20 c.3634G>A p mutation. A

new mutation was detected in Val1212lle. During the follow-up the basal cortisol value measured was 16.2 ug/dL. After this result and genetical diagnosis, hydrocortisone treatment was discontinued and diazoxide treatment was continued. The patient's blood sugar is followed closely, and the follow-up continues in terms of conversion to diabetes.

Conclusion: In conclusion, heterozygous INSR gene mutation causing hyper insulinemic hypoglycemia was detected in our case. This case is presented because INSR mutations are rare in the etiology of hyperinsulinism in hypoglycemic patients and also the detected mutation is new.

GH and IGFs

P1-98

Supporting the mental wellbeing of caregivers of children under growth hormone treatment: mix-methods evaluation of the Adhera® Caring Program

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Background: The emotional distress of caregivers (i.e., parents) of children with long-term conditions affects their self-management behaviors, including treatment adherence. These conditions are diverse and prevalent, including diabetes, obesity, and growth hormone disorders (GHD). The caregivers' emotional well-being is then a core aspect of their own quality of life, and their children's. Emerging digital therapeutics solutions may improve such caregivers' distress, leading to better adherence. The Adhera® Caring program is a mobile-based digital therapeutics solution for caregivers. This program includes: 1) self-management education, 2) mindfulness-based cognitive behavioral therapy. and 3) personalized motivational messages. The selection and personalization of the motivational messages were powered by Adhera Health's Health Recommender System which uses the caregivers' profiles and their message rating history to find the most relevant messages for them using a machine learning approach.

Aim: To assess the feasibility of using Adhera® Caring to support the mental wellbeing of caregivers of children with GH treatment as part of regular clinical practice.

Methods: A mixed-methods approach with two sub-studies (Clinical Trial Registration: NCT04812665). Caregivers of children with GHD that use the easypod® (Merck KGaA, Darmstadt, Germany) injection device with sub-optimal adherence are identified in the easypod® Connect Dashboard – a software providing access to patient adherence data. The first sub-study consists of a trial with caregivers (n=10), who were onboarded to the Adhera® Caring Program by their healthcare professionals. After 30 days, a semi-structured interview was conducted. The second sub-study consists of a prospective non-randomized study for the same type of caregivers (n=55) using the digital solution to assess their engagement, treatment adherence, quality of life, and mental well-being using validated questionnaires.

Results: The first sub-study was completed in 2021, showing a high engagement of caregivers with the solution (more than 90% adherence to educational content). The thematic analysis of the interviews revealed that some caregivers had negative emotional experiences (e.g., fear of needles) prior to enrolling in the digital program - often linked to poor child-parent communication. However, the Adhera® Caring Program's actionable education contents and mental well-being activities were useful to reduce the stress related to their child's condition self-management and the injection-related stress. The results of the second sub-study are expected by Q3 2022.

Conclusion: The Adhera® Caring Program shows a promising potential to support the emotional self-management of caregivers of children undergoing long-term pharmacological treatment.

P1-99

Survey to Investigate Adherence to Growth Hormone Treatment in Children: The Impact of COVID-19 Pandemic

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Introduction: Treatment adherence is crucial for the success of Growth Hormone (GH) therapy. Non-adherence rates have varied over a wide range from 5% to 80% in the literature. Several factors may have an impact on treatment adherence. Besides, with the COVID-19 pandemic that affected the whole world, there were problems with the hospital admission and routine controls of the patients who used GH treatment.

Objective: The survey's primary objective is to investigate adherence to treatment in patients with GH. The survey will also investigate potential problems in GH treatment during the pandemic.

Materials and Methods: The survey was sent to pediatric endocrinologists. Patient data, diagnosis, history of pituitary surgery, current GH doses, duration of GH therapy, who administers the therapy (mother and father, patient), duration of missed doses, reasons for missed doses as well as problems associated with GH therapy, and missed dose data in the recent year (after the onset of the pandemic) and causes were asked. The treatment adherence category was determined based on missed dose rates over the past month (0 to 5%, full adherence; 5.1 to 10% moderate adherence; >10% non-adherence).

Results: 427 cases from thirteen centers were evaluated. The median age of diagnosis of the cases (56.2% male) was 8.5 (0.13-16) years. GH treatment indications were isolated GH deficiency (61.4%), multiple pituitary hormone deficiency (14%), Turner syndrome (7.5%), idiopathic GH deficiency (7.5%), and SGA (2.8%), and other (6.8%). GH therapy was administered by 70% parents and 30% patients. Mean daily dose was 32.3 mcg/kg, the annual growth rate was 7.52±2.7 cm. GH adherence rate was good (70.3%), moderate (14.7%), and poor (15%), respectively. The reasons for non-adherence were mainly due to forgetting, being tired, inability to access medication, and pen problems. It was noteworthy that the COVID-19 pandemic had a negative effect on adherence in 22%. The problem with an appointment, taking the medication, and anxiety about going to the hospital were the main reasons. There was no difference between genders in the adherence rate. Non-adherence to GH treatment decreased statistically when the patient administered the treatment, increased age, the duration of the treatment, and COVID-19 pandemia. A non-statistical decrease was found in the annual growth rate as the skip rate increased.

Conclusion: During the COVID-19 pandemic, poor adherence was found to be 15%, and the duration of hormone use and advanced age are important factors. The pandemic period negatively affected compliance.

P1-100

Aetiology of familial short stature in children diagnosed with growth hormone deficiency: what do the genes tell us?

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Introduction: The diagnosis of growth hormone deficiency (GHD) is complex, involving the combination of auxological, laboratory, and radiological findings. This includes growth hormone (GH) stimulation tests, which are done to confirm the diagnosis. It has been discussed that these tests have low specificity, potentially leading to false positive results. Therefore, children with GHD are regarded as a heterogeneous group with varied causes of short stature. Next-generation sequencing (NGS) methods have the potential to elucidate the genetic aetiology in these patients.

Aims: To search for the genetic background of growth disruption in children with familial short stature (FSS) and diagnosed GHD.

Patients and Methods: From 747 children treated with GH in our center, 64 with FSS (life-minimum height in child and his/her shorter parent <-2 SD) and diagnosed GHD (stimulated GH cut off <10 ug/L in two tests with priming if appropriate) were enrolled to the study.

Before treatment with GH, the median height of the study cohort was -3.1 SD (IQR -3.6 to -2.7 SD), their IGF-1 concentration was -1.4 SD (IQR -2.0 to -1.2 SD) and maximum stimulated GH was 6.4 ug/L (IQR 4.8-7.9 ug/L). None of the children had multiple pituitary hormone deficiency or a pathology in the midbrain region on MRI. Patient DNA was analysed by targeted NGS panel containing 398 genes known to influence growth. All the variants with potential clinical significance were evaluated by the American College of Medical Genetics (ACMG) standards.

Results: Causative variants in genes affecting growth were found in 21/63 children. Among them, only two (10%) had a variant in a gene involved in the secretion or function of GH (*GHSR* and *OTX2* genes). Interestingly, 15 (71%) patients had a primary defect in the growth plate (genes *ACAN*, *COL11A1*, *COL11A2*, *COL1A2*, *COL2A1*, *EXT2*, *FLNB*, *FGFR3* [2x], *NPR2* [3x], *NF1*, *PTPN11* [2x]), 2 others (10%) had variants in genes impairing IGF-1 action (*IGFALS* a *HGMA2*) and two (10%) had syndromic short stature (genes *MBTPS2*, *SALL4*).

Conclusion: The genetic findings did not correspond with the diagnosis of GHD in most cases of FSS. The results reopen the question about the reliability of standard methods currently used to diagnose GHD.

P1-101

A rare heterozygous *IGFI* variant causing impaired IGF-I cleavage and postnatal growth failure: a novel disease mechanism with insights into IGF-I physiology

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Background: Pathogenic *IGFI* gene mutations causing childhood growth failure are rare. Only 5 autosomal recessive mutations, one *IGFI* copy number variant and 2 heterozygous frameshift mutations are reported. Heterozygous missense *IGFI* mutations have not previously been described.

Objectives: To identify and functionally characterise a novel missense *IGFI* variant in a patient with postnatal growth failure and delayed bone age. The patient had a normal birth weight (-0.2 SDS) but poor growth was observed from a few months of age. Height was -3.4 SDS and head circumference -1.6 SDS at 10 years of age. She had no dysmorphic features and normal development. Bone age was delayed by 2.5 years. A high peak GH was observed (17.1mcg/L). Baseline IGF-I levels were low/normal (144micrograms/L; -1.3 SDS) and responded poorly (increase <15micrograms/L) following IGF-I generation testing.

Methods: The patient was assessed on our unique targeted short stature gene panel. Functional analysis was performed using immunocytochemistry and furin cleavage assays. For the immunocytochemistry, HEK293T cells were transfected with wild-type and mutant *IGFI* constructs containing FLAG and HA tags. For the furin cleavage assays, whole cell lysates from HEK293T cells transfected with streptomycin tagged wild-type and mutant IGF-I constructs were incubated with furin to assess cleavage at the target site. IGF-I constructs designed for the furin assay lacked the signal peptide, meaning they could be harvested from the cell lysate and would not be secreted from the cell. Detection of constructs was performed by Western blot with 16% tricine gels to optimise separation of small proteins. Relative quantities were assessed using Image J analysis.

Results: We identified a novel heterozygous *IGFI* variant (102813333C>T, c.356G>A, p.R119H) which was exceedingly rare (gnoMAD frequency 0.004%) and predicted damaging by SIFT (CADD score 32). The p.R119H variant changed the first amino acid of the IGF-I E domain, the most critical residue for furin binding and highly conserved across species. Furin cleaves pro-IGF-I to mature IGF-I (E domain removal). Functional analysis showed that both wild-type and mutant IGF-I are able to translocate to the endoplasmic reticulum. Furin cleavage assay showed reduced cleavage of mutant p.R119H IGF-I compared to wild-type.

Conclusions: We report the first missense variant identified at the critical furin cleavage site, impairing the cleavage of pro-IGF-I to mature IGF-I. Our findings suggest the novel variant impairs pro-IGF-I cleavage, reducing mature circulating IGF-I levels. Pro-IGF-I is likely to be less biologically active than mature IGF-I, resulting in functional IGF-I deficiency and postnatal growth failure.

P1-102

Growth and growth delay in children with systemic juvenile idiopathic arthritis: A single center study

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Systemic Juvenile Idiopathic Arthritis (sJIA) is a chronic autoinflammatory disease, with significant complications that can give short-term and long-term disability with reduced quality of life. Growth delay and short stature are described in >40% of cases, with a complex pathogenesis.

Chronic inflammation, long-term corticosteroids treatment, hepatic involvement, malnutrition decrease IGF-1 and GH biological effects. Corticosteroids inhibit growth velocity, bone maturation, GH and IGF-1 synthesis and biological effects. Inflammatory cytokines increase IGF-1-receptor resistance and reduce osteogenesis.

Children with an early disease onset and/or frequent relapses and/or a bad control of the disease, have a higher risk of short stature. Furthermore, the GnRH-gonadotropin-gonadic axis is often impaired in adolescents with sJIA who show a bad control of the disease, with a worsening of growth delay. Moreover, puberty failure is associated with a reduced bone mass peak with future bone fragility.

We studied 25 patients (15 F, 10 M) (age 1-18 years), 22 treated with biological drugs (19 canakinumab; 4 tocilizumab; 1 anakinra; 1 sarilumab), 3 with corticosteroids in association with biological drugs. At the diagnosis, mean height in SDS was -0.03 (range: -3.37-1.68; Median: 0.2).

At the last follow-up visit, still in treatment with biological drugs, the patients improved the mean height in SDS: 0.19 (range: -3.43-1.82; Median: 0.4).

2 patients with persistent active disease with low control by biological drugs, needed the association of corticosteroids with the anti-IL-1 beta antagonist (canakinumab): they showed a significantly low growth velocity (-3.3 SDS).

Biological drugs improve growth velocity and puberty timing, inhibiting inflammatory cytokines and sparing corticosteroids. However, inhadequate growth persists especially in patients with a severe disease and/or in low responders or in patients with frequent relapses. An early window of opportunity for treatment with biological drugs shows a significant growth improvement. In our children growth was more compromised in younger children who needed the association of corticosteroids with biological drugs and a poor control of the disease. Many patients showed a reduced height in SDS at the diagnosis. However, most of them, improved height during the follow-up, because of an effective treatment strategy.

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P1-103

A novel *IGF1R* variant in a child with mild IGF1 resistance, normal birth weight, mild short stature and microcephaly

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Introduction: The insulin-like growth factor 1 receptor (*IGF1R*) gene, located on chromosome 15q26.3, encodes the 1367 aa tyrosine kinase receptor IGF1R which is involved in many processes, including growth. Few heterozygous mutations and deletions of *IGF1R* leading to IGF-I resistance have been described in patients with intrauterine and postnatal growth retardation, microcephaly and variable learning difficulties.

We report a not yet previously described *IGF1R* nonsense variant in a child with normal birth weight, only mild short stature, and microcephaly.

Case: A 9-year-old male presented at 5.4 years with mild short stature (Height -2.1 SDS) low BMI (-2.6 SD) and microcephaly (Head circumference -3.9 SDS). His height velocity was 6–7 cm/year increasing his height to -1.75 SD. Birth weight was normal (1.38 kg at 31+6 weeks (-1.25 SDS). He also has a squint, delayed developmental milestones, behavioural difficulties and requires learning support. There was no significant family history. Maternal height was -1.39 SDS; paternal height -0.89 SDS.

Results: IGF1 was consistently mildly raised [aged 5.4 years, 228 mcg/L (15.6-216.4), aged 6.6 years, 338 mcg/L (18-307)]; IGFBP-3 was around the upper normal range [4.1 and 5.4 mg/L (1.9-5.2)] with raised random GH concentration (8.7 mcg/L), in line with IGF1 resistance. Bone age was normal. Spine X ray showed mild scoliosis and brain MRI reduced white matter. CGH array was normal. Sanger sequencing of IGF1R showed a nonsense variant (c.1237C>T, p.Gln413*), generating a premature stop codon. This variant has not been reported in control databases (dbSNP,1000 Genomes, ExAC and gnomAD, Human Gene Mutation Database, ClinVar and LOVD). and has been classified as pathogenic using ACMG criteria and bioinformatic predictors (SIFT, PolyPhen-2, Mutation Taster). The truncated IGF1R lacks the beta-chain and will be unable to signal.

The mother had normal IGF1 and IGFBP3 concentration and did not carry the *IGF1R* variant. Paternal DNA was not available.

Discussion: In conclusion, the novel heterozygous nonsense *IGF1R* variant c.1237C>T (p.Gln413*) results in mild impairment of IGF1R signalling with mild GH and IGF1 overproduction, and a phenotype of mild short stature without SGA but with significant microcephaly. Our patient fulfils 3 of the 4 previously proposed criteria for IGF1 resistance. The phenotype is in line with a milder phenotype of IGF1 resistance and suggests that *IGF1R* should be investigated in patients with biochemical evidence of IGF1 resistance even in the absence of short stature or SGA.

P1-104

SARS-CoV-2 pandemic and GH treatment: new strategies to abate the distance

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SARS-CoV- 2 pandemic induced to develop new strategies to abate the distance between patients, families and paediatricians, especially in cases of patients who need long-term therapies. Furthermore, the need to minimize the inflow of children and adolescents affected by chronic diseases into the hospitals induced paediatric endocrinologists to limit visits and to consider a new setting to assist children in treatment with growth hormone (GH). Telemedicine and smart-working could contribute to maintain a good standard of care in the follow-up of children with GH deficiency, still in treatment with GH.

Patients were assisted by telephonic consultations guaranteed by the paediatricians of free choice and by the paediatric specialists. However, patients frequently needed a direct specialistic evaluation in the case of flares, abnormal laboratory parameters and adverse reactions to drugs.

We enrolled 85 children (50 M; 35 F); Medium age: 12.4 (4-16) years, with GH deficiency, in treatment with GH. A questionnaire were proposed to their parents, with questions about the assistance and problems linked to the disease.

The questionnaire highlighted many points:

- the central role of the follow-up by the paediatricians of free choice;
- the useful digital support strategies (pc, smart phone app, tele consult, etc);
- the worsening of dietary intake and increased caloric intake, associated with a decreased regular physical activity. These life style increased BMI in most patients.
- the important role of the paediatric endocrinologist consults in important decisions as vaccinations.

The new scenario induced paediatric endocrinologists to create new strategies to support patients with special needs, as GHD children and adolescents. However, these strategies can be maintained even beyond the end of the pandemic, as a good assistance practice.

P1-105

Early growth failure and untreated growth hormone deficiency in radiotherapy-treated long-term survivors of childhood brain tumor

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Growth failure is common in radiotherapy-treated long-term survivors of pediatric brain tumors. The aim of this study was to assess the changes in growth patterns before and after brain tumor diagnosis, the final height, and the risk factors for compromised growth. The incidence and treatment practices of growth hormone deficiency were analyzed.

Methods: A cohort of 73 long-term survivors of childhood brain tumor (median age 27.2 years) were studied after a median follow-up period of 20.4 years from diagnosis (IQR 14.9 to 22.9 years). Patients were treated in five university hospitals in Finland between 1970 and 2008. Growth curves, final height, and patient- and disease-related risk factors for compromised growth during different growth periods were analyzed. Laboratory analyses for growth hormone status were performed at the follow-up.

Results: Low IGF-1 level was found in 32% (24/73), and untreated growth hormone deficiency in 41% (30/73) of the patients at the follow-up. Growth failure was already evident at diagnosis, with a mean height decline of -0.6 SDS (standard deviation score) from birth (95% CI -1.15 to -0.05). Loss of growth potential continued after diagnosis, with a mean height SDS decline of -1.09 SDS (95%CI -1.51 to -0.66). At follow-up, 37% of the patients (27/73) had true adult short stature (height < -2 SDS). The mean height deficit when corrected for target height was -1.9 SDS (95% CI -1.45 to -2.40). Growth failure was associated with young age at diagnosis.

Conclusion: Adult short stature was common in radiotherapy-treated survivors of childhood brain tumor. The growth decline was already evident at diagnosis. Growth failure associated with young age at diagnosis. These patients had a high prevalence of low IGF-1 level suggesting untreated growth hormone deficiency in adulthood.

P1-106

Shox deficiency in children with short stature: Response to recombinant growth hormone therapy (rGH)

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Background: Short stature may be due to various pathological conditions or may be idiopathic. SHOX (Short Stature Homeobox on X chromosome) gene is involved in the regulation of skeletal growth and is a main cause of short stature on monogenic basis. The frequency of this condition in children with idiopathic short stature (ISS) was reported to range from 2 to 17%. The phenotypic spectrum is heterogeneous, varying from Léri-Weill dyschondrosteosis (LWD) to Langer's mesomelic dysplasia (LD) and ISS. The main characteristics associated with this condition, such as mesomelia of the limbs and Madelung's deformity, develop over time and usually appear during the second decade of life, especially in women. The use of recombinant growth hormone (rGH) for SHOX deficiency was approved from 2006 in USA and from 2014 in Europe. The aims of this study were to analyze the frequency and type of alterations of the SHOX gene in a population of children with short stature, and the response to rGH therapy

Patients and Methods: All patients with molecular diagnosis of SHOX deficiency were retrospectively selected from a total group of 747 children with ISS. Auxological parameters at birth and at the time of diagnosis were analyzed, In addition, response to rGH treatment was assessed in a subgroup of patients reaching 36 months of follow-up. Gentic diagnosis was made by sequencing and MLPA analysis of SHOX gene and its regulatory sequences.

Results: Pathogenetic variants in the SHOX gene were found in 82/747 children (11%). Unlike other series, the most frequent mutations were exonic variants. Therapy with rGH determined a significant increase in both growth velocity and height after 36 months (average increase of +3.60 SDS and +0.85 SDS, respectively).

Conclusions: Present data confirm that SHOX deficiency is a relevant cause of ISS. The different frequency of mutations in this series compared to other populations may be related to a different genetic background. Treatment with rGH is able to improve growth pattern in these children. Early diagnosis permits better catch-up growth. The type of genetic alteration does not influence the response to therapy, even if further studies with a larger sample size are needed.

P1-296

No differences in adult height outcome with personalized approach to Growth Hormone dosing– but gender differences were found

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Introduction: The goal of treating short children with growth hormone (GH) is to normalize adult height adjusted for mid parental height (MPH). We obtained adult height data on 87 patients (23 girls, 64 boys) treated with GH who originally participated in a randomized, prospective, open-label clinical trial with either personalized dose based on a prediction model (n=58), or standard dose (n=29). The children were either growth hormone deficient (GHD) according to both stimulation test and spontaneous secretion (33%), or had idiopathic short stature (ISS).

Aim: To evaluate height outcome in GH treated patients with personalized approach, and find possible gender differences.

Methods: The different dose regimes were compared for mean GH dose and difference between MPH and adult height. The patients were then divided in two groups according to gender. The gender divided groups were compared for mean (SD); IGF-1, delta IGF-1 and GH dose from start until end of treatment, age at GH start, difference between MPH and adult height. Percentage of GHD diagnosis were also compared. Mann Whitney U test and Qi Square test were applied. P-values <0.05 were considered statistical significant.

Results: No mean (SD) differences were found for the personalized dose group versus standard dose group:

Variables	Personalized dose group	Standard dose group	P-value
GH dose (µg/kg/d)	31 (11)	29 (13)	0.603
MPH-adult height (SDS)	0.16 (0.75)	0.36 (0.81)	0.401

Mean (SD) for girls and boys:

Variables	Girls	Boys	P-value
GHD (%)	30	34	0.720
GH start age (years)	7.9 (1.7)	6.5 (1.9)	0.004
GH dose (µg/kg/d)	31 (9.8)	29 (8.7)	0.357
MPH-adult height (SDS)	0.54 (0.66)	0.11 (0.78)	0.040
Delta IGF-1 (SDS)	1.48 (1.82)	2.26 (1.82)	0.044

26 (40%) of the boys and 15 (65%) of the girls had an adult height within 0.5 SDS from MPH. 25% of the males grew better than 0.5SDS from MPH while none of the girls did.

Conclusion:

- No differences in mean dose nor in adult height outcome were found between the groups treated with personalized approach or standard dose.
- Although the mean GH dose did not differ between the gender groups, girls resulted in an adult height further beneath MPH than the boys. An older age at GH start and lower delta IGF-1 during treatment could be the explanation for the findings.

P1-297

rhGH therapy in a patient with homozygous IGF1R mutation

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Background: IGFR1 gene plays a crucial role in growth and glucose metabolism. IGF1R mutations account for approximately 10% of children born SGA with no catch-up growth. rhGH therapy has been reported moderately effective in stimulating growth of children with heterozygous IGF1R mutation. To date, no data are available about the efficacy of rhGH in patients with homozygous mutations.

Case Report: We describe a 4 years-old girl referred for severe pre- and postnatal growth retardation. Height 77 cm (-6 SDS), weight 6.5 kg (-11 SDS), OFC 42 cm (< -2 SDS), pubertal Tanner stage I. She was born at 36 weeks of gestational age by consanguineous parents with a birth weight of 950 g (–4.12 SDS), length 39 cm (–3.20 SDS), OFC 24.5 cm (–5.53 SDS) associated with cardiac and CNS defects, atrophic left iris, bilateral sensorineural hearing loss and progeroid features with triangular face, sparse scalp hair, low set ears, hypoplastic alae nasi, micrognathia. Karyotype and array-CGH were normal. Whole Exome Sequencing showed homozygous c.2201G>T missense mutation in the exon 10 of IGF1R gene, never reported in literature. Parents were both carriers of monoallelic IGF1R mutation with a mild phenotype of short stature, in particular mother's height was 151 cm (-2.3 SDS) and father's height was 159 cm (-2.2 SDS). Paternal and maternal grandmothers had type 2 diabetes history. Proband's IGF1 level was 422 ng/ml (+2 SDS) and glucose metabolism (baseline glucose and insulin, OGTT, HbA1c) was normal. rhGH therapy was started at the dose of 42 mcg/kg/day. The height gain was +1 SDS in 2 years of therapy. However, after 2 yrs rhGH therapy was stopped for impaired glucose tolerance. OGTT 2 hours-postload glycemia 162 mg/dl and HbA1c 48 mmol/mol. At last visit (age 8 years and 6 months), height was 97.5 cm (-6.3 SDS) and weight 11 kg (-8.5 SDS) with a height gain of -3.2 SDS in 3 years off-therapy.

Conclusion: We first report a case of homozygous IGF1R mutation treated with rhGH. Our findings suggest that rhGH therapy may partially reduce the height deficit but can affect glucose homeostasis.

P1-298

Use of PDE5 inhibitors as a potential treatment for isolated growth hormone deficiency caused by alternate splicing of GH1 gene

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Mutations in the GH1 gene cause isolated growth hormone deficiency (IGHD) by affecting production, secretion, and stability of growth hormone as well as its binding to GHR. A smaller isoform of GH1 is inactive and is linked to IGHD. While studying the impact of small GH isoform, we noticed that cells with the short 17.5 kD version of GH looked different from the control cells. We found that the production of short GH isoform distorts the cell morphology, contributing to detrimental effects seen in the patients. We hypothesized that cellular distortion caused by small GH isoform and overall GH secretion can be a target and a tool for experimental approaches for reversing the damaging effects of small GH protein, thereby providing potential treatments for IGHD. It is known that increasing cAMP enhances 26S proteasome activity and the degradation of cell proteins, including the selective breakdown of misfolded proteins, and recently, an increase in cGMP levels has also been shown to regulate protein degradation. Inhibitors of phosphodiesterase 5 (PDE5; e.g., Viagra (sildenafil)), which raise cGMP by inhibiting its hydrolysis to GMP, are widely used for the treatment of erectile dysfunction and pulmonary hypertension, and stimulators of soluble guanylyl cyclases (riociguat), which stimulate cGMP synthesis, are used as treatments for pulmonary hypertension and heart failure. Using our model of cellular morphology changes, we investigated the impact of chemicals that enhance cGMP levels by inhibiting PDE5 or activating guanyl cyclases. The cells expressing a small isoform of GH consistently show distorted rounded morphology. Treatment with BAY 41-2272, a cGMP inducer slightly improved the cell morphology in small isoform GH expressing cells. BAY 41-2272 did not show any adverse effects of normal and WT GH expressing cells. Treatment of sildenafil to cells expressing 17.5 kD isoform of GH markedly improved the cell morphology compared to untreated cells, especially after 48h when a larger percentage of cells that were distorted (rounder shapes) regained the shape of normal cells expressing WT GH and no damage to cells expressing WT-GH was observed. Another PDE5 inhibitor tadalafil also caused a marked improvement in cell morphology caused by the expression of a small GH isoform. Overall, it seems the strategy to regulate the cGMP levels in cells transfected in small GH isoform works and needs further investigation. A detailed analysis of the impact of PDE5 inhibitors on GH expression and secretion will be presented.

P1-299

Three years of growth hormone (GH) treatment in young adults with PWS previously treated with GH during childhood: Effects on cognitive functioning

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Introduction: Most patients with Prader-Willi syndrome (PWS) have a mild to moderate cognitive impairment. Growth hormone (GH) treatment has positive short- and long-term effects on cognition in children with PWS. Few studies, however, have investigated the effects of GH on cognitive functioning in adults with PWS.

Objective: To investigate the effects of 3 years GH treatment on cognitive functioning in young adults with PWS who were GH-treated during childhood.

Design: Open-label, prospective study.

Setting: Dutch PWS Reference Center

Methods: Patients were treated with 0.33 mg GH/m^2/day (~0.012 mg/kg/day). Cognitive functioning was measured by Wechsler Adult Intelligence (WAIS) tests.

Results: 46 young adults with PWS with a median age of 19 (IQR 17 – 21) years were tested. Estimated mean (95% CI) Total, Verbal and Performance IQ remained stable during 3 years of GH treatment. Total IQ being 66 (63-69) at start and 67 (64-71) after 3 years, p=0.30; Verbal IQ being 65 (62-68) and 66 (62-70), resp., p=0.31 and Performance IQ being 67 (63-70) and 67 (63-72) resp., p=0.42. 24% of the young adults at start, and 34% after 3 years, had a Total IQ above 70, the cut-off for mental disability.

Conclusions: Three years of GH treatment with a lower dose in young adults with PWS maintains Total, Verbal and Performance IQ.

P1-300

Evaluation of the growth response of children with growth hormone deficiency according to peak growth hormone levels on provocative tests

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Objective: We aimed to evaluate the relation between the peak growth hormone (GH) levels on provocative tests and response to recombinant human GH (rhGH) therapy in patients with GH deficiency (GHD).

Methods: This was a cross-sectional, single-center, and retrospective study. A total of 518 patients who received rhGH therapy under the age of 16 in the Endocrinology Clinic of Akdeniz University Hospital between 1997 and 2021 were identified

through the hospital's digital database system. Patients who had any genetic or chronic illness as well as using medication that may affect growth and patients diagnosed with GH neurosecretory dysfunction, GH resistance, acquired GHD due to radiotherapy/chemotherapy/surgery were excluded from the study. Finally, 135 subjects who were diagnosed with GHD by using insulin tolerance test and L-DOPA stimulation test and treated with rhGH for at least two years were included in the study.

Results: The patients were classified as group I (Idiopathic GHD, n=119) and group II (Multiple pituitary hormone deficiencies or having pathology on MRI, n=16). The idiopathic GHD patients were classified into 3 subgroups according to the peak GH values on the provocative tests (group Ia: peak GH < 3 μg/L, n=34; group Ib: peak GH between 3 - 7 μg/L, n=71; group Ic: peak GH between 7 - 10 μg/L, n=34). Height standard deviation score (SDS), Δheight SDS, and height velocity (HV) SDS were all higher in group Ia at the end of the 1st year of the rhGH therapy (p=0.040, p=0.029, p=0.005). The height SDS was still significantly higher in group Ia (p=0.033) while the HV SDS and Δheight SDS were similar between the groups at the end of the 2nd year of the therapy (p=0.164 and p=0.522). 1st year HV SDS was significantly associated with midparenteral height SDS and peak GH value on provocative tests in multiple regression analyses (p=0.009, p=0.012).

Conclusion: It might be predicted that the lower the GH peak on provocative tests, the better the response to the treatment. The best HV is observed in the 1st year and the diagnosis should be checked in the patients who had low first-year HV and had not severely low GH peak on provocative tests.

P1-301

High prevalence of refractoriness in children tested for growth hormone deficiency with nocturnal spontaneous profile and subsequent arginine-insulin-tolerance test

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Introduction: Diagnosing growth hormone deficiency (GHD) in children is complex. Spontaneous growth hormone (GH) pulses during late night may influence the pituitary GH response to provocation tests. We evaluated refractoriness during arginine-insulin-tolerance test (AITT) when having a GH-peak during a short spontaneous nocturnal profile in children with short stature.

Methods: Altogether 257 children 0-18 years were examined with spontaneous nocturnal profile, with blood samples for GH levels every 30 minutes between 04.00 – 08.00, and subsequent AITT. They were classified in subgroups depending on their GH response at the spontaneous nocturnal profile and AITT, and medical records were reviewed retrospectively. Refractory children were defined as having a GH-peak ≥7 μg/L during spontaneous nocturnal profile, but no GH-peak ≥7 μg/L during AITT. Prevalence of refractoriness for cut off level GH ≥5 μg/L and GH ≥10 μg/L was also evaluated.

Results: In total, 44/257 children were refractory, corresponding to 17.1% of all individuals and 21.9% of children with at least one GH-peak ≥7 μg/L. The proportion of males (p=0.033) and the body mass index (BMI) standard deviation score (SDS) (p=0.037) was higher in the refractory group compared to all children with a GH-peak ≥7 μg/L. The proportion of children with an adequate hypoglycaemia <2.2 mmol/L did not differ significantly between refractory and non-refractory children. The period between last spontaneous nocturnal profile peak ≥ 7 μg/L and GHmax AITT, was 210 (30 – 390) minutes in median. The maximum GH-peak at AITT occurred 30 minutes earlier for children who did not have a peak ≥7 μg /L during the spontaneous nocturnal profile (p=0.004). Using the cut off GH ≥ 5 μg/L, 35/257 (13.6%) of the study population were refractory, and for the cut off GH ≥ 10 μg/L 34/257 (13.2%) were refractory.

Of all children, median age was 8.0 years, 138 (53.7%) were male and 212 (82.5 %) were prepubertal. The median height of the prepubertal children was -2.9 SDS. Only 7 (2.7%) were primed with sex steroids. Comorbidity that might affect the GH secretion and/or growth was found in 31.1% (n = 80).

Conclusions: A considerable number of children were refractory when examined with both spontaneous nocturnal profile and AITT, and among them few clinical characteristics were found. The possibility of refractoriness needs to be taken into consideration when evaluating children for possible GHD to avoid over diagnosing.

P1-302

A novel heterozygous STAT5B variant in a patient with resistant atopic dermatitis and short stature

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Introduction: Growth hormone (GH) exerts its effect through insulin-like growth factor 1 (IGF-I), an intracellular signalling molecule whose production is stimulated by STAT-5b after binding to the growth hormone receptor. STAT-5b deficiency, is characterized by short stature, immune dysregulation and chronic lung disease. And these occur as a result of disruption of the growth hormone axis. Our case is an example of STAT-5b gene mutation, which is a rare disease and it has been defined for the last 10 years.

Case: A 12-year-old male patient was admitted to our outpatient clinic with complaints of short stature and skin rash. He was born 900 gr by cesarean section at 26th gestational week and had a 3-month neonatal intensive care hospitalization history. He was hospitalized with severe acute bronchiolitis attack twice, 1 year and 2.5 years old. He was followed up with diagnosis of atopic dermatitis and hyperimmunoglobulin E for the last 3 years. In the family history; his mother's and father's height were 150 cm and 175 cm respectively, there was no consanguinity between mother and

father, and he had 2 healthy siblings. Anthropometric measurements; his height, weight and body mass index were 134 cm (SDS: -1.9), 25.7 kg (SDS: -2.54), and 14.2 kg/m2 (SDS: -2.15) respectively. The mid parental height SDS of the patient was -1.17. In his physical examination; he had erythematous eczematous lesions around the eyes, cheeks and chin, and xerosis on the hands, prominent forehead and saddle nose. His testicular volumes were 4/4 ml and pubic hair was tanner stage 1. Laboratory examinations revealed low IGF level (98.7 ng/ml SDS: -1.67) and IGF binding protein 3 (IGFBP3) level (3.75 ng/L SDS: -3.56). Bone age was 8 years-old. GH stimulation tests with L-dopa revealed low basal GH levels and reduced GH response (peak GH of 2.24 ng/ml). Prolactin level was found to be 12.3ug/l. Height velocity was 6 cm per year. A new heterozygous STAT5b mutation (C.1906+1G>A) was detected.

Conclusions: Children with homozygous Stat-5b gene mutation is characterized by severe short stature up to –6SDS, development of bronchiectasis after recurrent severe lung infections and chronic lung disease that may require lung transplantation, dysmorphic findings such as widespread eczema and ichthyosis on the skin, saddle nose and prominent forehead. We reported a case with a new heterozygote mutation whose growth, respiratory problems and immune system were mildly affected.

P1-303

Short stature due to a novel missense variant (695C>A) in the *GHR* gene: a case report

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Introduction: Laron Syndrome (LS) or primary growth hormone (GH) insensitivity is an autosomal recessive disorder due to variants in the GH-receptor (*GHR*) gene or to post-receptor defects. LS prevalence is estimated 1-9/1000000. We report a case of LS with a missense variant in the *GHR* gene not previously described.

Case: Female, Turkish, was referred to our clinic for short stature. Born at term, birth weight was 3890 g (1.68 SDS), length 48 cm (-0.83 SDS) and head circumference 36 cm (1.72 SDS). The parents are first cousins; target height was 160 cm (-0.44 SDS). At first evaluation at 8 months: length 59,7 cm (-4.15 SDS), weight 6.5 kg (-1.86 SDS), head circumference 42 cm (-1.24 SDS), prepubertal. The phenotype was characterized by frontal bossing, midface retrusion, depressed nasal bridge, chubby cheeks, thin lower lip, downturned mouth cornersface. Bone age was 6 months according to Greulich & Pyle atlas. The hematological tests showed low IGF-1 (10 ng/ml, range 8-131) and IGFBP3 (385 ng/ml, range 710-2760) levels, compared to laboratory reference values for sex and age. Due to a relevant reduction of growth velocity in the following six months (4.26 cm/yr, -5.02 SDS) a GH stimulation test was performed with normal GH peak (GH 38.9 ng/ml). Brain MRI was normal. Karyotype was 46,XX. Clinical Exome Sequencing showed the homozygous missense variant c.695 C>A (p.Ser232Tyr) in the *GHR* gene, yet undescribed. The parents were heterozygous carriers of the same variant. At the age of 2 years and 2 months, the baby started therapy with subcutaneous injections of mecasermin (starting dose 0.04 mg/kg twice daily), showing improvement in growth velocity and muscular tone. Dietary indications with adequate caloric intake, in order to prevent hypoglycaemia, were provided and specific evaluations (cardiological, ophthalmological and ENT evaluations) are regularly performed according to the treatment protocol.

Discussion: LS is characterised by a typical phenotype associated with biochemical findings such as high serum GH and low levels of IGF-1 More than 70 variants, ranging from deletions to point mutations including missense, nonsense, frameshift and splice-site variants, have been previously identified. Therapy with recombinant IGF-1 improves height, metabolic parameters and motor development. Our case presented clinical characteristics of LS (dwarfism, typical phenotype), the diagnosis was confirmed biochemically and genetically, and therapy was started early. It is interesting to underline the importance of surveillance of these patients to optimize therapy and prevent potential adverse consequences.

P1-304

Growth hormone deficiency and central hypothyroidism related to microarray abnormality involving a loss of ~111-kilobases (kb) within cytogenetic band Xq28 and a gain within cytogenetic band 20q11.22

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Chromosomal microdeletions and microduplications have been associated with syndromic forms of intellectual disability (ID). The Xq28 duplication syndrome is an X-linked intellectual disability syndrome characterized by variable degrees of cognitive impairment (typically more severe in males), a wide spectrum of neurobehavioral abnormalities, and variable facial dysmorphic features. All males reported to date with the syndrome have a moderate-to-severe intellectual disability. This case report showed different clinical characteristics related to microarray abnormality involving a loss of ~111-kilobases (kb) within cytogenetic band Xq28 and a gain within cytogenetic band 20q11.22.

We report a boy who presented at 7 years of age with special facial features, growth failure, and bilateral hydronephrosis (grade 3) due to posterior urethral valve which was previously operated on, sensorineural hearing loss (on hearing aids), speech delay. No other developmental or behavioral issue was reported by his parents. Measurements showed: Ht SDS = -5.3, BMI SDS = -0.02, mid parental HtSDS = -1.

Investigations showed: FT4: 10.7 pmol/L (low), TSH: 2.75 mIU/L, IGF1: 7.0 ug/L (Low) (-4SD), Glucose: 3.3 mmol/L,

Creatinine: 68 umol/L, Albumin Lvl: 43.3 gm/L, ALT: 13.6 U/L, Bicarbonate: 22 mmol/L. He had normal calcium homeostasis and electrolyte levels. Bone age was 3 years when the chronological age was 7 years.

He was started on L thyroxine 50 ug OD. Growth hormone stimulation test revealed severe GH deficiency with peak GH = 2 mcg/L. MRI of the pituitary showed pituitary hypoplasia. The patient was started on GH 0.05 mg/kg.

Microarray study showed the following abnormality: arr[GRCh37] Xq28(147806444-147917562)x1, arr[GRCh37] 20q11.22(33458005-33557168)x3. The analysis revealed two copy number changes. A loss of ~111-kilobases (kb) within cytogenetic band Xq28. The loss causes intragenic deletion of the AFF2 gene. The second change is a gain of ~99-kilobases (kb) within cytogenetic band 20q11.22, the duplicated segment contains GSS, MYH7B, GGT7, and ACSS2 genes.

Discussion: Mutations in the AFF2 gene cause fragile XE syndrome, with mild intellectual and learning disabilities. The 20q11.2 microdeletion is characterized by intellectual disability (ID), developmental delay, and facial dysmorphism, but a gain within the cytogenetic band 20q11.22 was not described before.

Conclusion: This patient with this peculiar genetic constitution: arr[GRCh37] Xq28(147806444-147917562)x1, arr[GRCh37] 20q11.22(33458005-33557168)x3 presented with severe growth retardation, GH deficiency, central hypothyroidism, sensorineural hearing loss, and pituitary hypoplasia.

P1-496

The Effect of Anastrozole Treatment on Height Gain in Pubertal Boys on Growth Hormone Treatment

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Introduction: In children receiving growth hormone (GH) therapy during puberty, epiphyseal fusion due to sex steroids often limits the height gain. Aromatase inhibitors may seem to help at this point despite the lack of evidence.

Herein, it was aimed to investigate the efficacy of anastrozole for add-on treatment in pubertal male patients receiving GH therapy.

Methods: This is a retrospective study comparing two groups of patients treated with GH either with or without anastrozole who achieved final height (FH) between 2006 and 2021: patients who had received only GH (GH-Only) and both GH and anastrozole (GH+A). Chronological age, bone age (BA), pubertal stage, height, height SDS were noted from the files of the patients who received GH+A therapy at 3 different times: at the beginning of GH (TIME1), when anastrozole was added (TIME2), and at the end of the whole therapy (TIME3). FH was noted in all patients (TIME4). Then, GH-Only patients with similar target height and exactly similar auxological parameters indicated above as the GH+A group at TIME1 were selected to create a matched group. Since there was no milestone in which anastrozole was added (TIME2) in the GH-only group, for each patient, the findings were noted at the CORRESPONDING TIME2 (same chronological age of its partner in the GH+A group when anastrozole was added). Comparisons of auxological parameters were made between the groups at TIMES1-4.

Results: A total of 48 cases (24 cases in each group) were included. There was no statistical difference in the matched parameters at TIME1 and FH (TIME4)(p=0.071) between GH+A and GH-Only. However, when the analysis was limited to the patients who received anastrozole ≥2 years, FH was found to be significantly higher with an average of 3.3 cm in GH+A than in GH-Only group (173.1±6.2 vs. 169.8±5.6 cm, respectively, p=0.044).

Advancement in BA was slower in the GH+A group than in the GH-only group in the mean anastrozole treatment period of 1.59 years (1.37±0.80/1.81±0.98 years, p=0.001). However, the growth rate in this period and the height reached at TIME3 were similar between GH+A and GH-only groups (p=0.133 and p=0.269, respectively).

Conclusion: It has been apparently shown that although the use of anastrozole for at least 2 years in addition to GH does not affect growth rate, it slows down the advancement in BA, thus, resulting in gain in FH.

P1-497

Metabolomics profile of children with growth hormone deficiency

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Background and Objectives: In recent years, a growing number of studies investigated the profile of serum metabolomics in health and disease. These studies have led to the discovery of novel biological biomarkers and causative agents for a variety of medical conditions. Here, we focused on profiling serum metabolites of children diagnosed with growth hormone deficiency (GHD).

Methods: We conducted a prospective study and collected serum samples from children aged 3-18 years arriving to a glucagon or arginine growth hormone stimulation test (GHST). Children with genetic syndromes or chromosomal abnormalities, systemic illness or end-stage renal disease were excluded from participation. An inadequate response to GHST was defined as peak serum GH concentration of 7.5 ng/mL or less. GHD diagnosis was made after two separate stimulation tests demonstrating inadequate GH response. We performed metabolic profiling analysis using liquid chromatography-mass spectrometry (LC-MS) that measured the levels of 951 circulating metabolites (including 280 polar metabolites and 671 lipids) in the serum samples. We compared the levels of these metabolites between cases and controls, and estimated the P-values using the two-sided Mann–Whitney U test. False Discovery Rate (FDR) was employed at the rate of 0.1.

Results: Serum samples of 68 children who were recruited to the study between November 2017 and March 2021 were analyzed. Mean age was 8.43 ± 3.68 years (median 8.22 years, IQR [5.19-11.62]), 45 (66.2%) were boys. Twenty-five (36.8%) children were diagnosed as having GHD and 43 (63.2%) children served as controls. There were no significant differences between the groups in age, sex, tanner stage, height and weight measurements at test initiation and the type of GHST preformed. Overall, 20 polar metabolites and 76 lipids were significantly different between the groups ($p<0.05$). Metabolites measured higher in children with GHD included Myo-Inositol, Creatine, N,N-Dimethylglycine and Pantothenate and metabolites with higher levels in the control group included Heptanoic acid and N-Octanoylglycine. However, following FDR correction, only one lipid metabolite, phosphatidylserine (PS) (40:3), which was higher in children with GHD, remained significant.

Conclusion: Unique metabolic profiles in children with GHD offer an opportunity for development of novel diagnostic tests and identification of altered biological pathways. We found 96 plasma metabolites which were significantly different in children diagnosed with GHD compared to controls. Additional and larger scale studies are needed to identify the potential utility of the serum metabolic profiles as a diagnostic tool for GHD.

P1-498

A Long-Acting Growth Hormone Module For Paediatric Growth Hormone Deficiency In The Global Registry For Novel Therapies In Rare Bone & Endocrine Conditions – The GloBE-Reg LAGH Study

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Introduction: Post-marketing surveillance registries provided extensive information about the safety and efficacy of daily growth hormone (GH) therapy during treatment. With the availability of novel long-acting GH (LAGH) therapies, it is important to determine whether the novel molecules or the different pattern of GH exposure lead to changes in the efficacy and safety profile. Therefore, new surveillance registries of LAGH are warranted.

Objective: Develop an international electronic platform to capture real world safety and efficacy data for children receiving LAGH for GH deficiency (GHD).

Methods: To capture key safety and efficacy data points for multiple different LAGH products, the project will rely on the GloBE-Reg platform, a new international registry project that has been designed to collect relevant real world data through a joint collaborative approach between scientific centres, industry partners and medical societies. The steering committee of GloBE-Reg consists of representatives from a wide range of paediatric endocrine organisations across the world as well as members of industry. The fields within the LAGH module will be guided by the GloBe-Reg LAGH Scientific Study Group and will have diagnosis and drug specificity. Electronic data entry by local institutions will focus on a group of core condition- and treatment-specific items, a group of optional broader data and data targeting specific research questions submitted by investigator groups.

Results: The core fields within GloBE-Reg have been developed to align with international accepted standards and the GloBe-Reg LAGH Scientific Study Group has started to meet and advise on the specific module for novel LAGH therapy in paediatric GHD. It is anticipated that the module specific fields shall be agreed by the third quarter of 2022 and the module will be live by the end of 2022.

Conclusion: GloBE-Reg LAGH is being developed to capture real world evidence for the safety and efficacy of LAGH in an

international cohort of children. GloBE-Reg will also use this approach to serve the needs of the endocrine community for assessing longer term clinical outcomes, which are particularly important to continuously expand our scientific knowledge and improve care in children. Additional modules may be developed for specific LAGH products and other therapies for growth disorders in partnership with industry. More information is available on the project's website: www.GloBE-Reg.net and by following @ globe_reg on Twitter.

P1-499

Long-term safety and effectiveness of recombinant human growth Hormone inKorean pediatric patients with growth disorders: 9-year interim analysis fromLG Growth Study

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This study aimed to evaluate the long-term safety and effectiveness of recombinant human growth hormone (rhGH; Eutropin®, Eutropin®Pen, Eutropin®AQ, and Eutropin®Plus, LG Chem, Ltd.) treatment in Korean pediatric patients. This observational study has been conducted since 2011, and the data were collected up to August 2021 for interim analysis. The incidence rates of all adverse events (AEs) were assessed for safety analysis, and the height velocity (HV), height standard deviation score (SDS) and inulin like growth factor-1 (IGF-1) were evaluated for efficacy. During the 9-year study, a total of 4,525 patients were enrolled, and 4,442 patients (male 58.2%, female 41.8%) were analyzed for safety. Of those patients, 2,923 (65.8%) had growth hormone deficiency (GHD), 650 (14.6%) were born small for gestational age (SGA), 606 (13.6%) were diagnosed with idiopathic short stature (ISS), 253 (5.7%) had Turner syndrome (TS) and 10 (0.2%) had chronic renal failure (CRF). The mean age at the screening was 7.6 years and the mean treatment duration was 3.7 years. AEs were reported in 1,337 (30.1%) patients, most AEs were mild. A total of 34 neoplasms were reported in 30 (0.7%) patients, most were benign and/or non-related to rhGH. Cumulative results of AEs showed that the proportions of patients experiencing adverse drug reactions (ADRs), serious adverse events (SAEs), and serious adverse drug reactions (SADRs) remained relatively stable throughout 9 years of follow-up (5.8% for ADRs, 3.4% for SAEs and 0.3% for SADRs). When the effectiveness was assessed in 1,612 patients followed-up for 12 months, HV was 9.1±1.8, 9.2±1.6, 8.9±1.5, 7.4±1.8, and 8.5±1.9 cm/year in GHD, SGA, ISS, TS and CRF patients, respectively. The height SDS significantly increased from baseline to 4 years in GHD (from -2.6±0.7 to -1.1±1.1), SGA (from -2.6±0.6 to -1.1±1.1), ISS (from -2.7±0.7 to -1.8±0.9), TS (from -2.9±0.9 to -2.2±0.9) and CRF (from -2.7±1.1 to -1.6±0.7) patients, respectively. IGF-1 SDS significantly increased from −0.7±1.0 to 0.8±1.6 at 12 months and maintained within 0 to +2 SDS throughout the study period ($p<0.0001$). These data demonstrated the safety of long-term GH treatment in Korean pediatric patients with GHD, SGA, ISS, TS, and CRF, and there was a significant height gain during the first 4 years of follow-up in all groups. In particular, the HV improved the most after in the first year of treatment.

P1-500

A patient-centric approach to connected health solutions in paediatric growth hormone therapy

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Background: There is a clear need for improved patient-centric approaches in the treatment of chronic conditions, including paediatric growth hormone deficiency (GHD). Greater understanding of the patient's treatment journey has the potential to inform clinical decisions and to improve clinical- and patient-reported outcomes. Connected Health (CH) combines state-of-the-art technologies, tools, methodologies and analytics to create new patient-centric health management models.[1] Emerging CH solutions and patient support programmes that address different challenges during treatment for GHD are increasingly transforming healthcare.[2]

Aim: To identify paediatric GHD patients' challenges on the treatment journey that could be addressed with CH solutions.

Methods: Between 2016 and 2021, a series of qualitative studies (interviews and focus groups) targeting paediatric GHD patients and caregivers were used to collect patients' perspectives. The collected data was analysed using grounded theory,[3] and the insights were then condensed for user journey mapping. User journeys visualise the interactions between individuals and a product over time and across different channels.[4]

Results: A patient-centric paediatric GHD patient journey emerged, comprising six main phases: *awareness, diagnosis, treatment planning, treatment initiation, treatment maintenance*

and transition. For each phase, relevant concerns and emotions faced by patients with paediatric growth disorders and their families were identified and mapped to the patient journey. These included: 1) pre-diagnosis concerns and uncertainty, 2) difficulties initiating contact with healthcare professionals due to insufficient communicative support, 3) increasing confusion and concern about the future, 4) concerns about whether self-management is being performed correctly, 5) the need to deal with inconvenient and hurtful routines, 6) uncertainty about the impact and role of adherence, 7) long-term therapy fatigue and 8) difficulties of change to self-administration during adolescence. Future opportunities using smart technologies may support patients in overcoming these challenges, which may improve treatment satisfaction and outcomes.

Conclusion: This qualitative analysis provides a detailed description of the patient journey from the perspective of patients receiving GH therapy for GHD that identifies the emotional sensitivities and perceived risks. This will help inform future development of effective CH interventions that improve both clinical- and patient-reported outcomes.

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P1-501

IGFBP-3 assessment in the work-up of short stature

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Background: The diagnosis of GH deficiency (GHD) is not straightforward in childhood and adolescence, requiring comprehensive clinical, anthropometric, biochemical, endocrine, and neuroradiological assessment. Although pharmacological GH stimulation tests are still considered the gold standard for GHD diagnosis, they are burdened by both poor specificity and side effects. Several studies have addressed the issue of sensitivity and specificity of IGFBP-3 assessment in the diagnosis of GHD, yielding conflicting data.

Aim: The objective of this study was to determine the value of IGFBP-3 assessment in the work-up of patients with short stature.

Methods and Results: We conducted a cross sectional retrospective study in a cohort of 455 subjects referred for short stature to our Unit. We performed GH stimulation tests and serum IGFBP-3 measurement in all subjects. We identified 25 GHD children (11F/14M; chronological age 5.5 ± 2.6 SDS) with height -2.9 ± 0.8 SDS and Tanner pubertal stage I at first evaluation. GHD diagnosis was based on the following anthropometric, endocrine, and radiological criteria: stature less than 2 SD score, delayed bone age (at least 1 yr), growth rate less than 25th centile, peak GH response to two different provocative tests less than 8 ng/ml to clonidine/arginine test (<19 ng/ml for GHRH + arginine test), brain magnetic resonance imaging (MRI) normal or positive for hypothalamus-pituitary abnormalities such as pituitary hypoplasia, stalk agenesis, and ectopic posterior lobe. Only 2 patients showed IGFBP-3 level < 3th centile (8%); in these two patients brain MRI abnormalities of pituitary gland were observed. Sensitivity and specificity of IGFBP-3 measurement were 17 and 97%, respectively.

Conclusion: Our results suggest that normal IGFBP-3 serum concentrations do not exclude GHD in more than 80% of patients. The low sensitivity of IGFBP-3 measurement makes it too inaccurate as a screening test in the work-up of children with short stature.

P1-502

A real life evaluation of rhGH efficacy in children born SGA

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Background: Children born SGA are at risk of becoming short adults. Although most children born SGA show catch-up growth in the first 24 months of life, approximately 10% remain below the 3rd centile throughout childhood and adolescence. The available evidence shows that GH therapy can increase adult height in short children born SGA although long-term response is variable and closely related to the 1st year response.

Aims: The aims of this study were: 1) to evaluate the response to 1st rhGH therapy and 2) the efficacy of long-term rhGH therapy on near adult height in SGA children.

Methods and Results: We conducted a retrospective case-control study in a cohort of 54 children born SGA treated with rhGH (mean age 6.7 ± 2.5; 16F/35M) compared with 47 untreated SGA (mean age 6.3 ± 2.9; 30F/21M) after 1 year of follow-up. GH dose was 0.23 ± 0.09 mg/kg/week. Mean duration of therapy was 5.7 ± 2.62 years. The mean height at first evaluation in SGA treated children was -3.1± 0.8 SDS vs -2.9 ± 1.22 SDS in untreated children. After 1 year of follow-up mean height in treated SGA was -2.6 ± 0.8 SDS vs -2.2 ± 0.63 SDS. Mean height gain was 0.5 ± 0.8 SDS (about 3.1 cm) in treated SGA vs 0.7 ± 0.9 SDS (about 4.3 cm)

in untreated subjects (p=0.1). Mean near adult height was -1.9 ± 0.6 SDS in 17 treated patients with mean height gain from baseline to near adult height of 0.55 ± 0.8 SDS (about 3.4 cm).

Conclusion: Our study show that the response to rhGH therapy is on average dissatisfying in the first year of treatment, with wide individual variability. The overall height gain from baseline to near adult height overlaps the same magnitude in SDS observed in the 1st year of therapy

P1-503

Adult height in patients with non-permanent, idiopathic and isolated growth hormone deficiency

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Background: GH secretion is classically assessed by provocative tests and, indirectly, by IGF-1 serum levels. However, their diagnostic accuracy is low.

The aim of the study was to evaluate the adult height (AH) in short patients with IGF-1 ≤-1,5 SDS.

Method: 52 short patients (height-SDS -2.6 (-3.1- -2.3), age 12.2 (10.2-13.7) y, 36 boys), with low height velocity (HV)-SDS (-1.6 (-3.2- -0.9)) and IGF-1 ≤-1,5 SDS (-2.2 (-2.8- -1.9)) were included in this retrospective analysis.

The case group consisted of 24 patients (13 boys) with non-permanent, idiopathic, and isolated growth hormone deficiency (GHD, low peak GH after two provotative tests, <10 μg/L with Arginine, Insuline tolerance test, and Clonidine or <20 μg/L with GHRH+Arginine; normal MRI; normal GH and/or IGF-1 concentrations at near AH). These patients were treated with GH (25 μg/kg/die) until the near AH was achieved.

The control group consisted of 28 patients (23 boys) with idiopathic short stature (normal peak GH after the provocative test, no evidence of other cause for their shortness). Values are reported as median (interquartile range).

Results: The AH-SDS, the Δ AH-SDS – H-SDS and the Δ AH-SDS – Target height(TH)-SDS were similar in both groups (-1.6 (-2.5 - -0.2), -1.8 (-2.6 - -1.1), p=0.3; 1.3 (0.5-2.2), 1 (0.5-1.5), p=0.08; -0.3 (-1.2 – 0.5), -0.2 (-0.9 – 0.5), p=0.7; respectively in cases and controls). BMI-SDS, HV-SDS, and pubertal stage were lower in cases than in controls, while TH-SDS was lower in controls. Age and IGF-1 SDS were similar in both groups.

The same analysis performed including only the 41 subjects born adeguate for gestational age with normal BMI (14 cases and 27 controls), confirmed that the AH-SDS, the Δ AH-SDS – H-SDS and the Δ AH-SDS – TH-SDS were similar in both groups (-2 (-3 - -1.6), -1.8 (-2.6 - -1.2), p=0.52; 1.1 (0.3-1.5), 1 (0.5-1.4), p=0.13; -0.8 (-1.5 – -0.1), -0.3 (-0.9 – 0.5), p=0.59; respectively in cases and controls). Age, gender, BMI-SDS, HV-SDS, IGF-1 SDS, IGFBP-3 SDS, bone age, and pubertal stage, were similar in both groups.

Conclusions: In this study, both treated patients with idiopathic GH and not-treated patients with idiopathic short stature reached the same AH within TH, with similar height-SDS gain. Thus, the efficacy of treatment with GH in these patients is questionable. This could be due to the low accuracy of provocative tests and IGF-1 measurement in the diagnostic process of GHD, leading to a misdiagnosis of idiopathic short stature as GHD.

P1-504

easypod® Augmented Reality: Usability and acceptability of a virtual reality mobile solution to support training of patients on a connected injection device

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Background: Smartphones are becoming increasingly popular and powerful across the globe, which, in turn, has provided unforeseen opportunities in the digital health space. The increased capabilities of smartphones have allowed the incorporation of Augmented Reality (AR) capabilities that merge input from their cameras with additional, augmented annotations and representations. While there has been research on the use of AR in managing paediatric diabetes,1 to the best of our knowledge this is not the case for patient education in the treatment of paediatric growth disorders. The easypod® AR application2 provides training on the safe and effective use of a connected injection device (easypod®) for recombinant human growth hormone (r-hGH) therapy. It is designed to complement and support the work of nurses involved in the training of patients and their caregivers.

Aim: This study investigates the nursing experience associated with the easypod® AR mobile phone application to support and train patients and their caregivers to administer their r-hGH injections.

Methods: In 2020, the easypod® AR mobile application2 was launched to support nurse-driven telehealth patient education. Nurses who had been involved in the training of patients using the easypod® AR app in countries where it has already been launched (including Hong Kong, Taiwan, Germany, Singapore, the UK, Australia and South Korea) were invited to participate in an online survey based on the Mobile App Rating Scale (MARS) using a 5-point scale (1-Worst to 5-Best).3

Results: In total, 23 nurses completed the online questionnaire. They positively rated the quality of the app across multiple

dimensions, including engagement, functionality and aesthetics. All reported mean scores were ≥3.0; the highest mean scores reported for each dimension were 4.0 for engagement (adaptation to the target group; standard deviation [SD], 0.74), 4.1 (SD, 0.79) for functionality (navigation) and 4.1 (SD, 0.67) for aesthetics (graphics).

Conclusion: The easypod® AR mobile application was well received by nurses involved in the training of patients with growth disorders and their caregivers for the administration of r-hGH, and demonstrates potential as an educational tool. Future studies are warranted to investigate the impact of such AR technologies on clinical practice and patient outcomes.

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Growth and Syndromes

P1-107

Identifying several patient-related factors that predicted permanent growth hormone deficiency (GHD)

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GHD is the most common endocrine disorder in children with short stature (~1 in 4000). Appropriate diagnosis should synthesize auxological, biochemical and neuroradiological data. However, until now there are significant controversies, especially from the laboratory interpretation. A false positive diagnosis can lead to a significant wasted expenditure and unnecessary exposure to rare potential adverse effects. Given these open issues about biochemical diagnosis of GHD in childhood once reaching adult, patients should be re-assessed to define persistent adulthood GHD.We aim to identify predictive factors for permanent growth hormone deficiency.

Methods: GHD patients followed and re-tested when reaching adult height with an insulin provocative test, defining permanent with a peak <15 mIU/L.Collected information included perinatal, at diagnosis and at follow-up anthropometry, biochemical data,pubertal data,mid-parental height,MRI.

Statistical Analysis: Descriptive anthropometric and hormonal characteristics analysis, prognostic factors for persistent GHD evaluated using a univariate logistic regression.A multivariate stepwise model was developed.

Results: 101 GHD patients using a cut off of 20 mUI/L in 2 provocative tests, who started GH treatment at a mean age of 8.1± 0.4 years, with a height of -2.25±0.8 and BMI -0.27± 0.1 SDS. At final height 29 (28.7%) were defined as persistent GHD.The persistent GHD group had a shorter height SDS (-2.56±0.1 vs -2.13±0.1,p<0.001),a higher BMI SDS (0.13±0.27 vs.-0.42±0.13,p<0.05) and a lower GH peak mIU/L (8.3±1.0 vs 12.8±0.5,p<0.001,means of 2 stimulation tests) at diagnosis,and at final height a lower IGF1 ng/ml (232.± 19.9 vs. 331±9.1,p< 0.001) and a higher BMI SDS (-0.15± 0.27 vs. -0.73±0.13,p< 0.01).The OR for persistent GHD of patients with height < -3 SDS and between -3/-2.5 SD was 7.3 and 3.2 times vs. those taller than >- 2.5 SDS.By logistic regression analysis the best predictive model included height and BMI SDS and the two GH peak and MRI at diagnosis. Evaluated by ROC curve this model has a discrimination capacity of AUC of 0.9, a 89% sensitivity, 81% specificity and a 94.2% positive predictive value, showing that a shorter height SDS at baseline, adjusted by the other covariates showed 4.4 times risk of persistent GHD at adulthood.Nevertheless, an abnormal MRI was the best predictor (OR 10.7 of persistent GHD) after adjustment for the other covariates.

Conclusion: A shorter height SDS at diagnosis is a good predictor of persistent GHD,especially when accompanied by higher BMI, lower GH peaks and abnormal pituitary MRI.

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Once-Weekly Somapacitan versus Daily GH in Children with GH Deficiency: The Randomized Phase 3 REAL 4 Trial

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Background: Growth hormone (GH) replacement therapy usually requires daily subcutaneous (s.c.) injections that can be burdensome for patients and their caregivers. Long-acting GH formulations aim to establish a less burdensome dosing regimen that is as safe and efficacious as daily GH to potentially improve adherence and clinical outcomes. Somapacitan, a long-acting reversible albumin-binding GH derivative, is in development for once-weekly s.c. administration in children with GH deficiency (GHD).

Design and Patients: REAL4 is a randomised, multi-national, open labelled, and active-controlled parallel group phase 3 trial (NCT03811535) investigating efficacy and safety of once-weekly somapacitan compared with daily GH (Norditropin®, Novo Nordisk). The trial comprises a 52-week main phase and 3-year safety extension. Two-hundred GH-treatment-naïve, prepubertal children with GHD (74.5% male) were enrolled and randomly assigned in a 2:1 ratio to receive 0.16 mg/kg/week s.c. somapacitan (n=132) or daily s.c. GH (0.034 mg/kg/day Norditropin®; n=68) for 52 weeks. Data presented here include secondary efficacy endpoints, including change from baseline to week 52 in height velocity standard deviation score (HVSDS), height SDS (HSDS), and bone age, as well as patient-reported outcomes (PROs) to assess disease and treatment burden.

Results: Non-inferiority in height velocity (cm/year) at week 52 was confirmed. Estimated changes in HVSDS and HSDS from baseline to week 52 were similar between once-weekly somapacitan (8.05 and 1.25, respectively) and daily GH (8.82 and 1.30, respectively) treatment groups, with no statistically significant differences. The mean estimated bone age to chronological age ratio advanced slightly and similarly in both groups (0.06 for somapacitan vs. 0.08 for daily GH), with no changes in skeletal proportions reported. PRO results demonstrate a similar reduction in disease burden between treatment groups from baseline to week 52. Treatment burden assessments at week 52 favour somapacitan over daily GH across all domains. The same high proportion of respondents (96%) found the somapacitan and Norditropin® FlexPro® devices to be easy or very easy to use, while a similarly high proportion of respondents (>90%) found the devices easy or very easy to learn to use. Safety was consistent with the daily GH profile.

Conclusions: The efficacy and safety profile of somapacitan was similar to the efficacy and safety profile of daily GH. Data from PRO questionnaires show that both treatments reduced the disease burden to a similar degree, while reduced treatment burden consistently favoured somapacitan over daily GH.

P1-109

Efficiency of the genetic study in the assessment of short stature in pediatrics

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Introduction: Short stature is a common disorder in children that can become a challenge for clinical and molecular diagnosis. Recent studies in genetics and the implementation of Next-Generation Sequencing (NGS) in growth disorders have demonstrated the great genetic heterogeneity of short stature and the existence of highly varied phenotypes. The absence of homogeneous clinical criteria for conducting studies makes it difficult to evaluate the efficacy of these new technologies.

Objectives: To assess the efficiency of genetic testing in patients with pathological short stature.

Materials and Methods: The patient cohort was selected from children (age < 18 years) with pathological short stature and a normal karyotype who attended a tertiary care hospital. Pathological short stature was considered if A) height -3SDS; B): height -2.5SDS with disproportion, associated pathological phenotype (dysmorphia, cardiopathy, intellectual disability etc.) or family history of short stature. Patients with malnutrition, treatment with drugs or chronic diseases that affect growth, as well as patients with GH deficiency due to hypopituitarism, were excluded. Genetic testing based on array and NGS techniques (NGS based panel or clinical exome) was performed sequentially according to standardized clinical criteria. Genetic testing was considered as conclusive when a pathogenic or probably pathogenic variant was responsible for the short stature.

Results: 71 patients (48% male) were recruited, between the years 2018-2021 (mean age 11 years), 26 (36%) for meeting criterion A and 45 (63%) for meeting B. In addition, 44.9% were small for gestational age, 38% had a pathological phenotype, 38% disproportion, and 49% had a family history of short stature. 87% (n=62) of the individuals were studied molecularly. 15% (n=9) were studied by array, 48% (n=30) by NGS techniques and 37% (n=23) by both techniques. Of all the arrays performed (n=32) only in one case was conclusive (0.03%) while of the total NGS studies (n=53, n=41exome and n=12 gene panel) in 50%, the genetic study was conclusive. The yield of the NGS study was 50% in the two

clinically established groups (11 in group A and 7 in group B), so no significant differences were found.

Conclusions: Clinical characterization of the individual is essential to improve the efficiency of genetic testing. NGS methods have a higher diagnostic rate (50%) than array, which, in the context of pathological short stature, has low efficiency. Larger series are required to define the performance of genetic testing in short stature.

P1-110

Characterisation of the first heterozygous missense *HMGA2* variant helps delineate the crucial functional roles of a novel growth gene

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Background: Silver Russell syndrome (SRS) is genetically heterogenous and around 30% of patients with clinical SRS have no genetic diagnosis. Mutations in *HMGA2* have recently been identified causing growth failure and an SRS-like phenotype. Despite strong evidence of the crucial role of *HMGA2* in growth across species, the mechanism of action of *HMGA2* in human linear growth is unclear.

Objective: Identify and functionally characterise an *HMGA2* mutation in a patient with growth failure and SRS features.

Methods: We used custom bioinformatic pipelines to filter genetic data generated from our novel targeted genome short stature gene panel. Comprehensive functional analysis of a novel *HMGA2* missense variant was performed using Immunocytochemistry and Electrophoretic Mobility Shift Assays (EMSAs). Our collaborators at The University of Mannitoba, Winnepeg generated novel transgenic mice with targeted mutations of *Hmga2* using CRISPR/Cas technology.

Results: We identified several novel heterozygous *HMGA2* mutations in patients with short stature and SRS features including the first heterozygous missense *HMGA2* mutation c.166A>G, p.(Lys56Glu) in a patient with pre- and post-natal growth failure; low BMI, triangular face, high arched palate and 3/6 NHCSS. The variant was inherited from her mother who had short stature (height -3.5 SDS) and similar facial features. This novel variant was of particular interest as it resides in a critically important region of *HMGA2*, adjacent to the second AT hook or DNA binding region. This missense variant substitutes lysine, a positively charged amino acid crucial for DNA binding at target sites, for glutamic acid, a negatively charged amino acid.

Immunocytochemistry identified that the wild-type and mutant c.166A>G constructs were able to translocate to the nucleus. EMSAs confirmed reduced binding of the mutant c.166A>G HMGA2 protein to target DNA sequences. Transgenic mice harbouring homozygous c.166A>G p.(Lys56Glu) mutations (*Hmga2*^{K56E}) displayed dysmorphic facial features similar to the phenotypes observed in SRS children. 3D reconstructed serial micro-CT images showed an overall shortening of the viscerocranium and asymmetry of the skull bones. *Hmga2*^{K56E} transgenic mice were fertile but small for gestational age and showed SRS-like dwarfism.

Conclusions: This novel c.166A>G mutation is the first heterozygous missense *HMGA2* mutation identified in a patient with growth failure and SRS features. The mutant HMGA2 protein could translocate to the nucleus but binding to DNA target sites was impaired. A novel transgenic *Hmga2*^{K56E} mouse model recapitulated the SRS phenotype seen in our patient, confirming the critical functional importance of this amino acid residue.

P1-111

Diagnostic yield of a multigene sequencing approach in children classified as idiopathic short stature

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Objective: Most children with short stature remain without an etiologic diagnosis after extensive clinical and laboratory evaluation and are classified as idiopathic short stature (ISS). This study aimed to determine the diagnostic yield of a multigene gene analysis in children classified as ISS.

Design and Methods: We selected 102 children with ISS and performed the genetic analysis as part of the initial investigation. We developed customized target panel sequencing, including all genes already implicated in isolated short stature phenotype. Rare and deleterious single nucleotide or copy number variants were assessed by bioinformatic tools.

Results: We identified 20 heterozygous pathogenic (P) or likely pathogenic (LP) genetic variants in 17 of 102 patients (diagnostic yield = 16.7%). Three patients had more than one P/LP genetic alteration. Most of the findings were in genes associated with the growth plate development: *IHH* (n = 4), *SHOX* (n = 3), *FGFR3* (n=2), *NPR2* (n = 2), *ACAN* (n = 2) and *COL2A1* (n=1); or involved in the RAS/MAPK pathway: *NF1* (n = 2), *PTPN11* (n = 1), *CBL* (n=1) and *BRAF* (n=1). The diagnostic yield was higher among children with severe short stature (35% vs. 12.2% for height SDS ≤ or > -3; p=0.034). No significant difference in the rate of positive genetic diagnosis was observed regarding familial short stature

(with 22.4%, without 9.1%; p=0.129) or presence of mild body disproportion (present 30.4%, absent 14.1%, p=0.116). None of these patients had clinical findings to guide a candidate gene approach.

Conclusion: A multigene sequencing approach is able to determine a genetic etiology of short stature in up to one in six children with ISS, removing the term idiopathic from their clinical classification. Additionally, knowing the genetic basis of these patient's short stature can allow precise genetic counseling, particularly relevant to children harboring variants in the RAS-MAPK pathway and potential to trigger the development of specific treatment protocols including the use of rhGH, and/or puberty modulators in patients with variants in *SHOX*, *IHH*, *NPR2*, and *ACAN* who already have some preliminary data associated a good short-term response to rhGH treatment and some particularities in relation to their growth pattern.

P1-112

Long-term follow-up of aromatase-inhibitor use in 3 family members with aromatase excess syndrome

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Introduction: Aromatase excess syndrome (AEXS) is a rare, autosomal dominant disorder, characterized by enhanced extragladular aromatization of androgens and estrogen excess. Genomic rearrangements in chromosome 15q21 are found to result in overexpression of the aromatase gene CYP19A1. In males it is characterized by pre- or peripubertal gynecomastia, hypogonadotropic hypogonadism, advanced bone age and short adult height. Only a few female patients have been described so far. The aim of this study is to report on a family with 4 family members with EAXS and to present the long-term effects of aromatase-inhibitor use in 3 of them.

Patients and Methods: 3 children (index patient, brother, sister) with AEXS treated with 3rd generation aromatase inhibitor, letrozole, were studied. Genetic analysis of the aromatase gene showed a 0.3-Mb deletion in 15q21, involving six of the CYP19A1 exons 1, all exons of GLDN, and DMXL2 exons 2-43, in the index patient, his father and his siblings.

Results: The index patient (male, 8 years old) presented with gynecomastia, accelerated growth and bone age (13 $^{6/12}$ years). With start of puberty, estradiol levels increased, whereas testosterone and androstenedione levels remained low. Gynecomastia progressed and a mastectomy was performed twice (ages 9 and 13 years). Presuming AEXS, a therapy with letrozole was initiated first at the age of 19 years. Although adult height was already reached (168 cm), low-dose letrozole treatment increased testicular volume, promoted virilization, improved physical strength and libido. No gynecomastia was observed under treatment. His younger brother presented at the age of 3 years with accelerated bone age (5 $^{6/12}$ years). Treatment with letrozole was started at the age of 7 years. Under treatment the patient developed no gynecomastia and reached a final height of 179 cm. His sister, who presented at the age of 6 years with premature thelarche, accelerated growth and bone age (10 $^{6/12}$ years), was treated with an estrogen receptor modulator (tamoxifen) followed by letrozole treatment for 1 year. Menarche occurred at age 13 $^{6/12}$ years and final height was 158 cm.

Discussion/Conclusion: We observed a phenotypic variability within family members with AEXS carrying the same genetic microdeletion in CYP19A1. When started early, treatment with aromatase inhibitors in children with AEXS was found to prevent the development of gynecomastia and improve final height. In adult life, treatment with aromatase inhibitors in a very low dose resulted in improved physical strength and libido.

P1-113

Development and testing of a novel 'GrowthMonitor' Smartphone App for growth monitoring and the detection of growth disorders

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Background: Childhood growth is an indicator of health/well-being. Growth monitoring identifies treatable conditions in apparently healthy children and prevents inappropriate referrals. Systematic growth monitoring is not currently a UK priority and growth disorders are frequently diagnosed late.

Objective: Develop and test the accuracy of GrowthMonitor, an app which enables families to measure a child's height at home as a cost-effective alternative to primary care growth monitoring.

Methods: 'GrowthMonitor' calculates height data using augmented reality. The app uses algorithms to calculate height expressed as standard deviations (HSDS) and distance from target height (THSDSDEV) relative to UK population-based height references. Patients were measured using the app in parallel to stadiometer (gold standard) height measurements, as part of routine

clinic visit. A subset of parents also used the app to measure their child's height at home. Precision and reproducibility were assessed with coefficient of variance across 3 consecutive app measurements for each patient. The relationship between the app and stadiometer measurements was assessed with linear regression. The error rate (%) was calculated as [Stadiometer height measurement (cm) – Mean GMA Measurement (cm)]/ Stadiometer height measurement (cm) x 100. Accuracy (%) was then determined as 100% - error rate. Recorded heights were compared with pre-established thresholds that discriminate normal/abnormal growth in ethnicity-matched populations. Predefined thresholds trigger green (normal), amber (monitor) or red (seek medical advice) app alerts. The primary target was to achieve 95% of app growth measurements within +/-0.5SDS of gold standard (stadiometer) measurements.

Results: A total of 88 (46M) patients had three consecutive height measurements made in clinic by the study team using the app. Linear regression showed a significant correlation between the app and the stadiometer height measurements (R20.99; p<0.0001). The average coefficient of variance for height measurements from the app relative to the stadiometer was 0.9%, indicating excellent precision. The average accuracy for the app measurements ±95% CI was 99.2±0.14%. The app provided height measurements within +/- 0.26SDS (95%CI: 0.22-0.30SDS) of the stadiometer. Height measured by parents (n=28) using the app at home also showed a significant correlation (R20.98; p<0.0001) with stadiometer measurements performed in clinic, with a two-tailed paired T-test value of 0.421 suggesting no significant difference in the height measurement methods (app vs. stadiometer).

Conclusion: GrowthMonitor produces accurate, reliable height measurements and can be used by parents/carers in the community to capture serial height measurements and can facilitate early referral/diagnosis of growth disorders.

P1-114

Metabolic status in prepubertal and pubertal children with turner syndrome

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Aim: To evaluate the metabolic status in children with Turner syndrome (TS) depending on the Tanner stage (pre-puberty and puberty).

Methods: The total studied group consisted of 85 children with TS from 8 to 17 years, who were regularly followed-up in the University hospital (Minsk) and age matched 72 healthy controls. TS was diagnosed in patients with characteristic phenotypic signs according to the results of karyotyping at the age of 8.2±5.16 years. 41 patients were in pre-puberty (mean age 11.86 (9.21;13.25) years vs 8.97(7.86;9.54) years in pre-puberty control group, p=0.001). 44 girls had II-V stage of sexual development according to Tanner (mean age 15.63 (14.37;17.03) years). Spontaneous puberty was observed in 13 girls. 31 patients underwent puberty initiation. Body composition using dual-energy X-ray absorptiometry, body mass index (BMI), serum concentrations of insulin, glucose, lipids were measured in all groups of patients.

Results: 68.2% of TS girls had normal body weight, 25.9% were overweight, 5.9% had obesity. Significantly higher values of BMI (20.52 (18.34;23.22) kg/m2 vs 18.35 (16.30;20.59) kg/m2, p<0.0001), SDS BMI (0.42 (-0.25;1.31) vs -0.19(-0.73;0.54), p<0.0001), higher percentage of total fat mass (36,2 (28,6; 42,3) kg vs 29,15 (25,63; 37,10) kg, p=0.002) and android region fat mass (36.9 (26.75;44.50) kg vs 30.30 (23.90;38.43) kg, p=0.005) insulin (9.35 (6.77;13.30) μIU/mL vs 6.95 (3.84;10.62) μIU/mL, p=0.011), HOMA-IR (1.99 (1.38;2.90) vs 1.48 (0.82;2.62), p=0.039) and triglycerides (0.86 (0.66;1.06) mmol/L vs 0.69 (0.54;0.90) mmol/L, p=0.007) were revealed in patients with TS compared with the control. There were no significant differences in the SDS BMI (p=0.993), percentage of total fat mass (p=0.285) and android region fat mass (p=0.113) in children with TS in pre-pubertal and pubertal groups. A direct correlation of BMI (ρ=0.435; p=0.003), percentage of total fat mass (ρ=0.346; p=0.022), percentage of fat mass of android region (ρ=0.426; p=0.004) with age was found in pre-pubertal girls with TS. This relationship was not revealed among patients in TS puberty subgroup and in the control subgroups.

Conclusions: Overweight and obesity were detected in 31.76% of girls with TS. Significant increase in the SDS BMI, percentage of total android region fat mass, insulin, HOMA-IR and triglycerides levels in TS patients compared to the control group are predictors of metabolic disorders. Relationship between BMI values, percentage of total android region fat mass with age in the pre-pubertal TS patients may indicate excessive accumulation of fat mass in conditions of estrogen deficiency.

P1-115

Validation of referral criteria for growth monitoring in Flanders based on height at the start of GH therapy in children with growth hormone deficiency and Turner syndrome

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Background/Aims: Length and weight of all children in Flanders are monitored every three years at school from the age of 3 years. The current criteria used for referral to specialized care are: height SDS < -2.5, height SDS between -2 and -2.5 SDS with a height SDS adjusted for parental height < -1.64, or a decrease in height SDS of more than 1 SDS in the past 3 years. The aim of this study is to investigate the sensitivity of the Flemish referral criteria to detect idiopathic/congenital growth hormone deficiency (GHD) and Turner syndrome (TS).

Methods: A cross-sectional analysis of data from children with idiopathic/congenital GHD and girls with TS included in the BELGROW register – a national register of all GH treated children – from January 2018 through December 2020. Height at the start of GH treatment and 2-3 years before GH treatment and parental heights (reported or measured) were retrieved from the database. Height SDS adjusted for parental height was calculated according to Hermanussen & Cole. The referral analysis only included prepubertal children below 10 years of age.

Results: In the 112 children with GHD (78 male), GH treatment was started at a median age of 8.86 years (P10, P90: 2.86, 13.11) and a median height SDS of -2.99 (-4, -1.77). In the 43 girls with Turner syndrome this was 9.63 years (5.42, 14.44) and a height SDS of -2.79 (-3.77, -1.83). In the 97 children younger than 10 years of age, a height SDS < -2.5 was reported in 56 (76 %) out of 74 children with GHD and in 14 (61 %) out of 23 girls with TS. The SDS adjusted for parental height was < -1.64 in 60 (81 %) and 18 (78 %) respectively. In children older than 3 years with data on pre-treatment height, 5 (10 %) out of 49 with GHD and 1 (6 %) out of 17 with TS had a height decrease > 1 SDS before the start of GH treatment.

Conclusion: In Belgium, GH treatment is started relatively late in children with congenital/idiopathic growth hormone deficiency and Turner syndrome, despite systematic growth monitoring at school. Height SDS adjusted for parental height was the most sensitive criterium for auxological detection of growth hormone deficiency and Turner syndrome, stressing the need of collection of parental height in school health surveys.

P1-116

Clinical and biochemical parameters of puberty onset in children with Silver Russell syndrome and children born small for gestational age

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Silver-Russell syndrome (SRS) is a rare heterogeneous syndrome associated with severe prenatal and postnatal growth retardation.

Context: There is little information on puberty onset and bone age trend in children with SRS.

Study Design and Partecipants: Retrospective observational study, including patients with a confirmed diagnosis of SRS divided in 2 molecular groups [11p15 loss of methylation, (11p15 LOM) and maternal uniparental disomy of chromosome 7 (mUPD7)] and small for gestational age (SGA) subjects recruited at the Pediatric Endocrine Unit, Istituto Giannina Gaslini, University of Genova (Genova, Italy), between November 2014 and October 2021.

23 SRS patients (10 11p15LOM; 13 mUPD7; 12 males; 11 females- mean age 11.3± 3.9 years), and 21 SGA subjects (14 males; 7 females - mean age 14.2 ± 1.9 years).

Outcomes: Clinical (thelarche-Tanner B2 in females; testis volume ≥ 4 ml- Tanner G2 in males) and biochemical puberty onset [Luteinizing hormone (LH), 17-bestradiol, testosterone]; PH2; bone age evolution evaluated from the age of 5 to the age of 11 years according to Greulich and Pyle; Body mass index (BMI) trend evaluated at different ages (from the age of 5 to 9 years) and at the age of puberty onset.

Results: Pubertal onset and pubarche occurred significantly earlier in SRS group than in SGA group (p 0.03 and p 0.001, respectively). LH, 17-bestradiol, testosterone were detected earlier in SRS than in SGA (p 0.01; p 0.0001). Within the SRS group, clinical signs of puberty onset occurred earlier in mUPD7 than in 11p15LOM

group (p 0.003). 4 SRS children (2 females and 2 males, 3 mUPD7 and 1 11p15LOM) experienced central precocious puberty and were treated with gonadotropin-releasing hormone analogs.

Early bone age delay in SRS children was followed by rapid advancement; the delta between bone age and chronological age in SRS group became significantly higher than in SGA group at the age of 9-11 years (p 0.007). Patients with 11p15LOM were underweight at the age of 5 years with a progressive normalization of BMI with the age and a BMI significantly higher than mUPD7 group (p 0.04) and SGA group (p 0.03) at the age of puberty onset.

Conclusion: Puberty onset occurred earlier in SRS than in SGA. Within the SRS group, clinical signs of puberty onset occurred earlier in mUPD7 than in 11p15LOM group.

P1-117

The elevated levels of Fetuin-A and FGF21 are correlated with metabolic indicators in Turner syndrome

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Objective: To find the roles of Fetuin-A and FGF21 in metabolic disorders through investigating the correlations between Fetuin-A, FGF21 with metabolic indicators in girls with Turner syndrome (TS).

Methods: A cross-sectional study of TS girls ranging from 5 to18 years and age-, body mass index (BMI)- matched healthy girls were recruited from the outpatients in Fuzhou Children's Hospital of Fujian Medical University. The anthropometric indicators including height, weight, waist circumference (WC) and hip circumference (HC) were measured and Tanner stages were recorded. The levels of triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), fasting blood glucose (FBG), fasting serum insulin (FIns), Fetuin-A and FGF21 were tested. Weight to hip ratio (WHR), weight to height ratio (WHtR), BMI, BMI-standardized deviation score (BMI-SDS), non-HDL and homeostasis model assessment for insulin resistance (HOMA-IR) were calculated. TS girls were divided into subgroups according to karyotype and Tanner stage, respectively.

Results: 71 TS girls (12.25 ± 3.97 years) and 71 healthy girls (11.95 ± 3.15 years) were assessed. The levels of Fetuin-A and FGF21 were significantly higher in TS group than the control [1.45 (1.23, 1.83) vs 1.25 (1.10, 1.56) mg/ml, 207.4 (101.23, 344.13) vs 153.9 (88.04, 250.39) ng/ml, respectively]. In TS group, Fetuin-A was positively correlated with FBG and HOMA-IR, while negatively correlated with age and Tanner stages; FGF21 was positively correlated with WHtR, HOMA-IR and TG, but negatively correlated with HDL-c. Independent correlations between Fetuin-A with Tanner stages and HOMA-IR, FGF21 with HDL ($p<0.05$) were found in TS respectively.

Conclusions: FGF21 resistance might exist even in the childhood of TS. FGF21 resistance and the elevation of serum Fetuin-A might involve in the glucolipid metabolic disorders in this population through regulating insulin sensitivity.

Keywords: Turner syndrome, metabolic disorder, insulin resistance, Fetuin-A, FGF21.

P1-118

A background review of several generic patient-reported outcome and clinician-reported outcome measures: Selecting measures for further evaluation in a qualitative study in achondroplasia

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Objectives: No validated achondroplasia (ACH)-specific patient reported outcome (PRO) or clinician-reported outcome (ClinRO) measures are available. A detailed review of generic PRO and ClinRO measures was performed to select relevant tools for further evaluation in a qualitative study.

Methods: Published literature describing medical challenges and impacts among children with ACH was reviewed to identify important concepts. Based on these findings, five PROs and one ClinRO were selected for further analysis.

Results: The most common symptoms were pain, ear infections/fluid, and low stamina/tiring easily. The most common impacts were difficulty reaching objects/high places, toileting, bathing/showering, washing, grooming, and running. These concepts mapped well to PRO (CHAQ, CHQ-CF45, Pain-NRS, PedsQL, PODCI, QoLISSY) and ClinRO (WeeFIM) measures (Table 1).

Conclusion: The QoLISSY, PedsQL, Pain-NRS, and WeeFIM were identified for further evaluation in a qualitative study of children with ACH and parents of children with ACH. The content, clarity, and relevance of these measures were evaluated during combined concept elicitation/cognitive debriefing interviews (presented elsewhere).

Table 1. Summary of measures reviewed

Measure	Assessment	No. of Items	Concepts	Psychometric properties demonstrated	Recommended Yes/No
CHAQ	Change in physical functioning in children with arthritis	30	Dressing and Grooming, Arising, Eating, Walking, Hygiene, Reach, Grip, Activities	Some	No; covers some key concepts, but only a parent version available
CHQ-CF45/ CHQ-PF50	Physical and psychosocial functioning and well-being in children/adolescents	45/50	Global Health, Physical Functioning, Social/Emotional, Social/Physical, Body Pain, Getting Along, Global Behavior, Self-Esteem, Mental and General Health, Change in Health, Family Activities, Family Cohesion	Not reported	No; lengthy and psychometric properties not evaluated
Pain-NRS	Pain severity	1	Pain	Not reported	Yes; commonly used to assess pain severity
PedsQL	Health related quality of life (HRQoL) in healthy children/ adolescents and those with acute/chronic health conditions	23	Physical, Emotional, Social, School Functioning	Some	Yes; covers physical, emotional, and social functioning
PODCI	Changes following pediatric orthopedic interventions for broad range of diagnoses	83-86	Upper Extremity and Physical Function, Transfer and Mobility Tasks, Sports/Physical Functioning, Pain/ Comfort, Treatment Expectations, Happiness, Satisfaction with Symptoms	Not reported	No; lengthy and psychometric properties not evaluated
QoLISSY (Core)	HRQoL in children/adolescents with short stature	22	Physical, Social, Emotional Functioning	Majority	Yes; covers physical, social and emotional functioning
WeeFIM	Need for assistance and severity of disability in children	18	Self-care, Mobility, Cognition	Some	Yes; covers areas of self-care not included in other measures

P1-119

Post-hoc subgroup analysis of Asian subjects from the pivotal phase 3 study of once-weekly somatrogon vs once-daily Genotropin

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Objectives: Somatrogon is a long-acting recombinant human growth hormone (GH) approved by the EMA as a once weekly treatment for children with pediatric GH deficiency (GHD). A global phase 3 study compared the efficacy and safety of once-weekly somatrogon with once-daily Genotropin in pediatric subjects with GHD. The objective of this subgroup analysis was to evaluate the efficacy and safety of once-weekly somatrogon vs once-daily Genotropin in the subset of Asian subjects.

Methods: This open-label phase 3 study enrolled 224 subjects who were randomized 1:1 to receive either once-weekly somatrogon (0.66 mg/kg/week) or once-daily Genotropin (0.24 mg/kg/week) for 12 months. Randomization was stratified by geographic region, peak GH level, and age. The primary endpoint of the study was height velocity (HV) at month 12; secondary endpoints included HV at month 6, change in height SDS at months 6 and 12, IGF-1, IGF-I SDS, and bone maturation. This subgroup analysis focused on 45 Asian subjects from Australia, Great Britain, India, New Zealand, South Korea, Spain, Taiwan and the United States of America.

Results: Within this subgroup of Asian subjects, both treatment groups (somatrogon:n=24; Genotropin:n=21) had similar demographic and baseline characteristics. The least squares mean HV at month 12 was 10.94 cm/year in the somatrogon group and

9.56 cm/year in the Genotropin group with missing data imputed; the treatment difference of 1.38 cm/year favored somatrogon. The lower bound of the two-sided 95% confidence interval of the treatment difference (somatrogon–Genotropin) was −0.14 for this subgroup, similar to that for the overall study population (−0.24), for which the efficacy of once-weekly somatrogon was demonstrated to be non-inferior to once-daily Genotropin. The observed HV at month 6 was higher in the somatrogon group than in the Genotropin group (11.23 vs 8.31 cm/year). The somatrogon group also showed greater improvement in height SDS and IGF-1 SDS from baseline at months 6 and 12, compared with the Genotropin group. Both treatment groups had a similar proportion of subjects with adverse events (somatrogon: 83.3%; Genotropin: 76.2%) and serious adverse events were recorded for one and two subjects in the somatrogon and Genotropin groups, respectively.

Conclusions: The efficacy and safety results from this analysis of Asian subjects in the global study are consistent with those from the overall study population, in which non-inferiority of once-weekly somatrogon to once-daily Genotropin was demonstrated.

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P1-120

Mosaic sex chromosomal abnormalities in male individuals with short stature: a new role for non-conventional techniques (whole exome sequencing, genome wide array analysis, SHOX MLPA) in making the genetic diagnosis

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The phenotype in male individuals with a mosaic sex chromosomal abnormality is heterogenous, but ambiguous genitalia, delayed puberty, disturbed spermatogenesis, and short stature are frequently seen. Genetic investigation in boys with idiopathic/isolated short stature usually includes SHOX gene analysis (sequencing and copy number detection by MLPA), genome wide array analysis, and/or whole exome sequencing (WES). In the Netherlands, conventional karyotyping is not part of this standard diagnostic workup.

Here, we present three cases in whom a mosaic sex chromosomal abnormality was identified by WES or SHOX MLPA. In two of them, short stature was the only clear clinical feature.

In case 1 (11 years, height SDS: -2,4), WES was performed (SNV and CNV analysis) with a bioinformatic filter for our short stature/skeletal dysplasia gene panel (565 genes). CNV analysis showed a terminal deletion of Yq11.221qter in ~50% of the cells and a deletion of the whole Y-chromosome in the remaining 50% of the cells. These results were confirmed by genome wide array analysis and are indicative for a 45,X/46,X,del(Y)(q11.221) karyotype.

In case 2 (30 years, height SDS: <-2,5, sitting index 0.56 (>P97), very mild Madelung deformity), SHOX MLPA showed a mosaic deletion of the entire SHOX gene. To further characterize the deletion, genome wide array analysis was executed, showing a deletion of the entire Y-chromosome in ~40% of the cells, indicative for a 45,X/46,XY karyotype.

In case 3 (15 years, height SDS: -2.45), a gain of the entire SHOX gene was identified by MLPA. Array analysis showed a terminal gain of Ypterq11.221 in ~75% of the cells and a terminal deletion of Yq11.222qter in all cells, indicative for a isodicentric Y-chromosome (idic(Y)). Karyotyping and FISH analysis on leukocytes could confirm the presence of this idic(Y) in mosaic form: 46,X,idic(Y)(q11.221)[20].ish idic(Y)(SRY++,CEP(Y)++)[5]/45, X[10].

These cases show that (mosaic) sex chromosomal abnormalities should be in the differential diagnosis of short statue in males, as they can result in i.e. delayed puberty, fertility issues, or cardiac problems. Early detection can provide new treatment options to influence height. Non-conventional/non-cytogenetic techniques (WES, array analysis, SHOX MLPA) might have a more prominent role in the genetic diagnosis of these chromosomal abnormalities in the near future. Conventional cytogenetics (karyotyping or FISH) remain necessary to investigate the structure of the abnormal sex chromosome and/or the mosaic status in different tissues.

P1-121

Qatar National standards for newborn weight, length, and Abdominal and Head Circumference by gestational age and sex: A part of the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project

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Introduction: This was a population-based retrospective data analysis. The study was part of the Vulnerable Newborn Study, approved by the Hamad Medical Corporation Institutional Review Board (IRB No MRC-01-21-277).

Setting and Participants: The population for this analysis comprised of a 4-year cohort data (January 2016 to December 2019) for births conducted in all HMC hospitals (representing 90% of all births in the country). The inclusion criterion for this analysis was term singleton live births, 37+0 to 42+6 weeks gestation, giving a final sample size of 80722 births.

The outcome variables recorded were gestational age (GA), gender, birth weight, length, and abdominal and head circumference. Other covariates recorded were maternal age, mode of delivery.

Women had a reliable ultrasound estimate of gestational age using crown-rump length before 14 weeks of gestation or biparietal diameter if antenatal care started between 14 weeks and 24 weeks or less of gestation. Newborn anthropometric measures were obtained within 12 h of birth by a well-trained anthropometric team using the same equipment at all sites. GA was calculated

stats	count	mean	SD	Interquartile range	p5	p10	p90	p95
Abdomen Circ. (cm)	63324	30.4	1.9	3	27	28	33	33.5
Maternal age	80720	29.6	5.3	7	21	23	37	39
Birth weight (g)	80722	3281.7	438.7	576	2580	2735	3845	4020
Placental weight (g)	80722	661.3	104.2	110	482	525	780	830
Head Circ (cm)	79850	34.3	1.3	2	32	33	36	36.5
Length (cm)	79002	50.8	2.0	2.5	48	48	53.5	54
Weight/length ratio	79002	64.4	7.0	9.4	--	55.6	73.3	--

by either the calculation from the last menstrual period or early obstetric ultrasound measurements.

Statistical Analysis: We summarized the distribution of variables using numbers and percentages, mean and standard deviation (SD). (table) Pearson correlation coefficients explored the relationship between variables. The adjustment was made for maternal age, gender, and gestational age. Analysis was done with STATA 14 software.

Results: 80722 pregnant women were enrolled during the study period. We calculated sex-specific observed and smoothed centiles for weight, length, and head circumference for gestational age at birth. The observed data were presented as the 3rd, 10th, 50th(mean), 90th, and 95th centiles according to GA and sex.

Conclusion: We have developed, for routine clinical practice, national anthropometric standards to assess newborn size that is intended to complement the WHO Child Growth Standards and allow comparisons across multiethnic populations.

P1-122

A Case of Derivative Chromosome 1 Accompanied by Y Chromosome Deletion

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Introduction: Derivative chromosome is a rearrangement involving two or more chromosomes or the presence of multiple abnormalities in a single chromosome and always contains intact centromere. Segmental anomalies such as inversion or translocation in derivative chromosome may result in partial duplication or deletion during meiosis. Chromosomal translocations usually result in miscarriage and multiple anomalies (common neurodevelopmental defects, growth retardation, severe malnutrition, reproductive failure, cardiac anomalies) are observed in newborns. Here, a case of derivative chromosome 1 accompanied by deletion in Y-chromosome will be presented.

Case: A 17-year-old male patient first entered our follow-up at the age of 12. He was born with term NSVY of 1800 g, followed up in incubator for 15 days after birth, operated for hydrocele-herniaundescended testis-cleft palate-tracheostomy, immobile due to widespread neurodevelopmental retardation, had feeding problems and intermittent catheterization due to neurogenic bladder. He also had levothyroxine replacement for primary hypothyroidism, multiple antiepileptics for epilepsy and had no parental consanguinity or similar disease in his family members. In physical examination, pathological short stature and severe malnutrition, hypertelorism, nasal root depression, low ear, narrow forehead, low nape hairline, micro-retrognathia, cleft palate operation scar, drop foot, hypospadias, flexion contracture of fingers were detected. He was prepubertal and testicles were bilateral atrophic at inguinal canal. AFP-beta HCG-AMH-inhibin B levels were normal. Reorchiopexy was applied in follow-up. His imaging showed corpus callosum agenesis and intermittent anterior pituitary hormone levels were normal. In the follow-up severe osteoporosis was detected in patient who developed femur fracture during physotheraphy and pamidronate treatment was given. There was no pituitary problem in LHRH stimulation test of the patient who had hypogonadotropic hypogonadism. Testosterone and vitamin D replacements were treated. Karyotype was reported as 45,X,der(1)(inv 1)(p13q44) t(1;4)(q44;p11). In microarray analysis deletion of 1,786 kb in 1p12, 6,912kb in 1q43q44 and 10,800kb in Yq11,221q11.23. was detected. In Y-microdeletion analysis, deletions were detected in AZFb,AZFc-d,AZFc-DAZ regions of Y chromosome and SRY was positive. The patient wasn't considered to be as mixed gonadal dysgenesis or Turner syndrome variant and the genetic pathology didn't pose an additional risk of gonadal tumors. Close follow-up of the case was decided.

Conclusion: Our case provides information about mutation spectrum of Y-autosomal translocation associated with dysmorphology. There is still more need to increase our observations about this spectrum.

P1-123

Single center analysis of the characteristics of 24-hour ambulatory blood pressure and related factors in patients with Turner syndrome

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Background and Objectives: In the patients with Turner syndrome (TS), the risk of hypertension is higher in childhood and adulthood. The aim of the study was to retrospectively analyze 24-hour ambulatory blood pressure monitoring (ABPM) in children and adolescents with TS and its related factors.

Materials and Methods: A retrospective study was conducted involving TS patients admitted to our pediatric endocrine specialist clinics, the First Affiliated Hospital, Sun Yat-sen University, between January 2012 and December 2018. All patients completed anthropometric measurement, 24-hour ABPM, testing of cholesterol (CHOL), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), blood urea nitrogen (BUN), creatinine (Cr), fasting glucose, fasting insulin, estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL) and progesterone (P), testosterone (T), 8 am cortisol, echocardiography and abdominal ultrasound.

Results: A total of 27 patients with TS were identified, ranging in age from 7 to 23 years old (13.41±4.88), and 9 patients with ambulatory hypertension were detected by 24-hour ABPM. Among these 9 patients, 1 patient had elevated mean daytime blood pressure (BP), 4 patients had elevated mean nighttime BP, and 4 patients had elevated mean daytime and nighttime BP. The circadian rhythm with dipper BP pattern accounted for 33.3%, non-dippers BP pattern accounted for 66.7% of which 4 patients were reverse-dippers. Twenty-one patients had a decrease more than 10% of pulse rate at night. Among 27 TS patients, 2 patients had heart disease (7.4%) and 3 patients had horseshoe kidney (11.1%). The mean diastolic blood pressure (DBP) of TS patients was negatively correlated with HDL-c ($P < 0.05$). No correlation was found between mean systolic blood pressure (SBP) or DBP and E2 and T ($P > 0.05$). The decrease rate of SBP at nighttime in TS patients was negatively correlated with FSH, LH, PRL and T (all $P < 0.05$). The decrease rate of DBP at nighttime was negatively correlated with FSH and LH (all $P < 0.05$). FSH, LH and PRL of the non-dippers BP group were higher than those of the dippers BP group (all $P < 0.05$).

Conclusion: In this study, the detection rate of ambulatory hypertension in TS patients was relatively high, among which non-dippers BP pattern accounted for the majority. Low HDL-c level might be one of the causes of hypertension in Turner syndrome. Sex hormone levels in TS patients might further affect BP, leading to the occurrence of hypertension.

P1-124

Analysis of Clinical Features and Causative Genes in 48 Children with Short Stature of Unknown Etiology

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Objective: To analyze the clinical features and causative genes in children with undiagnosed short stature and study the causative genes in our hospital.

Methods: Clinical manifestations, laboratory test and whole exome sequencing (WES) results of children with undiagnosed short stature who visited pediatric endocrinology department of our hospital from January 2018 to August 2019 were analyzed retrospectively. Causative genes were classified and analyzed according to different pathogenic mechanisms.

Results: A total of 48 children met the inclusion criteria, including 30 males and 18 females, aged 7.73 ± 3.97 years, and height standard deviation score was -3.63 ± 1.67 SD. Clinical manifestations included 33 cases (68.8%) with facial anomalies, 31 cases (64.6%) with skeletal abnormalities, 26 cases (54.2%) with perinatal abnormalities including 61.5% small for gestational age (SGA), 24 cases (50.0%) with endocrine disorders including 87.5% growth hormone (GH) peak concentration below normal, 21 cases (43.8%) with family history of short stature. Laboratory tests showed that GH peak concentration following stimulation test was 9.72 ± 7.25 ng / ml, IGF-1 SDS was -0.82 ± 1.42 SD, and the difference between bone age and chronological age was -0.93 ± 1.39 years. Potential causative genes were found in 25 cases through WES. 17 cases (68.0%) were pathogenic, 4 cases (16.0%) were likely pathogenic, and 4 cases (16.0%) were uncertain significance. A total of 15 genes were identified with pathogenic/likely pathogenic variants, which were classified as (1) affecting intracellular signaling pathways: PTPN11, RAF1, RIT1, ARID1B, ANKRD11, CSNK2A1, SRCAP, CUL7, SMAD4, TRPV4 and FAM111A; (2) affecting extracellular matrix (ECM) components or functions: ACAN, FBN1, COL10A1 and COMP.

Conclusion: Rare monogenic disease should be considered as probably etiology for children with severe short stature accompanied by facial anomalies, disproportionate body, skeletal abnormalities, SGA, GH peak concentration below normal and family history of short stature. WES played an important role in identifying the causes for children of short stature with monogenic disorders. This study indicated that affecting growth plate cartilage formation through intracellular signaling pathways and ECM components or functions were the main machenisms of causative genes leading to severe short stature in children. Further research will help to discover and study new pathogenic variants and gene functions.

P1-125

SHOX gene deletion as part of a contiguous gene syndrome at Xp22.31p22.33 deletions

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Background: Terminal or interstitial deletions of Xp (Xp22.2→Xpter) in males have been recognized as a cause of contiguous gene syndromes showing variable association of apparently unrelated clinical manifestations such as Leri-Weill dyschondrosteosis (SHOX), chondrodysplasia punctata (ARSE), mental retardation (NLGN4), ichthyosis (STS), Kallmann syndrome (KAL1), and ocular albinism (GPR143).

Case Reports: We report two cases of boys with the same clinical features including hycthyosis, hypoacusis, short stature with short long bones, mental retardation, hypotelorism, strabismus, choanal stenosis and bilateral cryptorchidism. Case 1 was a boy born at 38 weeks of gestational age with a normal birth weight and birth length. At the age of 6 years and 10 months he was 99.5 cm (-4.1 SDS) compared to mid- parental-height of 169.5 cm (-1 SDS). ArrayCGH showed a terminal deletion in Xp22.31-33 region, maternally inherited, extended 6,1 Mb, including genes KAL1, STS, ARSE, NLGN4, SHOX. We started rhGH therapy at a dose of 0.035 mg/kg/day, increasing growth velocity from to 3.5 to 8 cm/year in the following three years, with a height gain of +1.3 SDS. At the age of 13 years he presented a decrease in growth velocity of 2 cm/yrs with a testicular volume of 2 ml bilaterally. GnRH-stimulation test showed a hypogonadotropic hypogonadism, so testosterone therapy was started. Case 2 was a boy born at 33 weeks of gestational age with a normal birth weight and length. At the age of 5 years and 7 months his height was 97 cm (-3.23 SD) with a mid-parental-height of 169 cm (- 1.1 SDS) and growth velocity of 4 cm/year. Array CGH showed a deletion in the region Xp22.31-33, maternally inherited, extended about 9.7 Mb. He started rGH therapy at a dose of 0.029 mg/kg/day with a height gain of +1 SDS in 2 years.

Conclusions: The two children presented a large terminal Xp22.31-33 deletion. Case 1 is the first Italian case of this contiguous gene syndrome, Case 2 had the longest terminal deletion reported in literature. We suggest, in order to improve the severe short stature in these patients, to start early the rhGH therapy for SHOX gene deletion and to optimize the induction of puberty according to the deletion of KAL1 gene, although short stature is also related to chondrodysplasia punctate.

P1-126

Earlier menarche of mothers as a risk factor for daughters' early age at menarche and short stature in young Korean females: an epidemiologic study

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Background: Early age at menarche was associated with obesity, insulin resistance, metabolic syndrome, cardiovascular disease (CVD), and mortality in adulthood. Besides, a mother's age at menarche has been suggested to be a likely contributor to a daughter's early menarche. Therefore, this study aimed to determine whether a mother's earlier age at menarche is a risk factor for a daughter's early menarche, obesity, and short stature in young Korean females.

Methods: We analyzed 761 pairs of mothers and daughters from 16-30 years-of-age using age at menarche and anthropometric data from the 6th Korea National Health and Nutrition Examination Survey (2013–2015).

Results: Mothers with earlier menarche showed a higher prevalence of early menarche in their daughters (earlier, 35.6%; reference, 25.8%; later, 13.3%; $p < 0.05$) and percentage of short stature (< 152 cm) of their daughters (11.3% vs. 4.2% vs. 2.6%; $p < 0.05$). However, there were no differences in the prevalence of a daughter's obesity, according to a mother's menarche age. The odds ratio (OR) for early menarche (< 12 years) for a daughter of a mother with earlier menarche compared with the reference was 1.56 (95% CI, [0.99-2.46]) after adjusting confounders. The OR for short stature for a daughter of a mother with early menarche was 3.13 (95% CI, [1.44-6.81]) after further adjusting for age, the short stature of the mother, and age at menarche of the daughter.

Conclusion: In conclusion, earlier age at menarche of a mother increases the risk of early menarche and short stature of a daughter in young Korean females.

P1-127

Treatment response to growth hormone in a patient with heterozygous ROR2 mutation

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Introduction: 'Receptor tyrosine kinase-like orphan receptor 2 (ROR2)' is a transmembrane protein tyrosine kinase encoded by the ROR2 gene. Pathogenic mutations in ROR2 are involved in two diseases: biallelic loss-of-function mutations in Robinow

syndrome and monoallelic gain-of-function mutations in brachydactyly type B1. Recently, monoallelic loss-of-function mutations in ROR2 have been reported as a cause of isolated short stature. Here we reported the treatment response of growth hormone (GH) therapy in a patient with monoallelic loss-of-function mutation in ROR2.

Case: A 8.3 years old girl was referred for short stature. There was no history of chronic diseases, malabsorptive symptoms, feeding difficulties. She was born with a weight of 3160 gr (-0.4 SDS) at term after an uneventful pregnancy to parents who were non-consanguineous. Her developmental milestones were normal. Her mother's and father's heights were 155 cm (-1.4 SDS) and 148 cm (-4.6 SDS, arm-span 147 cm) (midparenteral height was 145 cm -3.1 SDS). Her height was 111.7 cm (-3.07 SDS), weight was 17.7 kg (-3.6 SDS). Bone age was 6.8 years. She had proportional severe short stature. She had no dysmorphic features except high-arched eyebrows and a pointed chin. She was prepubertal. Total blood count and blood chemistry analysis were normal, and celiac antibodies were negative. At the age of 9.5 years, her growth velocity (GV) was 4 cm/year (her height was 116.9 cm (-3.1 SDS), and bone age was 7.8 years). GH stimulation tests with L-dopa and clonidine showed peak GH responses of 2.8 and 9.8 ng/mL and daily subcutaneous rhGH was started at a dose of 0.2 mg/kg/week. Her GV was 7.9 cm for the first year. However, despite the improvement of GV, her bone age accelerated even more. After three years of rhGH, at the age of 12.5 years, her height was 137.9 cm (-2.8 SDS), bone age was 13 years, and puberty was at Tanner stage 3. Predicted adult height was 143.9 cm (-3.2 SDS) which was compatible with midparenteral height. We conducted a genetic analysis due to family history suggesting monogenic causes, and poor response to rhGH. Next-generation sequencing revealed a missense monoallelic c.315G>T(p.Glu105Asp) mutation in ROR2.

Conclusion: ROR2 has a significant role in the formation and development of chondrocytes and bone by a mechanism other than the GH pathway. This pathway explains the poor response to rhGH in our patient. So, genetic testing is important for guiding the therapy.

P1-128

Major opinion about motherhood among women with Turner Syndrome – International online survey

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Context: Turner Syndrome (TS) is associated with ovarian dysgenesis leading to infertility in most of the cases. There are some options for fertility preservation in patients with sufficient follicle numbers. The most recently studied are oocyte preservation and ovarian tissue preservation. Due to premature ovarian failure among TS girls, the procedure should be performed as early as possible.

The aim of this study is to gain the opinions of women with TS about motherhood based on the web-survey.

Material and Methods: A web-based questionnaire was designed and submitted to online forums for women with TS. One version was offered to women with TS living in Poland (https://docs.google.com/forms/d/e/ 1FAIpQLSdoo7E40aVgOOiMClFEucKC0NNvXld6JuPmLtq4vFpp5-2nBQ/viewform), while another was offered to international respondents (https://docs.google.com/forms/d/e/ 1FAIpQLScIYv1eIHe19vZX_sW4rayFFAsJH-fiBu0qSJj93d5tGsEkezw/viewform). The questionnaire was administered to women with TS who were over the age of 18 years. It consisted of 12 questions: 11 were single choice, while the other was multiple choice. The participants anonymously completed and submitted the questionnaires, thereby agreeing to the use of their data for study purposes.

Results: A total of 98 women (37 from USA, 20 from Poland, 19 from UK and Ireland) with TS answered the questions. Asked if they had motherhood options discussed with physicians 41 (41.8%) of participants responded negatively. 16 (16.3%) respondents do not want to have children, 58 (59.2%) would like to have children, 21 (21.4) have some (biological or adopted) and 3 (3.1%) do not know yet. Asked about the will of use ovarian tissues if they had been preserved in the adolescence 50 (51.0%) Respondents would be interested in such procedure, 22 (22.5%) would not be, and 26 (26.5%) do not know. Among 79 women who previously had expressed a desire of having children 48 (60.8%) would use preserved cells, 13 (16.4%) would not and 18 (22.8%) do not know.

Conclusions: The most of women with TS who would like to have children would use preserved cells if they had such option. Therefore the further investigation of fertility preservation among TS patients is necessary.

P1-129

Variegated mosaic aneuploidy syndrome in two severely undersized siblings

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Introduction: Variegated mosaic aneuploidy syndrome (MVA) is a rare autosomal recessive disease characterized by a variable percentage of chromosomal gains and losses, resulting in multiple mosaic aneuploidies, which explains a great phenotypic variety and may predispose to the development of cancer.

Bi-allelic mutations in CEP57 are the cause of MVA2.

CEP57 encodes a centrosome protein involved in microtubule stabilization and is crucial for maintaining proper chromosome separation during cell division.

The main features of MVA2 include intra and extrauterine growth retardation, facial dimorphism (triangular face, prominent forehead, micrognathia, low-set ears...), skeletal deformities (rhizomelic limb shortening, clinodactyly...), congenital hypothyroidism, congenital cardiac and vascular anomalies and normal or mildly impaired psychomotor development.

Description of the Case and Evolution: We present two siblings of 8 and 4 years, from Tangier, children of non-consanguineous parents.

The first sibling is an 8-year-old male, born at term, with severe intrauterine growth retardation and current harmonic short stature at -5.2DS, with low IGF1 and growth hormone (GH) insensitivity. Phenotypically he has microcephaly (-3.5DS), scaphocephaly, triangular face, prominent forehead, micrognathia and hypodontia. Clinodactyly of the 5th finger, bilateral cryptorchidism, non-compacted cardiomyopathy and corrected atrial septal defect. Functional humoral immunodeficiency requiring periodic treatment with immunoglobulins. Cervical-dorsal syringomyelia and intellectual disability with language delay.

The second sibling is a 4-year-old male, born at term, with both severe intrauterine and postnatal growth retardation with current height at -7DS, normal IGF1 and IGFBP3 and GH insensitivity. Phenotypically same facial features as his brother. Bilateral cryptorchidism, hypospadias, bilateral hip dislocation. Normal cardiological study and mild developmental delay.

Genetic study by clinical exome revealed that both siblings carried the pathogenic variant c.915_925dup(p.(Leu309Profs*9)) in CEP57. This pathogenic variant confirms the diagnosis of MVA2. Both were also heterozygous carriers of the pathogenic variant c.32465delA (p.(Asn10822Ilefs*5)) in TTN.

Conclusions: Few cases of bi-allelic mutations in CEP57 have been described in the literature.

We present two cases of MVA2 that present most of the clinical features described in the literature, including severe short stature without response to GH treatment.

This is a new case of variegated mosaic aneuploidy syndrome related to CEP57 without chromosomal alterations in peripheral blood.

No association of this syndrome with cardiomyopathy has been described; in our patients this could be explained by the concurrence of a TTN mutation.

The absence of aneuploidies in a single determination and tissue does not allow us to exclude the diagnosis of this syndrome.

P1-130

Osteogenesis imperfecta / Ehlers–Danlos (OI/EDS) overlap syndrome associated with a new COL1A1 variant (c.3235G>A, p.Gly1079Ser) in a girl with severe short stature and neuroblastoma

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Background: Osteogenesis imperfecta / Ehlers–Danlos (OI/EDS) overlap syndrome is a rare and recently described disorder of connective tissue, characterized by mutation of COL1A1 (17q21.33) or COL1A2 (7q21.3) genes, involved in alpha-1 and alpha-2 chains of type 1 collagen synthesis.

Patients with OI/EDS overlap syndrome could show a phenotype characterized by features of both osteogenesis imperfecta (bone fragility, long bone fractures, blue sclerae, short stature) and Ehlers Danlos syndrome (joint hyperextensibility, soft and hyperextensible skin, abnormal wound healing, easy bruising, vascular fragility).

Case Description: We described the case of a 10-year-old girl, born of unrelated parents, came to our observation with a severe and worsening height deficit (-3.06 SD) and reduced growth velocity (-2.16 SD) during the last year. She was born at full term (38 weeks of gestational age), with adequate weight (-1.48 SDS) and length (-1.57 SDS) for gestational age.

In the first months of life, genetic investigations for Prader Willi, Silver-Russell syndrome, CGH array and karyotype (negative) were performed because of the presence of hypotonia and difficulty in feeding.

At the age of 11 months, she was diagnosed with stage 4 MYCN nonamplified neuroblastoma with left adrenal and bone marrow invasion, successfully treated with left adrenalectomy and 6 chemoterapy courses.

On clinical examination, she displayed the compound phenotype of OI/EDS, characterized by skin hyperextensibility, bilateral ectropion, blue sclerae, joint hypermobility (Beighton score 7/9), osteoporosis and tooth enamel abnormalities.

Results: Laboratory tests for complete blood count, hepatic and renal function, electrolytes, thyroid hormones dosage and also the evaluation of vitamin D and parathormone levels were confirmed normal, similarly to growth hormone (GH) stimulated levels and mutational analysis of SHOX gene.

Next-generation sequencing (NGS) applied to the proband and her parents' genome showed the presence of a de novo heterozygous COL1A1 variant (c.3235G>A, p.Gly1079Ser), already described in the literature in association with type V OI.

Conclusions: Our case reported a new COL1A1 variant associated with OI/EDS syndrome. We also hypothesized that the association with the previous history of neuroblastoma could not be occasional, but influenced by the presence of COL1A1 mutation, whose role has been already described in some cancers behaviour and progression.

P1-131

SHORT syndrome in a twelve-year old boy-case report

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Background: "SHORT syndrome" is a rare condition and mnemonic for Short stature, Hyperextensibility, Ocular depression, Rieger anomaly and Teething delay. The features most consistently observed in SHORT syndrome are mild intrauterine growth restriction; mild to moderate short stature; partial lipodystrophy; and a characteristic facial gestalt (small chin, triangular shaped face, prominent forehand, abnormal positioning large ears and thin wrinkled skin). Insulin resistance may be evident in mild-childhood or adolescence although diabetes mellitus typically does not develop until early adulthood. The diagnosis is established with compatible clinical features and a heterozygous pathogenic variant in PIK3R1gene (5q13.1), encoding phosphatidylinositol 3-kinase regulatory subunit alpha.

Case Presentation: A 12-years-old male presented at the endocrinology clinic at the age of 3 years because of failure to thrive and short stature (3rd percentile).

The proband was born full term with IUGR features (Birth Weight: 2200gr, Length: 48cm, Head Circumference: 32cm) and dysmorphic facial characteristics, suggestive of Russel Silver syndrome. However normal genetic testing ruled it out.

He had normal male karyotype (46,XY), and the molecular karyotyping did not reveal any chromosomal aberrations.

During follow up, his height and weight were always below the 3rd percentile. At the age of 5, failing to demonstrate catch-up growth, treatment with growth hormone was initiated, showing moderate response.

At the age of 10, due to the combination of lipodystrophy, short stature and dysmorphic features, whole-exome sequencing (WES) study was performed, reporting no genetic alterations.

At the age of 11, while he was still under treatment with GH, he developed acanthosis nigricans. Oral glucose tolerance test was performed, revealing normal glucose response but severe insulin resistance.

This new finding in combination with child's phenotype, were highly suggestive of SHORT syndrome. Hence, a reevaluation of WES was requested, detecting a de novo mutation c.1945C>T (p.ARG649Trp, R649W) at the exon 15 of the gene PIK3R1, confirming the hypothesis. This mutation is thought to impair the PI3K/AKT/mTOR pathway which plays an important role in cellular proliferation and growth and appears to disrupt the insulin signaling pathway and thereby predispose the patient to insulin resistance and diabetes mellitus.

Discussion: This case also underlines the importance of reanalysis of WES when new clinical data emerge.

Diagnosis of SHORT syndrome is important for the appropriate personalized treatment, considering that GH administration can induce hyperinsulinemia which might aggravate insulin resistance and accelerate the onset of diabetes. Subsequently despite short stature, GH is not recommended.

P1-132

The Study of Growth in Thalassemic Patients

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Introduction: β-thalassemia is a chronic hereditary hemolytic anemia characterized by a defect in the synthesis of beta-globin chains, particularly common in the Mediterranean region, southern Asia, and the Middle East.

Transfusion programs and chelation therapy have considerably extended the life expectancy of patients. This has led to an increase in the prevalence of complications related to iron overload, growth retardation is extremely common in polytransfused patients with thalassemia.

Objectives: To describe the frequency of growth retardation and to evaluate the GH-IGF-I axis in a group of patients with polytransfused β-thalassemia.

To study the relationship between growth retardation and serum ferritin level, mean transfusion volume (VTM), duration of transfusion treatment, splenectomy, and compliance with chelation treatment.

Method: This is a descriptive, analytical and monocentric cross-sectional study which was carried out in the CHU Mustapha pediatrics department and which involved 87 patients (46 girls and 41 boys), followed regularly for several years for the most part, and treated by a transfusion regimen (more than 10 transfusions) combined with chelation therapy.

All patients were assessed by clinical history, somatic examination, measurement of height and weight, followed by blood samples for biochemical assessment, IGF1 assay, and hand X-ray for all patients.

Secondly, we performed a dynamic test for patients with growth retardation.

Results: Short stature (height <-2SD) was detected in 16 patients (18.4%). Among the 16 patients with short stature, 6 (37.5%) had severe growth retardation (<-3DS). 8 girls (50%) and 8 boys (50%) are affected by short stature; The average age of

patients with growth retardation is 16.3 ± 5.6 years. among the patients with short stature, three patients were labeled as growth hormone deficiency (GHD).

There is a statistically significant correlation between serum ferritin level and growth retardation (P=0.012), (OR=4.2).

Conclusion: This study confirms the need to screen for short stature and GH/IGF-I axis status in this group of patients. The presence of short stature does not appear to be correlated with efficacy parameters of transfusion and chelation therapy. Other mechanisms, in addition to iron overload, may therefore play a role in the pathogenesis of this clinical condition.

P1-133

Postnatal growth of infants born <2.5 kg: Small for gestational age (SGA) versus appropriate for gestational age (AGA)

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We studied anthropometric measures (z scores) from birth to 2 years in 115 infants who were born with birth weight <2.5 kg but > 1.5 kg. They were divided into two groups based on Fenton's preterm growth standards at birth. Group 1 (AGA) with weight z score (WAZ) > -2 (n = 100), and group 2 (SGA) with WAZ < -2 (n = 15). Postnatal growth data were evaluated based on the WHO growth standard without correction for prematurity.

Results: The gestational age (GA) was 32.2 +/- 2.5 weeks for the AGA group and 36.5 +/- 2.5 weeks for the SGA group.

AGA infants had a progressive gain in WAZ during the first 18 months (from -3.15 to -0.0). This was followed by stable WAZ thereafter. SGA infants had a progressive gain in WAZ (from -2.8 to -0.75) during the first 3 years of life and were still catching up during the 3rd year. At the end of the second and 3rd years, SGA infants had lower WAZ compared to AGA infants.

AGA infants had a progressive gain in LAZ during the first 24 months (from -3.5 to -0.17). This was followed by stable LAZ thereafter. SGA had a progressive gain in LAZ during the first 3 years of life (from -2.7 to -0.45) and was still catching up during the 3rd year of life. At the end of the second year, they were significantly shorter than AGA infants.

In the 2nd year, the SGA group had a significantly smaller head size (HCZ) compared to the AGA group.

In conclusion: Infants born <2.5 kg classified as AGA and SGA showed different patterns of postnatal growth in WAZ, LAZ, and HCZ. At the end of the 3rd year, SGA infants were lighter but not shorter compared to the AGA group.

WAZ		2mon	4 mon	6 mon	12 mon	18 mon	24mon	3 years
AGA	Mean	-3.15	-1.84	-1.27	-0.43	0.00	-0.24	-0.20
n = 100	SD	1.11	1.13	1.24	1.21	9.01	1.29	1.35
SGA	Mean	-2.82	-2.35	-2.00	-1.87	-1.59	-1.06	-0.74
n = 15	SD	1.54	1.79	2.14	2.16	3.01	0.94	0.89

LAZ		2mon	4 mon	6 mon	12 mon	18 mon	24mon	3 years
AGA	Mean	-3.50	-2.43	-1.78	-1.06	-0.65	-0.17	-0.26
n = 100	SD	1.35	1.21	1.23	1.24	11.27	2.03	1.21
SGA	Mean	-2.71	-2.49	-2.01	-1.53	-1.20	-0.78	-0.45
n = 15	SD	1.05	1.51	2.11	2.11	2.50	0.53	0.40

P1-134

Applying personalized medicine- From a unique endo-genetic clinic to a national project of certifying endocrinologists to perform genetic consults and testing

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Background: The rapid advancement in understanding molecular mechanisms, and the availability of genetic testing, has led to a paradigm change in many endocrine disorders. Making an accurate diagnosis enables tailored follow-up, treatment, and family genetic counselling. However, a cooperation is required, since the endocrinologist has a more profound understanding of the disorders, but the geneticist is usually better skilled in analyzing genetic results and using bioinformatic tools.

Object: To evaluate endocrine patients with suspected genetic disorders in a unique clinic performed by a physician with skills in both endocrinology and genetics, with the escort of senior physicians in both clinics. In parallel, certifying endocrinologists to perform genetic consults, send genetic tests and interpret the results.

Methods: A unique endo-genetic clinic was founded in the Schneider Children's Medical Center of Israel in 2018. The clinic is performed by a pediatrician, completing now a double fellowship in both pediatric endocrinology and medical genetics (5.5 years fellowship). Because of a very high demand and dozens of referrals, a new nation-wide project was initiated by the clinic in collaboration with "Clalit" health services- the largest provider of public and semi-private health services in Israel. The purpose of the project is to certify endocrinologists to perform genetic consults, send genetic tests, analyze the results, and apply them to all relevant family members. The first topic elected for the project was monogenic diabetes. After a short course, the physicians used a gene panel test funded by "Clalit", when patients met certain criteria.

Results: 169 genetic consults were performed until today in the unique endo-genetic clinic. The most common reason for referral was short stature (27% of consults) followed by monogenic diabetes (17%), recurrent hypoglycemia (7%), hypogonadotrophic hypogonadism (6%), obesity (6%), hypo\hypercalcemia (5%), CAH (5%) and more rare referrals including DSD, MPHD, overgrowth syndromes, hypergonadotrophic hypogonadism, bone metabolism abnormalities, thyroid abnormalities etc.

In our nation-wide project, six courses were given to a total of 48 pediatric endocrinologists from different clinics across Israel. Over 50 monogenic diabetes gene panels were sent by the certified physicians. Further courses in other topics were set for 2022.

Conclusions: To best apply personalized medicine, an endo-genetic clinic is a crucial and imperative component in every endocrine clinic. Yet, it is not enough. In order to make genetic consults and testing more readily available, it is up to the endocrinologists to perform these.

P1-305

Once-Weekly Somapacitan versus Daily Growth Hormone in Children Born Small for Gestational Age: 1-year Results from a Randomised Phase 2 Trial

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Treatment of short stature in children born small for gestational age (SGA) requires daily growth hormone (GH) injections that can be burdensome for patients and caregivers. Once-weekly somapacitan is a long-acting GH in phase 3 development for replacement therapy in children with GH deficiency. We report the 52-week results of the first phase 2, multinational, randomised, open-label, controlled, dose-finding trial (NCT03878446) investigating efficacy and safety of somapacitan as treatment for short stature in children born SGA compared with daily GH (Norditropin®, Novo Nordisk A/S). Sixty-two (62; 35.5% female) GH-treatment-naïve, prepubertal children received 0.16, 0.20 or 0.24 mg/kg/week subcutaneous (s.c.) somapacitan, or 0.035 or 0.067 mg/kg/day s.c. GH. All children were subsequently included in a long-term safety extension trial.

At week 52, the observed mean height velocity (HV) was 8.5, 10.3 and 10.6 cm/year for 0.16 (n=12), 0.20 (n=13) and 0.24 mg/kg/week (n=12) somapacitan, respectively, versus 9.4 and 11.2 cm/year for 0.035 (n=11) and 0.067 mg/kg/day (n=13) GH, respectively. The effect of the three somapacitan doses vs. GH on HV was not statistically significantly different. A similar pattern as seen for HV was observed for changes from baseline in height standard deviation score (SDS) and HV SDS. Dose-dependent increases in IGF-I SDS were observed with somapacitan and GH, and significant exposure-response relationships to HV were established for somapacitan. Among the somapacitan doses investigated, 0.24 mg/kg/week provided an IGF-I response most similar to that of 0.067 mg/kg/day GH.

All somapacitan doses were well tolerated; no safety concerns were identified. Reported AEs were mild to moderate; most were evaluated as unlikely related to treatment by the investigator. The tolerability profile was favourable and consistent with that of GH. Low-titre non-neutralizing hGH anti-drug antibodies were

detected in one child in the GH 0.067 mg/kg/day arm; none were detected in other treatment arms. One patient treated with somapacitan 0.20 mg/kg/week developed type 1 diabetes mellitus. This event was evaluated as not related to the treatment. Otherwise, there were no clinically relevant findings with respect to glucose metabolism.

In conclusion, these data support that 0.24 mg/kg/week somapacitan appears most efficacious of the somapacitan doses investigated in short children born SGA after 52 weeks of treatment. Furthermore, the safety and tolerability profiles of this dose are similar to those of 0.067 mg/kg/day GH.

P1-306

Bone age in children with achondroplasia

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Background: Bone age (BA) is commonly used in pediatrics to define skeletal maturity for medical and non-medical purposes. Normal range is represented by 2 standard deviations (SDs) above and below the mean. A BA greater than ±2 SDs from the chronological age (CA) is considered abnormal. BA in achondroplasia (ACH) has not been fully characterized; calculation is challenging given difficulties in comparing x-rays with standard radiographs if using the Greulich-Pyle (G&P) method and complexity of using the Tanner Whitehouse method. Few publications have described delays in BA in children with ACH. One study showed a delay of 1.4 years for males and 1.2 years for females, with a difference between CA and RUS (radius, ulna, short bones) BA of 0.9±1.1 for children <10 years and 1.6±0.9 for those >10 years of age. Another study described a mean delay in BA of 11.6 months for boys and 8.2 months for girls during early childhood. Here we describe BA at baseline in a group of children participating in the Phase 2 dose-finding PROPEL2 study evaluating the preliminary safety and efficacy of infigratinib in children with ACH.

Methods: Left-hand radiographs of 37 children with ACH (age 7.9±2.1 years; female n=25; Tanner stage 1) were evaluated for BA by a single reader using the RUS method (TW2). BA relation to CA was expressed as BA/CA and BA-CA overall and by sex. SD score (SDS) was calculated using SD data from G&P atlas.

Results: The mean±SD BA was 8.2±2.5 years (no difference vs the CA; p=0.1). BA/CA was 1.06±0.24 and BA-CA was 0.37±1.4 years. Mean±SD BA/CA was 1.12±0.23 in females and 0.93±0.22 in males, a statistically significant difference (p=0.026). Six children (16.2%; 5 female, 1 male) had a BA >+2 SDs for age and sex, indicating an advanced BA compared with CA. Four children (10.8%; 1 female, 3 male) had a BA that was delayed compared with CA (≥ 2 SDs for age and sex).

Conclusion: This analysis did not confirm previous findings suggesting a delay in BA in pre-pubertal children with ACH. BA in females was more advanced than in males in this study, but within the expected variability for the age group. This work suggests that BA estimation in children with ACH can be employed for the same purposes as in children without skeletal dysplasia.

P1-307

A Prospective Clinical Trial of Vosoritide in Hypochondroplasia: Baseline Demographics and Preliminary Results

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Objectives: Vosoritide is a C-type natriuretic peptide analog which binds its receptor on chondrocytes, leading to increased chondrocyte proliferation and differentiation via its inhibition of the ERK1/2-MAPK pathway. It was recently approved for increasing linear growth in children with achondroplasia. This is the first study to examine the safety and efficacy of vosoritide in children with hypochondroplasia.

Methods: This is a prospective, Phase II study of children with selected genetic causes of short stature including hypochondroplasia. Subjects must be prepubertal between the ages of 3 and 11 for boys and 3 and 10 for girls and have a height </= -2.25 SD. Subjects are followed for a 6-month observation period to establish a baseline annualized growth velocity (AGV) and then receive daily subcutaneous vosoritide (15 mcg/kg/day) for 12 months. The primary outcomes are rate of AEs and change in AGV from baseline. Pharmacokinetic studies and pharmacodynamic studies, using cGMP production as a pharmacodynamic marker, are completed at Day 1 and Months 6 and 12.

Results: To date, 26 subjects with hypochondroplasia have enrolled in the trial (23 with the Asn540Lys mutation). Median age at screening was 5.7 years (IQR 4.3, 8.1). Median baseline height is -3.3 SD (IQR -3.8, -2.8). 12 subjects have initiated on vosoritide and 7 have completed 6 months of therapy. Median AGV during

the observation period is 5 cm/yr (IQR 4.5, 5.8). At 6 months, median AGV was 7.4 cm/yr (IQR 6.8, 8) with a median increase in AGV of 2.1 cm/yr. The 6-month change in height standard deviation ranged from -0.09 to +0.49 SD with a median of +0.27 SD. There were no serious adverse events related to vosoritide treatment. One subject had a brief episode of syncope with her first injection which self-resolved, and she continued on therapy with no further incidents. PK parameters were similar to previously published parameters for vosoritide in children with achondroplasia. Analysis of cGMP levels as well as patient reported quality of life outcomes are ongoing.

Conclusions: This is the first clinical trial of vosoritide for children with genetic short stature with hypochondroplasia. Vosoritide treatment may work as a precision therapy to improve growth in multiple genetic conditions which interact with the ERK1/2-MAPK pathway.

P1-308

Postnatal growth failure of aggrecan deficient mice is due to impaired growth plate chondrogenesis

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Background: Heterozygous Aggrecan (Acan) mutations cause autosomal short stature (ISS) with advanced bone age, early-onset osteoarthritis and intervertebral disc disease (OMIM#165800) in humans. Cartilage matrix deficiency mouse ($Acan^{cmd}$) has a naturally occurring 7 bp micro-deletion in aggrecan gene. Heterozygous $Acan^{cmd}$ mice develop postnatal dwarfism with progressing age. However, the underlying cellular and molecular mechanisms causing the growth failure have not been characterized in detail.

Objective: To investigate the molecular mechanism of proportionate dwarfism in heterozygous Acan ^{cmd} mouse.

Methods: Heterozygous $Acan^{cmd}$ and wild-type (WT) male and female mice were assessed for skeletal and body growth, at 1, 3, 6, 12 and 24 weeks of age. Histomorphometric analysis was performed on Masson-Trichrome stained proximal tibial and femoral growth plates. Cell proliferation was assessed by EdU incorporation and assessed by confocal microscopy. Quantification of percentage matrix area was performed using Image J image analysis software.

Results: Heterozygous $Acan^{cmd}$ mice were born with a normal body size. However, postnatal growth was reduced resulting in a gradually worsening dwarfism with reduced total body length ($p < 0.0001$) as well as shorter tibial length ($p<0.0001$) and femoral length ($p<0.0001$) than their wild-type littermates. Histomorphometric analyses revealed that growth plate chondrocytes were more tightly packed with reduced matrix area ($p<0.001$) and increased proliferative column density in $Acan^{cmd}$ mice compared to wild-type mice. Interestingly, the number of resting zone chondrocytes, proliferative cells per column and hypertropic cells per column were reduced at 1 week of age. In contrast, the size of terminal hypertrophic chondrocytes were normal during early postnatal growth, but reduced at 12 and 24 weeks of age. Despite the differences in growth plate morphology, chondrocyte proliferation was similar in $Acan^{cmd}$ and WT mice. Interestingly, female mice exhibited a more pronounced growth phenotype than the males.

Conclusions: Heterozygous $Acan^{cmd}$ mice have a growth disorder that is similar to that in children with heterozygous ACAN mutations in terms of progression with age as well as in magnitude (10-15% smaller). Histomorphometric analyses suggest that the growth failure of aggrecan deficient mice is due to a combination of reduced matrix production and decreased size of the terminal hypertrophic chondrocytes. Further studies will elucidate the pathogenic mechanisms as well as the effect of estrogen on growth in aggrecan haploinsufficiency.

P1-309

International Standard Growth Charts Overestimates Stunting Prevalence in Indonesia Compared to the Indonesian National Growth Chart

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Background: Growth problems, such as stunting, are commonly found in daily pediatric practice. Stunting is a significant problem in developing countries, and is part of the Sustainable Development Goals (SDG) Goal 2 of ending hunger. In Indonesia, the rate of stunting in children under 5 years old is still considered high, despite improvement in quality of life due to rapid economic development. The rate of this improvement is unequal throughout the nation, where the capital city of Jakarta tend to see better growth compared to more rural areas including Papua. The Indonesian government has set ambitious goals to reduce the number of stunting by 2030 as part of its SDG targets, but the use of international (WHO and CDC) growth charts may be inappropriate in assessing growth of Indonesian children, and can lead to overdiagnosis and overtreatment of stunting. A more suitable reference chart is needed to accurately assess growth problems in Indonesia.

Methods and Aims: We performed an analytical cross-sectional study on 1.829 children in Nabire and 1.283 children in Jakarta, aged 6-12 years old. Anthropometric measurements were obtained and plotted on the CDC growth charts and Indonesian National Growth Charts to determine which chart is more suitable to monitor children growth in Indonesia.

Results: Children in Nabire were shorter and had lower BMI than children in Jakarta, with a mean height difference of 7.03 cm in boys and 6.89 cm in girls ($p=0.001$) and a mean BMI difference of 1.66 in boys and 1.39 in girls ($p=0.001$). Despite being shorter,

more children in Nabire had normal BMI, showing normal nutritional status. Less children were categorized as stunted-and-wasted using the Indonesian National Growth Charts.

Conclusion: Primary school-aged children in Nabire are shorter than children in Jakarta. Most of the short-stature observed in children in Nabire is not caused by stunting because the children showed no evidence of malnutrition. The Indonesian National Growth Charts better represent the growth status of Indonesian children compared to the CDC growth charts.

P1-310

The Prader-Willi phenotype and atypical 15q11.2-q13 deletions

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Introduction: Prader-Willi syndrome (PWS) is a rare genetic disorder resulting from the lack of expression of the PWS region (locus q11-q13) on the paternally derived chromosome 15. Either a paternal deletion of the PWS region (50%), a maternal uniparental disomy (mUPD; 43%), an imprinting defect (4.1%) or translocation (<1%) can lead to PWS. Deletions are almost always de novo and manifest either as a large type I or a smaller type II deletion. In more rare cases, atypical deletions are identified, smaller or larger than the typical deletions and with different breakpoints. These patients may show distinct phenotypical features. In this study, we report 8 patients with atypical deletions from our Dutch PWS cohort, which provide further information for unravelling the mystery of the genotype-phenotype correlations in PWS.

Methods: This was a prospective study in 8 patients with an atypical deletion in the PWS region. All patients are treated with growth hormone and regularly visit the Dutch Reference Center for Prader-Willi syndrome.

Results: All patients (6 males, 2 females) had a different atypical deletion. One patient had two separate deletions in the PWS critical region. The median (IQR) of the age at diagnosis was 9.7 (0.8; 23.7) months. Cryptorchidism was present in all males and 62.5% of the patients required tube feeding after birth. At the last examination, the median (IQR) age was 12.0 (5.4; 24.1) years. Hyperphagia was present in 50% of the patients and 75% had typical facial features. Three patients (37.5%) had another endocrine condition and 4 (50%) had scoliosis. IQ varied widely amongst the patients and four patients (50%) had intellectual disability (IQ<70) and 6 (75%) had developmental delay.

Conclusions: We report 8 patients with an atypical microdeletion in the PWS critical region. All patients had symptoms of Prader-Willi syndrome, but there were patients that did not show some of the core features, such as neonatal feeding difficulties, typical facial features, intellectual disability, hyperphagia and obesity. Our findings further advance the knowledge of and insight in genotype-phenotype correlations in PWS.

P1-311

Variability of the Noonan syndrome phenotypic spectrum in four patients carrying novel *LZTR1* gene variants

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Noonan syndrome is a genetic condition caused by dysregulation of RAS-MAPK pathway (RASopathy) characterized by great clinical variability and genetic heterogeneity. Many genes has been associated with the disease, including recently *LZTR1*, which is causative of both dominant and recessive forms.

Currently less than one hundred cases of Noonan syndrome has been associated with *LZTR1* variants then phenotype related to this gene is poorly known.

Here we describe phenotypic spectrum of three young subjects carrying three novel heterozygous missense variants in *LZTR1*. In patient 1 was identified variant c.686G>A p.(Cys229Tyr), in patient 2 variant c.164G>C p.(Arg55Pro), both resulted de novo. In patient 3 variant c.578A>C p.(Tyr193Ser) of maternal inheritance was identified.

Patient 1: 13 yo, boy. In pregnancy increased nuchal translucency had been found, with normal karyotype on CVS. He presented regular psychomotor development, typical facial features, no cardiac abnormalities, right cryptorchidism and a linear growth at the tenth percentile, below the genetic target. At 10 yo aplastic anemia was diagnosed which made necessary bone marrow tansplantation. After the oncohematological treatments he developed growth hormone and gonadotropin deficiency resulting in replacement therapy.

Patient 2: 16 yo, girl. The pregnancy was characterized by cystic hygroma with normal kariotype on CVS. She presented mild psychomotor delay, typical facial features, hypertrophic cardiomyopathy with severe mitralic insufficiency, hearing loss. For important oropharyngeal dysfunction with velopalatin incompetence and vomiting at 6 months a PEG was placed for feeding. At 14 yo she came to our attention with a complete pubertal development with untreated growth deficiency and final height at -2.8 SDS. MRI performed for a worsening of bilateral proptosis detected Chiari malformation with a cervico-dorsal (C4-D11) syringomyelia. Surgical decompression was made with a marked improvement in oral feeding and vomiting.

Patient 3: 6 yo, girl. The pregnancy was characterized by transient cystic hygroma with normal kariotype on CVS and normal fetal array-CGH. She presents typical facial features with mild psychomotor delay, no cardiac abnormalities and a regular linear growth at the tenth percentile, at low limits of the genetic target. The mother, carrying the same mutation, shows slight typical facial features, mild mitral prolapse with minimal mitral tricuspid and pulmonary insufficiency and episodic dizziness; brain and spine MRI were normal.

The patients carrying the three novel *LTZR1* variants show a broad phenotypic spectrum from a very severe to a very mild picture up to the absence of specific signs of Noonan syndrome.

P1-312

Global Increlex® Registry, post-authorisation surveillance registry monitoring the long-term safety and effectiveness of mecasermin in children and adolescents with Severe Primary IGFD (SPIGFD): objectives and study design

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Background: Severe primary insulin-like growth factor-1 deficiency (SPIGFD) is a rare growth disorder characterised by severe short stature. Replacement therapy with recombinant human IGF-1 (rhIGF-1; mecasermin [Increlex®]) is currently the only available treatment for children/adolescents with SPIGFD. We describe the methodology of the Global Increlex Patient Registry (NCT00903110), designed to monitor long-term safety and effectiveness of mecasermin during treatment and for a minimum of five years following end of treatment and/or until adult height is reached according to locally approved product information.

Methods: The registry is a multicenter, observational, open-label study ongoing in Europe from 2008, and has transitioned to a global registry with the inclusion of USA study sites. Eligible patients receive 40-120 μg/kg (0.04-0.12 mg/kg) mecasermin, twice daily, as prescribed by their physician. Table 1 presents outcome measures. Target enrollement is 500 patients.

Conclusions: The registry will allow for characterisation of the risk-benefit profile of mecasermin in patients presenting with SPIGFD in real-life settings.

Table 1. Trial outcomes

Primary
During the treatment period, up to 30 days after last dose: • Incidence of serious adverse events (SAEs)[a], all adverse events (AEs), targeted AEs, deaths and withdrawals due to AEs
Secondary
Within five years post treatment: • Incidence of SAEs[a] and all AEs, targeted AEs, deaths and withdrawals due to AEs in the overall population, and in children and adolescents exposed to mecasermin for at least three cumulative years excluding interruptions
During the treatment period, within five years post-treatment: • Incidence of special situations and concomitant medications
From baseline at least up to 5 years or until final adult height (FAH) is achieved: • Changes in height Standard Deviation Score (HtSDS) • Height velocity • Bone age development • Body mass index • Pubertal stage • Estimated differences between predicted adult height and FAH • Modeling to identify predictive factors of HtSDS change, height velocity, FAH, pubertal (Tanner) stage and bone age development
Periodically assessed until treatment stop: • Dose of mecasermin administrated • Duration of mecasermin exposure
Throughout the study: • Biochemical assessments: baseline growth hormone, IGF-1 and IGF binding protein-3 levels and binding proteins • Presence/absence of gene deletion/mutation
At baseline, year one, end of treatment and at FAH: • Changes in quality of life assessment using EQ-5D in patients aged four and over
At different timeframes (e.g. first three years after treatment initiation, three-five years and over five years): • Description of neoplasia (benign/malignant) and hypoglycaemia

[a]Including AEs of special interest of neoplasia

P1-313

Pathway to assess severe primary IGF-1 deficiency diagnosis in a real-life setting: data from the Global Increlex® Registry

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Background: Severe primary insulin-like growth factor-1 deficiency (SPIGFD) is a rare condition for which replacement therapy with recombinant human insulin-like growth factor-1 (rhIGF-1; mecasermin [Increlex®]) is approved for treatment in Europe and the USA. SPIGFD is defined as a height standard deviation score (HtSDS) ≤-3, and baseline IGF-1 <2.5th percentile (European indication) or ≤-3 SDS (USA indication) for age and gender, despite sufficient levels of growth hormone (GH; cutoff not defined). Differences in diagnostic workup for children may vary across geographies, depending on national reimbursement and genetic diagnosis policies.

Methods: The registry is an ongoing, multicentre, open-label, observational study monitoring safety and effectiveness of mecasermin in children/adolescents with SPIGFD (NCT00903110) in eight European countries and the USA (data not yet included). Eligible patients: aged 2–18 years, receiving mecasermin. This analysis describes clinical practices in real-life settings across Europe to assess SPIGFD diagnosis from data collected in the registry from December 2008–October 2021.

Results: At the time of data cut-off (4 October 2021), 259/306 patients enrolled in the registry were reported as diagnosed with SPIGFD. HtSDS based on local height charts and baseline IGF-1 was reported in 90.3% (n=234) and 92.7% (n=240) of patients with SPIGFD, respectively. Random GH and GH peak were reported in 68.7% (n=177) and 64.9% (n=168) of patients, respectively. Additionally, baseline IGF binding protein-3 (IGFBP-3) was reported in 69.1% (n=179) of patients and baseline GH binding protein (GHBP) was tested in four patients, none of whom presented with Laron syndrome. IGF-1 generation was reported in 43.2% (n=112) of patients with SPIGFD, and at least one genetic test was reported in 56.3% (n=144). The DPC/Immulite kit was the most frequently used IGF-1 assay (48.0%; n=71/148; median [min; max]: 65.0 [<1; 562] ng/mL). Between countries, proportion of patients with reported IGF-1 generation testing ranged from 18.8% (n=9/48) in France to 100% (n=21/21) in Poland, and the performance of at least one genetic test ranged from 19.0% in Poland (n=4/21), to 81.5% in Italy (n=22/27).

Conclusions: In children reported to have SPIGFD enrolled in the registry, HtSDS and baseline IGF-1 were reported in >90% of patients, while additional biochemical information including GH levels were less frequently reported, indicating that full reporting should be pursued. Recommendations on SPIGFD recognition and diagnosis should be produced and made available to the medical community in order to improve homogeneity in the diagnostic workup of these patients across countries.

P1-314

Klinefelter Syndrome: Clinical Spectrum Based on 21 years experience of a Pediatric Endocrinology Unit

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Background and Aims: Klinefelter syndrome (KS) is the most common chromosomal abnormality in men, but because of its highly variable phenotype and clinical unawareness, it remains largely under-diagnosed. Cardinal features include tall stature, gynecomastia, hypergonadotropic hypogonadism, azoospermia and infertility. Learning and behavioral problems are also common. Testosterone replacement therapy (TRT) helps to prevent or ameliorate many of the comorbidities associated with KS while improving quality of life. This study aimed to review the data of children and adolescents with KS, including age and presenting symptoms leading to diagnosis, associated comorbidities and clinical and laboratory findings.

Methods: Cross-sectional retrospective study conducted, based on clinical data of patients diagnosed with KS, followed from September 2000 to February 2022 at our Pediatric Endocrinology Unit of a tertiary referral hospital in Portugal.

Results: During the study period, 27 patients were identified. Classical 47, XXY karyotype was detected in 25 (92.6%) subjects and 2 (7.4%) had a karyotype consistent with KS variants. The median maternal age was 35 years. Most of the cases were diagnosed prenatally (n=14, 51.9%). Post-natal diagnosis was made after investigation of development delay (n=5; 38,5%), learning difficulties (n=3, 23,1%), gynecomastia (n=2, 15,4%), scrotal hypospadias (n=1, 7,7%), and/or suggestive phenotype (n=8, 29,6% of them only diagnosed during adolescence). The median age of first visit was eleven years. The most frequent clinical findings were gynecomastia (n=5, 18.5%), cardiac anomalies (n=4, 14,8%), tall stature (n=4, 14,8%), dental abnormalities (n=4, 14,8%), obesity (n=3, 11.1%), asthma (n=3, 11.1%), dyslipidemia (n=2, 7.4%), cryptorchidism (n=2, 7.4%), intellectual development disorders (n=12, 44.4%), hyperactivity and attention deficit disorder (n=11, 40.7%), behavioral and social inadequacies (n=8, 29.6%). None

showed thyroid pathology. At the age of 12 years or above, mean follicle stimulating hormone and luteinizing hormone values were 30,4 IU/mL and 10,4 IU/mL, respectively. Puberty onset occurred spontaneously in sixteen cases. Of those who needed TRT (n=19, 70,4%), all had an effective response, 89,5% (n=17) with no side effects. In 88,9%, there was small sized gonads. Spermogram was performed in five patients, which revealed azoospermia in all of them.

Conclusion: KS is an often-missed diagnosis when not detected prenatally. Typical physical features combined with developmental delay should raise clinical suspicion, justifying karyotype analysis, given the high prevalence of this syndrome. TRT is recommended at the beginning of puberty to mitigate long-term consequences of hypogonadism. Further studies are needed to establish optimal TRT, sperm cryopreservation in adolescents and therapeutic targets.

P1-315

A Novel PADI6 Variant as a Cause of Recurrent Miscarriage and Multi Locus Imprinting Disturbance within the same family

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Background: Genomic imprinting is the process by which preferential methylation of one parental allele results in parent of origin specific expression of particular genes. Methylation is established during gametogenesis and is maintained throughout development. Alterations in any of the processes in the establishment and maintenance of methylation can lead to aberrant imprinting, which can result in either reactivation of the original silent allele or the silencing of the previously active allele.

Many syndromes resulting from abnormal imprinting are recognized, most of them associated with abnormal growth patterns. In these individuals there may be abnormal methylation in one genetic locus or across multiple loci resulting in Multi Locus Imprinting Disturbance (MLID). Over the past few decades understanding of the genetic processes involved in the establishment and maintenance of methylation has increased. Mutations in ZFP57 gene are the most well recognized familial cause of MLID. In recent years a subcortical maternal protein complex (SMPC) within the oocyte, essential for early embryonic development, has been described, first in rats and subsequently in humans. Mutations in genes encoding these proteins have been reported in families with recurrent pregnancy loss and MLID.

Case Report: We present a case of a family with recurrent pregnancy loss and two siblings born with MLID. Sibling 1, born with severe IUGR and subsequent FTT, was diagnosed clinically with Silver Russell Syndrome. Methylation analysis at 11p15.5 revealed hypomethylation at the H19 and KCNQ1OT1 loci. Genome wide methylation analysis revealed hypomethylation at multiple loci throughout the genome. Sibling 2, also born with IUGR, developed hyperglycemia requiring insulin treatment during the first weeks of life, which subsequently resolved, compatible with a diagnosis of Transient Neonatal Diabetes Mellitus (TNDM). Methylation analysis revealed hypomethylation at 6q24.2 in the region of PLAGL1 in addition to abnormal methylation across multiple loci, with a different pattern to her brother. Sanger sequencing of ZFP57 in sibling 2 revealed no pathogenic variants. Analysis of maternal DNA including a panel of genes associated with recurrent pregnancy loss and MLID revealed a c.1069C>A homozygous variant in PADI6 (which encodes a SMPC protein component), resulting in substitution of Leucine for Isoleucine at position 357, close to where other variants associated with MLID have been described. This change has a frequency of 0.05% among Ashkenazi Jews with no homozygotes reported.

Conclusion: We believe this variant to be the cause of the recurrent pregnancy loss and MLID in the two siblings in this family.

P1-316

Curve matching to predict future growth in patients receiving recombinant human growth hormone: an interpretable and explainable method using big data

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Background: Prediction models demonstrate potential in predicting growth in patients receiving recombinant human growth hormone (r-hGH) for growth disorders. However, considerable information from patients is needed to calculate a predicted growth curve. The curve matching technique only requires height data. This technique identifies growth curves that are similar (matched) among real-world patients within a database. The growth curves of these 'matched' patients can then be plotted on the growth chart of the new patient to show and predict how this patient will grow.

Aim: To investigate the validity of curve matching to predict growth in patients with growth hormone deficiency (GHD) and those born small for gestational age (SGA).

Patients and Methods: Height data from the Easypod Connect Observational Study and data extracted from the easypod™ connect ecosystem were analysed. Patients' monthly height standard deviation scores (HSDS) by treatment duration (0–48 months) were calculated using the broken stick method, and missing data imputed (matching database). Patients with GHD and those born SGA, HSDS at start (-4, <-1 standard deviation [SD]), age at start (3–<16 years), a yearly increase in HSDS (0–24 months), and no

yearly decrease in HSDS (24–48 months) were selected. Validity was determined using the SD from the observed HSDS minus the weighted (proportion of good database matches) mean predicted HSDS curve of 25 other patients with best matching scores (residual analysis).

Results: Within the matching database, data for 3,213 patients (2,487 GHD; 726 SGA) with monthly HSDS were available. The observed database comprised 2,472 patients (1,897 GHD; 575 SGA) with 16,624 HSDS measurements. The error SD at 12 months (range 10–14) of treatment decreased from 0.3 when only HSDS at start is known to 0.2 when an additional measurement in the first three months of treatment was available. The error SD at 24 months (range 21–27) decreased from 0.3 when a measurement at start and between 4–6 months was available to 0.2 when a measurement at start and between 9–12 months was available. When measurements up until 13–24 months were available, the error SD was 0.3 at 36 months (range 33–39) and 48 months (range 40–48).

Conclusion: Curve matching is a valid technique that provides an interpretable and explainable visualisation and prediction of growth in patients with GHD and SGA. It may contribute to the early detection of unique or deviating growth curves, supporting clinical decision-making.

P1-317

Effects of combined treatment with rhIGF-I and metreleptin in a girl with the severe insulin resistance Rabson-Mendenhall syndrom

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We present the case of a now 11 years old girl with the ultra-rare severe insulin resistance Rabson-Mendenhall syndrome due to the previously undescribed compound heterozygous mutations exon 16: c.2986A>G (paternal) and intron 9: c.2029+1G>T (maternal) of the insulin receptor gene.

The phenotypic findings were composed of dystrophy (birth weight 1970g, small for gestational age), hyperglycemia (up to 400mg/dl), severe acanthosis nigricans and mild cardiac septal hyperplasia. Insulin resistance was pronounced (insulin level 2074mU/I), with development of diabetes mellitus. At 7 months of age, conspicuous tooth formation was evident. On ultrasound, polycystic ovaries could be detected at the age of 18 months. Furthermore, with increasing age, the presence of generalized lipodystrophy was evident.

Due to severe short stature and IGF-I deficiency (IGF-I -8,1SDS, IGFBP3 -9,42 SDS) treatment with recombinant IGF-I (0.12mg/kgBW/d) was initiated at the age of 2 years with a height SDS of -4.39 SDS. Satisfactory catch-up growth (height SDS -1.92 at the age of 9 years) and stable long-term blood glucose levels (HbA1C ≤6.2% until the age of 7 years) could be obtained. However, metabolic control worsened (HbA1C 8.3% and LDL-cholesterol 252 mg/dl at the age of 10 years). Therefore, an additional treatment with metreleptin s.c. was started (0.08mg/kgBW/d) BMI was -1,37 SDS. After 9 months, metabolic control improved (HbA1C 7.4%, LDL-cholesterol 167 mg/dl), but BMI further decreased to -1.98 despite good appetite.

Conclusion: To our knowledge, this is the first report of combined treatment with rhIGF-I and metreleptin in severe insulin resistance syndrome showing short-term improvement in metabolic control.

P1-318

The molecular study of Ras/MAPK pathway and treatment of short stature in Noonan syndrome

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Mutations in genes of the RAS/MAPK signalling pathway have been shown to cause several syndromes characterized by dysmorphic features, growth retardation, cognitive impairment, heart disease and cutaneous abnormalities. The GHrh treatment has been used to improve growth in children with Noonan syndrome.

Material and Methods: 201 cases of patients referred with clinical suspicion of S. Noonan and other RASopathies was studied. Analysis of the genes *A2ML1, BRAF, CBL, HRAS, KRAS, LZTR1, MAP2K1, MAP2K2, NRAS, PPP1CB, PTPN11, RAF1, RALA, RASA1, RASA2, RIT1, RRAS, RRAS2, SHOC2, SOS1, SOS2, SPRED1, NF1, NF2, SPRED1* was performed.

Growth and therapeutic response to GH in patients diagnosed with Noonan Syndrome who have continued to be followed up in our center have been analyzed.

Results: 1) 32.8% shown molecular alterations: 51 pathogenic. 8 probably pathogenic and 7 variants of uncertain significance. 28 patients had mutations in the PTPN11 gene: in this group the most frequent mutation (25%) was NM_0028343 (*PTPN11*): c922A>G (pAsn308Asp). 8 patients have mutations in *SOS1*, 5 in *NF1*, 4 in *BRAF*, 3 in *RAF1*, 3 in *RASA1*, 2 in *RIT1,* 2 in *LZTR1*, 2 in *MAP2K2*, 2 in *AZML1* and 1 in *GRIN2A*, *A2ML1*, *SHOC2*, *KRAS*, *CBL* and *SOS2* respectively.

2) Growth hormone treatment: Seven of these patients followed up in our center for short stature have received GH treatment. 1 male and 2 females had started treatment with GH in other indications (SGA and GH deficiency) previously a Noonan GH indication. They have reached adult height with a good response to treatment: the boy (*PTPN11* mutation) with a height SDS gain of +1.89 and the two girls: one with a *PTPN11* mutation and the

other with *SOS1* showed a gain of height of +1.15 and +1.19 respectively. The other four cases are girls and started treatment in the last year. The SDS for height at the start of treatment are less than -2.5 SDS and they have positive changes in height SDS.

Conclusion: -The clinical suspicion of Noonan syndrome and other RASopathies were confirmed genetically in 32.8% of the cases referred for study.

-Patients diagnosed with Noonan syndrome and treated with GH have a good therapeutic response.

-Molecular genetic analyzes are a useful tool for diagnostic confirmation and clinical and therapeutic orientation of patients with suspected alterations in the RAS/MAPK pathway.

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Analysis of trabecular bone score in girls with Turner syndrome

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Introduction: Short stature is the most common symptom of Turner Syndrome (TS). The height below the 3rd percentile is an indication for recombinant human growth hormone (rhGH) treatment. TS is also associated with gonadal failure and increased risk of fracture. Spinal trabecular bone score (TBS) is a novel bone imaging tool that can offer better bone evaluation in TS.

Aim: To evaluate TBS in TS, its association with rhGH therapy, and selected parameters related to the calcium-phosphate balance.

Study Group: The study group consisted of 52 patients with TS, diagnosed in one pediatric tertiary centre, aged 4.8 to 18.9 years who underwent dual-energy X-ray absorptiometry (DXA). Biochemical parameters were measured: IGF-1 (ng/ml), IGFBP-3 (ug/ml), 25-OHvitaminD (ng/ml), calcium (Ca, mg/dl), phosphate (P, mg/dl), alkaline phosphatase (ALP, U/l). Blood was sampled in the morning in fasting conditions. SDS for height, BMI, IGF-1, and IGFBP-3 was calculated. The obtained data was subjected to statistical analysis.

46 of patients were treated with rhGH given subcutaneously once daily at bedtime, in a dose 0.05 mg/kg/day. Six patient were never treated with rhGH because their growth was above 3 percentile. The patients were divided into three groups: X monosomy (group 1), numerical aberrations (group 2), and structural aberrations (group 3). Patients with coexisting endocrine diseases or other conditions which could interfere with estimated parameters were excluded.

Results: Mean age of TS patients was 12.5 +/- 4 years. Mean time of rhGH treatment in the whole group was 4.4 +/-3.3 years. The time of treatment with rhGH was the longest in group 1 (5.96) vs group 2 (3.21) and group 3 (3.40) (p=0.041).

There were no statistically significant differences in TBS by karyotype. There was a positive correlation between TBS and the age of the patients (0.78; p<001), time of GH treatment (0.34; p=0.0154), height SDS (0.29; p=0.0416), but no BMI SDS (0.21; p=0.141)

TBS correlated negatively with ALP (-0.46, p=0.021), and phosphorus (-0.69; p<0.001). The correlation between TBS and IGF-1 SDS was below statistical significance (-026; p=0.0845).

Conclusions: Normal value of TBS confirms that bone architecture is not disturbed in young girls with TS. Therapy with rhGH may have a positive effect on TBS and reduce fracture risk in TS although this process is more complex and demand prospective research.

P1-320

International versus Qatar national growth data for identifying small and large-for-gestational-age newborns: A population-based study in Qatar

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Background: To update the ongoing debate about the use of universal strict versus (local) national intrauterine growth charts, we compared the prevalence of small and large-for-gestational-age (SGA/LGA) infants according to international charts and national growth data.

Methods: We classified singleton births from 33 to 42 weeks of gestation in 2016 and 2019 from Qatar (N = 92431), SGA (birthweight <10th percentile), and LGA (>90th percentile). Using our national data (table 1), we calculated gender and gestational age-specific 10th and 90th percentiles which were used to estimate the proportions SGA/AGA/LGA. These growth data based on the customized chart's methodology were then compared to the international Intergrowth-21st newborn standards and Intergrowth-21st classification.

Results: SGA prevalence using national charts was 9.9% both in males and females. This prevalence was like the average prevalence reported by 15 European countries but significantly different (6.3%) when using the international intergrowth standard. LGA prevalence using national charts was 9.8 and 9.9% in males and females respectively. This prevalence was similar to the average prevalence reported by 15 European countries (10%) but significantly different (14%) when using the international intergrowth standard. (table 2)

Interpretation: Using international instead of national charts in Qatar could lead to growth-restricted infants being reclassified as having normal growth, while some normal infants could be reclassified as having excessive growth (LGA).

Table 1. Qatar data: 33 to 44 weeks liveborn

	I-AGA	I-SGA	I-LGA	Total
Q-AGA	70242	103	3825	74170
Q-SGA	3189	5957	0	9146
Q-LGA	9	0	9106	9115
Total	73440	6060	12931	92431

Table 2. Intergrowth versus Qatar data: 33 to 44 weeks liveborn

	males	females
Q-SGA	9.9%	9.9%*
I-SGA	6.3%	6.8%
Q-AGA	80.3%*	80.2%*
I-AGA	79.7%	79.2%
Q-LGA	9.8%	9.9%*
I-LGA	14.0%	14.0%

I= Intergrowth. Q= Qatar data
*p <0.01

P1-321

A Novel IGF2 Gene Variant of Paternal Origin Causing the Silver-Russell Syndrome Phenotype

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Introduction: Silver-Russell syndrome (SRS) is a rare, well-defined genetic disease characterized by intrauterine and postnatal growth retardation, short stature, triangular face, relative macrocephaly and body asymmetry.The most common molecular pathologies are loss of methylation (50%) of the imprinting center in the p15.5 region of the paternal 11th chromosome and maternal uniparental disomy of the 7th chromosome (5-10%).The IGF2 (insulin-like growth factor 2, MIM#147470) gene located in the imprinting center in the 11p15.5 region and expressed only from the paternal allele has a critical importance in the pathophysiology of SRS due to its varying expressions.Although SRS is often associated with epigenetic changes, IGF2 gene variants in the paternal allele can rarely be identified in the etiology.Here we present a case with SRS3(MIM#616489) with a novel variant in the IGF2 gene.

Case: A 3.6 years old male who was born at term with 2500 gr (-2 SD) was evaluated for short stature.His mother and father were from the same village.His height was -3.39SDS, body weight was -2.28SDS, BMI was 0.57SDS, head circumference was -0.88SDS.He had relative macrocephaly, prominent forehead, prominent ears, long eyelashes, midface hypoplasia, slightly elongated filtrum, microstomy, and thin lips.Extremity diameters were symmetrical, there was no hand-foot anomaly.The target height was 168.5cm (-1.24SDS)(Mothers'&Fathers' height SDS:-0.95/-1.56SDS).Peak growth hormone responses to L-dopa&clonidine were found as 2.79/7.21ng/mL, respectively. His bone age was 2 years. Pituitary MRI, ecocardiography, abdominal USG and bone survey were normal. Heterozygous variant of c.518dupC (p.Glu174ArgfsTer50) was detected in the IGF2 gene (NM_000612.6) with SRS1 sequencing panel.The variant was determined to be of paternal origin by Sanger sequencing analysis and it was planned to expand the segregation study to the upper generations. His growth rate was found 3.6cm/year in the follow-up period. The growth hormone treatment (dose of 0.3mg/kg/week) was started at the age of 6.3 years. With the growth hormone treatment, his growth velocity was measured by 4.4cm in the first three months of treatment.

Conclusion: Although SRS is a clinically diagnosable disease with a well-known follow-up, the etiology cannot be determined in 30-40% of patients with SRS phenotype. Paternally inherited IGF2 variants have been reported to be associated with the disease in only a few case reports.We think that experience should be increased in order to understand the formation mechanisms of the disease and possible phenotypic differences in subtypes arising from different mechanisms.

Keywords: Short stature, IGF2 gene, Silver-Rusell syndrome.

P1-322

Analysis of genetic variability in 134 women with Turner Syndrome using high-throughput next-generation sequencing

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Background: Turner syndrome (TS) affects 1:2,500 females and results from complete or partial loss of one of the X chromosomes. Typical traits associated with TS include short stature, primary ovarian insufficiency (POI), autoimmune diseases, and cardiovascular and endocrine disorders. Long-term follow-up is needed from the time of presentation into adult life. Several genetic mechanisms have been proposed to account for the development of TS-associated features. These include haploinsufficiency of pseudoautosomal region (PAR) genes, gene dosage effects of factors that escape X-inactivation, exposure of traits with a single X, or secondary effects of X chromosome loss on autosomal gene regulation. In this study we explored the possibility that a deficit of X-chromosome material associated with TS could have a secondary effect on genetic stability across the genome.

Aims: We aimed to investigate whether there are differences in genetic variability in the autosomes and X chromosome in women with TS compared to control groups, as a consequence of disrupted DNA replication/repair mechanisms secondary to loss of X gene(s).

Methods: Whole Exome Sequencing (Nonacus ExomeCG) was carried out in a cohort of 134 women with TS (karyotype groups: monosomy=75; ring=20; isochromosome=34; complex=5) and three control groups (46,XX=23; 46,XX non-TS POI=101; 46,XY=11). Next generation sequencing was carried out to a read depth of ~ 110X on an Illumina NovaSeq. Variant calling (Platypus 0.8.1), annotation (Qiagen Clinical Insight) and filtering (R 4.1.1)

was used to assess the number of variants in the autosomes and X chromosomes of TS women and control cohorts, as well as translation impact and pathogenicity (ACMG).

Results: Overall, 6,600,120 variants were detected after filtering. The total number of autosomal variants was not significantly different between TS groups (median monosomy=23,532; ring=23,632; isochromosome=23,538; complex=23,713) and controls (46,XX=23,625; 46,XX non-TS POI=23,374; 46,XY=23,376). In depth analysis of missense, frameshift, synonymous and stop gain/loss variants, and pathogenicity also showed no significant differences. For the X chromosome, the number of variations was proportional to the amount of X chromosome material present within each group, with no excess of disruption seen in TS cohorts, for total variants and subgroup/pathogenicity analysis.

Conclusions: No significant differences in genetic variability within the autosomes were found in this large cohort of TS women compared to controls. The number of X-chromosome variants was related to the complement of X chromosome material. These data suggest that morbidity in TS is not likely to be linked to global changes in genetic variability.

P1-323

Assessment of linear growth and weight gain after early infantile surgical repair of tetralogy of Fallot (TOF)

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The benefits of surgical repair on long term growth in children with tetralogy of Fallot (TOF) have been variable. Surgery undertaken beyond infancy has often been associated with a residual degree of growth impairment. Primary repair of during early infancy was adopted in many centres, if clinically indicated. We examined the effects of full early surgical correction of TOF on linear growth for 2 years postoperatively.

Anthropometric data of infants with TOF before and after full surgical correction of TOF were collected and analyzed for 2 years. These infants underwent early surgical correction (at mean age = 4.5 +/- 2 months). Growth data included length, weight, weight for age SDS (WAZ), Length SDS (LAZ), and weight for length SDS(WLZ).

Results: Before surgery WAZ, LAZ and WLZ were significantly decreased in TOF versus normal infants. Two infants in the TOF group had WAZ, LAZ and WLZ < -2.

After early surgical correction the WLZ increased significantly in the TOF and controls. Only 1infant with TOF had LAZ <2 and none had WAZ <-2. Infants with TOF grew in length at normal rate after surgery but without post- surgical catch-up in length.

Despite improvement of WAZ and WLZ in the TOF group, their LAZ and WAZ were significantly lower compared to normal infants at 1.7 +/- 0.3 years.

Conclusions: Early repair of TOF prevents growth delay associated with this form of cyanotic heart disease. Early infantile operation significantly improves weight gain and ensures normal linear growth.

Table. Growth data of infants with TOF before and after early surgical correction

TOF		G age Weeks	WAZ1	LAZ1	WLZ1
n =10	Mean	38.7	-0.84	-0.62	-0.99
	SD	1.29	0.91	1.56	0.98
Controls	Mean	39.5	0.00*	0.24*	0.17*
n = 50	SD	1.20	0.78	0.90	1.01

Age 2 (yr.)	WAZ2	LAZ2	WLZ2	D-LAZ	D-WLZ
1.67	-0.59	-0.57	-0.22#	0.05	(0.76) #
0.43	1.34	1.56	1.06	1.81	1.32
1.76	0.56*	0.14*	0.7*#	-0.12	0.50#
0.51	1.09	1.21	1.02	1.06	1.09

1= before surgery, 2= 1.7 +/- 0.3 years after surgery, *p<0.05 among groups, #p<0.05 after vs before surgery. D= delta change.

P1-324

The diagnosis of aortic dilatation in Chinese children and adolescents with Turner syndrome

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Objective: Patients with Turner syndrome (TS) have an increased risk of aortic dilatation (AD), which is associated with higher mortality. The diagnosis of AD in children is more difficult than that in adults. This study aimed to investigate the application of cardiovascular assessment criteria in diagnosing AD in Chinese children and adolescents with TS.

Methods: In this retrospective study, a comprehensive cardiovascular assessment was performed, according to the 2016 Cincinnati guidelines, in all patients with TS registered from 2017 to 2022 in the Shenzhen Children's Hospital. In total, 97 girls with TS (1.8-18 years) were included. Patients without structural congenital heart disease were divided into different body surface area groups. Accordingly, Chinese TS population Z-scores (CHTSZ-score) of the ascending aorta diameters were calculated for the AD cases and were compared with the TS-specific Z-score (TSZ-score).

Results: Aortic coarctation (CoA) was present in 12.4% (n = 12) of the patients. Eleven patients had AD (11.3%). The TSZ-score (ranged: -0.94-3.3) for AD diagnosis was significantly lower than the CHTSZ-scores (ranged: -0.76-8.6, p=0.009). The sensitivity to diagnose AD increased to 81.8% when a combination of the TSZ-score, aortic size index (ASI), and the ratio of the ascending to descending aortic diameter (A/D ratio) was applied in the assessment.

Conclusions: The combination of the ASI, TSZ-score, and A/D ratio may increase the sensitivity of the AD diagnosis. A reference for TSZ scores of children and adolescents with TS in China is needed.

Keywords: Turner syndrome, aortic dilatation, ascending aorta diameter, Turner syndrome-specific Z-scores.

P1-325

ERF mutation in a patient with Noonan-like phenotype, type 1 diabetes mellitus and epilepsy

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ERF protein is a major binding target of ERK1/2 kinases, key effectors of the RAS–MEK–ERK signaling cascade. ERF has a role as a negative transcriptional regulator of RAS/MAPK mitogenic pathway (1) and, in theory, a loss-of-function mutation (LOF) in ERF could cause a Rasopathy phenotype. To date, LOF variants of ERF have been reported in 45 individuals with craniosynostosis but without a Noonan-like phenotype. There is only one case report describing a patient with a Noonan-like phenotype and craniosynostosis caused by a germline mutation in ERF.

We report the case of a male with a Noonan syndrome-like phenotype, type 1 DM, focal epilepsy and a heterozygous ERF variant.

Case Report: Firstborn child of healthy non consanguineous parents, born at term by CT for breech presentation after a normal pregnancy. Birth weight 3200 g (-0,69 SD), length 49 cm (-0.98 SD). Postnatal adaptation was normal. Severe language delay was observed.

At the age of 13.5 yrs, he developed type 1 DM and subcutaneous insulin therapy was started. At 14 yrs, he suffered an episode of generalized tonic-clonic seizures. The EEG showed diffuse spikes and polyspikes, especially in centrotemporal regions and levetiracetam was initiated. No brain MRI abnormalities were detected. ECG showed high and asymmetric R waves.

He was referred to our unit at 14 yrs of age for dysmorphic features and intellectual disability. Auxological parameters: height 152.8 cm (1.83 SD), weight 39.1 kg (-2.22 SD for height age), OFC 56.4 cm (+1.2 SD for height age). Physical examination showed dolichocephaly, hyperthelorism, pterigium colli, pectus excavatum, hypercheratotic skin. Due to the clinical signs and ECG pattern an NGS panel for Rasopathies was performed which revealed ERF variant (p.Lys401GlufsTer10).

Conclusion: In the literature, there has been a recent report of a patient with a Noonan-like phenotype, craniosynostosis and an ERF gene mutation [2]. Our patient has similar clinical characteristics such as dolicochephaly, a Noonan-like phenotype, and an ERF mutation, supporting a pathogenetic role for ERF in Rasopathies. Moreover, he had ECG anomalies and epilepsy which are frequently reported in these conditions, and type 1 DM, expanding the ERF mutant phenotype. Further studies are needed to clarify the genotype phenotype correlation.

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P1-326

The relationship of the physical development of erosive gastroesophageal reflux disease in children

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The relationship between growth scores and gastroesophageal reflux disease has been extensively studied in the adult population. Single studies conducted in children

Objective: To study the relationship between anthropometric parameters and erosive gastroesophageal reflux disease in school-age children

Materials and Methods: 103 children with erosive GERD were included (65 boys, mean age 12.3±2.5 years). Children of primary school age (7-11 years) 43 children, older (12-18 years) - 60. The diagnosis was established on the basis of the Los Angeles classification. Patients are divided into two groups: erosive esophagitis stage A - 93, stages B and C - 10. The comparison group consisted of 30 children (11 boys, mean age 13.1±3.1 years) with chronic gastroduodenitis. Standard deviation coefficient (SDS) was used to estimate height and body mass index (BMI). Growth SDS values ≥2 were considered tall, ≤ 2 short stature. SDS BMI values ≥2 were considered obese. For statistical processing, the x2 criterion was used, values less than 0.05 were regarded as significant.

Results: Tall stature was detected in 16.5% (17/103) of children with esophagitis, in the comparison group there were no children with tall stature (0.0%) (p=0.018). Short stature - in 0.97% (1/103), in the comparison group in 1 child 3.3% (1/30, p=0.350). Among children of primary school age, tall stature is 23.2% (10/43), among children of senior school age in children 11.6% (7/60 p = 0.199). Obesity was found in 11.6% (12/103) of children with esophagitis, in the comparison group in 3.3% (1/30, p=0.178). In young children, obesity is in 16.2% (7/43), in senior school age in 8.3% of children (5/60, p=0.216). The proportion of patients with obesity among boys 15.3% (10/65), girls 5.2% (2/38, p=0.123).

In children with stage B+C esophagitis, tall stature was not observed (0.0%), in stage A in 18.2% (17/93, p=0.139). Obesity in the subgroup with stage B and C esophagitis in 10.0% (1/10), and in stage A in 11.8% (11\93, p=0.865)

Conclusion: Among children with erosive GERD, tall stature occurs in every sixth patient and significantly exceeds the

frequency in patients without esophagitis. Obesity is observed three times more often than in the comparison group, in every tenth child with erosive esophagitis, but the differences are not statistically significant. The influence of indicators of physical development on the severity of erosive esophagitis has not been established.

P1-327

A comprehensive assessment of patient-reported outcome measures in children and parents of children with achondroplasia: Results from a qualitative research and mapping exercise

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Objectives: Individuals with achondroplasia (ACH) experience medical, emotional and functional detriments during their lifetime. A comprehensive research initiative was conducted to include combined concept elicitation (CE) and cognitive debriefing (CD) interviews and mapping of concepts to identify the most relevant available patient-reported outcome (PRO) measures for inclusion in studies of ACH.

Methods: Combined CE/CD interviews were conducted with children with ACH (8–17 years old) and parents of children with ACH. Participants were interviewed via an online conferencing system that allowed the interviewer to share their screen with the respondent. Data from CE were used to map important concepts to PROs (QoLISSY, PedsQL, Pain-NRS) and the clinician-administered WeeFIM. Data from mapping and CD were used to confirm the measures were content valid, clear and relevant. The study was reviewed and approved by an IRB.

Results: Eight children (50% female; 13±2 years) and 18 parents (89% female; 42±6 years; 92% Caucasian; 72% educated to college degree level) were interviewed. Pain was the most common symptom for both children/parents (88%/83%), followed by feeling hot/sweaty (88%/78%). Children/parents reported difficulties with concentrating and remembering (50%/50%), sleep apnea (13%/50%), speech issues (63%/50%), ear infections (50%/78%), and balance problems (75%/56%). The most common impacts were difficulty reaching objects (88%/78%), toileting (25%/63%) and bathing (38%/56%). Mapping, based on concepts elicited during the interview including specific quotes, responses to questions from the QoLISSY, PedsQL, Pain-NRS and WeeFIM, confirmed that these measures cover the most important concepts. WeeFIM contains important concepts not contained in the 3 PROs such as difficulty bathing, dressing and toileting. All participants said that PedsQL and QoLISSY were easy to complete, and ≥90% said items were relevant. Although the PedsQL was considered by 67% of respondents to be easier to understand, 61% said the content of the QoLISSY was more relevant. Most participants (79%) recommended inclusion of both measures. Pain-NRS was considered clear (88%), relevant (88%) and easy to complete (81%).

Conclusions: This comprehensive assessment provides important information on ACH-related medical challenges and impacts from the perspective of the child and the parent. Results suggest the PedsQL, QoLISSY and Pain-NRS, in conjunction with the clinician-administered WeeFIM, map well to important concepts identified during interviews, and all measures were clear, relevant and content-valid to children with ACH and parents of children with ACH.

P1-328

A real-world study of persistence with daily growth hormone therapy among children with growth hormone deficiency in Japan

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Background: Paediatric growth hormone deficiency (pGHD) is treated with daily somatropin (recombinant human growth hormone) injections. High rates of discontinuation and poor adherence to treatment, which are associated with worse growth outcomes, have been documented previously, for example in the US and EU. Discontinuation of somatropin has not yet been evaluated using real-world data in Japan.

Objectives: To describe discontinuation of, and persistence to, daily somatropin treatment among children with pGHD in Japan.

Methods: This was a retrospective cohort study of children (≥3 and <16 years old) who were prescribed somatropin, using two Japan-based databases, Japan Medical Data Center (JMDC) and Medical Data Vision (MDV). Children were required to have ≥1 prescription for somatropin (first prescription = index date) within each study period (1st January 2002 to 30th June 2021 for JMDC and 1st January 2009 to 31st October 2021 for MDV) and ≥1 GHD diagnosis code without a somatropin prescription during the 6-months pre-index. Children were required to be continuously enrolled in the database ≥6 months preceding and ≥3 months following index date. Children were followed for up to 48 months post-index.

Early persistence was defined as proportion of children with >1 refill of somatropin subsequent to the initial prescription. Discontinuation was defined as the first observation of a gap in therapy (using >60 and >90-day gap thresholds) between successive somatropin prescription fill dates. Persistence was defined as continuous refills of somatropin with no gaps in therapy. Time to discontinuation/non-persistence was evaluated using Kaplan Meier methods, and Cox proportional hazards models identified predictors of time to discontinuation.

Results: Among the children included in this study (JMDC N=452, MDV N=573), most were male (JMDC 64.8%, MDV 60.0%). Mean age (standard deviation) was 8.8 years (3.6) in JMDC and 7.5 years (3.6) in MDV. Early persistence was high across both cohorts (JMDC 91.2%, MDV 83.4%). Using the more conservative 90-day gap definition for discontinuation, a sizable proportion of children discontinued over the follow-up period: JMDC 19% at 12 months, 35% at 48 months, and MDV 33% at 12 months, 54% at 48 months. No meaningful predictors of discontinuation were identified.

Conclusions: Despite high early persistence with somatropin, many children with pGHD in Japan were increasingly non-persistent over time: at 48 months post-index, one-third to one-half of children discontinued therapy. These results suggest a need for new strategies to support medication use over time among children with pGHD in Japan.

P1-329

Associations between eating patterns of adolescents and their height and weight, a comparison between genders

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Rationale: Adequate nutrition is essential for normal growth in childhood and adolescence. The high growth rate during adolescence demands high amounts of energy and various nutrients. During puberty, unlike infancy and early childhood, boys and girls of the same age have gender-specific nutritional needs. Our aim was to examine the associations between the dietary intake of male and female adolescents and their anthropometric measures.

Methods: This cross-sectional study included healthy prepubertal girls ≥9 years and boys≥10 years who were recruited to four groups: (a) short and lean (SL) girls (n=31), (b) SL boys (n=32) (height and weight <10th percentile for age and gender, and weight ≤height percentile), (c) control girls (n=24) and (d) control boys (n=24) (height ≥25th percentile, BMI 5th-85th percentiles for age and gender). Participants and their parents completed a 3-day food diary, and sleep, physical activity, quality of life, and self-assessment questionnaires.

Results: SL boys consumed less total energy, protein, and fat (P<0.05) but a similar amount of carbohydrates compared to male controls. However, energy, protein and fat intake per kg body weight were similar in both groups, while carbohydrate consumption/ kg was higher in the SL boys (P≤0.001) than in controls. SL boys consumed less iron (P<0.001), zinc (P=0.005), vitamin A (P<0.001), calcium (P=0.005) and vitamin C (P=0.034) than controls (absolute levels and percent of RDA), and reported less hours of sleep during weekdays (P<0.001).

SL girls consumed similar amounts of total energy, fat, and carbohydrates, and tended to have a lower total protein intake (P=0.059) compared to female controls. When adjusted to weight, intake of carbohydrates per kg was higher (P=0.007), and fat per kg tended to be higher in the SL girls (P=0.082), compared to control girls. Micronutrient intake was similar, except for a tendency towards lower vitamin A intake (absolute and percentage of RDA) in the SL girls compared to controls (P=0.069). No differences in sleep patterns were observed between the female groups.

No between-group differences (in both boys and girls) were observed in quality of life, self-esteem and physical activity level.

Conclusions: Nutritional quality and sleep habits of short and lean boys were poorer than that of controls. The quality of nutrition in short and lean girls was not clearly poorer than that of controls. The results highlight the need for surveillance and intervention to improve nutrition quality and sleep patterns in short and lean children, especially boys.

P1-330

The JAMP (Journey around Achondroplasia Medicines and Patients) Project: Results collected from two surveys to clinicians and patients in Italy

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Achondroplasia is a rare genetic condition caused by a recurrent pathogenetic variant in the *FGFR3* gene resulting in short limb skeletal dysplasia.

Due to the wide-ranging anomalies associated with achondroplasia (both peculiar clinical features and complications), a multidisciplinary team is often required for ongoing care, although the nature of specialists involved differs among countries.

Despite a European consensus on principles for the management of achondroplasia providing a basis for optimal care, differences in management approach may also be found not only between countries, but also within local/regional contexts. As for other rare diseases, data and literature are often limited, specifically at single country level.

We have structured two questionnaire-based online-surveys dedicated respectively to clinicians and parents/caregivers of patients with achondroplasia (reached through AISAC patient association) previously discussed with a panel of Italian experts. The surveys consisted respectively in 39 and 36 questions aiming to understand how achondroplasia is managed in clinical practice across Italian regions, to gain insight into the patient journey, and to identify possible grey areas of improvement and differences, of structural/organisational needs. Anonymised answers collected in a Microsoft Excel database were analysed and discussed with the panel.

We have collected from clinicians (18 hospitals, 25 experts) information on patient number and age, and experts involved for each step of the patient journey and their possible interactions, from diagnosis to management of complications, from limb-lengthening surgery approach to follow-up. We have collected additional information from parents/caregivers (42 surveys) from a different perspective in terms of diagnosis and its communication, patient needs, practical issues (e.g. distance from the reference center), perception of the limb-lengthening surgery, role of the patient association and of different specialists.

Despite the two different perspectives, we found a number of areas of improvement overlapping between clinicians and families, such as the need to reinforce psychological support, the need for more structured multidisciplinary teams and for a better follow-up and transition to adult care. Clinicians claimed for a more active involvement of territorial services throughout the patient journey, while patients recognized issues in terms of access to care.

The JAMP project provides important insight into the real-world management of achondroplasia in Italy for the first time and has the potential to help improve patient management and patient outcomes in this condition.

P1-331

Prevalence of Obesity from birth to 3 years of age in infants born large for date (LGA): Infants with weight for age (WAZ) catch down versus those without catch down during the first year of life

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Introduction: Infants whose weight is > the 90th percentile for gestational age are classified as large for gestational age (LGA). Catch-up and catch-down growth can be defined as an increase or decrease in WAZ by > 0.67 SD respectively during the infantile period. It was suggested that in LGA rapid catch-up and/or no catch-down during infancy may be associated with the development of overweight (OW) and obesity (OB) during childhood.

Aim of the Study: We evaluated the prevalence of OW and OB in a cohort of infants (n = 87) born LGA (birth weight (wt) > 4 kg) from birth to age 3 years. We compared the prevalence of OW and OB in those who had significant catch down > 0.67 SD during infancy to those who did not have catch down.

Results: In LGA infants, the prevalence of obesity (WAZ > 2) increased markedly from 24% at the end of their first year to 39% and 42.5% at the end of the second and third years of life respectively.

More than half of LGA children showed catch-down growth during infancy. Those with significant catch-down during infancy had a lower tendency to be OW and OB when they grow up. Compared to those without postnatal catch-down growth.

Conclusion: Infants born LGA had a significant tendency to be OW or OB during early childhood. Those who had caught down in WAZ during the first year had a lower prevalence of OW and OB at 2 years of age. (table 1)

Table. Effect of rapid WAZ catch down during 6 and 12 months on the prevalence of OW and OB at 3 years of age

	number	WLZ >2 <3	WLZ >3	Ob + OW
With Catch down >-0.67 WAZ at 6/12	45/87	11.4%	0	11.4%*
With Catch down >-0.67 WAZ at 1 year	32/87	8.3%*	0*	8.3%**
Without Catch down >-0.67 WAZ at 6/12	40/87	18.2%	21.2%	39%
Without Catch down >-0.67 WAZ at 1 year	56/87	22.5%	20%	42.5%

P value catch down vs no catch down * < 0.05, ** <0.001

P1-332

Growth Hormone Therapy Experience in a Patient with Hypotonia Cystinuria Syndrome

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Background: Hypotonia-Cystinuria Syndrome (HCS) is a rare autosomal recessive disease characterized by generalized hypotonia, nephrolithiasis, short stature, minor facial dysmorphism, hyperphagia, and rapid weight gain in late childhood. Microdeletion can be detected in part of the SLC3A1 and PREPL genes in these cases. Growth hormone deficiency is rarely seen in these patients and adequate growth can be achieved with growth hormone therapy.

Case: An 8-year-old male patient, who was followed up by the pediatrics nephrology and pediatric metabolism departments due to cystunuria and nephrolithiasis, presented with short stature. On physical examination, his height 113.5 cm (<3p, -2.61 SD), weight 44.1 kg (38p, -0.30 SD), body mass index 21.7 kg/m2 (+2.14 SD) were measured. He had mild mental retardation, bilateral downslanted palpebral fissures, blepharophimosis, bilateral large ears, small square hand, and bilateral short 5th metacarpal. Bone age was determined to be 8 years. The growth velocity rate was

insufficient in the annual follow-ups. The pituitary gland height was measured as 3.05 mm and there was an insufficient response to growth hormone stimulation tests. Growth hormone therapy was started and genetic analysis was planned for HSS. In the new sequence sequencing analysis, homozygous deletion was detected between exons 2 and 14 of the PREPL gene at the chromosome 2p21 locus. With 6 months of growth hormone treatment at a dose of 0.2 mg/kg/week, he increased in height by 6.3 cm (12.6 cm/year).

Conclusion: We shared our experience of using growth hormone therapy for 6 months in our patient, whom we thought to have hypotonia-cystinuria syndrome and confirmed by genetic diagnosis. Growth hormone deficiency is rarely seen in HCS. It should be considered in the differential diagnosis of syndromic short stature with disease-specific phenotypic features of HCS.

P1-505

The effects of one year of growth hormone treatment on growth and body composition in patients with Temple syndrome

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Background/Aims: Temple syndrome (TS14) is a rare imprinting disorder caused by maternal uniparental disomy of chromosome 14 (UPD(14)mat), paternal deletion of 14q32 or by an isolated methylation defect. TS14 is considered a Prader-Willi-like (PWL) disorder. Some patients with TS14 are treated with growth hormone (GH). However, evidence for the effectiveness of GH-treatment in patients with TS14 is very limited.

Methods: Seven patients with TS14 were included in a prospective GH study. We measured height and weight, and body composition by DXA scan. Of four additional patients, height and weight measurements were retrospectively collected.

Results: The median (IQR) age of the patients was 5.79 (4.71; 7.43). Median (IQR) height SDS at start was -1.35 (-2.95; -0.02) and after one year of GH treatment -0.50 (-1.50; 0.13). Height-SDS increased significantly (p=0.008). This increase was most notable in the first six months of treatment. Fat mass (FM) SDS did not significantly decrease and lean body mass (LBM) SDS did not significantly increase during one year of GH treatment. In patients below the age of 7 at the start of GH treatment, LBM SDS did increase significantly during the first six months of treatment (p=0.043).

Conclusion: Growth hormone treatment for one year improves height SDS in patients with TS14. FM SDS and LBM SDS did not change significantly during one year of GH, but LBM SDS did show a tendency towards improvement. The change in LBM SDS was more pronounced in patients below the age of 7 years at GH start. Our findings demonstrate that early diagnosis and early start of GH treatment is important for patients with TS14.

P1-506

A service evaluation on the management of Noonan syndrome in the West of Scotland

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Background: Noonan syndrome (NS) is a condition caused by pathogenic variants of the genes of the RAS-MAPK pathway. Its clinical manifestations are diverse and include congenital heart disease, short stature, ocular abnormalities, coagulation defects and structural renal anomalies. Our aim was to find out whether the patients with a genetic diagnosis of NS in the West of Scotland were managed according to the Management of Noonan Syndrome guidelines (DYSCERNE), with a focus on referrals for full cardiac evaluation, renal ultrasound, assessment of vision, coagulation screen, and referrals to endocrinology. We also analysed patterns of referrals between the different specialties.

Methods: Using the clinical and laboratory databases, we identified patients with possible NS in the West of Scotland over the 10-year period of 2011 to 2021. This included patients with a definitive genetic diagnosis as well as patients with a variant of unknown/uncertain significance (VUS). Clinical information and growth data were obtained from electronic records. A t-test was used to determine the significance in height difference between groups referred and not referred to endocrinology.

Results: 45 patients were identified; 40 had a definitive genetic diagnosis and 5 had a VUS with clinical features of NS. 96% of them had been seen by cardiology, but only 64% and 60% had had a coagulation screen and an assessment of their vision respectively. The renal ultrasound assessment was at 36% only. 12 patients were referred to endocrinology, although only 2 of them received Growth Hormone Therapy (GHT). Patients who were referred were generally shorter than those not referred. (Median Height SDS -2.17; Range, -4.09 to -1.28 for those referred, and Median Height SDS,-1.82; Range, -2.78 to -0.56 for those not referred). Paediatrics made the majority of referrals (from a single specialty) to genetics (58%) and endocrinology (56%) while genetics made the highest number of referrals to cardiology (50%). There were no referrals to endocrinology by genetics.

Conclusion: While most patients were referred for cardiology assessment, there is still much work to be done to improve referrals for renal ultrasound, assessment of vision and coagulation screen. The variation in management highlights the lack of awareness of the guidelines and the need for a lead physician/ MDT clinic to coordinate the assessments. The absence of referrals to endocrinology by genetics could be because GHT was not licensed for NS in Europe until recently; now that it is, we expect an increase in referrals to endocrinology.

P1-507

Vosoritide Improves Growth in Noonan Syndrome and Patients with *NPR2* Mutations

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Objectives: Vosoritide is a C-type natriuretic peptide (CNP) analog which binds its receptor on chondrocytes, leading to increased chondrocyte proliferation and differentiation via its inhibition of the ERK1/2-MAPK pathway. Rasopathies, including Noonan Syndrome, lead to increased signaling through this pathway. NPR2 encodes the receptor for CNP and heterozygous mutations in *NPR2* account for ~2% of cases of idiopathic short stature.

Methods: This is a prospective, Phase II study of patients with selected genetic causes of short stature including Rasopathies and *NPR2* mutations. Subjects must be prepubertal between the ages of 3-11 for boys and 3-10 for girls and have a height </= -2.25 SD. Subjects are followed for a 6-month observation period to establish a baseline annualized growth velocity (AGV) and then receive daily subcutaneous vosoritide (15 mcg/kg/day) for 12 months. The primary outcomes are rate of AEs and change in AGV from baseline. Pharmacokinetic studies and pharmacodynamic studies, using cGMP production as a pharmacodynamic marker, are completed at Day 1 and Months 6 and 12.

Results: To date, 3 subjects with Noonan Syndrome due to PTPN11 mutations and 3 subjects with heterozygous NPR2 mutations are enrolled in the study. Demographics and 6-month treatment response are listed in the Table. One subject with Noonan syndrome for whom growth response is available (VOS03) had previously been treated with growth hormone (GH) for 2 years. His AGV was 6.7 cm/yr while on GH, 4.1 cm/yr during the 6-month observation period, and 11.6 cm/year during the first 6 months of vosoritide treatment. There were no serious adverse events related to vosoritide treatment. cGMP levels were markedly lower in subjects with *NPR2* mutations as compared to Noonan Syndrome.

Conclusions: This is the first clinical trial of vosoritide for children with genetic short stature due to *NPR2* mutations or Noonan Syndrome. Vosoritide treatment may work as a precision therapy to improve growth in multiple genetic conditions which interact with the ERK1/2-MAPK pathway.

P1-508

Real-world experience with Vosoritide for achondroplasia: interim findings from an early access programme in France

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Introduction: Achondroplasia is caused by a pathogenic mutation in the FGFR3 gene, leading to impaired endochondral bone growth and multiple medical complications. Vosoritide (once daily, subcutaneous injection) has recently been approved by the European Medicines Agency (EMA) for treating achondroplasia in patients aged ≥2 years until closure of epiphyses. It has been made available in France via an early access program, a cohort Temporary Authorization for Use (ATU). We report on the early experiences (baseline clinical characteristics, initiation process and safety) of patients enrolled in the ATU within the French Centre of Reference for skeletal dysplasia (CRMR MOC) network.

Methods: The ATU was initiated on 24th June 2021. A consortium of French achondroplasia experts belonging to the CRMR MOC reviewed the ACH cases followed in the network, to confirm eligibility for treatment initiation. Scale up with prioritization of the oldest patients was proposed, within the children with achondroplasia aged ≥5 years with open epiphyses.

After treatment initiation and parent therapeutic education, the patient follow up includes visits at month 1, 3 and 6 and at 6-monthly intervals thereafter. Data are systematically collected to evaluate treatment compliance, adverse events and growth.

Subject ID	Sex	Age at screening	Diagnosis	Height SDS at screening	6 Month Rx ΔHeight SDS	Observation AGV	6 Month AGV	6 Month ΔAGV
VOS05	M	10y3m	NPR2	-2.65	0.24	2.8	7.2	4.4
VOS07	M	10y11m	NPR2	-3.34	0.41	0.5	9.7	9.2
VOS30	M	6y8m	NPR2	-2.25	Pending	Pending	Pending	Pending
VOS03	M	4y2m	Noonan	-3.75	0.74	4.1	11.6	7.5
VOS10	M	5y2m	Noonan	-2.25	0.36	5.9	9.2	3.3
VOS15	M	3y10m	Noonan	-2.31	Pending	2.7	Pending	Pending

Results: The first patient enrolled in the ATU on 27th of September 2021, and at the time of data-cut (13 December 2021), 29 patients were enrolled from 6 centers across France. At the start of treatment (baseline), 52% of patients were female with a mean age of 9 years, ranging between 7 and 13 years. The mean height was 106.9cm (range 92.0- 119.5cm) with height z-scores ranging between -3.9 and -7.7 in males and -3.4 and -6.0 in females. Mean weight was 26.2kg (16.8-60.8kg). No enrolled patients discontinued treatment and compliance was 100% with no patients reporting any missed doses. In total, there were 12 adverse events (AEs) reported among 7 patients. The majority of AEs were mild and included injection site reactions and vomiting, with the most common being injection site rash (4 events). There were no serious adverse events related to vosoritide treatment, and no AEs led to permanent treatment discontinuation.

Conclusions: Over a 3-month period in a real-world setting, the overall safety profile of vosoritide in children with achondroplasia was consistent with that observed in clinical trials. Ongoing monitoring and data collection from this early access program will be useful to establish the ongoing safety and effectiveness of vosoritide in the real world.

P1-509

Breast Satisfaction in adult women with Turner Syndrome – an international survey employing the BREAST-Q questionnaire

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Context: Turner syndrome (TS) is associated with short stature, delayed puberty, primary ovarian insufficiency, infertility, and other features. The majority of girls with TS require pubertal induction and life-long oestrogen replacement therapy. There is paucity of data in adult TS on the efficacy of pubertal induction, such as breast satisfaction. Patient-related outcome measures (PROMs) assess the quality of care and treatment from the patient's perspective. We have employed the BREAST-Q questionnaire, a validated and widely used PROM to assess outcomes of breast surgery, to explore breast satisfaction in Turner women.

Design: International survey on self-reported PROM (Breast-Q) in Turner Women matched to a control dataset.

Methods: We confirmed the suitability of the BREAST-Q pre-augmentation module for the study population through qualitative interviews. An online questionnaire was created, containing the four domains of the BREAST-Q pre-augmentation module, demographics and health history. The survey was online advertised through TS support groups (03-10/2018). Adult Turner women (age 18-45 years) were eligible. BREAST-Q scores were matched to normative data obtained from the Army of Women (AOW), an online community of healthy volunteers from the US.

Results: Eighty-three valid responses were received. 74 out of 97 total responses could be matched to the control cohort. Median age was 32 years (18-45 years) and 97% were White Caucasian. Median age at menarche was 15.5 years (12-34 years), 86% had received pubertal induction therapy as teenagers. We found significantly lower BREAST-Q scores in TS in the domains 'Satisfaction with Breast' ($p=0.021$), 'Psychosocial Wellbeing' ($p<0.0001$) and 'Sexual Wellbeing' ($p<0.0001$). TS who had received oestrogen replacement therapy reported lower scores compared to TS who had not received oestrogen therapy ($p<0.0001$). Lower BMI and previous growth hormone therapy were associated with lower breast satisfaction. There were no differences in other TS subgroups (age at menarche, BMI, karyotype and age at diagnosis).

Conclusions: TS women who received oestrogen replacement for pubertal induction self-report lower breast satisfaction scores and late menarche, suggesting that type, mode of delivery, dose and timing of hormone supplements should be studied prospectively.

P1-510

Temple syndrome: clinical findings and body composition

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Background/Aims: Temple syndrome (TS14) is an imprinting disorder caused by maternal uniparental disomy of chromosome 14 (UPD(14)mat), paternal deletion of 14q32 or by an isolated methylation defect. TS14 is considered a Prader-Willi-like (PWL) disorder and phenotypic features include pre- and postnatal growth retardation, hypotonia, feeding difficulties, precocious puberty, short stature and truncal obesity.

Methods: This study reviewed medical records of 15 patients with Temple syndrome who visited the Dutch Reference Center for Prader-Willi syndrome and PWL, from December 2018 to January 2022.

Results: The median (IQR) age of the patients was 9.02 (4.71; 12.47) years. Of the 15 patients, 9 had UPD(14)mat and 6 had an isolated methylation defect. The most common symptoms were intra-uterine growth retardation (IUGR) (100%), precocious puberty (100%), hypotonia (100%), small hands and feet (100%),

joint hypermobility (67%), small for gestational age (SGA) birth (67%), tube feeding after birth (60%) and psycho-behavioral problems (53%). The median (IQR) IQ was 91.5 (85.7; 98.0) Most patients were enrolled in special education (54%) despite the fact that very few had intellectual disability. The median (IQR) fat mass SDS was 2.07 (1.85 to 2.5) and median (IQR) lean body mass SDS -1.8 (-2.5 to -1.22). There were no significant differences in characteristics between patients with a UPD(14)mat and an isolated methylation defect.

Conclusion: TS14 is a clinically recognizable disorder, but patients do present with variable symptoms. The 15 patients in the current study, share a distinct phenotype of IUGR, SGA birth, precocious puberty, hypotonia, tube-feeding after birth, and psycho-behavioral problems. In later childhood and adolescence, many of the patients became overweight. The neonatal phenotype of TS14 is very similar to the one of PWS and, in order to avoid delay in diagnosis, testing for TS14 should be considered in patients presenting with a PWS phenotype in infancy, and in patients that were born SGA and present with precocious puberty in later childhood. TS14 might be fairly underdiagnosed.

P1-511

Clinical characterization of patients with SHOX variants regarding their functional classification

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Introduction: Short stature is frequently caused by SHOX variants causing functional deficiency. SHOX resides in the pseudoautosomal region (PAR1) of the sex chromosomes and SHOX/enhancer alterations result in a broad phenotypic range: from Langer mesomelic dysplasia, Léri-Weill dyschondrosteosis to idiopathic short stature (ISS). Growth hormone (GH) therapy is indicated for those individuals with short stature due to SHOX deficiency. A frequent limitation in molecular studies is the identification of genetic variants of unknown significance (VUS), limiting the access to GH therapy. Our purpose was to compare the clinical characteristics of patients with short stature with pathogenic SHOX variants versus those with VUS.

Methods: Retrospective observational study analyzing the results of SHOX positive genetic studies in patients of our Genetic Unit, Cadiz from 2015-2021. Molecular studies (MLPA, HRM, sequencing) were performed at the Institute of Medical & Molecular Genetics (INGEMM, Madrid). Patients were divided in two groups according to the genetic results: Pathogenic variants vs. VUS. Those with chromosopathies were excluded from the study.

Results: We found 13 patients with SHOX/enhancer alterations (5 deletions, 2 missense variants, and 6 duplications). All duplications were classified as VUS, while the remaining variants were classified as pathogenic. Clinical characteristics are summarized in table 1. Both groups had similar height z-scores. The only difference between groups was sitting height z-scores, which was significantly lower in the VUS group.

Conclusions: In our small series, patients with short stature and SHOX duplications (VUS) have a significantly lower sitting height SDS than those with pathogenic variants. No other phenotypic characteristic helped to differentiate between groups. This finding emphasizes the need to analyse larger cohorts, perform functional studies of their genetic variants and/or to continue to search for a different cause to their short stature.

	PATHOGENIC VARIANT	VUS	P-VALUE
Number of patients (n=13)	7	6	-
AGE (years)	10.08 (6.41-13.33)	8.41 (7.00-11.41)	0.617
SEX (male/female)	2/5	4/2	0.170
WEIGHT MEAN, RANGE (SDS)	-0.85 (-1.20--0.69)	-1.62 (-1.78--1.10)	0.046
HEIGHT MEAN, RANGE (cm)	127.10 (108.40-140.10)	116.40 (110.80-134.30)	0.866
HEIGHT MEAN, RANGE (SDS)	-2.18 (-3.04--1.08)	-2.3 (-2.61--2.01)	1.000
SITTING HEIGHT (SH) MEAN, RANGE (cm)	68.5 (58.80-75.50)	61.35 (60.90-72.50)	0.474
SH:H (RANGE)	0.55 (0.54-0.56)	0.52 (0.52-0.55)	0.116
SH MEAN, RANGE (SDS)	0.35 (0.27-0.72)	-0.07 (-0.26--0.01)	0.032
ARM SPAN (RANGE)	128.60 (107.50-134.30)	122.80 (106.50-143.50)	0.935
ARM SPAN:HEIGHT (RANGE)	1.01 (0.96-1.01)	0.99 (0.96-1.02)	0.850
X-RAY DYSPLASIA SIGNS (n)	3	1	0.318

P1-512

Physical Activity: An Underestimated Factor in the Management of Arterial Hypertension in Women with Turner-Syndrome?

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Introduction: Turner syndrome (TS) is a rare X-chromosomal disease, which affects one in 2500-3000 female newborns. TS is associated with a distinct cardiovascular morbidity and mortality. Arterial hypertension is present in up to 50% of young TS women and closely related to the onset of aortic dilatation and dissection. The effective management of arterial hypertension can be considered as crucial to improve overall cardiovascular outcome of TS women. In the general population, physical activity was demonstrated to be an effective tool in the prevention and management of cardiovascular diseases, including arterial hypertension. However, limited data on this research field is available for TS. This study investigated the influence of physical activity on cardiovascular morbidity in adult TS women.

Methods: An anonymous online questionnaire for adult TS subjects was established. The German version of the Global Physical Activity Questionnaire was used to assess Metabolic-Equivalent-(MET)-minutes per week for recreational activities. Acquired cardiovascular diseases were additionally determined. The achievement of ≥600 MET-minutes per week for recreational activities was tested against the presence of arterial hypertension, glucose and lipid metabolism disorders using a chi-squared or Fisher's exact test. The influence of MET-minutes per week for recreational activities on weight classification was tested utilizing an unpaired t-test. A p-value of <0.05 was considered statistically significant.

Results: In the present study, 83 TS women (mean age: 37.48±11.22 years) were included. Arterial hypertension was reported by 24.1%, glucose metabolism disorders by 4.8% and lipid metabolism disorders by 14.5% of TS participants. Excess weight was present in 49.4% of TS women. On average, TS women achieved 1052.77±666.00 MET-minutes per week for recreational activities. Women who did not achieve ≥600 MET-minutes per week for recreational activities reported significantly more often the presence of arterial hypertension (p=0.006) but not the presence of glucose or lipid metabolism disorders. Moreover, no significant differences in MET-minutes per week for recreational activities were assessed between different weight classifications.

Discussion: The results of this study underline that physical activity might play an important role in the management of arterial hypertension in adult TS women. Given the increased cardiovascular TS morbidity, patients should be strongly encouraged to implement healthy lifestyle habits in their daily routine. In the future, studies are required that investigate the effects of regular aerobic physical training on cardiovascular morbidity and mortality in TS.

Data of this abstract is included in a recent publication of our department (https://doi.org/10.3390/jcm11010167).

P1-513

Long-term effectiveness and safety of childhood growth hormone treatment in Turner syndrome from two large observational studies

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Patients with Turner syndrome (TS) have short stature, despite having normal growth hormone (GH) secretion. Treatment with recombinant human GH is recommended. The effectiveness and safety of Norditropin® (somatropin, Novo Nordisk) over ≤10 years of follow-up were investigated in two non-interventional studies: NordiNet® IOS (NCT00960128) and the ANSWER Program (NCT01009905).

Of 2,409 children with TS, 2,377 were included in the full analysis set (FAS); 1,513 in the effectiveness analysis set (EAS). In EAS, 1,273 (84%) patients were prepubertal; mean (SD) age and dose at start of GH treatment were 8.8 (3.9) years and 0.045 (0.011) mg/kg/day. Baseline insulin-like growth factor-I (IGF-I) SD score (SDS) was –0.86 (1.52). Duration of GH treatment (FAS) was 3.8 (2.8) years. Concomitant medication was prescribed to 873 (36.7%) patients (FAS), most commonly oestradiol (455; 19.1%) and levothyroxine (299; 12.6%).

Height SDS (HSDS) in EAS at baseline and during follow-up, based on national and three TS-specific references, are shown in the Table. TS-specific HSDS increased continually throughout follow-up, with near-adult HSDS reached by 264 (17%) patients (mean [SD] –1.99 [0.94]; change from baseline 0.90 [0.85]). During the study, 695 (46%) patients (EAS) entered puberty at mean age of 12.7 (1.9) years. Within FAS, mean IGF-I SDS at Year 10 was 0.91 (1.69); change from baseline 1.48 (1.70). Nonserious adverse reactions were reported in 33 patients (mostly headache [13 events]), serious adverse reactions in 10 patients (namely epiphysiolysis [3 events]), and GHunrelated serious adverse events in 24 patients.

Despite a relatively late start, TS patients responded well to GH treatment, without new safety signals identified. Our real-world data correlate well with previous studies.

Table. Mean (SD) HSDS

		Follow-up (years)									
Reference data	**Baseline**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
National	–2.62 (0.95)	–2.09 (0.95)	–1.80 (0.96)	–1.68 (0.94)	–1.65 (0.94)	–1.57 (0.88)	–1.53 (0.87)	–1.60 (0.88)	–1.70 (0.87)	–1.88 (0.85)	–2.00 (0.86)
Westerlaken, 1997	0.08 (1.16)	0.87 (1.09)	1.34 (1.13)	1.62 (1.12)	1.77 (1.14)	1.93 (1.12)	2.10 (1.12)	2.15 (1.15)	2.20 (1.08)	2.14 (0.95)	2.01 (0.91)
Cabrol, 1996	0.23 (1.15)	1.02 (1.09)	1.48 (1.14)	1.74 (1.12)	1.86 (1.13)	2.00 (1.11)	2.11 (1.11)	2.15 (1.08)	2.20 (1.02)	2.17 (0.89)	2.05 (0.85)
Ranke, 1988	0.55 (1.10)	1.28 (1.07)	1.73 (1.11)	1.99 (1.11)	2.12 (1.14)	2.28 (1.11)	2.44 (1.13)	2.48 (1.16)	2.49 (1.09)	2.40 (0.98)	2.24 (0.95)
Patients	1513 1475*	1142 1140*	965	772	597	460	326	238	165	97	52

*Ranke only

P1-514

Abstract Withdrawn

P1-515

Distinct Growth Characteristics in Angelman Syndrome

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Objectives: Angelman syndrome (AS) is a rare, genetic, neurodevelopmental disorder characterized by developmental delay with severe impairments in speech, motor and coordination dysfunction and unique behaviors, accompanied with distinct facial features and high prevalence of epilepsy and sleep problems. Despite few reports regarding short stature among AS patients, this feature has not been extensively studied and is not included in the clinical criteria defined in 2005. We investigated growth patterns among AS patients with respect to mutation type, growth periods, family history and endocrine abnormalities.

Methods: Data regarding growth and puberty of patients and their parents were collected from medical files of AS patients in the national AS clinic. The cohort was divided into two subgroups – deletion and non-deletion. Growth data was divided to four main periods – preschool, childhood, peak height velocity and final height.

Results: The cohort included 88 individuals (46 males), out of which 54 (61.4%) had the deletion subtype. There was a median of 3 observations per individual (range 1-10), which produced 280 data points distributed from birth to final height. Mean final height-SDS of the cohort was significantly lower compared to the general population (-1.23 ±1.26, p<0.001), and among the deletion subgroup it was significantly lower compared to the non-deletion subgroup (-1.67±1.3 vs -0.65±0.96, p=0.03). Final height-SDS was significantly lower compared to height SDS in preschool period (-1.32 vs -0.47, p=0.007). Patient's final-height-SDS was significantly lower than the parents' (Δfinal-height-SDS=0.94±0.99, p=0.002). IGF1-SDS was significantly decreased compared to the general population (-0.55±1.61, p=0.04), with lower values among the deletion group (-0.70±1.44, p=0.01). IGF1 was positively correlated with height-SDS (r=0.65, p=0.007). No significant changes were seen in timing of puberty.

Conclusions: AS patients demonstrate a unique growth pattern, with deceleration throughout life up to a significantly decrease in final height compared to the normal population, and even lower among the deletion subgroup, which could be attributed to decreased IGF1 levels. We propose to add short stature to the clinical criteria and develop adjusted growth curves for the AS population.

Keyword: Angelman syndrome, growth curves, short stature, height, weight, deletion, non-deletion, IGF1.

P1-516

Ovarian hilus cell hyperplasia: a rare cause of progressive virilization in a girl with Turner syndrome in the absence of Y chromosomal material

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Introduction: Turner syndrome is a relatively common chromosomal abnormality affecting 1:2000 girls. Virilization can occur in girls with Turner syndrome which is in most cases associated with the presence of an Y chromosome. Mosaicism is found in 25% of the karyotypes, in 6% of those the Y chromosome is present. This could lead to development of androgen producing gonadoblastoma/dysgerminoma. Active screening to search for Y chromosomal material is included in the international guidelines and prophylactic gonadectomy is advised. We present a case of a girl with virilization without the presence of Y chromosomal material.

Case Presentation: A 16 year old girl presented with progressive hirsutism, deepening of the voice and clitoromegaly since 6 months. Her medical history is unremarkable. Puberty started at the age of 13, she had normal breast development (Tanner 4), menarche did not yet occur. Biochemistry revealed high testosterone levels (9 [0,5-2,0] nmol/L) and high gonadotropins (LH 53 [2.4-12.6] IU/L, FSH 120 [3.5-12.5] IU/L), estradiol was relatively low with 39 [45-854] pmol/L and AMH was undetectable (<0,1ug/l). Karyotyping and micro-array showed an 46,X,del(X)(q22.1) [82]/45,X [18] karyotype. FISH showed no signs of Y chromosomal material in urine and buccal mucosa. Tumor markers (βHCG and AFP) were negative. MRI abdomen and whole exome sequencing showed no abnormalities. Urine and serum steroid profile showed an isolated high testosterone with normal values for the other steroids. After receiving the results of the diagnostic tests, she was treated with a GnRH analogue and 1mg 17-Beta-estradiol. This successfully repressed both the gonadotropin (LH 5,3IU/L, FSH 1,7IU/L) and testosterone (0,72nmol/l) levels, indicating that testosterone levels were gonadotrophin dependent and derived from the gonad(s). In addition, low AMH levels suggest a negligible follicle reserve. We concluded that the girl suffered from her testosterone producing gonads while fertility was unreachable. As such gonadectomy was indicated. There were streak ovaries with bilateral ovarian hilus cell hyperplasia and in the left ovary a hilus cell tumor. Biochemistry 6 weeks after gonadectomy showed normalization of testosterone (0,39nmol/L) and gonadotrophins (LH 6,8IU/L, FSH 15IU/L).

Conclusion: Due to ovarian insufficiency a sudden rise in gonadotropins may overstimulate hilus cells that are still responsive to gonadotropins, causing the production of testosterone and fast progression of virilization. Short acting GnRH analogues could serve as a diagnostic tool to determine whether testosterone production is gonadotrophin dependent and prevent further virilization while awaiting results diagnostic workup.

P1-517

Evaluation of Genetic Etiology in Children Born Small for Gestational Age with Persistent Short Stature: Preliminary Results

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Background: Approximately 10-15% of small for gestational age (SGA) newborns are at risk of having subnormal growth and persistent short stature. It is postulated that a large amount of persistent short stature results from genetic abnormalities, which are commonly characterized by dysmorphic features and developmental disorders.

Aim: To uncover the genetic etiology of syndromic short stature children born SGA.

Methods: We recruited 50 patients born SGA with syndromic short stature. Candidate gene analysis/fluorescence in situ hybridization (FISH)/methylation-specific multiplex ligation dependent probe amplification (MS-MLPA) was performed in children with a clinical suspicion for a specific genetic syndrome based on clinical and laboratory studies. Clinically undiagnosed cases and children with negative results using candidate gene approach underwent chromosomal microarray analysis (CMA). Children with negative results with the above analyses are enrolled for whole-exome sequencing analysis (WES).

Results: Of 22 patients with clinical suspicion of a recognized syndrome, 15 had positive results. Three patients were diagnosed with Silver-Russel syndrome using MS-MLPA and one with Williams-Beuren Syndrome by FISH technique. Pathogenic/likely pathogenic variants found in candidate gene analysis were as follows: *OBSL1* (n=4), *CUL7* (n=3), *COL1A2, CREBBP, NPR2*, and *GNAS* (n=1 each). Two pathogenic copy number variants associated with short stature were detected with CMA in the remaining 35 patients, namely 7p22 microduplication syndrome and 1q21.1 duplication syndrome. With this diagnostic algorithm, 17 (34%) patients had a definitive diagnosis.

Conclusion: Further genetic analyses may provide a definitive diagnosis in syndromic SGA with persistent short stature. Preliminary results of this study allowed us to improve the clinical management and present a clear explanation to families regarding the disease.

Keywords: Short stature, Small for gestational age, Syndrome, Genes and growth, Genetic etiology.

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P1-518

Variable post-operative growth pattern in infants with transposition of great arteries (TGA) after neonatal arterial switch operation

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The arterial switch operation (ASO) represents a remarkable success in the treatment of cyanotic congenital heart disease, with survival rates approaching 100%. The effect of infantile deep hypothermic circulatory arrest and hypoxia on post-operative linear growth is not studied.

Growth data were recorded and analyzed in 12 infants with d-TGA who underwent switch operation (anatomical correction) in the early neonatal period for 18 months.

Results: After the operation, 5/12 crossed down Length centiles by 1 SD or more and 1 infant crossed up centiles > 1SD. 6/12 crossed down WAZ by 1 SD or more during the 18 months after surgery. 18 months after surgery 2 infants had WAZ< -1.5. One infant had HCZ <-2 at birth which improved markedly to -0.28 during 18 months after surgery. HCZ increased by 1 SDS or more in 3/12 infants after surgery and decreased by 1SD or more in 4/12 after surgery. None of the children had HCZ < -2 at 18 months of age.

Weight/Length Z score (WLZ) was < -2 in 5/12 at birth and only in one infant 18 months after surgery. WLZ improved > 1SD in 7/12 of infants and decreased by 1 SD in one infant after surgery.

In Conclusion: Anatomical correction for d-TGA in the early neonatal period resulted in variable patterns of growth. The WLZ improved in most infants. None of the infants had LSDS or HCZ < -2 at 18 months. These data indicated acceptable linear growth, weight gain, and head growth in these infants.

P1-519

Learning outcomes of a MOOC supporting healthcare professionals in treating patients with growth disorders

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Background: There is a need to increase digital health literacy in paediatric endocrinology due to the rapid emergence of digital technologies. Massive open online courses (MOOC) provide an opportunity to rapidly increase digital health capabilities at scale, as previously demonstrated in diabetes.1 To our knowledge, there are no comparable examples in the field of growth hormone deficiency.

Aim: This study evaluates the impact of a new MOOC launched in 2021 entitled 'Telemedicine: Tools to Support Growth Disorders in a Post-COVID Era' by comparing pre- and post-course assessment scores as well as comments received from learners.

Methods: Learners' knowledge in the field was assessed with pre- and post- course surveys via the FutureLearn platform. Learners who completed all ten questions for both the pre- and post-course assessment were included in the analysis. Scores were evaluated by t-test to identify significant knowledge changes. All comments posted by learners on the course discussion forum were evaluated.

Results: By 17 December 2021, 219 learners had enrolled in the MOOC; 31 completed both the pre- and post-course assessments.

Table. Growth of infants with TGA 18 months after early neonatal corrective surgery

patients	LAZ1	LAZ2	WAZ1	WAZ2	HC Z1	HC Z2	WLZ1	WLZ2
1	2.08	1.18	0.87	2.53	0.35	0.07	-1.58	2.57
2	-0.03	-1.03	-0.16	-0.13	-1.24	-0.18	-0.37	0.57
3	0.1	-0.5	-1.1	1.05	0.02	0.75	-2.15	1.42
4	-0.17	-0.85	-0.43	-1.75	-1.67	-0.71	-0.63	-1.69
5	-0.71	-1.14	0.05	-1.67	0.45	-0.67	0.8	-1.53
6	-0.12	-1.73	-1.4	-3.27	-1.24	-1.93	-2.52	-2.45
7	0.22	1.39	0.92	-0.1	1.06	0.7	1.02	-1.22
8	0.93	-0.23	-0.14	-0.05	0.35	-0.69	-1.94	0.08
9	1.44	-0.65	-0.31	-1.27	-0.82	-2.13	-2.29	-1.33
10	2.61	1.89	2.01	0.51	1.14	-0.11	-0.46	-0.52
11	0.5	0.25	-0.04	0.53	0.35	0.15	-0.87	0.54
12	-2.14	0.06	-3.76	0.22	-3.61	-0.28	-4.35	0.24
Mean	0.39	-0.11	-0.29	-0.28	-0.41	-0.42	-1.28	-0.28
SD	1.27	1.11	1.42	1.52	1.37	0.89	1.51	1.45

Of these evaluated learners, 74% showed improved scores in the post-course assessment, resulting in a mean score increase of 21.25%. No learners achieved 100% in the pre-course assessment, while 12 learners (40%) achieved 100% in the post-course assessment. The highest score increase comparing pre- and post-assessments was 40% in 16% of learners. There was a statistically significant improvement in overall scores, rising from 58.1% ± 18.9% to 72.6 % ± 22.4% ($p<0.0005$) in the post-course assessment. Of the 132 comments analysed, 75 described an increase in knowledge, 39 stated that the course content was appropriate and 10 related to a positive impact on future learning and self-care. Some learners commented on the potential applicability of the course content to other therapeutic areas.

Conclusion: The MOOC multimodal eLearning model offers an innovative and successful channel to train large numbers of healthcare professionals. Digital health competencies gained included the management of growth disorders through e-health, research and evidence-based methods in eHealth, and e-health co-design. Our results indicate the value of MOOC digital learning to improve digital health literacy on a large scale.

Reference

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P1-520

A Case of Familial Short Stature: A Novel Variant of ACAN

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Introduction: Aggrecan,a chondroitin sulfate proteoglycan encoded by the ACAN gene,is an important structural component of the cartilage matrix.Variants in the ACAN gene are associated with a group of skeletal dysplasias called aggrecanopathy,which shows a broad phenotypic spectrum.It has been reported that some heterozygous variants in this gene are responsible for the etiology of familial or idiopathic short stature located at the lightest end of the spectrum.In some of these cases, advanced bone age(BA) and early-onset osteoarthritis can be detected.Here,a case of familial short stature with a newly identified variant of ACAN is presented.

Case: He was born 3000g at the time, there was a 4th degree consanguinity between his parents, and there were short individuals in his mother's family.His height was 103.2cm(-1.69SDS), weight was 15.7kg(-1.37SDS), and his BMI was 14.74kg/m^2 (-0.55SDS).Malar hypoplasia, X-leg deformity, shortened distal phalanx and pes planus were detected.His mother/father height was 138cm(-4.27SDS)/160.3cm(-2.58SDS),target height was 155.6cm(-3.5SDS).His BA was 5-6years old, chronic disease screening was normal, and nonossifying fibroma was detected in the distal metaphysis of the right femur in bone survey.When evaluated for low growth velocity at 9years 8months of age height 124.4cm(-2.03SDS), weight 32.25kg(0.16SDS), BMI 20.84kg/m^2(1.34 SDS), BA 10years 6months,his IGF-1 was 170ng/mL(-1/meanSD), IGFBP-3 was 4360ng/mL(-1/meanSD) and had insufficient response to two growth hormone stimulation tests.Anterior pituitary height was 3.6mm on pituitary MRI.In clinical exome sequencing analysis,heterozygous variant of c.6991T>C(p.Cys2331Arg) in the ACANgene(NM_013227.3) was reported.It was predicted that the variant could lead to significant changes in protein structure and function by in silico models.The variant was determined to be of maternal origin by Sanger sequencing analysis. At 12years and 3months of age,his BA was 11-11.5years,had Tanner StageII puberty and GH treatment at a dose of 0.2mg/kg/week was started.With the growth hormone treatment,his growth velocity was measured by 1.9cm in the first three months of treatment.

Conclusion: The prevalence of heterozygous ACAN variants in different short stature cohorts is 1.4-6%.ACAN defect should be considered in cases of familial or idiopathic short stature, in the presence of advanced BA and a gradual decrease in annual growth rate.Evaluating anamnesis, physical examination and laboratory findings together and supporting them with genetic analysis can provide important experiences in terms of diagnosis and treatment in the early period.

Keywords: ACAN gene, aggrecan protein, familial short stature.

P1-521

Case with HOXA gene cluster delete

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Entrance: HOXA gene deletions cause an appearance characterized by short stature, mild developmental delay, characteristic face, small hands and feet, short and large thumbs, and urogenital malformations. Clinical signs may vary according to the content of the deletion region.

Case: The case applied to our clinic with the complaint of short stature. It was learned that the patient was born at term 2500 gr and had bilateral undescended testis operation when he was 1 year old. Examination at 8 years 10 months showed a height of 116.7 cm (-2.57 SD) and a weight of 24 kg (–0.86 SD). Target height: 171.5 cm (-0,54 SD). Testicular volumes were pubertal. The case had mild neurodevelopmental retardation. He had a flattened nasal root, hypertelorism, prominent auricle, small hands and feet. He had proximal thumb on both hands, clinodactyly in the 5th fingers, shortness in the 5th metacarpals, and hypoplasia in the bilateral hypothenar region. There was short, broad thumb and fingernail hypoplasia on the feet. Pituitary MRI was normal.

Cranial MRI was reported as "a 16x15 mm arachnoid cyst located at the cerebellar medullar corner on the right". In bone survey; There was arcus fusion defect in S1 vertebra, bowing in bilateral radius, and bilateral coxa valga appearance. In the LHRH test, the LH peak was 12.8 IU/L pubertal. In growth hormone (GH) stimulation tests, the peak response to clonidine was 6.3 ng/ml, and the peak response to L dopa was 3.4 ng/ml. Growth hormone deficiency and precocious puberty were detected in the case. GH and GnRHa treatments were started. In the follow-up of the case, it was observed that it lengthened by 8.1 cm/year with GH and GnRHa treatment.

Conclusion: In this case, a 2.9 megabase deletion containing the entire HOXA gene cluster was reported in the 7p15.2-p15.1 region. This is the first case in which arachnoid cyst, precocious puberty and GH deficiency have been described in addition to short stature and bone deformities found in HOXA gene deletions. This is the first case in which GH and GnRHa treatments were given from HOXA gene deletion cases and height gain was achieved with these treatments. This case contributes to the genotype-phenotype correlation of HOXA gene deletions.

P1-522

Positive impact of the TuiTek® patient support programme on caregivers of patients receiving treatment for growth hormone deficiency in Argentina

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Background: Good adherence to recombinant human growth hormone (r-hGH) is crucial to achieve optimal growth outcomes in children with GH deficiency (GHD). Controlling factors that negatively impact adherence is difficult in clinical practice. In order to obtain a better understanding of caregiver behaviour, an Argentinian patient support programme (PSP) implemented TuiTek®, a personalised programme comprising behavioural change training, call guides and resource packs. It addresses four key dimensions commonly faced by caregivers: 1) disease and treatment coherence, 2) emotional burden, 3) treatment-related anxiety and 4) self-administration, and offers tools and strategies to improve each of these dimensions in cases where scores fall outside of the expected limits.

Aim: To evaluate the impact of the TuiTek® PSP on caregivers' perceptions of r-hGH adherence and treatment options in patients with GHD over three months in Argentina.

Methods: Nurses associated with the PSP delivered a personalisation questionnaire based on feedback received from 76 caregivers of patients with GHD who were undergoing r-hGH treatment using the easypod® auto-injector device in Argentina; risk assessment scores were established using a 5-point rating scale. Caregivers who were classified as 'high risk' in at least one of the four dimensions (defined as a score of 1–3 for disease and treatment coherence and self-administration; 3–5 for emotional burden and treatment-related anxiety) at the start of the programme received bi-weekly personalised telephone interventions and follow-up calls from PSP nurses over the course of three months. The caregivers were then reclassified in each of the four dimensions post-intervention. The Wilcoxon-sum rank test was used to analyse questionnaire-based scoring patterns between baseline and follow-up; $p<0.05$ was considered statistically significant.

Results: Of the 460 caregivers enrolled in the study, 170 (37%) were initially categorised as 'high risk' and 290 (63%) as 'low risk'. Of the caregivers in the 'high risk' group, 76 completed the entire three-month programme. Statistically significant differences ($p<0.05$) in questionnaire scores between baseline and follow-up were observed for 'disease and treatment coherence', 'emotional burden', 'self-administration' and 'treatment-related anxiety'. The percentage of caregivers considered to be at 'high risk' for 'emotional burden' decreased by 15%. Both 'disease and treatment coherence' and 'self-administration' improved by 100%; 'treatment-related anxiety' was reduced by 77.5%.

Conclusion: The TuiTek® PSP enabled nurses to provide more effective support for caregivers. This intervention could help caregivers to improve and maintain their child's adherence to r-hGH therapy with the goal of optimising clinical outcomes.

P1-523

The diagnosis of aortic dilatation in Chinese children and adolescents with Turner syndrome

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Objective: Patients with Turner syndrome (TS) have an increased risk of aortic dilatation (AD), which is associated with higher mortality. The diagnosis of AD in children is more difficult than that in adults. This study aimed to investigate the application of cardiovascular assessment criteria in diagnosing AD in Chinese children and adolescents with TS.

Methods: In this retrospective study, a comprehensive cardiovascular assessment was performed, according to the 2016 Cincinnati guidelines, in all patients with TS registered from 2017 to 2022 in the Shenzhen Children's Hospital. In total, 97 girls with TS (1.8-18 years) were included. Patients without structural congenital heart disease were divided into different body surface area groups. Accordingly, Chinese TS population Z-scores (CHTSZ-score) of the ascending aorta diameters were calculated for the AD cases and were compared with the TS-specific Z-score (TSZ-score).

Results: Aortic coarctation (CoA) was present in 12.4% (n = 12) of the patients. Eleven patients had AD (11.3%). The TSZ-score (ranged: -0.94-3.3) for AD diagnosis was significantly lower than the CHTSZ-scores (ranged: -0.76-8.6, p=0.009). The sensitivity to diagnose AD increased to 81.8% when a combination of the TSZ-score, aortic size index (ASI), and the ratio of the ascending to descending aortic diameter (A/D ratio) was applied in the assessment.

Conclusions: The combination of the ASI, TSZ-score, and A/D ratio may increase the sensitivity of the AD diagnosis. A reference for TSZ scores of children and adolescents with TS in China is needed.

Keywords: Turner syndrome, aortic dilatation, ascending aorta diameter, Turner syndrome-specific Z-scores.

P1-524

A Case with Growth and Developmental Retardation: 12q14 Deletion

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Introduction: Interstitial deletions on the long arm of the 12th chromosome are rare and often occur de novo. These deletions have been found to be associated with mental retardation, developmental delay, growth retardation and various congenital anomalies in different studies. In studies up to date, it has been determined all interstitial 12q deletions are clustered between five regions on this chromosome (HMGA2, GRIP1, LEMD3, MSRB3, and TMBIM4). Low birth weight, failure to catch up growth, short stature, learning difficulties, Buschke–Ollendorff lesions on skin and bone (ostepoikilosis in the non-sensitive, tight skin and long bone epiphysis and metaphyses, wrist, foot, elbow, pelvis and scapula) has been reported in 12q14 microdeletion syndrome. Located within the 12q14 microdeletion region; it has been reported that LEMD3 haploinsufficiency is responsible for skin and bone lesions and heterozygous HMGA2 deletion is responsible for growth retardation. Up to date different phenotypes of 12q deletions have been described in a total of 69 patients. Here a case followed up in our clinic due to pathological short stature and detected to have 2.7 Mb deletion in 12q14.2 region in microarray analysis will be presented.

Case: A three-year-old female patient with short stature was referred to our outpatient clinic. She was born from a consanguineous marriage at 37 weeks of gestational age and with 2600g birthweight. Her mother had hypothyroidism, father had diabetes and she had two healthy siblings. She was evaluated in gastroenterology division and using enteral nutrition currently. Anthropometric measurements were determined as; weight: 6.3 kg (-3.28 SDS), height: 61 cm (-5.12 SDS), BMI: 16.93 kg/m2 (0.24 SDS), target height: 151.15 cm (- 2.04 SDS). In physical examination; frontal bossing, high palate, small mouth, clinodactyly at the 5th finger of the left hand, short neck, hypoplasic midface, bulbous nasal tip, thin lower lip and pointed fingertips were detected. In laboratory examinations, nutritional tests were normal, IGF-1:126 ng/mL (-1/mean SDS) and IGFBP-3: 3460 ng/mL (+1/+2 SDS). Bone age was evaluated as newborn. Peak growth hormone response to the growth hormone stimulation test (with clonidine) was sufficient (peak:15.6 ng/mL). Bone survey was reported as normal. No organ pathology was detected in echocardiography and abdominal ultrasonography. Karyotype was reported as 46,XX.MLPA analysis for Russell-Silver syndrome was normal. A deletion of 2.7 Mb was detected in 12q14.2 region in microarray analysis performed in follow-up.

Conclusion: 12q deletions may present with pathological short stature and reinterpretation of microdeletions may help us understand the growth-related mechanisms of our experience of genotype&phenotype relationship better in affected individuals.

P1-525

Growth Hormone IGF-1 axis and treatment with Growth Hormone in PGM1 deficiency

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Background: Phosphoglucomutase 1 (PGM-1) deficiency is a congenital disorder of glycosylation caused by an impairment of glucose-1-phosphate and glucose-6-phosphate interconversion.

The clinical phenotype of PGM1 deficiency is variable and includes several endocrine manifestations such as recurrent hypoglycemia and short stature, which may be associated with the decreased levels of growth hormone (GH), insulin like growth factor-1 (IGF1) and insulin like growth factor-binding protein 3 (IGF-BP3) reported in PGM1 deficiency. The growth response to Growth hormone therapy in PGM1 deficiency has been reported so far only in one single case. GH effect on glucose homeostasis in PGM1 cases was not yet elucidated.

Objectives: To study the growth, IGF-1 axis, and glucose homeostasis in three patients with PGM1 deficiency prior and following GH therapy.

Case Report: Two girls and one boy presented at infancy and early childhood (4 -30 months) with dysmorphic features, short stature and recurrent severe hypoglycemic episodes associated with seizures. Laboratory tests showed evidence of growth hormone insensitivity with normal to high growth hormone response to stimulation tests but low-normal IGF-1 and IGF-BP3. Transferrin electrophoretic pattern was consistent with congenital disorders of glycosylation (CDG). Genetic workup revealed a homozygous mutation (c.112A>T, p.N38Y) in phosphoglucomutase gene at the two female patients and compound heterozygous

Table 1. Growth hormone axis and growth parameters of the patients

	GH stimulation test response	Basal IGF-1	IGF-1 after an IGF-1 stimulation test	Height SDS before GH treatment	Growth velocity during 1st years of GH treatment
Patient 1a	35 ng/ml	3.72 nmol/l	7.31 nmol/l	-2 SDS	7.2 cm/y
Patient 2b		2.72 nmol/l		-3.4 SDS	
Patient 3c	8 ng/ml	6.9 nmol/l	15.1 nmol/l	-3.07 SDS	7.47 cm/y

Blank squares- missing data
GH doses:
aPatient 1- 0.04 mg/kg/d. The treatment was intermittent due to financial issues.
bPatient 2 was not treated with Growth hormone due to parents' refusal.
cPatient 3- 0.033 mg/kg/d.

novel mutations (c.1140insT and c.1348G>T) in the male patient. Two patients were treated with recombinant growth hormone which led to reduction in the hypoglycemic events and increase in growth velocity.

Conclusions: Growth may be interrupted in PGM1 deficiency, with evidence of interrupted activity of GH. Growth hormone therapy may be beneficial and improve both growth and the dysregulated carbohydrate metabolism.

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A Case of Short Stature Presenting with Multiple Exocytosis

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Objectives: Trichorinophalangeal syndrome (TRPS) is a cause of syndromic short stature; and is characterized by typical dysmorphology, ectodermal dysplasia, and skeletal findings. There are two types of TRPS; TRPS-I caused by monoallelic pathogenic variants in the *TRPS1* gene, and TRPS-II caused by whole gene deletion. TRPS-II; also called Langer-Giedion Syndrome (LGS), in which multiple exocytoses can be seen in addition to typical TRPS features due to contagious deletion of the *EXT1* gene at the same chromosomal region. Here we describe an 8 years old girl with LGS, who also had anal atresia and vertebral fusion defects.

Case: An 8 years old girl was referred for short stature. She was born to unrelated parents at term with a birth weight of 3000 gr (-0.8 SDS). At 15 days of age, she had an operation for anal atresia. She began to walk at 24 months old, and talk at 30 months old. On her initial examination height SDS was -2.12 (113.7cm), weight SDS was -2.04 (18kg). She was noted to have large-pronounced ears, a bulbous tip of the nose, broad nasal root, hypoplastic alae nasi, long philtrum, fine and sparse hair, broad eyebrows, brachydactyly, short 5th metacarpal, pes planus, umbilical hernia, scoliosis, and multiple exocytoses. In addition imaging examinations revealed multiple exocytoses in long bones, costae, and pelvic bones; osteopenia in lateral vertebral radiograph; ivory epiphysis and cone-shaped epiphysis in phalanges, short metacarpals of the fifth finger, fusion anomaly in cervical-thoracic vertebrae and costal malalignment. LGS was considered in the etiology and a contiguous 10.14 Mb deletion involving 8q23.3-q24.12 was detected by array comparative genomic hybridization, leading to haploinsufficiency of *TRPS1, RAD21,* and *EXT1* genes.

Conclusions: Patients with LGS show clinical variability depending on the loss of genes in the deleted region. To date renal defects, ventricular septal defects persistent cloaca, prune belly, and annular pancreas have been described in several patients. Besides growth hormone deficiency, corpus callosum agenesis and hypothyroidism were previously reported in a few cases. Interestingly, our patient was found to have anal atresia and vertebral fusion defects which, to our knowledge, is a novel co-existing feature in patients with TRPS II. Our patient broadens the spectrum of disease, further description of these cases will highlight the genes responsible for additional clinical manifestations of the disease.

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The Cumulative incidence of SGA, AGA and LGA, Premature, Postmature, and Term birth in infants born between the 33rd weak and the 44th weeks of Gestation in Qatar

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Introduction: Prematurity, post-maturity, and significant deviations in birth weight are associated with significant morbidities and mortalities.

Aim: The aim of this study was to identify the cumulative incidence (CI) of premature, postmature, and term birth rates additionally to find out the prevalence of SGA, AGA, and LGA using INTERGROWTH-21 st fetal growth standards.

Methods: The study was part of the Vulnerable Newborn Study, approved by the Hamad Medical Corporation Institutional Review Board (IRB No MRC-01-21-277).

The population for this analysis comprised of a 4-year retrospective cohort data (January 2016 to December 2019) for births conducted in all HMC hospitals. These government hospitals account for about 90% of all births in the country. We included 92431 live births with the required data in this analysis.

The explanatory variables recorded were gestational age, gender, birth weight. We calculated the cumulative incidence of prematurity, SGA, AGA, and LGA (according to the intergrowth -21st standards) during the study period. GA was calculated by either the calculation from the last menstrual period or early obstetric ultrasound measurements.

Results: The percentage and the (CI) of Term, preterm, and post-term birth rate are presented in table 1. Between 2016 and 2019, preterm birth affected 1 of every 10 infants born in Qatar, similar to the preterm birth rate in the USA in 2019 was 10.2%.

The CI of SGA, AGA, and LGA is presented in table 2. 6.6% of our babies were born SGA. The birth rate of SGA, AGA, and LGA were very comparable to those reported from the European countries.

Conclusion: The use of the Intergrowth 21st international charts for defining SGA and LGA at birth showed that the prevalence rates of both are comparable with many European countries.

Table 1. Cumulative incidence of prematurity, term and post-term birth between 2016 to 2019 in Qatar (94568 live births 24 to 44 weeks gestation)

Cumulative Incidence	Ratio	Per 100 livebirths
Incidence of prematurity	0.0998	9.98
Incidence of Full Term	0.8992	89.92
Incidence of post maturity	0.0009199	0.0919
Incidence of stillbirth	0.007314	0.73142

Table 2. Cumulative incidence according to the weight of the baby

(InterGrowth-21st)	n	(%)
SGA (< 10th percentile)	4,880	6.6
AGA (10th to 90th percentile)	64,329	79.5
LGA (> 90th percentile)	11,513	14.0

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The SHOX gene between duplication and deletion: when the follow-up guides the treatment

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SHOX gene haploinsufficiency is a well-documented cause of short stature and skeletal abnormalities; SHOX duplications appear very rare and of uncertain clinical significance. If relatively extended, they can result in SHOX overexpression with normal or tall stature. Partial SHOX duplications seems to have a more deleterious effect on skeletal dysplasia and short stature than complete SHOX duplications. MLPA (Multiplex Ligation-dependent Probe Amplification) analysis of SHOX/PAR1 contributes to the identification of partial and complete SHOX duplications associated with Léri-Weill dyschondrosteosis (LWD) or idiopathic short stature (ISS), suggesting that they may represent a further class of mutations involved in the aetiology of LWD or ISS.

We describe the case of a 4-month-old infant with the prenatal diagnosis of mixed gonadal dysgenesis associated with mosaic karyotype 46,X,i(Y)(p10)[94]/45,X[13], confirmed, after birth, in peripheral blood lymphocytes karyotype. FISH showed an isochromosome of the short arm of Y i(Yp) containing SRY gene; MLPA showed 25% duplication extending from the telomere of the short arm to the boundary of the PAR1 region, including SHOX. The probe of VAMP7 gene, in Xq28 (PAR2 region), very close to the q-telomere X and Y, is 50% deleted.

He was born at 40.5 weeks, SGA (small for gestational age); weight: 2480g (-2.83DS), length: 47cm (-2.44DS), head circumference: 33cm (-1.82DS). At the admission: length 61cm (-2.22DS), weight: 5.860g (-2.12DS), head circumference: 40.5cm (-0.66DS); normal male external genitalia, PH1G1, with testicles of 2 ml in situ.

Haematological tests, carried out to exclude organic aetiology of short stature, showed normal results; TSH, fT4, ACTH, cortisol, IGF-1were in the normal range. Given the high risk of gonadoblastoma in subjects with chromosomal aberrations involving the Y chromosome, we tested, during the follow-up, alpha-fetoprotein, beta-chorionic gonadotropin checks and testicular ultrasound.

Blood chemistry investigations and testicular ultrasound during the follow-up, were normal. Over a four-year follow-up, the growth velocity, initially adequate, showed a slowdown at the last visit (0.31 cm/year: -6.97 SD on the Rikken scale). The coexistence in our patient of haploinsufficiency of SHOX (cell line 45,X) and duplication, raised a therapeutic dilemma, in which clinical data made the difference and guided therapeutic decisions. We adopted a "wait-and-see" attitude since growth was adequate for age; when a deflection of growth occurreded, we started growth hormone (GH) treatment, with satisfactory results.

Furthermore, our child was eligible to GH treatment for 2 reasons: he was born SGA and showed SHOX gene involvement.

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A case of Silver Russell Syndrome-like phenotype with abnormal methylation of the imprinted *GNAS* locus (20q13)

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Background: Silver Russell Syndrome (SRS) is characterized by pre- and postnatal growth failure, relative macrocephaly at birth, prominent forehead, feeding difficulties and body asymmetry. The diagnosis is clinical, the genetic mechanisms involved are different, in 50% of cases loss of methylation (LOM) at the paternal *H19/IGF2*:IG-DMR (chr11p15.5), in 10% of cases maternal uniparental disomy of chromosome 7 (UPD(7)mat), cases of maternal uniparental disomy of chromosome 20 (UPD(20) mat) are among the rarest causes of SRS/SRS-like phenotypes.

Case Presentation: A 13-month-old girl was evaluated for poor growth and feeding difficulties. Born from unrelated parents at 39 weeks with weight 2096 g (-2.75 SDS), length 45cm (-2.26 SDS), head circumference 30 cm (-3.16 SDS), at the first visit she showed length 64.8 cm (-4 SDS), weight 5680 g (-4.1 SDS), head circumference 42.5 cm (-1.99 SDS), prominent forehead, triangular face, mild hypertelorism, clinodactyly of the fifth finger, regular psychomotor development. Poor appetite and chronic constipation were reported. First level blood exams were negative. We suspected a Silver-Russell syndrome, analysis of the 11p15 region and UPD analysis of chromosome 7 were both negative.

At 2 years of age, she presented height 73.5 cm (-3.74 SDS), weight 6,750 kg (-6.46 SDS), head circumference 44.5 cm (-1.93 SDS), BMI 12.5 (-3.46 SDS), NHCSS score 4, given the clinical suspicion of SRS, MLPA multi-locus Imprinting was required which highlighted on chromosome 20 hypomethylation in the *NESP55* region and hypermethylation in the *GNASXL* and *GNAS-AS1* regions, in the absence of CNV in the region. SNP-array analysis is ongoing. The patient is followed with a multidisciplinary approach, GHr therapy was proposed.

Conclusion: About 60% of patients with clinical suspicion of SRS receive a genetic diagnosis; in case of negativity of the molecular tests for the 11p15 region and for the UPD (7) mat, the Consensus Statement of SRS proposes to evaluate CNV and/or analysis of the 14q32 region, followed by research of UPD 16 mat, UPD(20)mat or search for mutations of *CDKN1C* or *IGF2*.

Currently rare cases of SRS/SRS-like phenotype from UPD (20) mat are known, our case adds a further characterization of the phenotype. A better phenotypic characterization, deriving from the description of further cases, could make it possible to identify who to candidate with priority for the research of maternal UPD (20). Moreover the use of the multilocus MLPA technique will allow an easier identification of more cases.

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Proportions of abnormal growth parameters in extremely low birth weight infants (ELBW) during the first 3 years of life: weight Z score (WAZ), length Z score (LAZ), weight for length Z score (WLZ), and head circumference Z score (HCZ)

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Introduction: This study evaluated the postnatal growth of infants born with extremely low birth weight (ELBW) < 1 kg for 3 years.

Method: Anthropometric measures (z scores) from birth, 2,4.6,12,18,24, and 36 months were measured in 87 randomly selected infants who were born with a birth weight below 1 kg (9-2016: 9-2018). Their growth data were compared to standard growth for normal age and sex using WHO growth standards without correction for gestational age. All ELBW received preterm formula for an average of 4-6 months.

Results: Their gestational age (GA) at delivery ranged between 23 and 27.5 weeks. They had weight z score (mean +/- SE) (WAZ) = -7.7 +/-0.14, length Z score (LAZ) = -8.8 +/-0.25 and Weight for length Z score (WLZ) =-5.6 +/-0.39 and head circumference z score (HCZ) = -8.8 +/-0.3.

At birth, 97% of infants had WAZ < -2, 96% had LAZ < -2 and 98.5 % had WLZ <-2. By the age of 18 months, 18.7 % had LAZ < -2, 16.7% had WAZ <-2 and 6% had WLZ <-2. By the age of 3 years 10 % had LAZ < -2, 19 % had WAZ <-2 and 7.4 % had WLZ <-2. At 3 years of age, 14.8 % of infants had WLZ > 1 < 2 and 7.4% WLZ >2. At birth 98.5 % of infants had HCZ <-2 and at 3 years of age only 8.5% had HCZ <-2 denoting very good brain growth.

Conclusion: Infants born ELBW who were fed preterm formula had progressive improvement of growth parameters including WAZ, LAZ, WLZ, and HCZ. By the age of 3 years, 78% had normal WAZ, 90% had normal LAZ, 87% had normal WLZ, and 91.5% had normal HCZ. Overweight was detected in 7.4% of them at 3 years.

Table. Proportions of abnormal postnatal growth (%) in infants born With ELBW at different ages

	% at birth	% at 18 mon	% at 24 mon	% at 36 mon
WAZ <-2	97%	16.67%	14.00%	22.00%
WAZ <-1	100%	35.00%	34.00%	40.00%
WAZ >2	0	5.00%	14.00%	2.00%
WAZ >1	0	11.67%	38.00%	12.00%
LAZ < -2	96%	18.75%	14.00%	10.00%
LAZ <-1	98.5%	53.13%	38.00%	20.00%
WLZ <-2	98.5%	6.00%	17.14%	19.00%
WLZ < -1	100%	24.00%	28.57%	29.00%
WLZ >2	0	5.00%	5.71%	7.41%
WLZ >1	0	16.67%	14.29%	14.81%
HCZ <-2	98.5%	18.00%	8.5%	ND
HCZ <-1	100%	56.00%	31.43%	ND

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Two years of Postnatal linear and head growth of term Infants Born Large for Date (LGA): Those who had infantile Length Z score (LAZ) and/or head circumference Z score (HCZ) catch down versus those without catch down

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Introduction: Large for date (LGA) infants may have a higher tendency to become obese and tall. Catch-up and/or catch-down in linear growth, defined as an increase or decrease in length for age Z score (LAZ) by > 0.67 SD during the infantile period, may affect this tendency. Additionally, head circumference is well correlated with brain growth.

Aim: We evaluated the prevalence of tall stature (LAZ > 1 and> 2) and large head (HCZ > 1 and >2) in a cohort of infants (n = 87) born large-for-gestational-age at age 2 years. We compared the prevalence of tall stature and large head in those who had significant catch down > - 0.67 SD during infancy to those who did not have catch down.

Results: The prevalence of tall stature (LAZ > 1 and > 2) was significantly higher in the LGA group who did not have significant catch-down during infancy. (Table 1) The prevalence of large head (HCZ > 1 and > 2) was higher in LGA children who did not have significant catch-down during infancy. (Table 2)

Conclusion: According to our data, term LGA infants with no catch-down growth had an increased incidence of tall stature and large head size compared to those with significant catch-down growth. A large percentage of LGA infants have relatively large heads at 2 years of age.

Table 1. Effect of rapid catch down during 6 and 12 months on LAZ at 2 years

	number	LTZ >1 <2	LTZ >2	LT>1
With Catch down >-0.67 WAZ at 6/12	45/87	10/36 27.8%	3/36 8.3%	13/36 36%
With Catch down >-0.67 WAZ at 1 year	32/87	6/25 24%	1/25 4%	7/25 28%
Without Catch down >-0.67 WAZ at 6/12	40/87	11/39 28.2%	10/39 25%	21/39 53.8%
Without Catch down >-0.67 WAZ at 1 year	56/87	18/38 47.4%	12/38 31.6%	30/38 78%

P value catch down vs no catch down * < 0.05, ** <0.001

Table 2. Effect of rapid catch down during 6 and 12 months on head growth (HCZ) at 2 years

	number	HCZ >1 <2	HCZ >2	HCZ>1
With Catch down >-0.67 WAZ at 6/12	45/87	10/31 32.3%	2/31 6.5%	12/31 38.7%
With Catch down >-0.67 WAZ at 1 year	32/87	7/55 12.7%	3/55 5.5%	10/55 18.2%
Without Catch down >-0.67 WAZ at 6/12	40/87	11/25 44%	7/25 28%	18/25 72%
Without Catch down >-0.67 WAZ at 1 year	56/87	16/55 29.1%	7/55 12.7%	23/55 41.8%

P1-532

Cerebral aneurysms and kidney disease in a child with microcephalic osteodysplastic primordial dwarfism type II: novel homozygous mutation in the PCNT gene

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MOPD is known to be caused by homozygous loss-of-function mutations in a specific gene, PCNT. Both intra- and interfamilial clinical variability (even for the same variant) have been frequently observed, which makes it difficult to infer a genotype–phenotype correlation.

Pericentrin (PCTN) is a structural protein expressed in the centrosome that plays a fundamental role in anchoring protein complexes, regulating mitotic cycle and thus cell proliferation.

High levels of mitotic alterations in the cells of subjects with PCNT mutations suggested that the cells of patients with MOPD II are more susceptible to apoptosis resulting in a decrease in the total cellularity of the embryo with subsequent growth restriction into adulthood.

We report the case of a 7 year child that died for cerebral haemorrhage secondary to posterior arterial aneurysm.

Genetic analysis evidenced a novel homozygous variant (c.3019_3020del, p.Leu1007Serfs*50), predicted to cause premature truncation of protein synthesis.

This child presented with extreme short stature (-9,53 SDS) with no catch-up growth from birth, mental retardation, and distinctive craniofacial features. He had microcephaly, a high forehead with ocular proptosis and prominent beaked nose, micrognathia, a relatively proportionated small mouth with multiple dental caries, brachy-mesophalangy, arthrogryposis of the hands, equinus right foot, micropenis, hypotrophic-like right testis and non-palpable left testis, generalized hypotonus and resistance to dorsiflexion of the right lower limb due to the presence of tendon retraction, brisk and asymmetrical patellar osteotendinous reflexes. Total body skeletal survey showed multiple and distinctive bone anomalies.

Abdominal US showed bilateral increased echogenicity of the kidneys with poor corticomedullary differentiation, at variance with the usual findings of kidney cysts in these patients. A first MRI of the brain performed at presentation showed areas of gliosis with encephalomalacia and diffused hypo/delayed myelination, and a thinned appearance of the middle and anterior cerebral arteries. Intracranial hemorrhage due to a cerebral aneurism occurred at age 7 yr, and was associated at that time with the moya-moya malformation,

Unlike cases previously published in the literature, intracranial anomalies and kidney findings findings were evidenced very early in the life of this child.

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Central Precocious Puberty in McCune Albright Syndrome: a case report

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Introduction: McCune Albright Syndrome (MAS) is a rare disorder caused by somatic activating mutations of the *GNAS* gene, characterized by monostotic/polyostotic fibrous dysplasia, café au lait skin pigmentation and hyperfunctioning endocrinopathies. We report a case of MAS presenting with mild phenotypic characteristics and central precocious puberty (CPP).

Case: Indian female was referred to our clinic for premature thelarche. Second child, born at term by caesarean section due to foetal abnormal presentation. Pregnancy was physiological, parents were non consanguineous. Neonatal weight was 2678 g (-0.85 SDS). At birth a congenital vascular abnormality on the nose was treated with propranolol for 9 months. At first evaluation at the age of 1 year and 10 months length was 80.3 cm (-1.45 SDS), within the family range (target height 155 cm, -1.3 SDS), weight was 9.9 kg (-0.96 SDS), head circumference was 45.5 cm (-1.03 SDS). Puberal stages showed bilateral thelarche (B2), no pubarche. Bone age was correspondent to chronological age according with Greulich &Pyle atlas. Initial blood exams and pelvic ultrasound were compatible with prepuberty. Due to persistent thelarche and increased height velocity, the girl underwent a gonadotropin-releasing hormone (GnRH) stimulation test that confirmed CPP. Brain MRI was normal. Therapy with a GnRH agonist was started. Due to the discovery of a widespread café-au-lait spot on the left side of the abdomen and two other millimetric spots on the right side of the abdomen and left arm, with indented edges (not compatible with neurofibromatosis 1), genetic evaluation was requested. In the suspicion of a somatic mosaicism of the *GNAS* gene, digital PCR analysis was performed, both on DNA extracted from peripheral blood leukocytes and on circulating DNA extracted from plasma, revealing the variant c.605G>A in the *GNAS* gene. This variant, compatible with MAS, is present only in some cells (mosaicism) and appeared in the post-zygotic phase. Parents were not carriers of this variant. Other investigations were precociously performed according to guidelines; currently no other endocrinopathies have been found and no radiological bone abnormalities have been detected.

Discussion: MAS is characterised by a variable spectrum of phenotypes. Our patient presented a mild phenotype, probably due to mosaicism and early timing of diagnosis. Interestingly, the girl presented gonadotropin-dependent and not gonadotropin-independent PP, that is most frequently associated with the

syndrome. Precocious diagnosis was essential to start specific follow-up of the patient, allowing clinicians to promptly identify and eventually treat any other manifestations or complications.

Multisystem Endocrine Disorders

P1-135

Hypoaldosteronism without hypocortisolism - an unusual presentation of APECED syndrome

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Background: Automimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is an extremely rare autoimmune condition caused by AIRE (autoimmune regulator) gene mutations and characterised by a classic triad of 1) chronic mucocutaneous candidiasis, 2) hypoparathyroidism and 3) adrenal insufficiency. APECED can involve any endocrine or non-endocrine organ. Consequently, clinicians need to be mindful of the great variability in presentation.

Although adrenal insufficiency has been described as the initial endocrine manifestation of APECED syndrome, hypoaldosteronism without cortisol deficiency is not a recognised manifestation of APECED. We describe a young boy with atypical initial endocrine presentation.

Case: A 3-year-old British Caucasian male presented to the Emergency Department with a 3-month history of candida stomatitis resistant to nystatin and bilateral athlete's foot.

Weight and height were on the 90th centile, and the child was normotensive with no other abnormalities identified on full examination. Initial investigations for persistent candidiasis showed normal full blood count, renal, bone and liver profile, normal immunoglobulins and vaccine responses and negative Human Immunodeficiency virus screen. Unexpected low serum sodium (lowest value 128 mmol/L) resulted in specific investigations, which showed inappropriately elevated urinary sodium (44mmol/L). Paired serum and urine osmolalities were 276 mOsm/kg and 320mOsm/kg respectively. Serum ACTH (14ng/L) and cortisol (489 nmol/L) were normal. Low serum aldosterone (78pmol/L) and high renin (790mU/L) pointed towards isolated hypoaldosteronism. However, urine steroid profile did not show evidence of aldosterone synthase defect. Treatment with fludrocortisone (100micrograms daily) normalised serum sodium

In view of uncertain diagnosis of primary adrenal insufficiency due to normal serum ACTH and cortisol, we measured anti-adrenal antibodies (21-hydroxylase and 17-hydroxylase) which were elevated. Subsequent genetic testing confirmed compound heterozygous mutation in AIRE (c.769C>T p.(Arg257*) pathogenic variant and c.967_979del p.(Leu323Serfs*51) pathogenic variant).

Monitoring with 3-monthly serum cortisol and ACTH confirmed development of cortisol deficiency approximately 6 months after diagnosis of hypoaldosteronism (ACTH 2080ng/L; Cortisol 0 min 205nmol/L, 30 minutes 190nmol/L and 60 minutes 126nmol/L). Hydrocortisone replacement was commenced. To date the child has had normal bone profile and no other autoimmune endocrine or non-endocrine dysfunction.

Discussion: Hypoaldosteronism is a rare first endocrine presentation of APECED. APECED may pose a diagnostic conundrum even for experienced clinicians due to heterogenicity in presentation.

Presence of treatment resistant candidiasis in addition to any auto-immune endocrine disorder should act as a red flag prompting for consideration of APECED.

P1-136

Time Taken to Reach a Diagnosis In Children With XY DSD In Expert Endocrine Centres In Europe

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Background: Reaching a definitive diagnosis in individuals with XY DSD is challenging and the time taken to reach a diagnosis is an important clinical benchmark that has not been sufficiently explored in this group of conditions.

Objective: To evaluate the diagnostic process with a focus on the time to diagnosis in children with XY DSD reported via the e-reporting platform (e-REC) of the European Registries for Rare Endocrine Conditions (EuRRECa) project.

Methods: Endocrinologists (n=19) reporting new cases of XY DSD in children (n=166) over a two-year period, from July 2018 to August 2020, were approached to complete an online survey regarding the diagnostic process in the XY DSD cases that were reported.

Results: The survey was completed for 76 cases (46%) by 15 respondents (79%) from 14 centres within 9 European countries. The median age at first presentation was 0.6 years (range 0,18.3).

Clinical evaluation, biochemical tests and molecular genetic investigations were used to reach a diagnosis in 56 (74%), 46 (61%) and 29 (38%) cases, respectively and a combination of all three investigative modalities were used to establish a diagnosis in 11 (14%). Of the 76 cases, 54 (71%) and 15 (20%) were reported to have a confirmed or suspected diagnosis, respectively. In 41 cases (59%), the diagnosis was categorised as non-specific XY DSD. Amongst the 11 cases who had a combination of all three investigative modalities, only 4 (36%) had non-specific XY DSD whereas in the remaining 65 cases who did not have a combination of all three investigative approaches, the number of cases with non-specific XY DSD was 37 (56%), p=0.3. The overall median time from first presentation to the endocrine centre to diagnosis was 2 (1, 14) months. The median time taken to reach a diagnosis of a disorder of gonadal development (n=10) was 1 month (1,11) and a disorder of androgen action (n=4) was 2 months (1,4) months, whilst a label of non-specific XY DSD (n=26) was reached at 3 (1,14) months.

Conclusions: The use of detailed endocrine and genetic investigations in cases of XY DSD is variable and the time taken to reach a diagnosis in XY DSD depends on the underlying condition. Further clarity is required for the use of the term 'non-specific XY DSD', a term that may describe a case that has no identifiable hormonal or genetic abnormality of gonadal development, androgen synthesis or androgen action.

P1-137

First description of a child with a biallellic loss-of-function variant in the sulfate transporter SLC13A1

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Introduction: Sulfation is required for the metabolism of numerous compounds, including proteoglycans, steroid hormones, neurotransmitters, toxic chemicals, and drugs like acetaminophen. The sulfate transporter SLC13A1 is responsible for the intestinal absorption and the renal reabsorption of inorganic sulfate, but loss-of-function mutations in this gene have never been described in man. Here, we describe a male with a biallelic loss-of-function variant, i.e., R12X, in the SLC13A1 gene who was followed up until age 14 years.

Methods: Our patient underwent assessment of circulating sulfate level, renal sulfate excretion, sulfate loading (using intravenous N-acetylcysteine), and the degree of sulfation of various compounds.

Results: Our patient presented at age 7 months with prominent knees. Skeletal radiographs revealed remarkable generalized widespread skeletal abnormalities, characterized by a spiky widening of all metaphyses, ovoid-shaped vertebral bodies, slightly delayed epiphyseal ossification, irregular tarsal bones, and flared ribs, which gradually improved with age. Neurodevelopment was normal, except for the presence of autistic traits. Linear growth did not deviate from the population reference or from the target height range, although his trunk was relatively short compared to his legs (with a sitting height/height ratio of -2.0 SD score). Pubertal onset was age appropriate.

On evaluation, our patient's plasma sulfate level was low at 44 to 65 (normal range: 322-454) µmol/L, and his fractional sulfate excretion was around 100% (normal range: 13-34%). For comparison, his heterozygous mother had a fractional sulfate excretion of 45%. After the infusion of N-acetylcysteine, our patient's plasma sulfate level normalized, and 16 hrs later it was returned to baseline. In our patient the proportion of chondroitin sulfate disaccharides in urine was no different from his parents or from controls (92.6% vs. 90.8-96.1% vs. 92.5-94.5%). His serum cholesterol sulfate level was reduced at 443 (normal range: 500-1,236) ng/mL, and his serum steroid sulfate levels were all within the normal range.

Discussion: The homozygous variant R12X of SLC13A1 is characterized by a predominantly skeletal phenotype, which should prompt genetic testing.

P1-138

Long-term Growth and Endocrine Complications of Bone Marrow Transplantation in Children and Adolescents with Beta-Thalassemia Major: Comparison with Conventional treatment

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Introduction: The conventional approach to the treatment of Beta- thalassemia major (BTM) is based on the correction of hemoglobin status through regular blood transfusions and iron chelation therapy for iron overload. Allogeneic hematopoietic stem cell transplantation (HCT) remains the only currently available technique that has curative potential. No previous study compared the long-term growth and endocrinopathy changes among large cohorts of BTM patients on conventional treatment versus those treated with HCT.

Aim: The goal of this study was to find out the prevalence of long-term growth and endocrine changes after HCT in patients with BTM and compare these data with those occurring in BTM patients on conventional treatment.

Methods: We recorded, summarized, and calculated the prevalence of different growth and endocrine abnormalities in published studies (Pubmed, Google scholar) on children and adolescents with BTM in the past 30 years (n = 527). These data were compared to published data on 2 large cohorts of BTM children and adolescents who were on conventional therapy (n = 11744 and n=3817).

Results: Considerable growth and endocrine abnormalities were detected after BMT in patients with BTM. (~ 41% had growth impairment, ~37% had GH deficiency, ~30 % had gonadal abnormalities and ~10 % had thyroid anomalies). In comparison to prevalence data from 2 large cohorts of children on Conv therapy,

Table. Prevalence of growth and endocrine abnormalities in BTM after conventional (Conv) therapy versus after bone marrow transplantation (BMT)

	n =	BMT HCT	% abnormal	n =	Conv/ Zozani et al	%	p-value	n =	Conv/ Soliman et al	% abnormal	p-value
Growth abnormalities	527	218	41.4	11744	5743	48.9	<0.001	3817	1137	29.8	<0.001
Growth Hormone Deficiency	286	107	37.4	11744	3123	26.6	<0.001	ND	ND	ND	ND
Hypogonadism	868	269	30.9	ND	ND	ND	ND	3817	1755	46	<0.001
Thyroid abnormalities	611	62	10.1	ND	ND	ND	ND	3817	666	17.5	<0.001
Diabetes	72	5	6.9	ND	ND	ND	ND	3817	446	11.7	0.20

our analysis showed clearly that BMT cannot correct the endocrinological complications and therefore highly supported the set-up of simple universal measures that allow early identification and proper and timely management of these consequences. (table 1)

Conclusion: In Children with BTM who had BMT, annual assessments of growth, pubertal development, sexual, and reproductive function are recommended based on the high prevalence of growth and endocrinopathy after exposure to conditioning regimens.

P1-139

Cushing's syndrome in a girl with Carney Complex: A case report

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Background: Carney complex (CNC) is a rare autosomal dominant multiple endocrine neoplasia and lentiginosis syndrome, characterized by abnormal cutaneous and mucosal pigmentation, myxomas of the heart, skin, breast and other non-endocrine tumors. CNC is principally caused by loss-of-function mutations of PRKAR1A gene located at 17q22-24 coding for the regulatory subunit type I alpha of protein kinase A (PKA) gene. Cushing's syndrome is a rare disorder in pediatric age resulting from the prolonged exposure to excess glucocorticoids that can be a complication of CNC.

Case Presentation: We herein report a rare presentation of CNC in a 5 years old female patient who suffered from a rapid weight gain associated with changing of the facial physiognomy, acne, hypertrichosis, asthenia and an increased sedentariness. The patient was admitted to our department with the suspect of Cushing's disease, especially after that high levels of free urinary cortisol (>800ug/24h) were found. During the first screening the patient performed a blood count, a glycemic profile, an evaluation of thyroid, sexual and adrenal hormones, urine test as well as a blood pression monitoring. The patient also performed a low dose dexamethasone test that showed a lack of suppression of cortisol level with suppressed ACTH levels which confirmed an ACTH independent Cushing syndrome. Other important findings were the presence hypokalemic alkalosis (pH 7.47,K+ 1.9), kidney stones and hypertension which were treated during the hospitalization.

Although Cushing's disease was already confirmed, CNC was suspected given the anamnestic data of atrial myxoma, thyroid and testicular tumor, cutaneous fibromas and lentiginous lesions in the patient's father.

The first abdominal ultrasound exam did not show adrenal masses but successively an abdominal MRI confirmed the presence of hypertrophy of both adrenal glands with bilateral evidence of millimetric nodulations. A DNA test eventually confirmed a mutation (p.Arg97Ter) of the PRKAR1A gene compatible with CNC both in the father and the daughter.

Finally, the patient underwent a bilateral laparoscopic adrenalectomy and after the beginning of a substitution therapy a complete regression of the symptoms was obtained.

Conclusion: Cushing's syndrome is rare in children and physicians should always keep in mind the main red flags as rapid weight gain associated with changing of the facial physiognomy and short stature, hypertension and sudden modifications of behavior. When Cushing's syndrome is diagnosed, especially without adrenal mass, rare diseases as CNC should be considered searching carefully supporting clinical and anamnestic data.

P1-140

Prevalence of Endocrinopathies in Sickle cell Disease Patients on Conventional Therapy: Review of literature in the past 25 years

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Sickle cell disease (SCD) is a hereditary hemoglobinopathy characterized by abnormal hemoglobin production, hemolytic anemia, and intermittent occlusion of small blood vessels, leading to tissue ischemia, chronic organ damage, and organ dysfunction including endocrine organs. The aim of this work was to evaluate the prevalence of different endocrinopathies in children, adolescents, and young adults with SCD.

Methods: We performed an electronic search in PubMed, Google Scholar, and Web of Sciences to evaluate the global prevalence of growth hormone impairment and different endocrinopathies in SCD in all publications in the past 25 years.

Results: Sixteen studies were included from 9 countries (USA, Canada, UK, Brazil, Jamaica, Egypt, Turkey, Saudi Arabia, and Bahrain) after 2000. The total number of patients was 1286. Most patients were children and adolescents <16 years. The pooled prevalence of hypogonadism/delayed puberty was 21% %. The pooled prevalence of GH deficiency in short SCD children with height SDS < -2 was 24.6%. Clinical and subclinical hypothyroidism occurred in 5.76% while diabetes and dysglycemia occurred in 10.9%. The prevalence of vitamin D deficiency was 62.3%.

Conclusion: Our study revealed that near one-fifth of SCD patients suffered from hypogonadism and/or delayed puberty. One-fourth of short SCD children (HAZ < -2) had GH deficiency. Dysglycemia and diabetes mellitus occur later in life in 10.9% of SCD patients. Regular evaluation of growth and close monitoring of endocrine function for early and timely management of these abnormalities besides conventional treatment (hydroxyurea, and regular blood transfusion and chelation therapy in those with transfusion-dependent SCD) could significantly reduce these abnormalities. (table)

	Studies (No)	Patients (No)	%
Hypogonadism/ delayed puberty	11	779	20.95
GH deficiency	2	100	24.6% of short SCD
Diabetes mellitus and impaired glucose tolerance (IGT)	5	656	10.90
Clinical and subclinical Hypothyroidism	5	413	5.76
Vit D deficiency	3	184	62.30

P1-141

A Case with Primrose Syndrome and What He Taught

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Introduction: Primrose syndrome was defined in 1982. It is characterized by characteristic facial appearance, macrocephaly, global developmental delay, intellectualdisability and calcification in the outer ear. It occurs with loss-of-function mutations in the ZBTB20-gene. This gene is a transcriptional gene suppressor regulator and is effective on neurogenesis, glucose homeostasis, and postnatal growth. Here, a case with Primrose syndrome will be presented.

Case: The patient who applied with the cause of prolonged-jaundice at the age of 40 days, was born 2620 grams at term, received mechanical ventilation during the neonatal period, and there was no consanguinity between the parents. On physical examination, his general condition was good, vitalsigns were normal, height 52 cm, body weight 4500-grams, anterior fontanel 3x3cm, posterior fontanel closed, syndromicfacial appearance. In the examinations, TSH was 2.5μIU/ml, free T4 0.76ng/dl, free T3 3.61pg/ml. Glucose was 94mg/dL, Na was 136mEq/L, K was 4.44 mEq/L. anterior pituitaryhormones: Cortisol 3.0 μg/dl, ACTH 37 pg/ml, FSH 3.11 mIU/ml, LH 1.80 mIU/ml, total testosterone 103.39ng/dl, IGF1 46.7ng/ml, prolactin 20.89ng/ml. The peak cortisolresponse of the case to the low-dose ACTH stimulation test was 14μg/dl. Central adrenal insufficiency and central hypothyroidism were considered in the patient, hydrocortisoneand LT4 treatments were started. Neuroimaging wasperformed with the preliminary diagnosis of hypopituarism. The corpus callosum was found to be thin, and the lateralventricles were wide. Hearing test was abnormal. No visionproblems were detected. In the microarray analysis performedwith the diagnosis of panhypopituarism, 3q11.2q13.31 deletion and ZBTB20 haploinsufficiency were detected. Thefindings were reported to be associated with Primrose syndrome, which is caused by loss of ZBTB20 function.

Conclusion: Neurodevelopmental problems, hearing loss, corpus callosum dysgenesis, ataxia, seizures and endocrinological problems such as congenital hypothyroidism, growth hormone deficiency, delayed puberty and diabetesmellitus have been reported in Primrose syndrome. Central hypothyroidism and adrenal insufficiency accompanying this syndrome have not been reported before in the literature, and considering that the hypopituitarism in the patient may be associated with axis maturation failure, the treatment was planned to be discontinued gradually. The case with Primrose syndrome diagnosed early will be followed up for a long time and it will increase our experience in terms of endocrine effects. Literature and genetic data enable us to prevent unnecessary drug use in the follow-up of patients.

P1-142

Two causes of short stature and delayed puberty in one patient: craniopharyngioma and celiac disease. A case report

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Introduction: Craniopharyngioma, a benign tumor, develops in the sellar/parasellar region. Diagnosis is usually late. Symptoms include severe headaches and vomiting, visual impairment, visual and olfactory hallucinations and at least one hormonal deficiency.

Celiac disease is caused by an immune reaction triggered by gluten in the small intestine. Over time, due to inflammation, it causes malabsorbtion which can affect growth in children.

Case Report: We present the case of a 15 years and 8 months old girl, diagnosed with short stature 3 years prior to presentation. Due to parental decision, she was not further investigated or treated. At 14, she was diagnosed with cataract.

Clinically, the patient has a significant delay in growth (SDSt=-4.37). No signs of puberty. Pale skin. Normal bowl movements and diuresis. No signs of neurological impairment.

Blood tests reveal a mild anemia and pituitary pluri-deficiency: low levels for IGF-1, cortisol, FSH, LH, estradiol, FT4 and "abnormally" normal values for ACTH, TSH. Stimulating tests for hGH and cortisol confirm pituitary insufficiency for both. Bone age corresponds a 13 year-old. The karyotype was 46, XX. Gastroenterology evaluation reveals an unexpected diagnosis of celiac disease (tTG IgA >10x, EMA>10x). Ophthalmological evaluation suggests an inflammatory etiology for her cataract (uveitis sequelae detected in the left eye). Eye fundus exam reveals a mildly discolored optic nerve papilla, with clear contour and no edema. The field of sight cannot be evaluated due to her impaired sight by the cataract. We perform a pituitary contrast MRI which shows a 50/30/23 mm tumor in the sellar region, with the aspect of a craniopharyngioma. Neurosurgery evaluation confirms the suspicion and recommends surgical excision. Surgery is scheduled for July 2022, due to family request. Substitution therapy is initiated with Levothyroxine, Hydrocortisone and Estradiol. Prophylactic anticonvulsivant medication is recommended until surgery. Gluten-free diet is initiated.

Conclusions: Short stature, especially when associated with pubertal delay, can have multiple etiologies which do not exclude each other.

When there are no neurological or ocular symptoms, cranyiopharingioma can be a very late diagnosis.

In short stature cases which associate anemia, gastroenterological evaluation is important, even if the patient does not have digestive symptoms. When specific antibodies are >10x higher than normal, biopsy is not needed for diagnosis of celiac disease.

Growth hormone substitution can be administered only after complete resection of the craniopharyngioma. In our patient, we do not expect to recuperate much of the height deficit, due to the patient's age.

P1-333

Emerging phenotypes linked to variants in *SAMD9* and MIRAGE syndrome

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Background: Heterozygous *de novo* variants in *SAMD9* cause the complex multisystem growth disorder, MIRAGE syndrome. Core features are myelodysplasia, infection, restricted growth, adrenal hypoplasia, genital/gonadal phenotypes, and enteropathy. However, the range of additional associations is expanding and includes disrupted placental development, poor post-natal growth, and other endocrine features. Milder phenotypes are also described, such as hypospadias in boys born small for gestational age (SGA), and normal adrenal function. Some children present with isolated myelodysplastic syndrome (MDS/monosomy 7) without MIRAGE features.

Aims: We investigated: 1) the range of reported *SAMD9* variants, clinical features and possible genotype-phenotype correlations; 2) whether *SAMD9* disruption affects placental function and leads to pregnancy loss/recurrent miscarriage (RM); 3) if pathogenic variants cause isolated fetal growth restriction (FGR).

Methods: A systematic literature review was undertaken of *SAMD9*-associated conditions, focussing on position/type of variant, pregnancy and growth data, and associated endocrine features. Genetic analysis of *SAMD9* was performed using next generation sequencing (NGS) in products of conception (POC, n=26) and RM couples (n=48; individuals n=96), and in children with FGR (n=44), SGA (n=24), Silver-Russell Syndrome (SRS, n=8), (total n=198).

Results: SAMD9 variants are currently reported in 117 individuals (MDS/monosomy 7, 65 (55%); MIRAGE, 52 (44%)). Increasingly, children with MIRAGE features are reported without an adrenal phenotype (12/52, 23%). Compared to MDS, MIRAGE-associated variants cluster in specific domains of SAMD9. Disruption of arginine residues is more common with adrenal dysfunction. MIRAGE patients without adrenal dysfunction were heavier at birth (median 1515 g versus 1020 g; $P < 0.05$) and born later (median 34.5 weeks versus 31.0; $P < 0.05$) compared to children with adrenal insufficiency. Hypospadias is a common feature, but 46,XX girls remain underreported. Additional endocrinopathies include hypothyroidism, hypo- and hyper-glycaemia, short stature and panhypopituitarism. Single cell RNA sequencing showed higher SAMD9 expression in late trimester human placenta, but no pathogenic variants in SAMD9 were identified in POC or RM couples. NGS analysis showed no likely pathogenic variants or enrichment of rare variants in SAMD9 in FGR, SGA and SRS cohorts.

Conclusions: MIRAGE syndrome is more phenotypically diverse than originally reported and includes children with neonatal growth restriction and multisystem features but without adrenal insufficiency. Other endocrinopathies are emerging and long-term follow-up needed. MIRAGE is likely underdiagnosed in the neonatal setting, especially in 46,XX girls. Reaching a diagnosis has important implications for personalised multidisciplinary management. Nevertheless, SAMD9 variants are not common in fetal growth disorders without additional features.

P1-334

Multi-continent comparison of the prevalence of short stature and undernutrition in children and adolescents with homozygous sickle cell disease: Africa, USA, Europe, and Middle East area

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Background: Poor growth and under-nutrition are common in children with sickle cell disease (SCD). This review summarizes evidence of impaired linear growth and weight gain in children with SCD in different regions of the world in the past 25 years.

Methods: A literature search was conducted on Medline/PUBMED, Google scholar, and SCOPUS, for studies published in English during the past 25 years, using the keywords sickle cell combined with nutrition, anthropometry, growth, height and weight, body mass index.

Results: Twenty-one studies (cross-sectional and longitudinal) were included in the final anthropometric analysis. The prevalence of short stature (Height SDS (HAZ)< -2 and underweight (weight for age Z score (WAZ) or BMI Z score BMI Z < -2 was calculated in each study. Prevalence data from each region complied and the three regions were compared using proportion statistics.

We reviewed eight studies from North America and Europe, nine from Africa (Egypt, Nigeria, Cameroon, Central Africa, Ivory Coast, Senegal, Ghana, and Zambia), and 5 from the Middle East area (Yemen, Qatar, Iraq, Bahrain, and Oman). Most studies were observational with wide variations in sample size and selection of reference growth data. Results of cumulative prevalence per region are presented in the table. The prevalence of short stature and underweight and wasting were significantly higher in SCD children from the Middle East and Africa compared to Europe and USA. The higher prevalence of growth impairment in African children with SCD can be explained in part by the high occurrence of nutritionally related growth abnormalities in non-SCD children in these countries (around 25% of children) which adds to growth impairment in SCD.

Conclusions: The high prevalence of growth abnormalities in children and adolescents with SCD necessitates close monitoring of growth and nutritional status as an essential requirement for early diagnosis and proper management of growth failure and nutritional intervention.

Table. Prevalence of growth abnormalities in SCD in different regions of the World

Region	Africa	Europe/USA	Middle East
Number of studies	9	8	5
Total No	12018	733	310
HAZ <-2SD	20%	15.4%	33%
p-value	A vs E 0.0024	E vs M <0.0001	M vs A <0.0001
Total No.	3200	1435	199
WAZ or BMI Z<-2SD	43.54%	9.64%	51.5%
p-value	Avs E <0.0001	E vs M <0.0001	M vs A 0.0282

A = Africa, E= Europe and USA, M = Middle East

P1-335

Early endocrinological deficiencies can anticipate the diagnosis of mitochondrial diseases: Phenotype evolution of a rare *MT-TG* gene variant

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Mitochondrial diseases are multisystemic disorders which often involve endocrine system, as defective oxidative phosphorylation can lead to decreased hormones production or secretion and all steroid hormones are synthesized in the mitochondria. Endocrine dysfunctions can therefore represent the initial symptoms of these pathologies and the incidence of various endocrinopathies varies between different mitochondrial disease. Diabetes mellitus is the most frequently described endocrinopathy but hypothalamic dysfunction with multiple pituitary hormone deficiencies and end-organ dysfunctions have also been reported.

In mitochondrial diseases a correlation between specific mutations and phenotype has been found. Only a few of the reported mutations in mitochondrial genes reside within *MT-TG*, that encodes $tRNA^{Gly}$. Here we report the second observation of a patient with a specific rare mutation in *MT-TG*, presenting similar endocrine features extended to a GH deficiency.

The patient is an 18-year-old female. Psychomotor development was normal but mild intellectual disability was diagnosed during childhood. At 6 yo GH stimulation tests with peak respectively at 3.30 and 1.45 µg/l were performed for progressive slowing of growth rate. Recombinant human GH treatment was started. At the age of 12 for lack of spontaneous pubertal development oestrogen replacement therapy was started for diagnosis of

hypogonadotropic hypogonadism. At the age of 14, L-thyroxine treatment was also started for onset of central hypothyroidism. Brain MRI showed normal midline structures.

In addition to endocrinological problems, she also presented severe sensorineural hearing loss at the age of 6 for which she underwent bilateral cochlear implantation. Retinal dystrophy was diagnosed at the age of 15 and at 17 yo she underwent surgical correction of bilateral cataract.

Karyotype (46,XX), array-CGH, genetic analysis with targeted resequencing using multigenic panels for hearing loss, hypogonadism and hypopituitarism were carried out without identifying pathogenic mutations.

At the age of 18 she presented tonic-clonic seizures, EEG showed diffuse epileptic discharges and increased serum CPK and lactate levels were found. Brain CT scan showed diffuse basal ganglia ad cerebellar dentate nuclei calcification. The suspicion of mitochondrial pathology was raised and confirmed by muscular biopsy (diffuse ragged red fibres and COX negative fibres). Molecular analysis of mitochondrial DNA identified the m.10038G>A variant in *MT-TG* gene with 53% heteroplasmy level in peripheral blood and 88% in skeletal muscle.

The rare variant was previously reported in an adult patient (Pool O.V. et al., Neurol Gen 2020) with several similar phenotypic features: GH deficiency, epilepsy and extensive intracranial calcification were not previously reported.

P1-336

Prevalence of Short Stature and Endocrinopathy in β-thalassemia Major Patients on Conventional Therapy in the Mediterranean and the Middle East countries

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Blood transfusion and iron chelation are conventional treatments for β-thalassemia (BTM). However, iron overload in parenchymal organs and endocrine glands still occurs in a good number of these patients.

Objective: To evaluate the prevalence of iron-related complications (short stature, growth retardation, and growth hormone deficiency) in BTM.

Methods: We performed an electronic search in PubMed, Google Scholar, and Web of Sciences to evaluate the prevalence of growth hormone impairment and Endocrinopathies in BTM in the Mediterranean and Middle-east countries in the past 20 years.

Results: Fourteen studies were included from 14 Mediterranean and Middle East countries after 2000. The total number of patients was 4477. The overall mean age of the participants was about 16.5 years. The pooled prevalence of short stature (ST) was 35.9 %. The pooled prevalence of hypogonadism/delayed puberty was 45.6%, hypothyroidism was 10.3%, diabetes and dysglycemia was 16.3% and hypoparathyroidism was 7.9%.

Conclusion: Our study revealed that near a third of thalassemia patients suffer from growth impairments. Hypogonadism is still the most common endocrinopathy occurring in these patients (45.6%). Dysglycemia occurs after 10 years of age in 16.3% of these patients. Regular evaluation of growth and close monitoring of endocrine function for early and timely management of these abnormalities besides regular chelation therapy could significantly reduce these abnormalities.

	Cyprus	Greece	Itlay	France	Iran	Turkey	Egypt	Tunesia	Morocco	West Bank
Number	436	262	1861	378	220	252	100	28	78	309
Hypogonadism/ delayed puberty%	35.2	42	49	35	35	50	57	46.5	42	ND
DM/IGT%	9.4	18.5	4.9	6.9	8.7	9.3	8.8	60	ND	
Short Stature /GHD%	35	32		20.1	39.3		49	57	36	14.6
Hypothyroidism%	5.9	4	6.2	11.1	7.7	29	7	21	9	
Hypoparathyroidism%	1.2	4	3.6		7.6	4	ND	3.6	ND	8

	Dubai	Oman	Saudi Arabia	Qatar	Total
Number	382	30	81	60	4477
Hypogonadism/ delayed puberty%	52.5	73	52.7	23	45.6
DM/IGT%	10.5	26.7	Nd	15.5	16.3
Short Stature /GHD%	ND	ND	21	25	32.9
Hypothyroidism%	6.5	3.3	14.8	8	10.26
Hypoparathyroidism%	10.5	10	11.1	23	7.9

P1-337

Alopecia totalis at the onset of polyglandular syndrome type 1

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Background: The decreased immune tolerance caused by mutations of the autoimmune regulatory gene (AIRE) lead to a spectrum of variable organ specific autoimmune disorders known as autoimmune polyglandular syndrome type 1 (APS-1). The rarity of the syndrome and the heterogenous clinical manifestations at the onset of the disease may delay the diagnosis. Only when two major components of the triad chronic mucocutaneous candidiasis – hypoparathyroidism – Addison disease (AD) are present, the diagnosis is usually made.

Case Report: We present the history of an eight year old boy with moderate mental retardation who was diagnosed with APS-1 two years after the onset of the first manifestations of the autoimmune disorder. At the age of 5 he was investigated for alopecia totalis that was followed by Lyme disease from a few months before, according to his past medical history. It is important to highlight that he also presented nail dystrophy at that time. Because of the noncompliance of his parents, we lost track of our patient until approximately 2 years later, when he presented at the emergency room for abdominal pain, nausea and vomiting, diarrhea, fatigue, muscle weakness and an altered mental status. After intravenous saline, potassium and glucose infusion, his seric sodium dropped at 110 mEq/L and malignant hyperpotassemia was associated; therefore adrenal insufficiency was suspected and the diagnosis of AD was confirmed after adequate glucocorticoid and mineralocorticoid replacement therapy. Furthermore, the clinical diagnosis of APS-1 was made 5 months later, based on the clinical assessment of an oral candidiasis associated with the previous diagnosed conditions: AD, alopecia and the nail dystrophy.

Discussions: Although alopecia is a frequent feature of APS-1, its emergence during childhood is uncommon, as it typically appears around the age of 40. Lyme disease may have influenced the disease onset, considering the fact that infections can trigger autoimmune diseases. We found literature data drawing a connection between the antigenic stimulus provided by Borrelia infections and the setting of alopecia. Another particular feature is that AD was the first diagnosed disease as a major component of the APS-1, while studies report that it is the least prevalent and the last to occur. A classical presentation of the syndrome would have made the life threatening adrenal crisis easier to diagnose.

Keywords: autoimmune polyglandular syndrome type 1, alopecia totalis, Lyme disease, Addison disease.

P1-338

Age of Estrogen Therapy Affects on Final Height in Girls with Chronic Kidney Disease and Short Stature

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Introduction: We investigated the age of starting Estrogen replacement therapy as a key parameter for reaching near normal Final Height (FH) in Chronic Kidney Disease (CKD) girls with growth retardation. Although Growth Hormone (GH) therapy significantly increase final height in children with CKD, these children's final height remain under normal population height in several studies. As normal puberty is a key point to reach normal final height, unmet needs of CKD children in the case of both delayed puberty and delayed thelarche may be the missing subjects. In fact, endocrinologists neglect onset of puberty and only add estrogen when they can confirm delayed puberty after 13.5 yrs old that lead to not so arbitrary final height in spite of GH treatment.

Method: This open label, quasi-experimental designs, matched controlled clinical trial was performed on CKD girls with short stature and delayed thelarche or delayed puberty according to clinical and laboratory investigations. Participants group 1 and 2 had been treated with GH, and Ethinyl Esradiol (EE) was administered from 11yrs old with delayed thelarche and 13.5 yrs old with delayed puberty in group 1 and 2 respectively. Group 3 was selected from patients that did not accept to start GH or EE till 15 years old. The effect of the age of starting EE on FH, GH therapy outcomes, bone density, and calcium profile were evaluated.

Result: Finally 16, 22, and 21 patients analyzed as group 1, 2, and 3 respectively. Mean Mead Parental Height (MPH) in group 1, 2, and 3 had not significant difference between groups. GH therapy significantly enhanced mean final height in groups 1 and 2 in comparison with group 3 (β= -4.29, P<0.001). Also multivariable backward linear regression illustrated significant negative association between final height and age of starting EE (β=0.26, P<0.001). mean femoral and lumbar bone density were significantly enhanced after GH and EE therapy (P value: <0.001).

Conclusion: We recommend to pay more attention to the effect of delay the onset of puberty on growth spurt and final height. Therefore, in spite of serious concern about closure of growth palate because of estrogen replacement therapy, we should not limit it only for after 13.5 yrs old girls and starting EE from 11 yrs old in short stature girls that have no clinical or laboratory sign of sexual maturity till 11 yrs can help to enhance the cost effectiveness of GH therapy.

P1-339

Treatment-resistant hypokalemia and arterial hypertension: a prismatic case of low renin childhood hypertension

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We report on a 17-year-old female patient with cramps in hands and legs since 6 months. She showed hypokalemia with high need of potassium substitution (128mmol K= 1.3 mmol/kg/d), arterial hypertension (mean 154.5/92 mmHg), polydipsia and polyuria without nocturia or salt craving.

Her PMH revealed neuroblastoma stage III with high-dose chemotherapy, stem cell transplantation and obesity (36.8 kg/m2).

Further investigation showed aldosterone 77.5 ng/dl (norm values: 2-10ng/dl), renin 1 ng/l (8.3-43.4 ng/l), aldosterone-renin-ratio (ARR): 77.5. A GS-MS steroid profile from 24h urine revealed excretion of tetrahydroaldosterone of 2-fold of the upper norm.

A saline loading test (2l NaCl 0.9% in 4h), showed inadequate suppression of aldosterone values (basal: 16.6 ng/dl, after SLT: 10.8 ng/dl, normal: 2-10 ng/dl). Thus suspicion of primary hyperaldosteronism was rised. There was no evidence of pheochromocytoma (normal metanephrines and normetanephrines in urine). An NGS panel diagnostic for hereditary hypertension and familial forms of hyperaldosteronism was unremarkable (CYP11B1/ CYP11B2, CUL3, KLHL3, KCNJ5, etc). A CT abdomen showed discrete bilateral adrenal hypertrophy without definite evidence of a mass.

A captopril test showed insufficient aldosterone suppression with suppressed renin. Adrenal vein catheterization followed for subtype differentiation of primary hyperaldosteronism: peripheral blood: cortisol 6.2 µg/dl, aldosterone: 28.2 ng/dl, A/C: 4.5; left suprarenal vein: cortisol 1363 µg/dl, aldosterone: 2148 ng/dl, A/C: 1.5, ratio cortisol AV/ cortisol PV: 219.13; right suprarenal vein: cortisol 281.7 µg/dl, aldosterone: 1205 ng/dl, A/C: 4.2, ratio cortisol AV/ cortisol PV: 45.29. There was no lateralization of the aldosterone/cortisol quotient (ratio A/C right/ A/C left: 2.8), consistent with CT morphologic evidence of bilateral NNR hyperplasia without definite space-occupying lesion.

In synopsis, we found primary hypokalemic hyperaldosteronism with bilateral adrenal hyperplasia. Therapy with spironolactone was started (50 mg/d), potassium substitution could be discontinued and blood pressure normalised.

P1-340

A novel SPINT2 missense mutation (c.386A>G; p.Y129C) causes syndromic congenital sodium loss diarrhea: The first case report in China

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Background: Congenital sodium diarrhea (CSD) is a monogenic disorder caused by specific genetic defects that increase sodium content in the stool, resulting in intractable diarrhea. There are two categories of CSD depending on whether it involves other congenital malformations: non-syndromic congenital sodium loss diarrhea (non-sCSD) and syndromic congenital sodium loss diarrhea (sCSD). For non- sCSD, the identified causative genes include SLC9A3 and GUCY2C, while sCSD is primarily caused by SPINT2 mutations.

Methods: A case of a 7-month-old male with typical diarrhea with fecal sodium and bicarbonate loss who was diagnosed with sCSD and treated in the Second Xiangya Hospital of Central South University in November 2020. Clinical data were collected, including data of genetic sequencing results and clinical manifestations.

Results: Whole-gene exon sequencing revealed a homozygous missense mutation in the 4th exon of the SPINT2 gene in this patient (c.386A>G;p.Y129C), which caused a change in amino acid 129 from Tyr to Cys. We use software simulations of the mutant and wild-type proteins as well as existing knowledge of wild-type SPINT2 and a similar mutant to inform discussion on the consequences of this amino acid change on the structure and function of SPINT2, and how this can manifest clinically as sCSD. We followed the patient until the final outcome, unfortunately, the patient died at the age of 17 months due to severe systemic infection and secondary hemophagocytic syndrome.

Conclusion: Here, we provide evidence for the first time of this novel SPINT2 mutation being involved in the pathogenesis of sCSD as well as the first reported case of sCSD in China. These findings could have implications for genetic counseling for future pregnancies in parents who have children with sCSD.

P1-534

Successful treatment of neonatal Cushing in a paediatric patient with McCune Albright Syndrome (MAS) by using metyrapone suppositories

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We present the case of a now 20 months old female patient, in whom we diagnosed MAS on the basis of pseudoprecocious puberty and hypercorticism at the age of 10 months. Medical history and photodocumentation suggested that symptoms of hypercorticism were present soon after birth. At age 4 months thelarche had occurred, followed by vaginal bleeding at age 5 months. At first presentation at our outpatient clinic, the girl was severely short (-5 SDS), with only minimally advanced bone age, Tanner stages were B3, P3-4. The endocrine evaluation confirmed peripheral ovarian and adrenal over-secretion. Additional findings included hepatopathy, hypertriglyceridemia, hypercholesterinaemia, proteinuria, and secondary arterial hypertension.

In light of the hepatopathy, we decided to start the off-label treatment with metyrapone. Being aware of the challenges of this treatment with the only available product (gelatine capsule containing liquid metyrapone) and reports on local irritation and significant side effects after the oral and intrarectal administration of liquid metyrapone, diluted or undiluted, we decided to go for the rectal application as suppositories. Just one previous case report mentions the unsuccessful attempt of using metyrapone suppositories, without further information on the preparation or dosage.

Our hospital pharmacy developed the preparation technique. The suppositories were characterized in terms of detectable metyrapone content, storage stability, as well as release of metyrapone from the matrix. The storage stability of metyrapone in the dosage form was studied over a period of six weeks at 4°C. Within the first three weeks the drug content varied by ± 3% and, during the whole timeframe, less than 10% was degraded. The release of metyrapone from the suppository was characterized using the flow-through cell, optimized for lipophilic formulations according to the European Pharmacopoeia (type C). A rapid disintegration of the dosage form after 6 minutes was followed by a gradual release and dissolution of metyrapone.

We started with the dose of 300mg/m2/day (one administration every 6h), with the intention to "block and replace", using repeated measurements of serum morning and 23:00 cortisol, salivary cortisol and 24h urine steroid profile. After two weeks, we discharged our patient with normal cortisol levels, without additional hydrocortisone substitution and with a total dose of 900 mg/m2/day. Triglycerides and cholesterol normalised after 8 months, arterial hypertension after 1 month, growth velocity improved progressively.

Conclusion: we present the first successful, long-term use of metyrapone as suppository, with no adverse side effects and striking clinical and biochemical improvement.

P1-535

Case Report: HAX1 Mutation/Kostmann Syndrome: A close cooperation between pediatric endocrinologists and hem-oncologists is crucial!

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Purpose: Clinical problems caused by impaired molecular function of inborn errors of immunity (IEI) genes are not limited to the immunological system but can also affect the endocrine system. An autosomal recessive form of severe congenital neutropenia also known as Kostmann syndrome (KS) is caused by mutations in the gene encoding the mitochondrial protein HAX1. Knowing that most endocrine disorders associated with IEI are hypofunction, a close cooperation between the two specialties hem-oncology and endocrinology is crucial for an early diagnosis, a timely start of supplementation therapy and an appropriate management for favorable long-term outcomes in patients with KS.

Method: Clinical histories, auxology, pubertal development, laboratory and medical imaging findings of two patients with compound-heterozygous HAX1 deficiency (HAX 1 c.130_131insA, p.W44* (het.); c.430dupG, p.V144Gfs*5 (het.)) were evaluated.

Results: We report of two syrian sisters from non-consanguine parents age 13.5 and 14.5 years with KS, hypothyroidism, short stature, delayed puberty as well as premature ovarian insufficiency. LH/FSH-levels were elevated while Estrogen-, InhibinB-, and AMH-levels were low (hypergonadotropic hypogonadism). The TSH-level and thyroid autoantibodies (TPO-Ab, TG-Ab) were increased while the FT4-level was low. The Ovarian tissue-antibodies were negative and via ultrasound no ovaries were detectable. Chromosome analysis was normal 46,XX. Bone age was delayed.

Conclusions: HAX1 is an ubiquitously expressed protein and therefore mutations in the HAX1 gene can have an effect on numerous body functions such as growth, thyroid and gonadal function besides the immunological functions. Since the introduction of recombinant human granulocyte colony-stimulation factor (G-CSF), most patients with KS enjoy a normal life span and a greatly improved quality of life - but short stature and infertility definitely have a major impact on a patient´s quality of life.

So we must be even more vigilant and screen regularly at not too great intervals for dysregulations in the endocrine system to ensure a normal child development. Negative long-term consequences on growth, peak bone mass and reproduction should be

avoided at all means. This case report emphasizes the crucial role of a close cooperation between pediatric hem-oncologists and endocrinologists and it highlights the need for an interdisciplinary approach in patients with KS.

P1-536

A case of septo-optic dysplasia and congenital hypothyroidism in a patient affected by Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome

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Septo-optic dysplasia (SOD) is a rare congenital disorder characterized by a classic triad of optic nerve hypoplasia, agenesis of septum pellucidum and corpus callosum, and hypoplasia of the hypothalamic-pituitary axis. Up to date, a shared consensus is not available and the diagnosis relies mainly on clinical and neuroradiological findings. Even though few genes have been described as responsible for this syndrome, the precise causes of SOD remain unknown and a combination of genetic predisposition and prenatal exposure to environmental factors are believed to play major roles in its occurrence.

Here we report the clinical case of a 2 years old boy affected by SOD associated to psychomotor delay, nystagmus, congenital hypothyroidism, and a growth delay. He was born at term after a pregnancy characterized by a decrease of fetal growth since 32th gestational week. At birth the patient presented with adequate length and head circumference but was small for gestational age for weight. Starting from the first month of life he showed psychomotor delay and nystagmus. The newborn screening resulted slightly positive for congenital hypothyroidism; in consideration of the persistent mild neonatal hyperthyreotropinemia (TSH 10-12 mU/L) with FT4 values within, at 30 days of life levothyroxine therapy was started at dosage of 5.7 µg/kg/day. Brain MRI showed a form of SOD characterized by partial segmental agenesis of the corpus callosum, agenesis of the septum pellucidum, optic nerve hypoplasia and a small pituitary gland with small median pituitary stalk. When he was one year old his weight was -3.72 SD, his length -3.27 SD; blood tests showed undetectable IGF1. In consideration of the growth delay and the neuroradiological findings, therapy with growth hormone was started at dose of 0.15 mg/kg/week. A whole exome analysis detected a novel heterozygous de novo variant c.1069_1070delAG in SON gene, reported as pathogenic and responsible of Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome, a multisystemic neurodevelopmental disorder mainly characterized by intellectual disability, facial dysmorphisms, visual abnormalities, brain malformations, feeding difficulties and growth delay.

Peculiar clinical features, neuroradiological findings, multiple hypotalamic-pituitary alterations might suggest the presence of a complex disorder that could not be easly recognised in the first years of life. As far as we know this is the first case of a form of SOD with hypothyoidism in a patient affected by ZTTK syndrome suggesting a possible relationship between septo-optic dysplasia and SON gene alterations. These patients require a longlasting and multidisciplinary follow-up.

P1-537

A case report of Pituitary Stalk Interruption Syndrome caused by novel compound heterozygous mutations in the KATNIP gene

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Introduction: Pituitary stem interruption syndrome (PSIS) is a congenital anomaly of the pituitary gland characterized by the absence or thinness of the pituitary stalk, an ectopic posterior pituitary gland and a hypoplastic or aplastic anterior pituitary gland. Our case is an example of this rare syndrome.

Case: A 12-month-old male patient was referred to us by pediatric urology for micropenis and undescended testis. He was born 3250 gr as term birth by spontaneous vaginal delivery, had a history of hospitalization in the neonatal intensive care unit for 2 days due to jaundice. In the family history; parents were healthy, there was no consanguineous history, the previous pregnancy of the mother was terminated due to anomaly. Anthropometric measurements; his height, weight, head circumference were 67 cm (SDS:-2.08), 10.2 kg (SDS: 0.65), 45 cm (SDS: -0.37) was respectively. In the physical examination; he had frontal bossing, sparse hair. Testicular volumes were 1/1 ml, stretched penile length was 1,5 cm, other system examinations were normal. Laboratory examinations revealed central hypothyroidism, prolactin deficiency, low IGF-1 and IGFBP3 levels (Table 1).

Table 1. Laboratory findings

Hormonal Tests	Patient results (Reference Ranges)
Thyroxine	**11,14 (11,4-19,4pmol/L)**
TSH	0,96 (0,88-5,42 uIU/ml)
Cortisol	**6,8 (0,54-15,9 µg/dl)**
ACTH	9,8 (<46pg/ml)
Prolactin	**0,82 (3,9-31,45ng/ml)**
IGF-1	**29,7 (0-129 ng/ml SDS (: -2,42)**
IGFBP 3	**0,673mg/L (SDS: -2,08)**

After showing low basal cortisol, ACTH stimulation test was performed with 1 mcg synacthen®. Peak cortisol level was 20.3µg/dl, adrenal insufficiency was excluded. In hCG stimulation test, total testosterone level was 3.28 ng/ml dihydrotestosterone level was 330.81 pg/ml, which was normal. GH stimulation tests with L-dopa and glucagon revealed low basal GH levels and reduced GH response (peak GH of 0,12 ng/ml, 0.55 ng/ml, respectively). Pituitary magnetic resonance imaging was requested from the patient with multiple pituitary hormone disorders. Empty Sella and ectopic neurohypophysis were detected. Genetic analysis was

performed. A new mutation KATNİP (NM_0,15202,5) c1461g>A, KATNİP (NM_0,15202,5) c4035delC compound heterozygote was detected. Since the mutation was compatible with Joubert syndrome in genetic database, the patient was followed up in the pediatric neurology department for neurological involvement. The treatment were initiated for central hypothyroidism, micropenis and GH deficiency with l- thyroxin, androstanolone and somatropin.

Conclusions: In conclusion, in our case we present a rare case of Joubert syndrome caused by a new mutation in the KATNIP gene, which resulted multiple pituitary hormone deficiency without any neurological finding.

P1-538

Capillary hyperglycemia in infants - A manifestation of endocrinological urgency, or not

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Capillary hyperglycemia in critically ill infants is a situation with numerous interfering factors, from acute illnesses to concomitant use of medications and may or may not be a manifestation of endocrinological urgency. Clinical case: Female patient, 2 months old, with failure to thrive, hepatomegaly without cholestasis, polyuria and compensated metabolic acidosis. On admission, capillary blood glucose levels above 200 mg/dL were measured even without concomitant use of corticosteroids or glucose infusion. The Pediatric Endocrinology consultancy was called urgently to evaluate the patient in ICU for suspected neonatal diabetes and insulin therapy decision. Reviewing the case: patient referred to Hospital de Clínicas de Porto Alegre for suspected inborn error of metabolism. She had presented hypoglycemia at the hospital of origin and received intravenous glucose, as well as Dexamethasone and Ganciclovir, which had been discontinued for more than 24 hours after our hospital admission. She persisted with high capillary blood glucose between 200-300 mg/dL and acidosis. The genetic team's diagnostic suspicions were lysosomal or mitochondrial diseases. Laboratory tests were requested to prove hyperglycemia: at the same time capillary blood glucose was 265 mg/dL the plasma glucose was 83 mg/dL and serum and urinary ketones were negative. At this moment it was thought that this capillary hyperglycemia could be due to a cross-reaction with another substance similar to glucose. The literature shows that some glucose monitoring devices may show cross-reactivity between enzymes on the test strip with drugs or with other substances such as galactose, maltose and xylose, which may result in false hyperglycemia. This occurs in glucose monitoring systems using dipsticks based on glucose dehydrogenase pyrroloquinoline quinone or glucose-dye-oxidoreductase methods. Although initial measurements of normal bilirubin and transaminases did not suggest a diagnosis of galactosemia in this patient, total galactose was measured, which was elevated (350 mg/dL).

Conclusion: When facing a case of hyperglycemia, it is always important to confirm with plasma glucose. Remember that capillary blood glucose monitoring systems may cross-react with blood glucose-like substances. The consequence of these possible changes can range from delay in diagnosis of other more complex health conditions to erroneous and unnecessary administration of life-threatening insulin. It is also worth emphasizing that in countries that do not have routine screening for galactosemia in the heel prick test, the diagnosis of galactosemia may be suggested due to factitious hyperglycemia by measuring capillary blood glucose.

P1-539

Rett syndrome patients: Do they need pediatric endocrinologist's care?

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Background: systematic data about endocrinopathies in Rett syndrome (RTT) patients are still scarce and not univocal.

Objective: to assess the prevalence of endocrinopathies in a pediatric population of RTT patients.

Design: retrospective observational single center study.

Methods: 29 caucasian patients (28 girls,1 boy) with genetically confirmed diagnosis of RTT were enrolled (mean age:13.2±5.4 years, range:3.3-18 years). The patients were referred from the Rett Center of our Hospital for endocrinological evaluation. All the patients underwent clinical assessment (height, weight, BMI, pubertal staging) and hormonal workup. Thyroid ultrasonography (US) was routinely performed. Pelvic US and bone densitometry (DEXA) were performed in postpubertal girls. Midline defects were excluded by brain MRI.

Results: 27 patients (93.1%) presented MeCP2 deletions, with R255X and R306C being the most prevalent. Only 2 patients exhibited less common genotypes, respectively CDKL5 and FOXG1 deletions. Overall, 24 patients were treated with anticonvulsant drugs.

- Short stature: 16 patients (55.2%) had a height <-2 standard deviation score SDs (median -2.88 SDs, range:--2.0/-4.33) and below target height. Of these, 6 girls also had BMI<-2 SDs and 5 had thyroid dysfunction. Celiac disease and GH deficit were excluded.
- Malnutrition: 10 patients (34.5%) had severe underweight (median BMI -3.15 SDs, range: -2.5/-8.2SDs), in absence of other chronic diseases.
- Obesity: 6 patients (20.7%) had BMI>2 SDs (median BMI +2.39 SDs, range: +2/+2.5 SDs), 2 of them with basal hyperinsulinemia.
- Gonadal function: among the 19 post-pubertal girls, 4 had a history of precocious puberty and one premature isolated pubarche. 9/19 (47.4%) patients claimed menstrual cycle abnormalities (secondary amenorrhea and oligomenorrhea); all of them had body weight alteration (5 were overweight and 4 underweight).

- Thyroid abnormalities (5 patients,17.2%): central hypothyroidism (1 patient), subclinical hypothyroidism (1 patient), Hashimoto's thyroiditis in euthyroidism (1 patient), and thyroid nodules (2 patients).
- Hyperprolactinemia: 6 patients (20.7%) exhibited high prolactin blood levels, with occurrence of galactorrhea in one case, during anticonvulsant therapy.
- Bone health: 9 patients (31%) had vitamin D deficiency. DEXA highlighted osteopenia in 4 patients and osteoporosis in 5 patients (one of them requiring biphosfonate).

None of the genotypes of our patients was significantly associated to a specific endocrine phenotype.

Conclusions: in our RTT pediatric population, short stature was the most frequent endocrinological report, followed by poor weight gain and menstrual cycle abnormalities.

Bone health concerns are relevant in RTT, for both motor impairment and skeletal abnormalities.

In the context of a multidisciplinary approach, endocrinological evaluation should be recommended in RTT patients.

P1-540

Screening for hypoparathyroidism in beta thalassemia major: About a series from Constantine

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Introduction: Endocrine complications observed in patients with thalassemia major (TM) are mainly secondary to martial overload. Hypoparathyroidism (HPT) is a late and rare complication, typical of the 2nd decade of life in transfusion-dependent thalassemia patients (TDT). It is usually associated with other iron overload conditions (diabetes, hypogonadism, heart failure, etc.). The incidence of PTH varies from 1.2% to 20% depending on the center. Men are more frequently affected than women (male/female ratio = 1.35).

Patients and Methods: Prospective descriptive study conducted at the endocrinology department of the CHU of Constantine over two years concerning polytransfused BTM patients. All our patients underwent a clinical examination, a hormonal assessment (somatotropic, gonadotropic and thyrotropic function) and a haematological evaluation. A phosphocalcic assessment was performed by measuring corrected serum calcium, phosphorus and PTH levels as well as vitamin D.

Results: A total of sixty-four patients were enrolled in the present study; hypoparathyroidism was found in 12 patients (18.75%), the mean age was 21.66 years, male predominance was not present in our series as we have more affected women than men (8 women and 4 men), the male to female ratio was 4:8. The most common endocrinopathy associated with hypoparathyroidism was hypogonadotrophic hypogonadism, followed by growth retardation in our patients.

Discussion: PTH is the consequence of iron deposition in the parathyroid glands and resulting tissue fibrosis or suppression of parathyroid secretion induced by bone reabsorption resulting from increased haematopoiesis secondary to chronic anaemia.

PTH is asymptomatic in most beta thalassaemics, but may be diagnosed on the occasion of symptomatic hypocalcaemia contrasting with normal or low PTH levels, sometimes with a relatively severe clinical picture involving tetany and convulsions. Recently, brain CT abnormalities (calcifications) have been reported in TM patients in relation to hypoparathyroidism.

The high frequency of PTH in our patients may be partly related to poor compliance with chelation therapy in line with what has been reported in the literature.

Vitamin-calcium treatment was started in all our patients with hypoparathyroidism.

Conclusion: Iron overload remains a real problem, even in countries where iron chelation therapy is widely available and properly monitored. Early detection of endocrine complications is mandatory to improve morbidity and quality of life of these patients. Since asymptomatic hypocalcaemia is common in these TM patients, it is wise to recall the importance of checking the phospho-calcium balance from the second decade of life in TM patients.

P1-541

Severe Systemic Pseudohypoaldosteronism Type 1: 10 years of evolution

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Background: Type 1 pseudohypoaldosteronism (PHA1) is a rare syndrome characterized by unresponsiveness to aldosterone. Diagnosis is established by high levels of aldosterone and plasma renin activity, associated with findings of hypoaldosteronism (hyponatremia, hyperkalemia and metabolic acidosis). When the inheritance pattern is autosomal recessive it expresses as a severe systemic disease and the mortality rate is high, especially in the neonatal period.

Case Report: Male child with irrelevant gestational history. He had one sister with Chediak-Higashi syndrome but no parental consanguinity was found. Systemic PHA1 due to homozygous mutation in intron 3 of the SCNN1A gene was diagnosed in the neonatal period (severe hyperkalemia, hyponatremia, dehydration and acidosis). After numerous life-threatening crises he was discharged at five months-old under fludrocortisone, sodium supplement 33mEq/kg/day and cation-exchange resin. Until 2-years-old, medication was administered by nasogastric tube. He always maintained tight control of electrolyte balance and therapeutics but he was admitted several times in the emergency room with hypovolemic shock, requiring intensive treatment, and frequently nebulizer salbutamol and calcium gluconate. These incidents became less severe and less frequent with increasing age. Fludrocortisone and cation-exchange resin were stopped at 3-years-old. Hydrochlorothiazide was started from 18-months-old until 4-years-old. Sodium supplement ranged from 28-55mEq/kg/day. At 18-months-old, he had a tonic-clonic seizure in apirexy and after that six simple febrile seizures occurred (the last at 6

years-old). Electroencephalogram and brain magnetic resonance were normal. The child had an atopic dermatitis-like rash that worsened in hot environments, but has not occurred since 5-years-old. During follow-up, transient asymptomatic hypoglycemia and subclinical transient hypothyroidism were diagnosed. ACTH, cortisol, C-peptide, insulin, IGF-1 and ACTH stimulation-test were normal and there was no need for treatment. He underwent adenoidectomy and tonsillectomy for snoring and repeated upper respiratory tract infections, at 6-years-old. He was under a development stimulation program and actually, he is attending the 5th year of school with reasonable performance. WISC-III at 6-years-old, showed a lower IQ (75) and reassessment at 10-years-old showed similar results (72). He thrived very poorly during the first two years, and actually at 10-years-old, he maintains failure to thrive (height -2.2SDS, weight -0.9SDS) but regular growth velocity. He is prepubertal and his only medication is sodium supplementation (26mEq/kg/day).

Conclusion: Management of PHA-1 patients is challenging since there are no evidence-based recommendations and the long-term prognosis remains unclear. A multidisciplinary approach and rigorous follow-up are essential to have a controlled disease and an adequate growth and development.

Pituitary, Neuroendocrinology and Puberty

P1-143

Use of the 100,000 Genomes Project to identify the molecular basis of rare endocrine disorders within a tertiary paediatric endocrinology centre

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Introduction: The UK 100,000 Genomes Project (100KGP) recently investigated the genetic basis of rare disease using whole genome sequencing. The genetic aetiology of most rare paediatric endocrine disease remains unexplained.

Methods: Children with genetically unexplained rare endocrine disease attending a subspecialist paediatric endocrinology clinic underwent whole genome sequencing as part of the 100KGP. Parental DNA was obtained where possible. Virtual gene panels were applied and bioinformatic analysis used to filter and prioritise variants. Variant pathogenicity was classified using ACMG guidelines, and relevance to clinical phenotype assessed at multidisciplinary (endocrine and genetic) meetings.

Results: A total of 177 children were recruited (58.8% male (n=104); 66.7% trios (n=30), 17.8% duos (n=8), 15.5% individuals (n=7)). Diagnoses included septo-optic dysplasia (32.2%, n=57), congenital hypopituitarism (26.5%, n=47), short stature (11.9%, n=21), isolated growth hormone deficiency (16.4%, n=29), hypogonadotropic hypogonadism (4.0%, n=7) and other rare endocrine conditions (9.0%, n=16). Multiple pituitary hormone deficiencies were present in 50.8% (n=90). Of the 82.2% (n=149) children with pituitary imaging, most had structurally abnormal pituitary glands (85.9%, n=128).

A genetic diagnosis was obtained in 25.6% (n=45) of children. Within this group, heterozygote variants were detected in 66.6% (n=30) in several genes (*ACTB, ACAN, ARID1B, EP300, PTPN11, SIX3, TBL1X41, ADNP, KRAS, PTCHD1, GRIN2A, SMC3, DEPDC5, GLI2, IGF1R, NPR2, NF1, N2RF1, CLCN7, DPF2, EFNB1, FGFR1, FGFR3, TGIF1, ZNF148*). These were confirmed de novo in 23.3% (n=7). Homozygous or compound heterozygote variants were found in 31.1% (n=14) within *AIRE, PKHD1, TYR, CHD7, DHTKD1, CEP57, BBS1, CPS1, GHRHR, TBC1D32,* and *CLPP*. One patient had variants detected in both *GLI2* and *LHX4*. Diagnoses were associated with extra-endocrine features in 44.4% (n=20).

There were fewer genetic diagnoses in children with septo-optic dysplasia compared to those with other pituitary conditions (15.8% versus 30.3%, p=0.042). There were more genetic diagnoses in children with developmental delay (35.9% versus 19.5%, p=0.016) and other extra-endocrine features (34.8% versus 8.1%, p=<0.001) compared to those without. There were no significant associations between obtaining a genetic diagnosis and patient gender, pituitary gland structure, or number of pituitary hormone abnormalities.

Conclusion: A genetic diagnosis was achieved in a significant proportion of children recruited to the 100KGP. This knowledge empowers families and demonstrates the value of integrating next generation sequencing approaches into standard clinical care. Several genetic diagnoses identified influenced clinical management. Expanding this analysis to include other coding and non-coding regions may yield further diagnoses.

P1-144

Precocious puberty and other pubertal disorders in females during the Italian lockdown and the coronavirus 2019 (COVID-19) pandemic

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Background: At present few data have clearly showed an increased frequency of idiopathic central precocious puberty (CPP) in females during the COVID-19 pandemic. The role of environmental factors is not fully understood and various hypotheses have been formulated.

Aims of the Study: To evaluate retrospectively the incidence of newly diagnosed CPP and other pubertal disorders (premature thelarche, early puberty, fast puberty and precocious menarche) in two regions of Italy (Tuscany and Emilia–Romagna) during and after the lockdown for COVID-19.

Patients and Methods: The study included 440 females evaluated for pubertal disorders into the Centres of Florence, Parma, Reggio Emilia and Modena between the 1 January 2020 into the 31 December 2021. Subjects with endocrine or chronic diseases were excluded. Monthly incidence rates and clinical features were compared with a control group of patients evaluated for the same problems into 2019.

Results: Our data confirmed a higher frequency of CPP in females (261 patients, mean age 7.6 ± 0.6 years, without significant differences between the diagnoses carried out in 2020 and 2021) compared to 2019 (52 cases, mean age 7.5 ± 0.7 years, $p < 0.0001$). Interestingly, CPP cases were significantly higher also in the first two months of 2020, so before the start of Italian lockdown and just before the Sars-COV-2 pandemic was declared (21 cases vs. 7 in the same period of 2019; $p < 0.0001$). Our preliminar data seem also to suggest an increased frequency of the diagnoses of premature thelarche (54 patients in 2021 and 31 patients in 2020 vs 21 patients in 2019, respectively $p < 0.0001$ and < 0.05; between 2020 and 2021: $p < 0.0001$), early puberty (31 patients in 2021 and 25 patients in 2020 vs 16 patients in 2019, respectively $p < 0.0001$ and $p < 0.05$), fast puberty (20 patients in 2020 vs 5 patients in 2019 and 2021; respectively, $p < 0.0001$) and precocious menarche (9 patients in 2021 vs 3 patients in 2019 and 4 patients in 2020; $p < 0.0001$).

Conclusion: Our data, on the one hand, confirm an increase in the frequency of new cases of CPP during and after the lockdown for COVID-19 pandemic, but also show an increase, albeit differently distributed in these 2 years of epidemic, in other pubertal development disorders. Interestingly, this could delineate different factors involved in the genesis of these disorders. Further studies and insights appear necessary to better explain these aspects.

P1-145

Spatial navigation and memory in transgender male adolescents treated with gender affirming hormones

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Background: Spatial navigation is an essential human skill that helps individuals track their changes in position and orientation by integrating self-motion cues. Meta-analyses indicate that males, on average, perform better than females on a number of spatial tasks. Sex steroids, mainly androgens, modulate the remodeling of synapses in the prefrontal cortex and hippocampus, a limbic brain area with critical influence on spatial and contextual memory. Androgen-induced plasticity might be more pronounced during peri-adolescence to young adulthood when the executive network is under rapid development. In both males and females, testosterone levels have been associated with spatial ability. Transgender males receiving testosterone have been reported to have enhanced performance on visual memory, mental rotation and 3D spatial memory tasks. To date, performance on the virtual Morris Water Task, examining spatial navigation and memory, has not been examined in transgender male adolescents.

Objective: To examine spatial navigation and memory in transgender male adolescents receiving gender-affirming testosterone treatment compared to cisgender male and cisgender female adolescent controls.

Methods: Cross-sectional, single-center study from the Israeli Pediatric Gender Clinic. Spatial navigation was assessed using the Virtual Morris Water Maze Task in 28 transgender male adolescents receiving gender-affirming testosterone treatment, 26 cisgender male and 30 cisgender female adolescents. Participants were asked to find a hidden platform while navigating in a virtual water tank according to spatial cues located on the surrounding walls (4 blocks of 4 repeated attempts each). Data extracted from medical records included LH, FSH, estradiol and testosterone blood levels, and testosterone and Gonadotropin releasing hormone analogs (GnRHa) duration of treatment. Outcome measures: latency and path length to hidden platform.

Results: Transgender male adolescents (mean age 17.1±1.7 years) were treated with GnRHa and testosterone (mean duration of 17.9±11.2 and 19.4±14.8 months, respectively). Mean peak testosterone blood levels were 24.3±8.1 nmol/L. Transgender males

and cisgender males performed significantly faster than cisgender females (p = 0.022), with a shorter path length in the first block of the task (p = 0.020). Correlations were not found between peak testosterone blood levels or duration of treatment and task performance.

Conclusion: Transgender male adolescents, receiving gender-affirming testosterone treatment, demonstrate spatial memory and learning that is comparable to cisgender males and enhanced compared to cisgender females. Further longitudinal research on the impact of gender-affirming hormonal treatment on cognitive functions is required, especially in peri-adolescence.

P1-146

Spectrum of Endocrinopathy in Children with Ectopic Posterior Pituitary (EPP)

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Introduction: Ectopic posterior pituitary (EPP) is a radiological diagnosis likely caused by a migration defect that occurs during pituitary development. We aim to describe the clinical characteristics and hormonal deficiencies seen in patients with EPP.

Method: Longitudinal observational study performed in a single [HK1] [NM2] centre from 1993-2020. As per MRI findings, cases were divided into three cohorts 1) C1: EPP only [n=8 (9%)] 2) C2: EPP + PSIS (Pituitary Stalk interruption Syndrome) [n=44 (49.4%)] and 3) C3: EPP + Cortical abnormalities (CA) [n=37 (41.6%)].

Results: 89 patients were identified with EPP (55 male (61.8%)). The median duration of follow up was 9.85 years (IQR 3.96).

Table 1. Characteristics of Cohort

	C1	C2	C3
Median Age at presentation (in years)	2.73	2.36	1.2
Symptoms at presentation			
Short Stature	4 (50%)	19 (43.2%)	7 (18.9%)
Hypoglycaemia	2 (25%)	21 (46.7%)	22 (48.9%)
Incidental MRI finding	2 (25%)	4 (9%)	0
Ophthalmology Referral	0	0	8 (21.6%)

Table 2. Spectrum of Endocrinopathies

	C1	C2	C3	p- value
Isolated GHD	5 (62.5%)	8 (18.2%)	5 (13.5%)	0.009
GHD+ACTHD+ TSHD	0	30 (68.2%)	29 (78.4%)	<0.005
GHD+ACTHD	0	2 (4.5%)	1 (2.7%)	1.00
GHD+TSHD	1(12.5%)	3 (6.8%)	1 (2.7%)	0.489
ACTHD+TSHD	0	1 (2.3%)	0	
Isolated TSHD	0	0	1 (2.7%)	
Hypogonadotropic Hypogonadism	0	20 (45%)	12 (32.4%)	0.04
Age of GHD (mean ± SD)	6.02± 3.40	3.68 ± 3.12	2.96 ± 3.06	
Age of ACTHD (mean ± SD)	0	3.26 ± 4.53	1.68 ± 2.64	
Age of TSHD (mean ± SD)	3.86	3.29 ± 4.05	1.97 ± 2.84	
No hormone deficiency	2 (25%)	0	0	

GHD: growth hormone deficiency
ACTHD: Adrenocorticotrophic hormone deficiency
TSHD: Thyroid stimulating hormone deficiency

GHD was the single most frequent endocrinopathy across all cohorts (n=83, 93.2%). C2 and C3 both had evidence of MPHD with 72.8% within these groups having GHD, ACTHD and TSHD. ACTHD was the earliest endocrinopathy to present at 1.68 years in C3 and 3.26 years in C2. This was followed by TSHD which presented at 1.97 years in C3 and 3.29 years in C2. GHD developed before 5 years in C2 and C3 and after 5 years in C1.

Discussion and Conclusion: The presence of other abnormalities in addition to EPP were associated with progression to multiple pituitary hormone deficiency (MPHD). EPP with normal pituitary stalk and no CA is a strong predictor for isolated GHD rather than MPHD.

P1-147

Prevalence of polycystic ovarian syndrome (PCOS) in girls with history of idiopathic central precocious puberty (ICPP)

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Introduction: The prevalence of PCOS in adolescents and young women was established at 4.3%. Whether women with a history of ICPP are at increased risk for PCOS is still controversial.

There is no clear evidence that ICPP girls treated with GnRH analogues (GnRHa) are more likely to develop PCOS than their age-matched peers.

Objectives: To assess the prevalence of PCOS in adolescents with a history of ICPP and further compared the prevalence with ICPP girls who have not received GnRHa treatment.

Materials and Methods: A retrospective cohort study was performed. PATIENTS: 142 post-menarche girls with a history of ICPP diagnosed between 2000 and 2012 from the outpatient Endocrine Division. Girls were evaluated at gynaecological age (GA) ≥ 2.5 years. Patients with incomplete clinical reports were excluded (n=48). Data collected included: age at menarche, menstrual cycle characteristics, body mass index (BMI), and clinical signs of hyperandrogenism (HA): hirsutism (Ferriman-Gallwey score >8) and severe acne. Serum total and free testosterone levels were determined. PCOS diagnosis was defined by criteria for the adolescent population: > 2.5 years of GA with cycle disorder, clinical and biochemical hyperandrogenism. Other endocrine disorders were excluded. After the whole cohort analysis, patients were analyzed with respect to whether or not they received GnRHa treatment. STATISTICS: Data are expressed as mean ± standard deviation (SD). Mann-Whitney U-test and Fisher´s exact test were used accordingly.

Results: Mean ± SD chronological age (n=94) was 15.6± 1.9 years, and 63 were treated with GnRHa. The mean BMI was 23.6±3.8. Menstrual disorders were found in 27/94 girls (28.7 %). Clinical HA was present in 34/94 (36%). Biochemical HA was found in 22/94 (23.4%). Eleven out of 94 patients (11.7%) met the diagnosis criteria for PCOS. There were no differences in BMI or in the frequency of menstrual dysfunction, clinical hyperandrogenism or hyperandrogenemia between treated and untreated patients. The relative risk (RR) of developing PCOS was 2.5 (95 % CI 1.25-5.24) in our cohort with a history of ICPP compared to a historic population of healthy adolescents. The RR was not higher between the group of patients who received treatment with GnRHa and those who did not.

Conclusion: Adolescent girls with a history of ICPP have an increased risk of PCOS. This risk seems not to be related to GnRHa treatment.

P1-148

Usefulness of Next Generation Sequencing in the Molecular Diagnosis of McCune-Albright Syndrome in Peripheral Blood

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Introduction: McCune-Albright Syndrome (MAS) is a rare congenital disorder caused by post-zygotic activating mutations in GNAS gene. Due to the mosaic pattern of this disease, mutation abundance is frequently low in several tissues, including blood cells. The emergence of next-generation sequencing (NGS) methodologies has allowed the analysis of millions of DNA fragments simultaneously and independently, enabling detection of low mutation abundance.

Aim: To establish the molecular diagnosis of patients with MAS using NGS analysis.

Methods: We selected 18 patients (13 girls and 5 boys) with at least 2 out of 3 classic clinical features of MAS. Of them, 14 and 17 patients had café au lait skin spots and fibrous dysplasia, respectively. All girls presented peripheral precocious puberty. In addition, hyperthyroidism and acromegaly were identified in 5 (2 girls e 3 boys) and 3 (all boys) patients, respectively. DNA was extracted from peripheral blood and analyzed through a targeted gene panel for endocrinopathies by NGS (Agilent SureSelect XT). DNA samples were prepared and pair-end sequenced on the Illumina NextSeq 500 platform (High Output - 300Cycles). The sequences were aligned using GTKA program. Using the Integrative Genomics Viewer (IGV) program, BAM files were visually analyzed for genomic regions 20:57484420-57484421 and 20:57484595-57484597 (GRCh37/hg19), where GNAS mutations associated with MAS are located. Allelic variants represented for 6 or more independent reads with no strand bias were considered as a positive result after 35 negative controls analyzes.

Results: The mean read depth per sample for two codons (201 and 227) was 269 (range 180-317) and 499 (range 363-686), respectively. Conventional base calling programs (Freebayes) using protocols for analysis of germline variants did not detect variants in GNAS associated with MAS. The visual analysis in IGV revealed GNAS mutations in 7 of 18 (38.8%) patients. The p.R201C and

p.R201H mutations were identified in 4 and 3 patients, respectively. The allele mutation abundance ranged from 2.8% to 19%. Inconclusive molecular results were obtained in 5 patients due to low reads (≤ 5) and/or strand bias: p.R201H (≤5 reads), p.G227H (strand bias), and p.G227R (3 reads and strand bias). Conclusion: NGS represents a more sensitive tool for identifying GNAS mutations in peripheral blood, even with low abundance, in patients with MAS, with the advantage of analyzing multiple positions.

P1-149

Validation of Puberty Interpreter, a mobile application-based evaluation of pubertal disorders

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Background: Assessment of pubertal disorders is challenging for the pediatricians causing unnecessary evaluation on one hand while missing pathology on the other. The paucity of pediatric endocrine centers further adds to the problem in resource poor settings. We have developed puberty interpreter, a mobile application that provides instantaneous guidance regarding diagnosis and management of children and adolescents with concern for pubertal disorders based on the input of age, tanner staging (breast, pubic hair, and menarchal status in girls; testicular volume and pubic hair status in boys), and growth parameters (height and height SDS for bone age).

Aim: To evaluate the predictive accuracy of puberty interpreter in children and adolescents with concerns of early or delayed puberty.

Methods: The study involved the development and validation of the mobile application. The diagnostic algorithm was based on published protocols for evaluating pubertal disorders using clinical data (height, age, pubertal status, and bone age). The algorithms were then uploaded to our Mobile application. The guidance provided by the application was compared to clinical diagnosis in 408 children (126 boys) presenting with concern for pubertal disorders (247 with early and 161 with delayed puberty).

Results: The application guidance was concordant with clinical diagnosis in 401 (98.3%) cases. Discordance with clinical diagnosis included an erroneous diagnosis of central cause in a boy with CAH with triggered puberty and the labelling of three girls with central cause as peripheral. In subjects with delayed puberty the application guidance included an inaccurate diagnosis of obstructive cause in a girl with acquired hypogonadism, CDGP in a girl with hypopituitarism and Complete androgen insensitivity syndrome in a girl with systemic disease.

Conclusion: Puberty Interpreter based guidance for the assessment of pubertal disorders is expected to allow a rational point of care evaluation in the community.

P1-150

Pubertal dysfunctions in intracranial germ cell tumours

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Introduction: Paediatric intracranial germ cell tumours (IC-GCTs) are often accompanied by precocious or delayed puberty, either at diagnosis caused by tumour itself or during follow-up as consequence of treatments.

Aims: We examined the prevalence of pubertal dysfunctions in a cohort of paediatric patients with IC-GCTs at diagnosis and during follow-up.

Methods: We recorded clinical, radiological, histopathological, and hormonal data. Pubertal dysfunctions were diagnosed clinically and confirmed biochemically and classified as: 1) pseudo-precocious puberty (PPP) (gonadotrophin-independent); 2) central precocious puberty (CPP) (gonadotrophin-dependent); 3) hypogonadotrophic hypogonadism (HH).

Results: Twenty-five of 52 patients (56% males) with IC-GCT treated at Royal Marsden Hospital between January 1996 and December 2019 displayed a pubertal disorder (median follow-up 75.7 months, range 0.5-249.9 months). 68% had germinomas, 16% teratomas, 16% mixed GCT. IC-GCTs were suprasellar (64%), pineal (24%) or bifocal (12%). Patients underwent biopsy (72%), surgery (24%), chemotherapy (80%) and radiotherapy (100%).

Low gonadotrophin levels were found in 20 cases (10 females, 10 males), along with clinical evidence of either arrested or delayed puberty, at a mean age of 17.5 years for males and 15.1 for females. This condition was already present before tumour diagnosis in 2 patients. One female patient with suprasellar germinoma manifested secondary amenorrhoea, probably due to hypothalamic dysfunction and concomitant polycystic ovarian syndrome; combined oral hormonal replacement therapy was started with benefit. PPP was evident in 3 patients at diagnosis: in one case it reverted spontaneously accordingly with tumour cure and concomitant reduction of HCG levels; one patient subsequently developed CPP and received therapy with an agonist analogue of gonadotropin-releasing hormone for 5 years; one more subject was initially treated with bicalutamide and anastrozole for 14 months and then with triptorelin after he developed CPP. Finally, one subject manifested CPP 3.7 months after the completion of oncologic therapies and received treatment with triptorelin. No cases of hypergonadotrophic hypogonadism due to chemotherapy-related gonadal toxicity were reported in our cohort.

Conclusion: Patients with IC-GCTs are at risk of pubertal dysfunctions, especially suprasellar germinomas. Associated pubertal disorders can be heterogeneous, from HCG-driven PPP to CPP or HH, and may change over time, therefore specialist follow-up is required.

P1-151

The effect of a GnRH analogue injection on the circulating levels of kisspeptin-1 in girls with suspected central precocious puberty

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Introduction: Kisspeptin stimulates the gonadotropin releasing hormone (GnRH) neurons in hypothalamus initiating puberty. However, it is not known whether GnRH inhibits kisspeptin secretion by negative feedback and whether there are any associations between circulating levels of kisspeptin and other hormones, like ghrelin, important for the onset of puberty.

Methods: Thirteen girls with suspected central precocious puberty performed an adjusted GnRH stimulation test twice, placebo-controlled in a randomized order, at Örebro or Uppsala University Hospital, Sweden. Blood was sampled 0, 30, 60, 90, 120 and 150 min after the iv injection of either Relefact LHRH® or saline. The protease inhibitor 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF) was added to the sampling tubes to a final concentration of 2 mg/ml. An ELISA kit from LifeSpan BioSciences, Inc. (No LS-F8231) was used for the analyses of Kisspeptin-1 levels. The levels of acylated ghrelin were analyzed with Millipore® Human Ghrelin (Active) ELISA kit (#EZGRA-88K). Serum ultra-sensitive estradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), insulin and glucose levels were analyzed using the usual clinical methods.

Results: The median Kisspeptin-1 level at baseline was 39 pg/ml (min–max: 0.1–221.3 pg/ml). The area-under-the curve for Kisspeptin-1 levels was not significantly lower after the GnRH injection as compared to the placebo injection. We did not find any significant correlations between the levels of kisspeptin-1 and acylated ghrelin, estradiol, LH, FSH, or insulin. However, we could see a positive correlation between kisspeptin-1 and glucose levels at baseline (Spearman's rank test, rho = 0.63, p=0.021).

Discussion: We did not find evidence of a negative feedback mechanism between GnRH and kisspeptin in girls with suspected central precocious puberty since the circulating levels of kisspeptin-1 were unaffected by an intravenous injection of a GnRH analogue. However, paracrine actions in the hypothalamus cannot be ruled out by this study. The positive correlation found between kisspeptin-1 and glucose levels is in accordance with previous findings in both adults and children, suggesting a possible role for kisspeptin signaling in glucose metabolism.

P1-152

COVID-19 and precocious puberty: Does BMI play a role?

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Background: Since COVID-19 the number of girls referred to pediatric endocrinologist for suspected precocious puberty (PP) and early puberty (EP) has increased. The aim of the study was to evaluate the incidence, the anthropometric, biochemical and radiological characteristics of PP during the COVID-19 pandemic, compared to previous years.

Methods: We retrospectively evaluated medical records of 464 females (F) referred to academic pediatric endocrinology center for suspected PP/EP from January 2016 to June 2021 (Group1: January 2016-March 2020, n=295; Group2: March 2020-June 2021, n=169). At first visit (V1) 289F had Idiopathic CPP (Group1 n=175; Group2 n=114) of which n=89 met the Rapidly Progressive Idiopathic CPP criteria (RP-ICPP; Group1 n=45; Group2 n=44) and n=200 for Slowly Progressive Idiopathic CPP (SP-ICPP; Group1 n=130; Group2 n=70). Additional n=44 of the SP-ICPP met the RP-ICPP criteria (Group1 n=27; Group2 n=17) at a second assessment (V2). Girls were classified by age at diagnosis (<6; 6-6.99; 7-7.99; >8 years). The total number of RP-ICPP was 133 (n=27 no-caucasians).

Results: We found a higher incidence of RP-ICPP in Group 2 compared to Group1 (36% vs 24%, p<0.05, respectively); comparing the annual RP-ICPP incidences, 2021 showed the highest (p<0.05). RP-ICPP in Group1 and Group2 differed in age at diagnosis (7.96±0.71 vs 7.61±0.94; p<0.05) and in the time interval between thelarche and diagnosis (0.93±0.75 vs 0.74±0.64 yrs, p=0.05). We found a progressive increase in the number of girls Group2 in each age group<8 years (<6 years n=4 vs n=2; 6-6,99 years n=7 vs n=4; 7-7,99 years n=34 vs n=20), and a significant inverted proportion in girls >8 years (n=41 Group1 vs n=21 Group2, p<0.05). There were no differences between Group1 and Group2 for any anthropometric, biochemical and radiological parameters analyzed, except for blood glucose and cholesterol HDL levels (both highest in Group2 (p<0.05)). These data were confirmed in the total group and only in caucasian girls. By regression analyses we found that age at diagnosis was anticipated in Group2, regardless of BMI SDS. Analyzing the subgroup of patients with V2, BMI SDS V2-V1 was not different (-0.12±0.5 in Group1 vs 0.11±0.44 in Group2, p=0.17).

Conclusions: During the Covid-19 pandemic the number of girls with suspected PP/EP resulted 1.79 fold increased, with a 1.5 time higher incidence of RC-ICPP. BMI doesn't seem to play a role, but further studies are needed to understand the etiology and primarily the role of metabolic parameters.

P1-153

Urinary gonadotrophins as markers of puberty in girls and boys during late childhood and adolescence: Evidence from the SCAMP Cohort

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Introduction: Urinary gonadotrophins measurement is a non-invasive method for evaluation of pubertal development and may have utility in population studies.

Objectives: To investigate the utility of urinary gonadotrophins as a noninvasive biomarker of puberty in boys and girls.

Methods: School-based adolescent cohort study with two time points for collecting school time urine samples and self-reported assessment of puberty through the Pubertal Development Scale (PDS) approximately two years apart. FSH and LH were measured by immunoassay and corrected for creatinine excretion.

Results: A total of 941 samples from 741 girls and 1,198 samples from 899 boys aged between 11-16 years were analyzed. Samples were mainly collected at a median age of 12.3 yrs (range11.1,13.2) and 14.2 yrs (13.4,15.7); uFSH:Cr ratio showed median annual change of -0.101 IU/mmoL (95%[-0.143,-0.038]) for girls and -0.124 IU/mmoL (95%[-0.156,-0.090]) for boys; uLH:Cr ratio showed an annual change of +0.013 IU/mmoL (95%[0.004,0.020]) and +0.017 IU/mmoL (95%[0.012,0.021]) in girls and boys, respectively. The annual change for uLH:FSH ratio was +0.028 (95%[0.021,0.035]) and +0.035 (95%[0.027,0.043]) in girls and boys, respectively. Correlation coefficients between uFSH:Cr, uLH:Cr and uLH:FSH ratio with age in girls were r=-0.075, r=0.106 and r=0.148, respectively. In boys, correlation coefficients between uFSH:Cr, uLH:Cr and uLH:FSH ratio with age were r=-0.113, r=0.163 and r=0.287, respectively. In subgroup analysis of 59 samples from girls and 233 samples from boys, collected within 90 days of PDS, were analyzed for correlations with self-reported pubertal development. In girls, uFSH:Cr ratio showed negative correlation with self-report breast development (r=-0.52), composite PDS score (r=-0.53) and PDS-derived pubertal categories (r=-0.50); uLH:FSH ratio showed positive correlations with self-report breast development (r=0.29), self-report menarchal status(r=0.35), composite PDS score (r=0.39) and PDS-derived pubertal categories (r=0.45) and uLH:Cr ratio revealed negligible correlations. In boys, all three parameters revealed negligible correlations with self-reported pubertal development, PDS composite score and PDS-derived pubertal categories. In girls, ROC curve analysis showed that uLH:FSH ratio of 0.071 provided sensitivity of 80% and specificity of 65% to predict post-menarcheal status on PDS self-report.

Conclusions: In girls aged 11-16 years, increase in urinary LH:FSH ratio is associated with increase in self-report pubertal development and urinary LH:FSH ratio represents a valid non-invasive biomarker of puberty in population studies. Associations between urinary gonadotrophins and self-reported pubertal development in boys are negligible.

P1-154

Reference values in pelvic ultrasonography for a Spanish population of healthy girls between 6 and 12 years old

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Background: Pelvic ultrasonography (PUS) of the uterus and ovaries allows the diagnosis of changes in sexual development. However, the reference values used in Spain originate from old studies conducted in other countries.

Objective: To determine reference uterine and ovarian measurements by PUS and according to pubertal status and bone age in a Spanish population of healthy girls aged between 6 and 12 years.

Materials and Methods: Descriptive cross-sectional study performed on 221 healthy girls from 2017 to 2019. Ovarian and uterine measurements were described and associated with chronological age, bone age, and Tanner stage. ROC curves were used to assess the predictive value of tests for Tanner stage II.

Results: We described reference values for all PUS uterine and ovarian measurements assessed. Subjects in Tanner II (thelarche) had a mean age of 9.7 years (SD = 1.1). Fundal–cervical ratio changed from 1:1 to 2:1 at 12 years of chronological age (62.5% with 1:1 ratio; $p < 0.0001$) and 13 years of bone age (2:1 in 85.71%, $p < 0.0001$). Mean uterine length for Tanner II was 4.065 cm (SD = 0.736); mean ovarian volume was 2.466 cm3 (SD = 1.719). Bone age, ovarian volume, and uterine length were good predictors of Tanner stage II.

Conclusion: This is the first study providing reference uterine and ovarian PUS values in a Spanish population of healthy girls aged 6 to 12 years. Use of updated data characteristic of a specific population increases the diagnostic accuracy.

Breast development		Tanner I N = 108	Tanner II N = 55	Tanner III N = 44	Tanner IV N = 13
Uterine length (cm)	Mean ± SD	3.475 (0.416)	4.065 (0.736)	5.594 (1.037)	6.934 (0.931)
Anteroposterior diameter of the Fundus (cm)	Mean ± SD	0.610 (0.166)	0.865 (0.750)	1.866 (0.746)	2.683 (0.522)
Anteroposterior diameter of the cervix (cm)	Mean ± SD	0.572 (0.135)	0.717 (0.257)	1.214 (0.342)	1.500 (0.214)
Mean ovarian transverse diameter (cm)	Mean ± SD	1.189 (0.228)	1.367 (0.297)	1.621 (0.275)	1.781 (0.267)
Mean ovarian antero-posterior diameter (cm)	Mean ± SD	0.984 (0.191)	1.167 (0.303)	1.422 (0.297)	1.677 (0.361)
Mean Ovarian longitudinal diameter (cm)	Mean ± SD	2.369 (0.399)	2.700 (0.460)	3.195 (0.465)	3.530 (0.353)
Mean ovarian volume (cm3)	Mean ± SD	1.466 (0.534)	2.466 (1.719)	3.989 (1.714)	5.550 (1.681)

P1-155

Evaluation of the influence of the gonadotropin-releasing hormone agonist therapy on growth and body mass index in girls with idiopathic central precocious puberty

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Objective: We aimed to examine the auxological findings of the girls diagnosed with idiopathic central precocious puberty (CPP) at the end of the Gonadotropin-releasing hormone analogs (GnRHa) treatment and to investigate the effect of related factors on the height gain of those patients.

Methods: This study was designed as single-center, descriptive, cross-sectional retrospective study. A total of 43 patients who were diagnosed with idiopathic CPP and treated with GnRHa between 2012 - 2021 were included in to study.

Results: The mean chronological age (CA) of the subjects was 7.39 ± 0.76 years at the treatment initiation and 10.93 ± 0.21 at the end of the therapy. The mean treatment duration was 3.96 ± 1.37 years. A decline in height standard deviation score (SDS) from 1.20 ± 0.14 to 1.02 ± 0.06 during the therapy was observed (P<0.001). The bone age (BA)/CA ratio was decreased and predictive adult height (PAH) was increased at the end of the therapy (P<0.001; P=0.001). Both the rates of overweightness and obesity were increased (38.6% to 50% and 9% to 15.9%) when the treatment onset compared with the end of therapy. At the end of the treatment; the mean body mass index (BMI) SDS of the overweight patients was still higher compared to the normal-weight group and the change in BMI SDS during the treatment in the overweight group (BMI median: 1.39 to 1.81; ΔBMI: 0.42) was higher than the change in the BMI SDS in the subjects with normal weight during the treatment (BMI median: 0.32 to 0.46; ΔBMI: 0.14) (P<0.001). There were no significant correlations between pre-treatment BMI and height parameters (pre- and after-treatment height SDS as well as pre- and after-treatment PAH SDS). While Δheight and height velocity (HV) at the 1st year were higher at the patients whose treatment was initiated before the age of 7 years; both pre- and after-treatment height and PAH SDS were similar in two groups (P<0.0001; P<0.032; P=0.528; P=0.768; P=0.928; P=0.858).

Conclusion: A decrease in bone maturation rate and an increase in PAH were observed with GnRHa treatment which had a positive effect on height potential. The HV at 1st year and Δheight were higher when the treatment was initiated under the age of 7. An increase in BMI during the therapy has been also demonstrated especially in subjects who were overweight before treatment.

P1-156

Cushing´s disease in children and adolescents: Experience of a single tertiary center

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Cushing's disease (CD) is rare entity especially in pediatric patients. It is associated with significant morbidity. Early diagnosis and treatment is important for optimal outcome.

Aim: To evaluate the clinical, biochemical, pathology, treatments and outcome in a cohort of CD pediatrics patients in a single tertiary center.

Subjects and Methods: Retrospective review of 27 medical records of CD (chronological age (CA) <18 years (y) treated between 1992-2021. Data analyzed were: clinical, biochemical, radiological (MRI), bilateral inferior petrosal sinus sampling (BIPSS), histological features, therapeutic interventions and outcomes.

Results: CA at diagnosis (Mean ± SDS) 12.64 ± 2.52 years(y) (range(r) 5.88-17.32 y). F/M 1.45/1.Time between initial clinical signs and diagnosis was 1.44 ± 1.17 y. Features at diagnosis (%) were: Weight gain 92.5, Facial changes 77.8, striae 51.8, hirsutism 44.5, dorsal hump 44, acne 40.7, acanthosis nigricans 40.7, Hypertension 33.3, Pubertal delay or arrest 29.6,Growth retardation / Short stature 26, and others. Mean ± SD Height was -0.84 ± 1.09 (r:-2.68 to 0.03), weight 1.6± 1.46 (r: -0.54 to 4.76), BMI 1.78±0.76 (r: -0.7 to 2.8). Hypercortisolism was confirmed by UFC in 26/27 patients (96.2%) median 312 ugr/m2/day (r: 53-2005), SFC 23.00 hrs in 10/10 (100%) 1.06 ± 0.68 ugr/dl, Suppression test with dexametasone 18/18 (100%). High doses dexamethasone suppression test was positive in 15/16 patients, one patient did not inhibit. MRI showed microadenomas in 12 patients, macroadenomas in 7(3 invasive). Eight MRI (29,6 %) did not show adenoma. BIPSS were done in these patients. Central hypercortisolism were confirmed in 7 and one had ectopic Cushing (Carcinoide tumor in thymus). Transsphenoidal surgery (TSS) was performed in 22 /26 patients (excluding ectopic). 2 patients lost during follow-up, 1

received medical treatment and 1 craniotomy surgery. Histology confirmed ACTH+ adenoma in 17/23 (74%). The remission rates post-surgery was 66.6 % (16/24). Eight patients had persistent hypercortisolism. In these, second surgery, external pituitary Radiotherapy, gamma knife stereotactic radio-surgery, o medical treatments were underwent. Bilateral adrenalectomy was performed in one, who died. There was no recurrence after remission.

Conclusion: We reported the experience in our cohort of 27 CD patients seen in a single center over 30 years. The early diagnosis is essential to controlling hypercortisolism and prevents complications. Pituitary surgeon with experience of TSS in children is a priority. Post-surgical remission was similar to others series and same patients need second-line therapy. Recurrence is rare in this age group.

P1-157

Effect of gonadotropin-releasing hormone agonist monotherapy and combination therapy with growth hormone on final adult height in girls with central precocious puberty

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Objective: This study aimed to compare clinical parameters, including final adult height (FAH), in girls with central precocious puberty treated with gonadotropin-releasing hormone agonists (GnRHa) with and without growth hormone (GH).

Methods: This retrospective study reviewed data of 210 girls with precocious puberty who had reached FAH in a long-term trial of GnRHa treatment. The subjects were divided into the GnRHa treatment group (n=188), and the combined GnRHa+GH treatment group (n=22). Chronological age, bone age, height, height standard deviation score (SDS), predicted adult height (PAH), FAH, Tanner stage, and hormone levels were assessed during the treatment period.

Results: At the start of treatment, PAH was 156.35 ± 6.34 cm in the GnRHa monotherapy group and 150.41 ± 5.32 cm in the GnRHa+GH group (P<0.001). At the end of treatment, PAH was 166.25 ± 5.26 cm in the GnRHa group and 164.07 ± 4.99 cm in the combined GnRHa+GH treatment group, which had increased compared to the start of treatment. The FAH in the GnRHa group and GnRHa+GH combination group were 161.07 ± 4.78 cm and 159.63 ± 3.8 6 cm, respectively, without significant difference. In addition, the height gain (FAH−PAH) was significantly higher in the GnRHa+GH group than the GnRHa group (9.22 ± 6.03 cm vs. 4.72 ± 5.01 cm, P<0.001).

Conclusion: In girls with central precocious puberty, the height gain in the FAH compared to PAH at the start of treatment was significantly higher with the GnRHa+GH combination treatment.

P1-158

Clinical Findings and Endocrine Follow-up of Childhood Craniopharyngioma Cases

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Introduction: Craniopharyngioma is a low malignant potential tumor of embryological origin of the sellar/suprasellar region. It occurs with various symptoms and signs such as headache, vomiting, vision loss and endocrinological disorders. It was aimed to evaluate the presentation findings and endocrinological disorders in the follow-up in childhood craniopharyngioma cases.

Methods: The patients followed up with the diagnosis of craniopharyngioma between 2009 and 2022 in Gazi University Faculty of Medicine Pediatric Endocrinology Department were included in this study. Clinical, laboratory and imaging findings were reviewed retrospectively.

Results: Twenty-two cases (mean age 8.5±3.6 years,72% under 10 years old,68% male) were included in the study. The most common complaints were headache 63%(n=14) and visual impairment 59%(n=13). At the time of admission, at least one pituitary hormone deficiency was detected in 50%(n=11) of the cases. Short stature was accompanied by 41%(n=9) and hypothyroidism was accompanying in 36%(n=8) cases. Although the majority of tumor localization was in the suprasellar region (45%), it was most commonly caused by the infundibulum in 36%(n=8). Compression of the chiasm was observed in 77%(n=17) of the cases. Tumor size was greater than 3 cm in 63%(n=14) of the cases, total excision was applied to 36%(n=8) of the cases. Postoperative radiotherapy was applied in 22%(n=5) and re-operation was applied in 18%(n=4) cases. Multiple pituitary hormone deficiency after surgery was detected in 90%(n=19) of the cases. The incidence of hypothyroidism was 86%(n=19), adrenal insufficiency and diabetes insipidus were observed in 81%(n=18) cases, while transient inappropriate ADH syndrome was observed in 6 cases and central salt loss was observed in 2 cases. In the follow-up, obesity was observed in 41%(n=9) cases and hyperlipidemia was observed in 27%(n=6) cases. While the mean body mass index SDS of the cases was 0.49±1.38 at the time of admission, it was 1.18±1.63 at the last control. 50% of the cases(n=11) received growth hormone treatment.

Conclusion: Because craniopharyngiomas grow slowly and are usually diagnosed late, tumor sizes are quite large at the time of diagnosis. Depending on the size of the tumor/resection before and after surgery, endocrinological problems are frequently observed. Especially in cases with growth arrest, headache and vision problems should be questioned and care should be taken for early diagnosis.

P1-159

Final adult height and bone mineral density of the children who were treated with gonadotropin releasing hormone analogues near the age eight

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Aim: Central precocious puberty (CPP) is defined as premature activation of the hypothalamic–pituitary–gonadal (HPG) axis before the age 8 in girls. Precocious puberty starting at a very young age causes a severe loss in height potential and should be treated with gonadotropin releasing hormone agonists (GnRHa). However, there are controversial results about the benefit of the GnRHa treatment in girls whose CPP is initiated near the age 8. This study evaluated the effectiveness of GnRHa treatment on final height of 160 girls with CPP in this specific age group. Moreover, it has been also investigated if this therapy had any negative effect on bone health.

Method: This retrospective study was conducted on 117 girls with CPP who were diagnosed near the age 8 (7-9 years old). The girls, who's the treatment were initiated between the ages 8-9 years (n=71) and 7-8 years (n=46) were included to the group 1 and 2 respectively. Predicted height (PAH), target height (TH) were calculated at the beginning of the therapy according to medical records and final adult heights (FAH) were obtained also from the records. Age of onset of the treatment, the duration of GnRHa therapy, anthropometric measures of the children and bone mineral density z-scores (n=52) after the treatment were also recorded. Girls' PAH, TH and FAH were also compared between groups. Paired t test was also performed to assess the difference between PAH and FAH.

Results: The mean age of the girls at the beginning of the treatment was 8.59±0.27 in group 1 and 7.50±0.47 in group 2. The durations of GnRHa therapy were 1.97±0.54 and 2.91±0.61 in group 1 and 2 respectively. The TH (160,53±5,49 vs160,57±4,94), PAH (158,72±5,23 vs 158,35±5,57) and FAH (162,42±5,32 vs 162,14±5,70) were not statistically different between groups. Multiple regression analysis demonstrated that major determinant factor of the FAH was baseline height SDS (Beta: 0.572, $p<0.001$). However, FAH was improved approximately 4 cm from the PAH in both groups ($p<0.001$). There were not any girls with osteoporosis after treatment. However, 4/52 girls had a BMD z-score between -1 and -2.

Conclusion: GnRHa may improve FAH even the treatment is delayed after the age 8 without a serious negative effect on BMD. However, as this improvement is limited for this age group, the therapy option should be individualized and should not be considered for all children.

P1-160

Central diabetes insipidus following immunization with anti-COVID19 BNT162b2 Comirnaty vaccine

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Introduction: The coronavirus disease 19 (COVID19) pandemic urged to develop new vaccines to reduce the morbidity and mortality associated with this disease. Recognition and report of potential adverse effects of these novel vaccines (especially the urgent and life-threatening ones) is therefore essential.

Case Presentation: A 16-year-old boy presented to the Paediatric Emergency Department with polyuria (9 liters per day), polydipsia and concomitant weight loss (- 6 Kg) over the last four months. His past medical history was unremarkable. Onset of symptoms was referred to be few days after second dose of anti-COVID19 BNT162b2 Comirnaty vaccine. The patient was admitted to the Paediatric Department. The physical exam was normal, without neurological abnormalities. Auxological parameters were within normal limits (height -0.12 SDS, weight +0.35 SDS). Daily fluid balance monitoring confirmed polyuria and polydipsia (IN 6,250 L / OUT 7,100 L). Biochemistry laboratory analysis and urine culture were normal (Sodium levels 141 mEq/L). Serum osmolality was 297 mOsm/Kg H2O (normal values 285-305), whereas urine osmolality was 80 mOsm/Kg H2O (normal values 100-1100), suggesting diabetes insipidus. Hormonal tests showed no significant impairment of anterior pituitary function. Test with Desmopressin was performed and confirmed the diagnosis of central diabetes insipidus. Brain MRI revealed pituitary stalk enlargement (4 mm) with contrast enhancement, and loss of posterior pituitary bright spot on T1 weighted imaging. Even in absence of pituitary enlargement, those signs were consistent with neuroinfundibulohypophysitis. Immunoglobulin levels were normal. Low doses of oral Desmopressin were sufficient to control patient's symptoms, normalizing serum and urinary osmolality values and daily fluid balance at discharge. Brain MRI after 2 months showed stable thicken pituitary stalk and detectable small posterior pituitary. Due to persistence of polyuria and polydipsia, therapy with Desmopressin was adjusted by increasing dosage and number of daily administrations. Clinical and neuroradiological follow-up is still ongoing.

Conclusion: Hypophysitis is a rare disorder characterized by lymphocytic, granulomatous, plasmacytic, or xanthomatous infiltration of the pituitary gland and stalk. Common manifestations are headache, hypopituitarism, and diabetes insipidus. To date, only time correlation between SARS-CoV-2 infection and development of hypophysitis and subsequent hypopituitarism has been reported. Further studies will be needed to deepen a possible causal link between anti-COVID19 vaccine and diabetes insipidus.

P1-161

Causal Effect of Age at Menarche on the Risk for Depression: Results from a Two-Sample Multivariable Mendelian Randomization Study

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Background: A fair number of epidemiological studies suggest that age at menarche (AAM) is associated with depression, but the reported effect sizes are small, and there is evidence of residual confounding. Moreover, previous Mendelian randomization (MR) studies to avoid inferential problems inherent to epidemiological studies have provided mixed findings.

Methods: To clarify the causal relationship between age at menarche and broadly defined depression risk, we used 360 genome-wide significantly AAM-related single nucleotide polymorphisms (SNPs) as instrumental variable and data from the latest GWAS for broadly defined depression risk on 807,553 individuals (246,363 cases and 561,190 controls). Multiple methods to account for heterogeneity of the instrumental variable (penalized weighted median, MR Lasso, contamination mixture method), systematic and idiosyncratic pleiotropy (MR RAPS), and horizontal pleiotropy (MR PRESSO and multivariable MR using three methods) were used. Body mass index, education attainment, and total white blood count were considered pleiotropic phenotypes in the multivariable MR analysis.

Results: In the univariable (inverse-variance weighted (IVW): OR=0.96, 95% confidence interval=0.94-0.98, p=0.0003) and multivariable MR analysis (IVW: OR=0.96, 95% confidence interval=0.94-0.99, p=0.007), there was a significant causal effect of AAM on depression risk.

Conclusions: The present study supports conclusions from previous epidemiological studies implicating AAM in depression without the pitfalls of residual confounding and reverse causation. Considering the adverse consequences of an earlier AAM on mental health, this finding should foster efforts to address risk factors that promote an earlier AAM.

P1-162

Complications of non-endocrine pituitary tumors in children, in the city of Oran

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Background: Non-endocrine pituitary tumors (NEPT) correspond to expansive processes, developing at the expense of non-endocrine pituitary lodge structures. Our objective is to evaluate their prevalence and their incidence rates in Oran, Algeria.

Patients and Methods: This is a cross-sectional descriptive multicenter study in the town of Oran study. Data were collected prospectively from Avril 2014 to Mars 2015 and retrospectively from Avril 1998 to Mars 2014.

Results: 35 pituitary tumors were collected in children (age ≤15 years), 33 were non-endocrine pituitary tumors (NEPT): 12 girls and 21 boys, mean age=11.3 years. Standardized incidence ratio (SIR) 1case/100000/year. Mean consultation time was 10.5±8.3 months. Circumstances of discovery: headaches-visual disturbances (70.0%), growth retardation (20.0%), polyuropolydipsia syndrome (6.6%) and incidentalomas (3.4%). Epileptic seizures reported in 6.7%. In all of the NEPT in children, the most frequent physical signs were those of pituitary insufficiency (60.0%), Diabetes insipidus (16.7%), hypothalamic syndrome (10.0%) and cranial pair involvement (6.7%). The Complications: hypothalamic syndrome 30.8%, epilepsy 11.5%, diabetes insipidus 23%. Neuropsychiatric complications (55.1%), ophthalmological (79.8%), blindness 23%, hydrocephalus 68.7% and visual impact: altered visual field (22.1%), low visual acuity (41.9%), blindness (9.3%), occulomotor disorders (18.6%), pallor or papillary atrophy (34 .9%)

Conclusion: NEPT are more frequent and more voluminous. Their significant loco regional morbidity requires awareness for early diagnosis.

P1-163

Stress and Hyperprolactinemia: Can a Stimulation Test be Used to Evaluate?

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Background: Prolactin is a peptide hormone produced by the anterior pituitary gland. Hyperprolactinemia can be caused by stress, but pathological causes of hyperprolactinemia could be due hypothyroidism, medications or hypothalamic/pituitary tumors. It is important to differentiate between the causes of hyperprolactinemia. The best way to accomplish this is via a rest test. One way to accomplish this would be to measure prolactin levels as a part of a hormone stimulation test.

Objective: To use a hormone stimulation test as a rest test to evaluate whether stress is the cause of hyperprolactinemia in patients.

Methods: A retrospective chart review (N: 526) was done to select patients who completed either a growth hormone stimulation and/or a Lupron stimulation test. Growth hormone stimulation test patients received L-Dopa and Arginine. Lupron stimulation test patients received Leuprolide acetate. Prolactin levels were measured at the time of IV catheter insertion(baseline) and then at the 3-hour time point.

Results: Data showed that elevated baseline prolactin levels decreased to normal at the 3-hour time point in patients who completed the hormone stimulation test.

Conclusions: Our data showed that elevated baseline prolactin levels decreased to normal levels at the 3-hour time point in patients who completed a hormone stimulation test. Medications used during the stimulation testing and circadian rhythm effects could also be implicated, but will need to be examined further. This study demonstrates that a hormone stimulation test may be a good way to examine the cause of hyperprolactinemia in patients.

P1-164

Familial Central Precocious Puberty: A case of three siblings with MKRN3 mutation

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Introduction: We report a series of three siblings, two girls and one boy, diagnosed with Central Precocious Puberty (CPP) respectively at the age of 5.66, 6.67 and 8.5 years, carrying a mutation in the gene encoding the makorin RING finger protein 3 (MKRN3), usually responsible for the development of familial CPP.

Methods: We diagnosed CPP in all the patients by performing a GnRH test. We also dosed basal levels of LH, FSH, 17-beta-estradiol (E2) and testosterone. To further support the diagnosis, we assessed the bone age with X-ray of the left hand. Moreover, we performed pelvic ultrasounds and brain MRIs in the female patients. Given the recurrence of CPP in 3 out of 3 siblings, we decided to perform, on patients and parents as well, a Next Generation Sequencing (NGS) panel studying the most frequently implied genes in the occurrence of CPP (KISS1, KISS1R and MKRN3).

Results: When referred to our centre, all three patients showed clinical signs of precocious puberty. GnRH test showed elevated GnRH-stimulated LH levels confirming the initial hypothesis of CPP. Basal levels of LH and FSH were not consistent with a prepubertal status. One of the two girls showed elevated E2 levels (16.1 pg/mL). Both the girls and the boy had advanced bone age (approximately one year more than the chronological age). Pelvic ultrasounds showed signs of pubertal activation (longitudinal uterine diameter was 37 mm for both girls). Brain MRIs for the study of the pituitary gland, performed on the two girls, did not show secondary causes of pubertal activation. This last exam was deemed unnecessary for the boy, considering the highly probable genetic aetiology. NGS panel revealed, in all three patients, a paternally inherited variant of MKRN3 gene (c.475_476insC; p.Ala162GlyfsTer15), which leads to the introduction of a premature stop codon, as already reported by previous literature. MKRN3 is a maternally imprinted gene located in the Prader-Willi syndrome critical region (chromosome 15q11-q13). Therefore, even if the transmission is described as autosomal dominant, the father may be not affected as in our case.

Conclusions: MKRN3 mutations are the most frequent genetic cause of CPP, in particular in the familial settings. Thus, when there is a familial history of CPP – two affected siblings or a father and at least one child – genetic studies could precede the brain MRI. Furthermore, the maternally imprinted mode of inheritance of MKRN3 gene makes the diagnosis remarkably challenging.

P1-165

The effect of metformin on the onset of menarche and the final height of obese girls

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Background/Aims: Obese girls experience precocious puberty which could influence their final height. We studied the effect of metformin on their body weight, final height, onset of menarche, and bone age.

Methods: In a prospective study, 63 obese girls aged between 8 -13 years old were treated with metformin (500-1000 mg/daily and compared with control at the outpatient pediatric endocrine clinic of Loghman Hakim Hospital in Tehran for 5 years.

Results: Metformin differed control in significantly decreasing body weight, delaying menarche and bone age progress, and increasing final height.

Conclusion: Metformin could decrease the body weight, delay the menarche and improve the final height in the obese girls.

P1-166

Metabolic setup in infants with panhypopituitarism

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Congenital panhypopituitarism is a rare cause of impaired metabolism in early infancy.

Many guidelines for neonatal hypoglycemia include evaluation of pituitary hormones, but other parameters of metabolism (either mineral, lipid or hepatic) are rarely taken into consideration and don't regularly suggest hormonal investigation. Therefore the diagnosis of multiple hormonal deficiencies is often late at that age.

Although many reports point to the impaired bile discharge, a little is known about the underlying mechanisms of the metabolic events in infants with multiple deficiencies of pituitary hormones.

A retrospective study of the metabolic parameters in five infants aged 1-18 months with congenital panhypopituitarism (two siblings with septo-optic dysplasia) was performed. Growth parameters were within normal range for the gestational age in all, however all three boys had micropenis and cryptorchidism. All five have recurrent and severe fasting hypoglycemic events during the first month (1-15 days) ranging from 0,2-2,1 mmol/l. In two the hypoglycemia resolved after establishing the feeding regiment, and in the other three after the therapy with hydrocortisone. Low levels of IGF1 and IGFBP3 and GH stimulation tests performed at 2 years were established in all. TSH deficiency (low TSH and T4) was established in three patients. Low ACTH and consecutive decreased cortisol level was detected in all.

Moderate elevation of total bilirubin (290..315 umol/l) and liver enzymes were detected in four, while excessive cholestasis was detected in one patient (persistent direct bilirubin above 250 umol/l with predominant elevation of AST (369 U/L), alkaline phosphatase (208) and hyperlipidemia. This child had most severe ACTH and cortisol deficiency. Metabolic screening of FFA, carnitines and electrolytes were normal, while hyperlipidemia was found in other two infants. MRI of the pituitary was performed in four, all with structural defects.

Existence of the triad of hypoglycemia, jaundice and hyperbilirubinemia in neonatal period should raise suspicion of hormonal deficiency despite normal growth parameters in infants. It is not clear which of the hormones has the major role in hepatic dysfunction, however data showed that low ACTH and cortisol levels are predominant in cases where cholestasis occur. Treatment with glucocorticoids as a first hormone should be replaced immediately after establishing the diagnosis since it is mandatory for the resolving the hypoglycemia and metabolic dysfunction.

P1-167

A PROP1 Compound Heterozygosity with Pituitary Enlargement

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A PROP1 homozygous mutation was found in an 8 years old boy who was referred for fatigue, general slowness, dry skin, normal weight and slow growth. His T4 and TSH were low, while tests of pituitary reserve were normal as well as the concentrations of ACTH and cortisol. FSH/LH/T/E were in the pre-pubertal range. TRH test resulted in no increased TSH and T4, confirming the pituitary origin of the defect. MRI of the pituitary hypothalamic region revealed an enlargement of the anterior pituitary gland, a mass lesion of 10 mm. The pituitary stalk was normal and neurohypophyses was normally located. Substitution with sodium L-thyroxine resulted in increased growth velocity. Control MRI of the pituitary hypothalamic region after 6 years revealed a pituitary mass of 2mm. At the age of 14 years, the boy had testicle size of 2ml and no signs of puberty. At the age of 15 years, GnRH test resulted in unresponsive FSH/LH and testosterone. Substitution with chorionic gonadotropins resulted in increased growth velocity, testicle size and pubarche. At the age of 16 years the ACTH serum concentrations were 25.8 pg/mL (0.0-46.0), while cortisol serum concentrations were 3.09 ug/dL (6.7-22.6). Corticotropin realizing hormone test is pending. At the age of 16 years GH was low at two tests of pituitary reserve (<0.5 ng/ml). IGF-1 was low, IGFBP-3 had normal values for age and gender. His height is 164 cm (mother 158, father 172), his bone maturity is 13 years and he started GH treatment. Clinical exome sequencing revealed that the proband is a PROP1 compound heterozygote with c.358C>T (p.Arg120ys) inherited from the mother, and the c.301_302del (p.(Leu102CysfsTer8) inherited from the father. The sequential pituitary hormone deficiency unusually begun with TSH deficiency, continued with gonadotropin deficiency, followed by GHD and finished with central hypoadrenocorticism.

Keywords: combined pituitary deficiency, PROP1, pituitary mass.

P1-168

Are Obese Cases with Precocious Puberty Diagnosed Late?

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Introduction: Today, excessive nutrition and obesity are the leading environmental factors affecting this puberty. We planned to investigate the prevalence of obesity in our patients who received GnRH analog therapy in our clinic, and the distribution, clinical features and laboratory findings of our patients with and without obesity.

Methods: In the study, female patients who received GnRH analog therapy in the Pediatric Endocrinology outpatient clinic of Ankara City Hospital between August 2019 and December 2021 were divided into 2 groups, obese and non-obese, according to body mass index (BMI). SPSS 26.0 program was used for statistical analysis. The rates of the two independent groups were compared with the "Chi-Square" test, the medians of the two independent groups with the "Mann-Whitney U" test, and the mean of the two independent groups with the "Student t-test". Statistically, $p<0.05$ was considered significant.

Results: The mean±SDS age of 108 patients who received GnRH analogue therapy was 8.2±0.9 years. The most common complaints of the cases were breast enlargement 69.4% (n:76), hair growth 6.5% (n:7), breast growth and hair growth together 17.6% (n:19), menarche 5.6% (n:6). The most common breast tanner stage at presentation was stage 3; pubic hair was stage 1.

While 26.9% (n: 29) of the cases were obese, 73.1% (n: 79) were non-obese. The mean±SDS age at presentation was 8.3±0.8 in

obese cases and 8.2±0.9 in non-obese cases. In the physical examination at presentation, the most common breast tanner staging was stage 3 in both obese and non-obese cases. Obese cases were taller at presentation than the non-obese group (p=0.004). In addition, the bone age of the obese group at the time of admission was found to be higher than the non-obese group (p=0.01).

Conclusion: In our study, the age of admission and initiation of treatment in obese cases and non-obese cases were similar. Bone age at the time of admission of obese cases was more advanced, and it is compatible with the literature, and also their height at admission was longer in obese cases

It is considered as a positive gain in terms of height gain during the treatment.

P1-341

Proposal of a diagnostic flow-chart for the diagnosis of central precocious puberty (CPP) in females

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Introduction: In females with precocious thelarche (PT) (< 8 years), elevation of morning luteinizing hormone levels (mLH) may be indicative of pubertal activation of the pituitary gonadal axis. However, this approach could not be satisfactory in real life management of PT due to the risk of reduced specificity and sensitivity of the mLH thresholds. We propose a diagnostic flow-chart based on basal and stimulated gonadotrophins integrated with bone age and ultrasound uterine diameters to screen CPP in females.

Patients and Methods: The clinical, radiologic and hormonal data of 213 consecutive girls with PT who underwent GnRH stimulation test (GnRHST) to exclude CPP were retrospectively evaluated from 2017 to 2020 at our Centre. Bone age was assessed by Greulich-Pyle method, uterine diameters by B-mode ultrasound scans. CPP was diagnosed by LH peak ≥ 5UI/L after GnRHST. Retrospectively a diagnostic flow-chart was created evaluating mLH against the stimulated LH peak, bone age, basal FSH, FSH/LH ratio, longitudinal uterine diameter and uterine volume.

Results: According to the statistical analysis (ROC curves, Younden index) the following features and thresholds were found associated to CPP: mLH ≥0.5 UI/L, FSH ≥3.5 UI/L, mLH/mFSH ≥0.16 UI/L, uterine volume ≥ 3.6 cc, longitudinal uterine diameter ≥41 mm, bone age advancement >1.8 years. According to mLH we subdivided the patients (pts) in 2 groups: group 1 (≥0.5UI/L) group 2 (<0.5 UI/L), however we found respectively 19% of false positive in group 1 and 17 % of false negative in group 2. Therefore we subdivided the pts more accurately in 3 groups according to mLH: group A, 31 pts: ≥ 1,5 UI/L; group B, 36 pts: 0.5-1.4 UI/L; group C,146 pts: <0.5 UI/L: CPP was found in 100% of pts of Group A, 34% of group B and 17% of group C. In Group C, 41 pts (28%) without any of the clinical features reported above did not show CPP, in the remaining 105 pts with at least one feature 25/105 pts has CPP.

Conclusion: Our data seem to confirm the correlation between mLH and LH peak. GnRHST seems not necessary to diagnose or exclude CPP in cases with mLH levels ≥1.5 IU/L and in cases with <0.5 UI/L without any puberty-associated clinical features. In the other pts with low levels of mLH a careful evaluation of other basal hormonal levels and other positive predictive features should advice the GnRHST evaluation case by case.

P1-342

Redefinition of LH cut-off to earlier diagnose evolutive precocious puberty after triptorelin stimulation test

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Introduction: Precocious puberty (PP) is defined as the appearance of thelarche before the age of 8 years, in girls. The gold standard for the diagnosis is represented by the increase of LH level after stimulation with native GnRH, but a feasible alternative involves the administration of GnRH analogues. This test is poorly standardised and currently literature lacks of defined values to confirm the activation of the hypothalamic-gonadal axis, since they depend on the type of stimulus and on the methods used. Since 2002, in Verona, Italy, triptorelin has been used as analogous, with a LH cut-off of 15 IU/L measured 4 hours after the stimulus. Nevertheless, many girls have recently presented LH values below the cut-off despite signs of pubertal progression.

Aims: To identify a new threshold of LH post triptorelin stimulation to allow an earlier diagnosis of PP in girls with pubertal progression; to verify whether other parameters, such as the longitudinal diameter of the uterus, the bone age progression and estradiol levels after the assay, can be considered a valuable method to refine the diagnostic process.

Methods: We enrolled 186 females meeting the following criteria: thelarche onset between 4-8 years and GnRH analogue assay performed between 2015-2019 without showing any activation of the axis. 62 patients of this cohort repeated a triptorelin test due to a rapid clinical progression of puberty. The GnRH analogue assay was performed by injecting 100 mcg/m^2 of triptorelin and measuring LH, FSH and estradiol levels before and four hours after the stimulus. All females underwent clinical evaluation, pelvic ultrasonography, and bone age.

Results: Patients presenting an activation of the axis at the second assay showed retrospectively significantly higher levels of post-stimulus LH at the first test when compared to those whose LH was inferior than 15 IU/L at the second test. They had significantly higher basal levels of LH, LH/FSH ratio and growth velocity. Statistical analysis led us to the identification of a new threshold for post-stimulus LH of 8.5 U/L (sensitivity: 83%, specificity: 76%, negative predictive value: 98%).

Conclusions: A post-stimulus LH value of 8.5 IU/L after triptorelin administration has been identified as the new cut-off to allow a diagnosis of PP in the early stages of hypothalamic-gonadal axis activation avoiding the repetition of the test for the progression of pubertal clinical signs. On the contrary, the other parameters analysed did not result conclusive for the diagnosis.

P1-343

Subcutaneous Triptorelin stimulation test for diagnosing central precocious puberty in girls

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Objective: Central precocious puberty (CPP) is defined as early activation of the hypothalamic-pituitary-gonadal axis. The gonadotropin releasing hormone (GnRH) stimulation test has become widely used in the evaluation of CPP. However, intravenous GnRH is often not readily available for commercial use. Therefore, we aimed to evaluate the diagnostic accuracy of the Triptorelin test compared to the GnRH test.

Methods: A total of 656 girls were referred to Ajou University Hospital for evaluation of precocious puberty between 2020 and 2021. A total of 390 patients underwent the GnRH stimulation test using intravenous GnRH (Relefact, 100ug) from May 2020 to Mar 2021, and a total of 266 patients performed the test using Triptorelin (100ug) from April 2021 to December 2021. The inclusion criteria for this cohort were (i) objective breast budding appeared before the age of 8 years and (ii) advanced bone age more than 1 year over the chronological age. During simulation test, serum luteinizing hormone (LH) and follicle stimulation hormone (FSH) levels were acquired at 0, 30, 45, 60, 90, and 120 min after the injection.

Results: Of the 656 subjects, 217 (33.1%) were included in the pubertal response group and 439 (66.9%) were in the prepubertal response group. Triptorelin test mainly showed the peak of LH level at about 60 minutes, and then showed a tendency to decrease gradually. In the examination using Relefact, the peak value of LH appeared mainly at 30 minutes and then showed a tendency to gradually decrease. Based on the ROC curve, the highest diagnostic accuracy for CPP (AUC = 0.998, sensitivity 96.9%, specificity 89.3%) at 120 min was at a LH level above 4.65 IU/L.

Conclusion: In situations where intravenous GnRH stimulation test is limited, subcutaneous triptorelin stimulation test can be considered as an alternative. In addition, a single LH measurement obtained 120 minutes after triptorelin stimulation may be adequate for diagnosing CPP.

P1-344

Puberty patterns in boys with X-linked congenital adrenal hypoplasia

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Background: X-linked congenital adrenal hypoplasia (adrenal hypoplasia congenita, AHC) is a rare life-threating disorder due to pathogenic variants in the *NR0B1* gene. It encodes DAX-1, an orphan nuclear hormone receptor, that acts as a transcription factor and is expressed in the adrenals and hypothalamus-pituitary-gonadal (HPG) axis. Therefore, apart from primary adrenal insufficiency, patients present incomplete or absent puberty and infertility due to hypogonadotropic hypogonadism (HH). However other puberty patterns were described including normal puberty, peripheral precocious puberty, ACTH-dependent precocious puberty, and GnRH-dependent precocious puberty. Here, we present a cohort of patients with AHC and different puberty patterns.

Material and Methods: 11 patients from 6 families were studied. Pathogenic variants in the *NR0B1* gene were identified by direct sequencing and the deletion encompassing *NR0B1* and *MAGEB1-4* genes by array comparative genomic hybridization.

Results: All patients presented with neonatal onset of adrenal insufficiency with salt-losing. None of the patients exhibited cryptorchidism and/or micropenis – clinical red flags of HH in infancy. One patient presented with acquired cryptorchidism of the left testicle at the age of 10 years and 8 months. Adrenals were described as hypoplastic on ultrasound in 3 out of 11 patients. Five out of 6 patients that achieved pubertal age developed hypogonadotropic hypogonadism and were subsequently treated with testosterone. Remaining patient developed central precocious puberty (CPP) at the age of 8 years and 10 months with fast progression, that was subsequently arrested before final completion (decrease in testicular volume, lack of increase of inhibin B concentration). Hormonal assessment during minipuberty was performed in 3 patients. However, its prognostic value for future puberty is of limited value, as only one patient achieved pubertal age. The hormonal profile was normal (LH 4.2 U/L, FSH 1.8 U/L, testosterone 4.6 nmol/L), however the patient exhibited CPP with subsequent arrest.

Conclusions: Although AHC is mostly associated with HH, different puberty patterns may be observed. It is important to follow-up on HPG function, as it may be disrupted with time. Systematic hormonal assessment of minipuberty in patients suspected of AHC should be performed in order to investigate its prognostic value for future puberty.

P1-345

A cause of familial central precocious puberty: A Novel variant in the DLK1 gene and low serum DLK1 levels

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Background: Genetic factors play an important key role in regulating the timing of puberty. The premature activation of pulsatile release of gonadotropin-releasing hormone (GnRH) before 8 and 9 years of age in girls and boys causes central precocious puberty (CPP). Pathogenic variants in DLK1 are associated with isolated familial CPP. Here, we report three siblings with a diagnosis of CPP with novel variant in DLK1.

Case Report: Patient 1 (P1) is the first-born child of nonconsanguineous parents. Birth weight (BW) was appropriate for gestational age (AGA) with -1.3SDS. She was referred to the pediatric endocrinology outpatient-clinics for breast development at the age of 7-years. At presentation, height and body mass index (BMI)-SDS were +1.82 and +0.2 respectively. Pubertal stage was Tanner 4. Bone age (BA) was 10.5 years, predicted adult height (PAH) (-1.3SDS) was below the target height (+0.1SDS). She received GnRH analog(a) between the age of 8.7 and 10.8-years. Menarche occurred at 11.3-years of age. Patient 2 (P2) was younger sibling of P1. BW was -1.2SDS. She presented due to early menarche at the age of 9-years. At presentation, height and BMI-SDS were +2.2 and -0.7 respectively. Pubertal stage was Tanner-3. BA was 12-years, PAH was calculated as -0.94SDS. GnRHa treatment has been planned, however the family was lost to follow-up. After 7-years, we recontacted the family and patients were summoned. AH-SDS of P1 and P2 was -1.2 and -1.4, respectively. Molecular analysis revealed a novel heterozygous c.357C>G (p.Tyr119Ter) variant in DLK1.The segregation analysis showed paternal origin of this variant. Same variant was also in the 6-year-old sister (P3). At follow-up of P3, breast development started at the age of 7.5-years. At this time, height and BMI-SDS were -1.2 and -0.7 respectively. Pubertal stage was Tanner-2. BA was 9.5-years and PAH-SDS was calculated as -2.2. Hormonal profile was as follows LH 2.3 mIU/mL, FSH 3.3 mIU/mL ve E2 37.6 pmol/L. Thus, GnRHa treatment was started. Recently, serum DLK1 levels were measured in 3 siblings and parents by ELISA assay, which were low in 3 siblings. These results supported the loss-of-function in DLK1.

Conclusion: The study has shown that the paternally inherited variant in DLK1 lead to protein truncation with early "stop" codon formation, which is associated with familial CPP. By molecular analysis, opportunity to make predictions, provide early diagnosis, and follow-up/treatment opportunities for CPP were provided for family members.

P1-346

In between isolated premature thelarche and central precocious puberty: when DHEAS makes the difference

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Background: Precocious puberty (PP) in girls is most frequently an idiopathic gonadotropin-releasing hormone (GnRH)-dependent PP, being thelarche the typical first sign. It is well established that increased dehydroepiandrosterone sulphate (DHEAS) levels are associated with premature adrenarche and may characterize PP too. However, its relationship with signs of hypothalamic-pituitary-gonadal (HPG) axis activation and estrogen exposure is still to be elucidated.

Aims: assessing the association between DHEAS levels and other parameters of HPG activation in girls with precocious thelarche.

Methods: at this aim, 37 girls (median chronological age-CA 7.7 years, range IQ 6.8-8.1) referring to the Endocrine Clinic for suspected PP were consecutively enrolled. In all patients the following data were collected: basal and stimulated (GnRH test at 2.5 mcg/kg) LH and FSH levels, basal ACTH, cortisol, DHEAS, androstenedione, testosterone, 17-α hydroxyprogesterone, 17-β estradiol levels, pelvic ultrasound (US) and hand and wrist X-ray for bone age (BA) assessment.

Results: Median DHEAS values were 447 mcg/L (range IQ 229-909), 0.81 SDS (range IQ -0.78-2.52), being >2 SDS in 13/37 patients. In all patients, other adrenal function tests were in the normal range. Out of 37 girls, 19 showed a pre-pubertal response to GnRH test (LH<5 mIU/L). Higher DHEAS levels were found in this group vs girls with pubertal LH peak (2.07±2.61 SDS vs 0.17±1.56 SDS, P=0.011). At logistic regression DHEAS values>2 SD for age-adjusted reference range were associated with pre-pubertal LH response to GnRH test (P=0.007) and lower levels of estradiol levels (P=0.03). No other difference was found between patients with elevated DHEAS concentrations and others regarding hormonal parameters and US values.

Conclusion: In the presence of signs of HPG axis activation and estrogen exposure, pubertal GnRH test response confirms PP. Our data suggest that elevated DHEAS concentrations, in the absence of HPG axis activation and detectable estradiol levels, may drive estrogenization signs. Indeed, an estrogen receptor concentration-dependent transactivity action of DHEAS has already been described in vitro studies. Moreover, this condition can be different from a mere normal variant of PP thus requiring an appropriate follow-up and eventual therapeutic approach. Further studies are needed to support our findings and to insight into their impact in patients' management.

P1-347

Congenital hypogonadotropic hypogonadism and Cornelia de Lange Syndrome share clinical phenotype and genetic background

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Background: Congenital hypogonadotropic hypogonadism (CHH) is caused by impaired function of GnRH neurons, which clinically manifests by incomplete or absent puberty and infertility. The phenotype may be broader with other developmental anomalies such as anosmia, which is known as Kallmann syndrome. To date, there are more than 40 genes in which mutations underlie CHH. Cornelia de Lange Syndrome (CdLS) is characterized by facial dysmorphia, psychomotor delay, growth impairment and upper limb malformations. A subset of CdLS patients present cryptorchidism, micropenis, delayed puberty, and hyposmia/anosmia. Heterozygous mutations in 7 genes (SMC3, NIPBL, SMC1A, RAD21, HDAC8, BRD4 and ANKRD11) involved in the cohesion complex underlie CdLS. Given the clinical overlap between CHH and CdLS patients, we hypothesised that they may share the genetic background.

Methods: Whole exome sequencing (WES) was performed in CdLS patients with signs of CHH (n=4) as well as CHH patients in search of pathogenic variants in known CdLS genes. In vitro assays were performed on identified mutants. GnRH3:GFP zebrafish model was used to explore the role of SMC3 and NIPBL in GnRH neuron development.

Results: WES identified rare sequencing variants (RSV) in NIPBL (p.P2761Cfs*4, p.R2298C) and a de novo missense RSV in SMC3 (p.C549Y) in 3 patients exhibiting signs of CHH and CdLS. None of these variants were seen in the control population in gnomAD. NIPBL p.R2298C has been reported in CdLS patients and is considered to be pathogenic. NIPBL p.P2761Cfs*4 may escape nonsense-mediated decay and thus lead to a truncated NIBPL protein lacking 39 amino acids on the N-terminal region. SMC3 p.C549Y is located in the hinge domain of SMC3 and enhances the hinge binding to SMC1 in vitro. Further we identified two protein truncating variants in NIPBL (p.E2656*, p.E2696Sfs*6) and a RSV in SMC3 (p.R199K) in three CHH patients without diagnosis of CdLS. Both Nipbl and Smc3 are highly expressed along the GnRH migratory path from the nose to the hypothalamus. Knock down of Smc3 and Nipbl in GnRH-GFP zebrafish led to reduced GnRH neuron numbers, indicating their implication in GnRH neuron biology.

Conclusions: Pathogenic variants in cohesion genes (NIPBL and SMC3) underlie CHH with or without CdLS and implicate cohesion complex in GnRH neuron biology. Transcriptomic and DNA accessibility (ATAC-seq) studies in zebrafish and fibroblasts from the SMC3-mutated patient are underway to further explore the common mechanism of these two rare developmental diseases.

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A homozygous Y443C variant in the RNPC3 is associated with severe syndromic congenital hypopituitarism and diffuse brain atrophy

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Context: Biallelic RNPC3 variants have been reported in a few patients with growth hormone deficiency, either in isolation or in association with central hypothyroidism, congenital cataract, neuropathy, developmental delay/intellectual deficiency, hypogonadism and pituitary hypoplasia.

Objective: To describe a new case with syndromic congenital hypopituitarism and diffuse brain atrophy due to RNPC3 mutations and to compare her clinical and molecular characteristics and pituitary functions with previously published cases.

Case Report: A twenty-year-old female presented with severe growth, neuromotor and developmental delay. Her weight, height and head circumference were 5135 gr (-25.81 SDS), 68 cm (-16.17 SDS), and 34 cm (-17.03 SDS), respectively. She was prepubertal, and had dysmorphic facies, contractures and spasticity in the extremities, and severe truncal hypotonia. There were no radiological signs of a skeletal dysplasia. The bone age was extremely delayed at 2 years. Investigation of pituitary function revealed growth hormone, prolactin, and thyroid-stimulating hormone deficiencies. Whole-exome sequencing revealed a novel homozygous missense (c.1328A>G; Y443C) variant in RNPC3. Cranial MRI revealed a hypoplastic anterior pituitary with diffuse cerebral and cerebellar atrophy.

Conclusion: The Y443C variant in RNPC3 associated with syndromic congenital hypopituitarism and abnormal brain development. This report extends the RNPC3-related hypopituitarism phenotype with a severe neurodegenerative presentation.

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Use of urinary gonadotropins for the evaluation of the minipubertal profile in term newborns and infants within the first six months of age

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Background: The activation of the hypothalamus-pituitary-gonadal (HPG) axis during the first months both in males(M) and females(F) is named as minipuberty. Urinary gonadotropins (uGn) represent an unexpensive and non-invasive method of assessing pubertal development and they have recently been used also for studying minipuberty.

Aims of the study are: 1) to describe the urinary hormonal pattern (uLH, uFSH, testosterone – uT, oestradiol-uE) during minipuberty in a group of healthy full-term infants. 2) to identify the relationship between urinary hormone levels and environmental factors, anthropometric measurements, anogenital distances (AGD).

Methods: Prospective longitudinal study of healthy singleton full-term infants, AGA. Patients were evaluated soon after birth (T0), at three months (T3) and at six months (T6). Anamnestic data, anthropometric measurements, ano-penile distance (AGD-AP), ano-scrotal distance (AGD-AS) for M, ano-fourchette distance (AGD-AF) and ano-clitoris (AGD-AC) for F, were collected at each time-point. Urine samples were collected at T0,T3 and T6. Data are expressed as mean ± SD.

Results: 139 neonates (91M) were enrolled. The table summaries hormonal values and AGDs in M and F at the three times of the study. For M, statistically significant differences were found for uLH, uFSH, and uT at T0 compared to T3 and T6. For F, uFSH and uE but not uLH at birth were higher, compared to values at T3 and T6. uGn levels along the study both in M and F changes significatively according to: anthropometrics of the infant, maternal age, occupational status of the mother, pre-pregnancy BMI and breast feeding. AGDs also change significantly according to uGn, maternal data and breastfeeding.

Conclusion: The use of uGn is confirmed as a reliable and easy-to-use method even during the first year of life. The trend of uGn during minipuberty seems to be influenced by environmental factors which could have an impact on the subsequent development of the infant.

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Phenotypic characteristics of a cohort of patients with Septo-Optic Dysplasia followed in a Tertiary Centre

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Introduction: Septo-optic dysplasia (SOD) is an uncommon, highly heterogeneous entity of multifactorial etiology, consisting in the association of 2 or more of the following characteristics: ophthalmological abnormalities [most frequently optic nerve hypoplasia (ONH)], midline brain abnormalities [such as aplasia/hypoplasia of the septum pellucidum (SP) and/or corpus callosum (CC)] and variable degree of hypotalamo-pituitary insufficiency (HPI)

Objective: To describe the phenotypic findings, prevalence and age of presentation of HPI in a cohort of patients with SOD.

Materials and Methods: A retrospective electronic chart review of SOD patients diagnosed and followed at a tertiary endocrine centre between January 2000 to January 2020.

Results: We included 151 patients (50% women) and excluded 19 (2 deceased, 17 due to lack of data at the time of diagnosis or loss of follow-up). 21% (n= 32) of patients were classified as SOD-plus (associated with any cortical malformation) and the rest were classified as classic SOD. 41% (n=60) of patients had all 3 diagnostic features. The most frequent findings were: ONH (90%) and HPI (74%), followed by aplasia/hypoplasia of SP (49%) and less frequent aplasia/hypoplasia of CC (3.4%). Of these, the most

	T0		T3		T6	
	M	F	M	F	M	F
uLH mUI/ml(SD)	0.81 (1.82) * §	0.14(0.19)	0.21(0.22)*	0.13(0.12)	0.18(0.16)§	0.15(0.13)
uLFSH mUI/ml(SD)	2.01(3.52) * §	1.33(1.88)° ^	0.92(0.33)*	3.15(3.1)°	0.89(0.56)§	3.62(3.31) ^
uT (ng/ml)(SD)	9.95(5.22) * §	\	0.41(0.41)*	\	0.22(0.16)§	\
uE (pg/ml)(SD)	\	862.2(1240.49)°^	\	22.8(9.96)°	\	23.61(11.31)^
AGD-AS cm(SD)	1.9(0.6)	\	3.5(0.88)	\	3.97(1.11)	\
AGD-AP cm(SD)	4.9(0.6)	\	6.84(0.89)	\	7.3(1.14)	\
AGD-AF cm(SD)	\	1.2(0.3)	\	1.7(0.56)	\	2.04(0.62)
AGD-AC cm(SD)	\	3.9(0.6)	\	4.6(0.81)	\	5.2(0.97)

common association was ONH with HPI (49%), followed by ONH with midline brain abnormalities (45%) and less frequently, midline changes associated with HPI (6%). The diagnosis of HPI was made in most cases in children under 4 years of age (87%) and only in 3% in those over 8 years of age. Central hypothyroidism (94%) and secondary/tertiary adrenal insufficiency (73%); were the most common followed by growth hormone deficiency (58%), diabetes insipidus (32%), precocious puberty (7%) and hypogonadotropic hypogonadism (7%). Other common findings were cognitive delay (66%), seizures (40%), behavioral disturbances (9%), and autism spectrum disorder (5%).

Conclusion: ONH and HPI should be a warning sign for the early diagnosis of SOD allowing to perform a prompt treatment in order to reduce the associated morbidity and mortality. Hormonal deficiencies can manifest themselves in the course of the evolution of the disease, being more frequent in children under 4 years of age, falling progressively until 8 years. However, it is important to maintain active surveillance until physical maturity is complete.

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Evaluation of Early Puberty in Patients with MC2R Deficiency

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Background: Melanocortin receptor 2 (MC2R) is expressed in the adrenal cortex and has a major role in the control of the hypothalamic-pituitary-adrenal axis. It is reported that the ACTH receptor MC4R has an impact on premature adrenarche. The melanocortin signaling system is reported to have leptin mediated effect on the regulation of GnRH neuron activity and has an important role in the onset of puberty and fertility.

Objective: To evaluate the early onset puberty of patients with primary adrenal insufficiency (PAI) due to MC2R gene mutation.

Patients and Method: Four patients with PAI from three unrelated families were included in the study. The age of PAI diagnosis was between 1 day-11 months, and all of the patients presented with hypoglycemia, hypoglycemic convulsion, and hyperpigmentation. Clinical diagnosis was also molecularly confirmed in all patients, with homozygous MC2Rvariant c.560delT (p.V187Afs*29). Clinical data regarding anthropometry, puberty, and laboratory were evaluated retrospectively. MKRN3, DLK1, KISS1, and KISS1R were screened by Sanger sequencing.

Results: The mean age at onset of puberty was 8.4 years (range; 7.4-9.5) in boys (Patient(P)1, P2, and P3), and it was 8.5 years (range; 7.4-9.5) in girls (P4, P5, and P6). Tumor markers were negative and there was no evidence of adrenal rest/tumor in testes/ovaries. GnRH analog treatment was administered due to rapidly progressive puberty in P2, P3, and P6. The final heights of P1 and P2 were below the target height with -2.6 SDS and -0.7 SDS respectively. Menarche of P4 and P5 occurred at the age of 11 and 11.3 years respectively. No pathogenic variants were detected by Sanger sequencing.

Conclusion: Molecular studies related to CPP did not explain underlying mechanism. ACTH receptor-MC2R gene mutation, onset, and regulation of puberty may be related. Thus, puberty should be closely followed in patients with MC2R mutation.

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Random Luteinizing Hormone Concentrations for Monitoring Central Precocious Treatment Efficacy

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Background: A decrease in random LH concentration is observed after initiation of treatment for central precocious puberty (CPP), but the suitability of random LH concentrations for assessing efficacy is controversial. Although Neely et al. reported that random LH values frequently fail to demonstrate suppression to prepubertal levels,[1] Lee et al. demonstrated that a cutoff of random LH <0.6 IU/L may be adequate for monitoring suppression.[2] We present secondary analyses of random LH data from the pivotal trial of the first small-volume, long-acting, subcutaneously administered GnRH agonist for CPP, approved in 2020.[3]

Methods: 62 children (60 girls, 2 boys) with treatment-naïve CPP received 2 doses of 45 mg subcutaneous leuprolide acetate at 24-week intervals over the 48-week study period. Luteinizing hormone concentrations were assessed using a validated central Cobas ECLIA assay with a lower limit of detection of 0.100 IU/L. Random LH was defined as LH at time 0 or another visit where a stimulation test was not performed. Blood samples for random LH measurement were taken at baseline and weeks 4, 12, 20, 24, 36, 44, and 48.

Results: Mean random LH decreased from 1.9 IU/L at screening to ≤0.6 IU/L from week 12 to 48. 63 to 71% of children achieved random LH <0.6 IU/L from week 12 to 48. Of patients who achieved both arrested growth (decreased bone age to chronological age ratio and no progression of Tanner stage) and peak LH <4 IU/L at week 24, 68% had random LH <0.6 IU/L at week 24. Strong correlation was not seen between peak and random LH concentrations.

Conclusions: Random LH concentrations decreased significantly following treatment initiation and most children attained a random LH <0.6 IU/L.[2] There were insufficient data to suggest a strong correlation between peak and random LH concentrations. These data support further research into the use of random LH for monitoring CPP treatment efficacy. Physicians should continue to monitor all relevant hormone levels and clinical symptoms that confirm suppression of pubertal progression per standard of care.

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A novel missense variant in the gene encoding Fatty Acid Synthase (*FASN*) associated with a unique multi-system disorder including hypopituitarism and hypoparathyroidism

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Whole exome sequencing performed on a male patient with a unique complex phenotype revealed a novel *de novo* missense variant in *FASN* (c.6395C>T, p.A2132V), encoding Fatty Acid Synthase. The patient presented with panhypopituitarism (GH, TSH, LH, FSH and ACTH deficiencies), short stature, sensorineural deafness, hypoparathyroidism, retinal dystrophy, and developmental delay. He was 127cm tall at the age of 21 and failed to respond to GH treatment [IGF-1 generation test: no response to 2.8mg/m2/day GH]. He was completely prepubertal (LH 0.8U/L, FSH 2.6U/L, Testosterone <0.69nmol/L) with a bone age of 12 years. A trial of recombinant IGF-1 failed to improve his growth. He died at 26 years of age following a collapse of unknown etiology.

The variant was not present on control databases, including the GnomAD browser. Human embryonic brain expression analysis using in situ hybridisation revealed *FASN* mRNA transcripts in the diencephalon and hypothalamus at Carnegie stages (CS) 16, 19, 20 and 23, and in Rathke's pouch (the primordium of the anterior pituitary) at CS16 and CS19 only.

FASN is a crucial multienzyme with seven different catalytic activities, essentially converting acetyl-CoA and malonyl-CoA into long-chain saturated fatty acids such as palmitate. Murine null *Fasn*-/- embryos die before implantation and *Fasn*+/- embryos die in early postnatal stages. Murine *Fasn* is expressed in multiple tissues including the brain, parathyroids, liver and adrenal.

Biochemical investigation of the patient revealed high triglyceride concentrations (3.81-6.49mmol/L; NR 0.38-2) throughout an 18 hour fast. He mobilised free fatty acids but 3-hydroxybutyrate failed to increase, suggesting a defect in fatty acid oxidation or ketone body synthesis. He maintained normoglycaemia with normal hormone responses to fasting, except for an undetectable IGF-1 (<25ng/ml) and IGFBP-3 (1.17mg/L). A glucose tolerance test was abnormal; plasma glucose did not decrease at the expected rate.

We measured *de novo* fatty acid synthesis in cultured patient and control fibroblast cells with 13C-labelled glucose, with and without a C75 fatty acid synthase inhibitor. The 13C-fatty acids, derived from 13C-glucose, were analysed by mass spectrometry. Preliminary data showed that more C13-glucose was incorporated into *de novo* synthesised palmitic acid in the control cells, suggesting reduced fatty acid synthesis in the patient.

Our data suggest that *FASN* p.A2132V is pathogenic and contributed significantly to the complex patient phenotype, consistent with recent studies (Bowers M *et al*.,2020) suggesting that neural stem/progenitor cells (NSPCs) in the rodent brain are governed by Fasn-dependent de novo lipogenesis for proliferation.

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Single centre experience of using 6 monthly GnRH analogues in the paediatric population

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Background: Gonadotropin releasing hormone (GnRH) analogues are used in central precocious puberty to inhibit the progression of puberty. Generally, patients are treated with intramuscular depot preparations once every 10 to 12 weeks. Recently, a 6-monthly formulation has been made available for clinical use. The aim of this project was to evaluate the efficacy and acceptability of 6-monthly triptorelin in a routine clinical setting at a tertiary children's hospital.

Methods: Patients on 12-weekly GnRH analogue therapy as well as patients who were newly starting on GnRH analogue therapy were offered the 6-monthly triptorelin (Decapeptyl SR 22.5mg). Clinical data was collected on the 34 patients currently on the 6-monthly preparation.

Results: The mean age of diagnosis was 7.4 years (+ 1.4SD; range: 2-9) and 32/34 (94%) patients were female. All patients were commenced on triptorelin for central precocious puberty. Triptorelin was switched from 12-weekly formulation to 6-monthly at an average age of 8.1 years (+1.6SD; range: 2-10). 94% of patients have had one dose of the 6-monthly medication to date, with the remaining 6% having had two doses. 24% of patients have been reviewed since commencing 6-monthly triptorelin and no progression in puberty has been noted. The injections have been tolerated well, with no side effects noted. The patient feedback has been positive with the need for less frequent injections and visits to the hospital.

Conclusion: The results show that 6-monthly triptorelin has been well tolerated and effective in inhibiting pubertal progression over a short-term course. Long-term data needs to be analysed, but the initial results are promising. The 6-monthly preparation has the potential to reduce the costs and the burden on limited healthcare resources.

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Serum ghrelin and neuropeptide y concentrations and their relationship with gonadotropins and anthropometric parameters in girls with idiopathic central precocious puberty, premature thelarche and premature adrenarche

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Orexigenic molecules such as ghrelin and neuropeptide Y (NPY) can contribute puberty as directly or indirectly. Our aim is to investigate the changes in the levels of orexigenic peptides ghrelin and neuropeptide Y at the onset of puberty in girls with idiopathic central precocious puberty (ICPP), premature thelarche (PT) and premature adrenarche (PA), and to determine their relationship with gonadotropins and anthropometric parameters.

Subjects and Methods: Eighty-four girls aged 24-96 months with signs of puberty such as breast budding, pubic and axillary hair and 24 prepubertal girls were included in this study. Prepubertal girls were the control group. The girls with breast budding were diagnosed with precocious puberty or PT according to Gonadotropin Releasing Hormone (GnRH) test, bone age, and basal follicle stimulating Hormone (FSH)/Luteinizing Hormone (LH) ratios. Only those with pubic and axillary hair were defined as premature adrenarche. Height and weight measured. Ghrelin and NPY concentrations were evaluated during diagnosis.

Results: There was no significant difference in NPY concentration between the 3 groups with pubertal findings and the control group ($p>0.05$). Ghrelin concentration differed between the four groups ($p<0.05$). Ghrelin concentration was significantly higher in girls with PT compared to girls with ICPP ($p=0.023$). No correlations were found between gonadotropins and both ghrelin and neuropeptide Y concentrations in three groups ($p>0.05$). The body weight standard deviation score (SDS) and body mass index SDS were significantly higher in girls with PA than in girls with PT and ICCP ($p=0.011$ and 0.024, respectively). No correlation was also found between neuropeptide Y and anthropometric parameters in all three groups ($p>0.05$). A positive significant correlation was found between ghrelin and body weight SDS in girls with premature thelarche ($r:0.397$, $p=0.04$).

Conclusion: Girls with PA were more overweight than girls with PT and ICCP in our study. However, we found that body weight increased as ghrelin concentration increased in girls with PT. Although we could not find a relationship between ghrelin and gonadotropin concentrations, the fact that ghrelin concentration is higher in girls with PT than in girls with ICCP may suggest that decreased ghrelin levels initiate pubertal progression through different mechanisms.

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Use of the arginine-stimulated copeptin test in polyuric syndrome in paediatrics. Experience in three patients

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Introduction: Differential diagnosis of partial central diabetes insipidus (PCDI) and primary polydipsia (PP) can be challenging.

Copeptin is the C-terminal segment of the vasopressin precursor peptide that represents a novel and stable biomarker. Arginine infusion produces a nonosmotic stimulus that causes an increase in copeptin concentrations in healthy subjects.

Arginine-stimulated copeptin concentrations have been used to differentiate between patients with central diabetes insipidus (CDI) and PP, setting a copeptin value of 3.8 pmol/L at 60 min as a cut-off point in adults.

Objective: To evaluate the efficacy and safety of the arginine-stimulated test in paediatrics.

Patients and Methods: Three patients with polydipsia-polyuria syndrome. After water restriction/desmopressin test, arginine-stimulated test was accomplished. Time points: basal 0',30',60',90',120'. To verify the safety of the test, vital signs and blood tests were monitored.

Results: Patient 1: 5-year-old boy with sudden polydipsia-polyuria syndrome. The 15-hour water restriction test resulted in a maximum urinary osmolality (Osmu) of 601 mOsm/kg that increased up to 845 mOsm/kg after desmopressin. Arginine-copeptin test showed a flat curve with a low copeptin at 60'. Polydipsia-polyuria syndrome clearly improved on desmopressin treatment. MRI showed a small and hypoplastic adenohypophysis with absense of the neurohypophysis signal.

Patient 2: 12-year-old boy with syntelencephaly and severe optochiasmatic atrophy, dysgenetic corpus callosum, without alterations in the hypothalamic-pituitary region. He presented a long-standing polydipsia-polyuria syndrome. The 17-hour water restriction test resulted in a maximum Osmu of 495 mOsm/kg that increased up to 687 mOsm/kg after desmopressin. Arginine-copeptin test showed a flat response but with values above the cut-off point. Desmopressin was started without improvement, therefore it was suspended. Polydipsia-polyuria syndrome improved spontaneously afterwards.

Patient 3: 13-year-old boy with sudden polydipsia-polyuria syndrome. In the basal analysis, he presented plasma osmolality of 303 mOsm/Kgm and water restriction was not performed. Osmu of 98 mOsm/kg increased up to 507 mOsm/kg with desmopressin. Arginine-copeptin test showed a flat curve with low copeptin at

60'. MRI showed an absence of the neurohypophysis and thickening of the pituitary stalk, etiological study pending.

Conclusion: The arginine-stimulated copeptin test is a safe procedure and can represent an alternative to the diagnosis of CDI.

Table 1. Arginine-stimulated copeptin test

	Patient 1	Patient 2	Patient 3
	Copeptin (pmol/L)		
Basal	2,4	3,8	1,61
30'	2,5	4	1,48
60'	2,3	4,13	1,78
90'	1,8	3,8	1,98
120'	2,4		1,47
Diagnosis	PCDI	no-CDI	CDI

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The Prolactin (PRL) – Growth Hormone (GH) Relationship during Growth Hormone Stimulation Tests

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Background: Despite many similarities between the structure, receptors and proliferative and growth promoting actions, the interrelationship between PRL and GH in clinical conditions has received little attention.

Aim: To determine the PRL response to GH stimulation tests.

Subjects: Prepubertal and early pubertal boys (n=581) and girls (n=502) with short stature.

Methods: Data was retrieved from the computerized records of the Endocrine Laboratory. Peak GH and PRL levels during GH stimulation tests with glucagon (Gluc), clonidine (Clon) and clonidine with arginine (Clon+Arg), were determined by radioimmunoassay. Statistical analysis was performed by ANOVA with repeated measurements.

Results: The comparative values of peak GH and PRL (mean ng/l ± SD) are shown in the Table.

Whereas Gluc stimulated both GH and PRL to similar levels, Clon alone or combined with Arg suppressed PRL secretion ($p<<0.0001$). It is also evident that in both boys and girls, Clon±Arg are superior to Gluc in GH stimulation. The higher GH levels during Clon+Arg can be attributed to the pubertal stage.

Conclusion: Our study helps to select the appropriate PRL function test in relation to GH.

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Pathogenic and Low-Frequency genetic determinants in children with Central Precocious Puberty

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Background: Central precocious puberty (CPP) due to premature activation of GnRH secretion results in early epiphyseal fusion and to a significant compromise in the achieved final adult height as well as psychological consequences. So far only a limited number of genetic determinants have been associated with the pathogenesis in children with CPP. In this original research, rare sequence variants in *MKRN3, DLK1, KISS1*, and *KISS1R* genes were investigated in patients with CPP.

Methods: Fifty-four index girls and two index boys with CPP were first tested by Sanger sequencing for the *MKRN3* gene. All children (n = 44) negative for pathogenic variants with Sanger, underwent whole exome sequencing (WES) by Next Generation Sequencing (NGS). The frequencies and status of the newly identified novel and rare variants of the present study in genes known to be related with pubertal timing were compared with an in-house Cypriot control cohort (n = 43). The identified rare variants were firstly examined by in silico computational algorithms and confirmed by Sanger. Moreover, a genetic network for the *MKRN3* gene, mimicking a holistic regulatory depiction of the crosstalk between *MKRN3* and other genes was created.

TEST	BOYS				GIRLS			
	n	AGE (y)	GH peak	PRL	n	AGE (y)	GH peak	PRL
Gluc	264	9.6 ± 4.4	9.0 ± 5.3	8.6 ± 6.7	217	9.0 ± 3.6	9.0 ± 5.4	9.4 ± 7.6
Clon	178	9.8 ± 3.8	12.4 ± 6.2	6.5 ± 3.8	160	9.5 ± 3.3	11.1 ± 6.0	6.7 ± 3.5
Clon+Arg	139	12.9 ± 2.7	14.9 ± 7.3	6.8 ± 3.5ł	125	11.6 ± 1.9	15.8 ± 7.6	6.6 ± 3.3

PRL: Gluc vs Clon/Clon+Arg $p<0.0005$

Results: Three previously described pathogenic *MKRN3* variants were identified in 12 index girls with CPP, with one (p.Gly312Asp) being exclusively found among seven probands of the Cypriot CPP cohort and never reported before, indicative of a founder effect phenomenon. Seven other CPP girls harbored rare likely pathogenic upstream variants in the *MKRN3*. Among the 44 CPP patients submitted to WES, nine rare *DLK1* variants were identified in 11 girls, two rare *KISS1* variants in six girls, and two rare MAGEL2 variants in five girls. Interestingly, the frequent variant rs10407968 (p.Gly8Ter) of the *KISS1R* gene appeared to be less frequent in the cohort of patients with CPP.

Conclusion: The outcomes of the present study highlight the importance of the *MKRN3*-imprinted gene in the development of CPP and its key role in pubertal timing. Furthermore, they also emphasize the importance of an approach that aligns genetics and clinical aspects, which is essential for the management and treatment of CPP.

P1-359

Primary Granulomatous Hypophysitis with Panhypopituitarism, presenting as Aseptic Meningitis in a 14-year-old boy

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Background: Hypophysitis is an uncommon inflammatory disorder of the pituitary gland and is classified both clinically (primary versus secondary) and histologically (lymphocytic, granulomatous or xanthomatous). Primary hypophysitis is exceptionally rare in the paediatric population with only a few cases reported, the majority being Lymphocytic Hypophysitis.

Case Report: We present the case of a previously healthy 14-year-old boy who attended the emergency room with a 2-day history of fever, headache and vomiting. Initial clinical and laboratory examination were compatible with a diagnosis of bacterial meningitis and intravenous antimicrobial therapy was commenced. After two days of treatment, fever subsided but he continued to complain of headaches and vomiting. CSF culture at this stage was sterile. MRI was performed to rule out Sinus Vein Thrombosis. On MRI a heterogenously enhancing mass-like lesion, involving the hypothalamus, pituitary gland, and stalk, with a necrotic component was demonstrated. Differential diagnosis included a malignant, infectious, or inflammatory process. Laboratory work up revealed panhypopituitarism with central hypothyroidism, hypocortisolism, and low IGF1 and gonadotrophins. Corticosteroid treatment was initiated and after 48 hours Levothyroxine was added. Within 48 hours of initiation of therapy, clinical signs of Diabetes Insipidus emerged, and the diagnosis was confirmed by laboratory testing. Due to the uncertainty regarding the diagnosis, trans-sphenoidal biopsy was performed. Pathology revealed an epithelioid granulomatous process with stellate morphology and disintegration in the central part of the granulomas, present in the anterior pituitary gland tissue. A presumed diagnosis of Granulomatous Hypophysitis was made. Comprehensive work up to rule out a secondary cause was normal, including viral and bacterial serology (Herpes, Enterovirus, CMV, Parainfluenza, Adenovirus, Syphilis, Brucella, Echinococcus and Toxoplasma), a full autoantibody panel, tumour markers, Lysozymes, and TB culture. A decision was made to treat with a 12-week course of Pulse Steroids. Follow- up MRI scans after completion of treatment showed complete regression of the pituitary-hypothalamic process with an atrophic pituitary and thickened stalk. Subsequent dynamic testing of the pituitary-gonadal and growth hormone axis confirmed gonadotrophin and growth hormone deficiency. Growth hormone treatment was commenced with a good response, and subsequently, recombinant LH for induction of puberty. The patient remains under regular MRI surveillance and endocrinology follow-up. No recurrence of the lesion has been demonstrated radiographically. Pituitary function has not recovered.

Conclusion: We present what is, to our knowledge, the first reported case of Idiopathic Granulomatous Hypophysitis in a pediatric patient, presenting clinically as aseptic meningitis with concurrent panhypopituitarism.

P1-360

Somatostin analogs in a 15 year old boy with gigantism

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Introduction: Pituitary gigantism is caused by a somatotroph pituitary tumor that occurs before epiphyseal closure and is associated with increased morbidity due to the systemic effects of chronic hormonal excess. It is an extremely rare disease, with an estimated incidence of 8 per million person-years.

Therapeutic modalities for pituitary gigantism are the same as those for acromegaly and include surgery, medication and radiation. Medical treatment plays an important role in acromegaly and gigantism. In recent years, novel therapies and novel combinations of existing drugs have been studied in preclinical and clinical trials in order to improve clinical outcomes and reduce side effects.

Objective: To describe the case of an adolescent with gigantism, who was treated with surgery, followed by somatostatin analogues.

Case: A 15-year-old boy was referred to endocrinology for postoperative evaluation. He had partial resection of an invasive pituitary macroadenoma. His family/personal history was unremarkable. Recently his height was above his genetic potential, enlarged feet/hands, poor school performance, headache, dizziness, sleepiness and visual disturbances. Workup showed high levels of IGF1 933 ng/ml (Normal:211-512) and GH 50.3 ng/ml, with hypothyroidism, secondary adrenal insufficiency and normal

gonadal function. An invasive pituitary macroadenoma was seen at MRI and ophthalmological evaluation showed bilateral temporal hemianopsia. Postoperative pathology confirmed a somatotropic adenoma (+ GH and PRL), Ki67 3% and P53 3%. No AIP, MEN1 or CDKN1B gene abnormalities were found.

Post-surgery outcome: He suffered from diabetes that required insulin pump during one year, and he persisted with high levels of IGF1 and BP3. He was treated with octreotide (30mg/month) and cabergoline (1 mg/week) for 2 years, with initial improvement of IGF1 levels and visual field, but 8 months ago he had a relapse (worsening visual fields) and was started on pasireotide. Since then, he has had stable IGF1 levels (411 ng/ml), normal glucose metabolism, stable MRI without significant changes, and improved visual fields.

Conclusions: As pituitary gigantism is rare and disease control is difficult to achieve, medical treatment with somatostatin analogues is a useful resource. In this case it showed adequate safety and a moderately good response, especially in regard to his visual fields, avoiding the need for second surgery or radiotherapy for the time being.

P1-361

Blue Light Exposure and Exposure Duration Effects on Rats' Puberty Process

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Introduction: In the last 10 years, blue light (BL) sources such as tablets and phones has increased in every age group. Especially due to the Covid-19 pandemic, screen exposure has also increased in childhood. However, the effects of BL exposure in the puberty process aren't clear.

We aimed to examine the effect of BL exposure and exposure time on puberty

Methods: Immature eighteen 21-day-old female Sprague Dawley rats were divided into three groups consisting of six rats in each group: Control Group (CG), Experiment Group-1 (EG-1), Experiment Group-2 (EG-2). CG rats were maintained under standard conditions with 12/12-hour light-dark cycles. The rats of EG-1 and EG-2 were exposed to BL (450-470 nm / irradiance level 0.03 uW/cm2) for 6 hours and 12 hours, respectively. Rats were exposed to BL until the first signs of puberty and then they were euthanasiad. Serum FSH, LH, Estrodiol, testosterone, DHEA-S, leptin, melatonin were studied by ELISA method. Ovaries and uterus were dissected for histomorphological examination

Results: The medians of the pubertal entry days of the CG, EG-1 and EG-2 were 38th, 32th, and 30th days, respectively. (p: 0.001) A negative correlation was found between the puberty entry day of the groups and the exposure to BL and the duration of exposure. (r:-0.910, p<0.001)

The FSH, testosterone, DHEA-S, leptin levels of all groups were similar. (p> 0.05) However, LH and estradiol levels of EG-1 were higher compared CG. (p:0.027) There was a negative correlation between BL exposure, exposure time and melatonin levels (ro:-0.537, p: 0.048) Ovarian tissue was compatible with pubertal period in all groups. As the BL exposure time increased, capillary dilatation and edema in the over tissue increased. Prolonged exposure caused polycystic over like (PCO-like) morphological changes and apoptosis in granulosa cells.

Conclusion: Our study is the first to show the effects of BL exposure on puberty. In our study, we showed that exposure of BL and the duration of exposure lead to early puberty. PCO-like, inflammation and apoptosis were detected in the ovaries with the increase in BL exposure time.

There are studies showing that there is an increase in cases with precocious puberty and acceleration in puberty pace during the closure period compared to the pre-pandemic period. In our study, we experimentally demonstrated the effects of BL exposure on puberty and the relationship between increased exposure time.

P1-362

Negative impact of brain tumors on the neurocognitive functions of childhood cancer survivors

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Introduction – Scope: Childhood cancer has an impact on the neurocognitive functions of growing children and adolescents. The aim of this study, which is the first of its kind in Greece, was to examine the differences in neurocognitive abilities between children and adolescents survivors of brain tumors (BT), and survivors of other types of cancer.

Method: Study participants were cancer survivors aged 7 to 15 years, without any major mental health disorder, for whom ≥ 1 year had elapsed from completion of cancer treatment. Cognitive

function was measured with the Hellenic (Greek) version of the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) which measures full-scale intelligence qK. Mavrea1K. Mavrea1uotient (FSIQ), verbal IQ (VIQ) and practical IQ (PIQ).

Results: A total 70 childhood cancer survivors were evaluated, with an average age (±SD) of 11.29 (±2.60) years. Survivors of BT had significantly (p = .011) lower mean (± SD) FSIQ (82.06 ± 23.45) than acute lymphoblastic leukemia (ALL) survivors (100.09 ± 20.19) or survivors of other types of cancer (108.56 ± 15.65). Regarding PIQ, survivors of BT demonstrated significantly (p = .005) lower mean (± SD) scores (40.50 ± 14.05) than survivors of ALL (51.57 ± 9.15) or other types of cancer (54.11 ± 7.98).

Conclusion: This research demonstrated the negative impact of BT on the neurocognitive functions of cancer survivors during the sensitive developmental periods of childhood and adolescence.

P1-363

Medium-and long-term follow-up observation of the efficacy and safety of GnRHa in the treatment of five cases of central precocious puberty caused by hypothalamic hamartoma

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Background: Hypothalamic hamartoma (HH) is the most common cause of organic central precocious puberty (CPP). Gonadotropin-releasing hormone analogue (GnRHa) is widely used in the treatment of HH combined with CPP, but there is no report on the medium-and long-term efficacy and safety of HH in China.

Objective: To investigate the medium-and long-term efficacy and safety of GnRHa in the treatment of children with CPP caused by HH.

Methods: Five children with CPP caused by HH were treated with GnRHa vary three to eight years. Tanner stage, sex hormone level, glucose and lipid metabolism, bone age and PAHtSDS were evaluated at baseline, during the follow-up period and after treatment.

Results: The initial age of breast enlargement or vaginal bleeding in girls was 0.25 to 5.67 years old, testicular enlargement in 1 male was 4.5 years old, whose Tanner stage was I to III, age of first visit was 0.5 to 5.92 year-old, the level of sex hormone elevated at the onset. Besides, the younger the age of onset, the faster the progress of sexual development. After 3 months of GnRHa treatment, the breast development of 4 girls subsided, Tanner stage was B1 to B2, Two girls with vaginal bleeding did not experience vaginal bleeding after 2 months treatment. The testicular volume of the boy was smaller than before. Five patients were followed up regularly during the treatment. The bone age of four female was controllable during the treatment, $\Delta BA / \Delta CA < 1$, and the bone age of one man was poorly controlled during the treatment, $\Delta BA / \Delta CA = 1\text{-}1.5$. The PAHtSDS of five patients were improved. During the follow-up period, 5 children had no abnormal glucose and lipid metabolism, 1 female patient stopped GnRHa treatment at the bone age of 12. After stopping the drug, she began to develop breasts again. Menarche occurred one and a half years later, and her menstruation was regular. GV was 4-5.2cm/y after stopping the drug.

Conclusion: The age of onset of CPP caused by HH is young, the level of sex hormone at onset elevated, and the bone age is significantly advanced. GnRHa treatment of precocious puberty caused by HH can improve PAHtSDS during the medium-and long-term follow-up period, there is no abnormality in glucose and lipid metabolism, the growth rate is normal after drug withdrawal, spontaneous menarche can occur, and the drug safety is good.

Keywords: Hypothalamic Hamartoma, Central Precocious Puberty, GnRHa, Efficacy, Safety.

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Pneumonia as the first manifestation of pediatric pulmonary carcinoid tumor

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Pulmonary carcinoid tumors represent well-differentiated pulmonary neuroendocrine tumors, which include typical and atypical carcinoids. This type of lung tumors is rare, but represents the most common primary malignant lung tumor in children and adolescents, especially the typical carcinoids. They can be asymptomatic at the time of diagnosis or can present with nonspecific findings like recurrent pneumonia, cough, and hemoptysis.

We report the case of a 15-year-old girl reffered for MEN1 screening due to recent diagnosis of typical pulmonary carcinoid. Her personal history revealed the debut of events two years ago with an episode of pneumonia and hemoptysis which was followed by gradually visual impairment. She was referred for more investigations which led to the CT scan describing the right pulmonary tumor and multiple disseminated liver nodules and the MRI showing an increased pituitary volume (14 mm diameter) and bilateral ocular tumors.

Biochemical screening and genetic testing excluded MEN1 diagnosis. Cg A, urinary 5HIIA, NSE tumor markers were normal, except Serotonin which was two times the upper limit of normal values.

Octreotide scan was performed and showed the octreoscan-positive right pulmonary tumor and octreoscan-positive choroidal, pituitary and liver metastases.

Thus, the patient started systemic treatment with somatostatin analogs and was referred to the oncology department for systemic chimiotherapy regimen.

In conclusion, typical pulmonary carcinoids represent a small percentage of pediatric tumors and their diagnosis is difficult to establish due to their nonspecific symptoms. Typical lung carcinoids have an excellent prognosis following surgical resection. They rarely metastasise, which emphasizes the particularity of this

case and the need for an increased awareness of this rare form of lung cancer. There isn't a consensus between societies and their management guidelines regarding optimal treatment scheme in the metastatic lung NET, so there is a need for more studies. Therefore, an early and accurate diagnosis may lead to an appropriate treatment scheme with a substantial impact on prognosis.

P1-365

Etiology and clinical features in childhood panhypopituitarism

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Introduction: Panhypopituitarism is a deficiency of two or more pituitary hormones. Etiological causes of panhypopituitarism include pituitary developmental disorders, traumatic damage, inflammatory and neoplastic diseases affecting the pituitary, and vascular disorders. In this very rare condition, symptoms and signs related to anterior and posterior pituitary hormone deficiency can also be seen, as well as symptoms and findings related to etiological factors causing panhypopituitarism.

Aim: In our study, it was aimed to determine the etiological causes and clinical features of the cases followed for panhypopituitarism.

Method: The files of the patients with panhypopituitarism who were followed up in Gazi University Faculty of Medicine, Pediatric Endocrinology outpatient clinic between 2009 and 2022 were retrospectively analyzed. Etiological and clinical features of the cases were evaluated. The datas were evaluated with the SPSS 26 program.

Results: 55 cases, 21 male (56.4%) and 24 female (43.6%), were included in the study. The age at diagnosis of the cases was 8.4±4.7 (0.1-17.5) years. 71% of the cases were prepubertal. The presenting symptoms were 39.9% vision loss, 38.2% headache, 21.8% polyuria, 18.2% polydipsia, 14.5% short stature, 10.9% thyroid dysfunction, 9.1% hypoglycemia, 5.5% vomiting, 3.6% cholestasis. The etiologic cause was intracranial mass in 71% of the cases. Intracranial masses; It consisted of 43.6% craniopharyngiomas, 18.1% tumors, and 9.1% pituitary adenomas. Central hypothyroidism in 89.1% of cases, central adrenal insufficiency in 78.2%, growth hormone deficiency in 74.5%, diabetes insipidus in 58.2%, hypogonadotropic hypogonadism in 52%, 10.9% of cases low prolactin was detected. In cases of congenital panhypopituitarism, the presenting symptoms were hypoglycemia and/or cholestasis. Genetic mutation was detected in 5 of the cases with pituitary developmental disorder.

Discussion and Conclusion: Hypopituitarism in childhood may have either a congenital or an acquired basis. Craniopharyngiomas and intracranial tumors and traumas are among the most common causes of panhypopituitarism in children. Among the rarer causes, genetic disorders leading to deficiency of transcription factors involved in pituitary development are seen. In our study, craniopharyngiomas were the most common cause in the etiology of cases with panhypopituitarism, which was consistent with the literature. The most common reasons for admission were headache and vision loss. Pituitary masses should be kept in mind in cases with headache and visual disturbances in the pediatric age group and the cases should be examined in terms of pituitary insufficiency. Congenital panhypopituitarism should be considered in infants with hypoglycemia and cholestasis.

P1-366

Hemorrhagic pituitary apoplexy due to pituitary adenoma: description of two cases in two adolescent males

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Context: Pituitary apoplexy is rare endocrine emergency, resulting from ischemia and/or hemorrhage and necrosis of a pituitary tumor (typically an adenoma). Children and adolescents show severe headache sometimes associated with cranial neuropathies from compression of the optic chiasm or the cavernous sinus.

Case Presentation: A 15-year-old boy was admitted with severe headache and vomiting since 3 days, without visual disturbances and neurological defects; normal auxologic parameters, Tanner stage G3Ph3.MRI showed a hemorrhagic intrasellar mass, hyperintense on T1 with a not homogeneous hyperintense fluid level on T2-weighted sequences. Hormone tests showed a central hypoadrenalism revealed by a low-dose ACTH test (cortisol peak 165 mcg/l), a central hypothyroidism (FT4 5.8 ng/l, TSH 1.65 mU/l), low levels of IGF-1 for pubertal stage (93 nmol/l) with severe insufficient response to dynamic tests; slightly elevated prolactin levels (87 mcg/l) and adequate LH, FSH and testosterone. Visual acuity and visual field were normal. In the suspicion of a pituitary hemorrhagic apoplexy in a pre-existing prolactinoma, hydrocortisone, levothyroxine, hGH and cabergoline 0.75 mg/week (doubled after 2 weeks) were started. The 3-months MRI check showed a reduction of the lesion. Weight and BMI improved and puberty progressed.

A 14-year-old boy was admitted for intense throbbing headache since 2 days, associated with vomiting and photophobia without visual disturbances and neurological deficits; height +0.64 SDS (MPH +1.57 SDS), BMI +1.93 SDS; Tanner stage G4Ph4. Brain CT showed "widened appearance of the sellar cavity with an expansive intra and suprasellar formation"; MRI revealed an expansive formation (maximum longitudinal diameter 17 mm) with oval morphology and signs of intralesional bleeding, that exerted a mass effect on the optic chiasm by deforming it upwards. The picture was compatible with hemorrhagic pituitary apoplexy on a possible underlying adenoma. Visual acuity and visual field were normal. Hormonal tests showed hyperprolactinemia (237 ug/l,nv 4-23) with normal remaining pituitary tropins. cabergoline 0.75 mg/week was started. MRI at 8 weeks showed a significant reduction in volume of the lesion (max 12 mm).

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In both patients, an exome sequencing analysis is ongoing to search genetic defect causative of pituitary adenomas in childhood.

Conclusions: Even rare, it is critical to identify rapidly this entity due to the possible acute hypopituitarism that requires urgent steroid replacement; early surgical intervention is recommended on those with neurological defects. Our patients presented a similar clinical and radiological picture with a very different hormonal outcome.

P1-542

Clinical Manifestation and Treatment Outcomes of Pheochromocytoma and Paraganglioma in Children and Adolescents: A 26-year Single- Center Experience

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Purpose: Pheochromocytoma (PCC) and paraganglioma (PGL) (PPGL) are rare neuroendocrine tumors, and there is little information on how to treat them in children and adolescents. The objective of this study was to demonstrate the clinical presentation and treatment outcomes in children and adolescents with PPGL in a single Korean tertiary care hospital.

Methods: Korean patients diagnosed with PCC and PGL before the age of 21 were studied retrospectively for 26 years at a single center. We describe age, gender, family history, clinical characteristics, laboratory findings, pathologic findings, therapeutic approaches, and treatment outcomes.

Results: Of the 23 patients, 14 had PCC and 9 had PGL. At the time of diagnosis, the median age was 16.8 years (range: 6.8–20.8 years). Hypertension (41.7%) was the most prevalent presenting symptom, followed by headache (39.1%), palpitation (17.4%), and perspiration (17.4%). The plasma or 24-hour urine catecholamine and/or metabolite concentrations were markedly elevated in 14 patients (100%) with PCC and 8 patients (88.9%) with PGL, but were normal in one patient with carotid body PGL. Genetic tests were performed in 15 patients, and seven patients showed mutations in RET (n = 3), SDHB (n = 3), and VHL (n = 1). All patients had complete excision surgery, and three patients with metastasis.

Conclusion: According to this study, pediatric PPGL is extra-adrenal and bilateral, with a higher risk of genetic mutations. Genetic screening tests are strongly advised, and lifelong follow-up is required to detect recurrence and metastasis, given the hereditary predisposition to pediatric PPGL. Further research with a larger sample size and routine genetic screening is needed to better understand the genetic conditions and long-term prognosis of PPGL.

P1-543

Klotho response to treatment with GnRH agonist in children with central precocious puberty

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Background: Klotho is an anti-aging protein acting as a circulating hormone. Major physiologic activities attributed to klotho include regulation of phosphate and calcium homeostasis, aging, adipogenesis, and glucose metabolism. Pubertal children had higher klotho than prepubertal. Insulin like growth factor-1 (IGF-1) directly promotes klotho shedding. Klotho levels significantly correlated with IGF-1 standard deviation scores (SDS).

Objects: Elevated klotho levels during puberty may be associated with elevated IGF-1 concentrations, which may also be observed in central precocious puberty (CPP). We investigated the effect of GnRH agonist treatment on klotho levels in children with CPP and factors related with change of klotho levels.

Methods: Klotho levels were measured in 82 CPP girls aged 8.42 ± 0.65 years treated with GnRH agonist between March 2020 and May 2021. All subjects had samples obtained between before and 6 months after the treatment. Klotho levels were measured using an α-klotho ELISA kit. A compared t-test was used to compare continuous variables between before and 6 months after the onset of GnRH agonist treatment groups. Pearson's correlation analysis was examined to determine the relationship between α-klotho and other clinical variables. Subjects after 6 months of GnRH agonists treatment were considered prepubertal girls, and receiver operating characteristic curve used to discriminate the ability of α-klotho to detect CPP.

Results: After GnRH agonists treatment, peak LH, peak FSH, estradiol, alkaline phosphatase, and IGF-1 SDS were statistically significantly decreased in all subjects (p<0.001). α-klotho levels decreased from 2529.36 ± 999.51 pg/mL to 2147.50 ± 789.62 pg/mL (p<0.001) after 6 months of treatment with GnRH agonists. After adjusting for age and BMI SDS, α-klotho levels showed positive correlations with peak LH (r=0.274, p=0.014) before treatment, but no correlation after treatment. α-klotho showed a weak correlation with IGF-1 SDS when analyzed including all subjects before and after treatment after adjusting for age and BMI SDS (r=0.157, p=0.05). The area under the curve for α-klotho was 0.686 (95% confidence interval: 0.594–0.777, p=0.012) with 59.4% of sensitivity and 73.4% of specificity.

Conclusions: The results of this study suggest the role of α-klotho as a possible marker to detect CPP. Further studies to compare klotho levels between patient with CPP and prepubertal children and to establish cut-off levels for CPP are needed in the future.

P1-544

Long term effects of continuous subcutaneous infusion of recombinant LH and FSH during infancy on testicular function in congenital hypogonadotropic hypogonadism

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Context: We previously observed that continuous subcutaneous infusion (CSI) of gonadotropins in infants with congenital hypogonadotropic hypogonadism (CHH) can mimic the hormonal pattern of minipuberty.

Objective: Describe the peripubertal outcome in gonadotropins CSI treated patients.

Patients: A retrospective study was realised in Bicetre Hospital between 2004 and 2022. Follow-up data and long-term observations were available for 7 boys with HH, aged 12,9 years [12,6-13,3]; 4/7 with combined pituitary hormone deficiencies (CPHD) and ectopic neurohypophysis; 3/7 with isolated HH (IHH). 5/7 patients have cryptorchidism; Patients were treated at the mean age of 5.8 months [0.25-11] with rhLH and rhFSH CSI at a daily rate of 50 and 75-150 UI, respectively. As a retrospective control cohort, we provide data of eleven untreated CHH boys (age: 14,6 years [13–17.4 years], 6/11 with combined pituitary hormone deficiencies (CPHD) and ectopic neurohypophysis; 5/11 with IHH.

Results: In response to early gonadotropin CSI, serum testosterone and inhibine B levels increased from 0,02 ng/ml to 1,32 ng/ml [1,12-3,36] and from 90 [5-145] to 328 [185-578] pg/ml, respectively. Testicular volume (TV) increased from 0.28 ml [0.2-0.4] to 0.75 ml [0.4-0.9]. Orchidopexy was realized in 2/5 patients. Penis reached normal dimensions. In long-term follow-up, FSH and LH values were very low in the two groups. Inhibine B values available in 7/7 boys (35 pg/ml [19-134]), significantly differ from the controls (6 pg/ml [5-34]) (p=0,04)); TV was also significatively better in the CSI treated group (0,78ml [0,5-3]) versus untreated group (0,3ml [0,13-2,6] (p=0,012).

Conclusion: We describe the first long-term follow-up data in CHH boys treated with gonadotropin CSI. These results suggest that the effects of the gonadotropin infusion seem persistant at the beginning of the puberty. Follow-up should be continued until the end of puberty to assess spermatogenesis in these patients.

P1-545

X-Linked Central Precocious Puberty Associated with *MECP2* defects

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Background: Genetic causes of central precocious puberty (CPP) has been increasingly recognized, extending our knowledge of the triggering factors of human pubertal timing. Distinct etiologies remain to be elucidated in sporadic and familial cases. Methyl-CpG-binding protein 2 (MECP2) is a chromatin-associated protein that can activate or repress gene transcription, playing a role in neuronal maturation. It is encoded by *MECP2* gene located at chromosome Xq28, with high brain expression. Loss-of-function mutations in *MECP2* are usually associated with Rett syndrome, a severe neurodevelopment disorder with female predominance characterized by regression of acquired skills, such as communication and hand movements, seizures, and intellectual disability. Early pubertal development (early thelarche, pubarche and, less often, menarche) has been demonstrated in typical Rett syndrome girls.

Objective: We investigated whether *MECP2* defects are associated with an idiopathic CPP phenotype with or without mild neurodevelopmental abnormalities.

Methods: A total cohort of 331 multiethnic idiopathic CPP patients (310 girls; 38% familial cases) was investigated for MECP2 allelic variants. 133 CPP patients underwent multigene sequencing studies based on large-scale approaches (whole-exome sequencing n=62; targeted gene sequencing n=71) and a further 198 CPP patients were analyzed through MECP2 Sanger sequencing. Immunohistochemistry and immunofluorescence studies were performed in pubertal female mice to determine Mecp2 expression in hypothalamic nuclei.

Results: Three rare heterozygous exonic variants in MECP2 gene were identified in 5 girls from 4 unrelated families with CPP: a *de novo* p.Arg97Cys variant in two monozygotic twin sisters with CPP and microcephaly; a *de novo* p.Ser176Arg variant in one girl with sporadic CPP, obesity and autism; and a p.Ala6_Ala8dup insertion in two unrelated girls with sporadic CPP (one of them with a maternally inherited variant). These three exonic variants were predicted as likely damaging by in silico proteomic tools. Additionally, one rare heterozygous 3'UTR insertion in MECP2

(c.*36_*37insT) was identified in two unrelated girls with sporadic CPP (one with a maternally inherited variant and other with a *de novo* variant). These CPP girls did not manifest typical Rett syndrome. In female mice, experiments identified abundant staining for Mecp2 in multiple hypothalamic nuclei (arcuate, suprachiasmatic, and paraventricular) and co-localization of Mecp2 and GnRH within GnRH neurons, demonstrating Mecp2 expression in key hypothalamic nuclei responsible for GnRH regulation.

Conclusion: We identified rare dominant *MECP2* defects in multiple unrelated idiopathic CPP girls with or without mild neurodevelopmental abnormalities, revealing a new X-linked form of premature reactivation of the hypothalamic-pituitary-gonadal axis.

P1-546

Change of menarcheal age in schoolgirls living in Istanbul over the last 12 years

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Background: Menarche is the endpoint of a complex sequence of maturational events but is the unique marker of female puberty. Timing of menarche is a strongly heritable trait. However, secular trends suggest that lifestyle and/or environmental factors are important.

Objective: To assess the trend in age at menarche (AAM) in Istanbul over the last 12 years, and compare the patterns according to socioeconomic status (SES), education and body mass index (BMI).

Method: A cross-sectional study carried out between March 2022 and April 2022 on schoolgirls aged 9-18 years. A predesigned, pretested, structured and self-administered questionnaire was filled anonymously by the students. The data of AAM was included in the statistical analysis if the time of AAM is remembered precisely for months and years. A probit model was used to calculate the median AAM. The effect of the pandemics on AAM was assessed by comparing menarcheal age among the girls born before and after 2021. The findings were compared with those from the study performed 12 years ago at the same region of Istanbul.

Results: 1211 schoolgirls out of 7000 gave consent and filled the survey. The mean age was 13.8±1.7 years (median 14.2). The AAM was reported in 929 girls. The median AAM was 11.72 years (95% CI 11.41-11.91). The median AMM was reported 12.01 years (95% CI 11.92-12.11, n=679) and 12.03 years (95% CI 11.88-12.19, n=250) among girls attaining menarche before and after 2021 (p=0.02). The AMM was positively correlated with maternal AAM (p<0.0001) and negatively correlated with BMI-SDS, maternal and paternal education status (p<0.0001, 0.002, 0.009; respectively). The girls with BMI-SDS≥1.5 (n=86) had earlier menarche than the ones with BMI-SDS<1.5 (n=843) (mean 11.44 vs 12.1 years, p<0.0001). AAM was not significantly different among girls born with low birthweight (n=91) than the others (n=838) (median 11.99 vs 12.02 years, p=0.65). Among mother-girl pairs who reported AAM data (n=812), girls had a mean of 0.88 years (median 0.93) earlier menarche than their mothers. AAM was lower than that reported 12 years ago as 12.74 years (p<0.0001).

Conclusion: The present study denotes a significant downward trend in the menarcheal age of the girls living in Istanbul over the last decade. Although our findings suggest a strong contribution of genetic factors and BMI on AAM, but they do not support the influence of pandemics on AAM.

P1-547

Project to improve paediatric post-neurosurgical fluid management and to reduce the risks associated with Diabetes Insipidus (DI), Syndrome of Inappropriate ADH (SIADH) and Cerebral Salt Wasting (CSW)

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Background: Complex fluid balance problems are well established post-neurosurgery and traumatic brain injury (TBI). The triple-phase response requires fluid management strategies reactive to urine output as patients shift between DI and SIADH. Prevalence of CSW is controversial; but ensuring sodium homeostasis is central to safe fluid management. To improve clinical care for these complex patients an audit of existing institutional guidelines was undertaken. New guidelines were developed with structured educational packages for specialist teams involved, and subsequent assessment of their impact.

Method: Two periods were audited using set standards (table-1), before and after the quality improvements. All data was collected from the CQUIN neurosurgical database and electronic medical records; included were all paediatric patients having neurosurgical operations for posterior fossa (PFT) and supratentorial tumours (STT), plus TBI. A literature review of evidence-based practice, initial audit data and stakeholder feedback was used to develop new clinical guidelines and nursing standard operating procedures. Principles were of strict monitoring and adaptive fluid management strategies, implemented for all with active step down. Structured educational packages were designed for specialty medical and nursing teams involved to improve knowledge, consistency of approach and team working.

Results: Audit-1 January2017-June2018, n=80; Audit-2 January2020-June2021, n=30 (reduced neurosurgical operation numbers due to COVID-19 pandemic). All patients were managed within a high dependency setting; 26-33% initially in paediatric

intensive care. Step-down was to a neurosurgical/neurorehabilitation ward. Results comparison (table-1) demonstrated clinical, fluid balance and biochemical monitoring improvement. The number of clear fluid management plans documented post-operatively increased, leading to early recognition and management of evolving fluid-balance abnormalities. However, the recommended adaptive fluid management strategy was not always used. The endocrine team were involved earlier and in all complex cases. Significant Na fluctuations (>12mmol in 24 hours) remained similar (5vs6patients). These represented complex pituitary-hypothalamic pathology, plus one TBI. Feedback from patients and professional teams was of increased awareness, improved consistency of approach and communication.

Conclusion:

- Clinical guidelines revised using audited data, evidence-based literature review and stakeholder consultation have been adopted with effective change.
- Patient safety improved through effective post-neurosurgical fluid management and multi-professional team working.
- Regular feedback and continued education will identify areas for further improvement.

Table 1.

Standard	Audit-1	Audit-2	Fisher's test
Complete fluid balance charts	51%	77%	0.063
Fluid management plan post-op	64%	71%	0.7813
Electrolytes post-op	78%	94%	0.1816
Electrolytes 4-8hrly	18%	35%	0.1848
Endocrine team Involvement	14%	35%	0.0735
DDAVP prescription with endocrine team	60%	100%	0.444

P1-548

Legal degree of disability in childhood-craniopharyngioma survivors during long-term follow-up: Results of the HIT-ENDO study

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Background: Cranioparyngiomas are rare low-grade embryonic malformational tumors of the sellar/parasellar region. The prognosis after diagnosis during childood and adolescence is influenced by endocrine and hypothalamic long-term sequelae. A legal status of the degree of disability (GdB), according to the German Social Code Book V that is worthy of support provides financial means for psychosocial rehabilitation and participation of craniopharyngioma survivors. The aim of this study was to determine the association of clinical/psychosocial characteristics and quality of life (QoL) indicators with the resulting GdB.

Patients and Methods: HIT-Endo is a German registry study on craniopharyngioma patients aged ≤ 18 years at diagnosis and included before the year 2000. In a sample of 108 patients, the degree of disability and the association with endocrine, ophthalmological, neuropsychological and psychosocial parameters was analyzed after a mean follow-up period of 16 years (95% CI: 9.8-36.4). The Pediatric Quality of Life (PEDQOL) and the German daily life ability scale Fertigkeitenskala Münster-Heidelberg (FMH) questionnaires were used to assess health-related QoL and functional capacity, respectively.

Results: 44 patients (41%) did not receive a GdB, three patients (3%) received a GdB of 30-40, 43 patients (40%) a GdB of 50-90 and 18 patients (17%) the maximal GdB of 100. Higher GdB were associated with lower education, higher body mass index standard deviation and a higher degree of visual impairment and hypothalamic involvement of the craniopharyngioma. Patients with a GdB of 100 reported loss in physical and cognitive function, as well as fatigue, dyspnea, and pain conditions, and limitations in social and occupational contexts. They further had a lower functional capacity (FMH) when compared to those with a smaller GdB.

Conclusion: The GdB is associated with psychosocial and physical impairments and reflects the long-term consequences of craniopharyngioma during childhood and adolescence. A low functional capacity score as assessed by FMH may indicate a high GdB in later life of craniopharyngioma survivors.

P1-549

Genetic causes of combined pituitary hormone deficiency

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Introduction: CPHD is characterized by impaired production of GH and one or more other pituitary hormones. Genetic defects causing CPHD typically result in insufficient anterior pituitary gland development.

Aim: The aim of the study is to determine the genetic etiologies that lead tocombined hormone deficiencies. Todetermine phenotype genotype relationship with or without extra-pituitary anomalies.

Material and Methods: 27 CPHD cases between 2000 and 2022 were included inthe study. Genetic analyzes were performed with clinical exom sequencing panel based next-generation sequencing.

Results: The history, physical examination and radiological findings of 27 cases are listed in Table 1. Mutation frequency was

33,3 %. POU1F1 gene mutation was found in 3 patients (33%). PROP1, LHX4, HESX1, OTX2, FOXA2 and GLI2 mutations were detected in one patient each. Dysmorphic features as unilateral preaxial polydactyly, coloboma in the eye, strabismus and epicanthus were detected in the case with OTX 2 variant, coarse facial appearance, hypertelorism, right kidney agenesis in FOXA2 variant; cleft palate, micrognathia in GLI2 variant; microcephaly, flattened nasal root in HESX1, frontal bossing, low-set rotated ears, frontal bossing in LHX4 variant. Clinical and molecular features of the genes are summarized in Table2

Conclusions: Phenotype-genotype relationship is essential for follow-up and treatment options of CPHD.

Table 1. Clinical data of 27 patients withCPHD

	Clinical feature	Results
General data	Gender: M/F	70/30%
	Age at diagnosis (median)	3.10 (min-max: 0.04 -15.2)
Birth data	At term/preterm birth	78/22%
	Micropenis	53%
	Cryptorchidism	32%
	Prolonged neonatal jaundice	26%
Hormon deficiencies	At diagnosis	
GH	70%	
TSH	15%	
ADH	4%	
ACTH	11%	
Auxological data	Height SDS at diagnosis	-2.3 ± 1.4
MRI imaging data	Hypothalamic–pituitary abnormalities	81.5%
		48%
	• Anterior pituitary hypoplasia or aplasia	19%
		3.5
	• APH+ EPP	11%
	• Pituitary stalk abnormalities	
	• Neuropituitary ectopia	

P1-550

Clinical description of ten paediatric patients with rapid-onset obesity and clinical signs of ROHHAD-NET Syndrome

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Rapid-onset obesity with central hypoventilation, hypothalamic, autonomic dysregulation (ROHHAD) syndrome is a rare disorder characterized by respiratory failure and autonomic dysregulation with endocrine abnormalities. Some of these patients could also present with neuroendocrine tumors (ROHHADNET).

Aim: To evaluate the clinical, biochemical, treatments and outcome in a cohort of pediatrics patients with ROHHAD-NET syndrome follow in a single tertiary center

Subjects and Methods: Retrospective review of 10 medical records of ROHHAD-NET syndrome followed between 2007-2021. Data analyzed were: clinical, biochemical, therapeutic interventions and outcomes.

Results: Rapid onset obesity, identified for all 10 patients, was the first clinical sign (mean age at onset (MAO) 5.28 years). Neurobehavioral disorders were also an early manifestation presenting in 5 cases with a MAO of 5 years. Seven patients had central hypoventilation (MAO 6.8 years) and required BPAP mask

Table 2. Clinical and hormonal findings of combined pituitary hormone deficiency patients with mutations

Patient	PROP1	POU1F1	LHX4	HESX1	FOXA2	GLI2	OTX2
Number of patients	1	3	1	1	1	1	1
Gender	M	M/M/F	M	F	M	M	F
Week of gestation at birth	38 w	32w/34 w/38w	39w	37w	38w	38w	38w
Weigh SDS at diagnosis	-1.67 SDS	-0.89 SDS -0.36 SDS -0.4 SDS	-0.12 SDS	-2 SDS	-2 SDS	-2.7 SDS	2.5 SDS
Height SDS at diagnosis	-4.04 SDS	-2.86 -0.45 -2	-0.27	-2.2	-2.2	-1.6	-2.6
Hormone deficiencies/at diagnosis	GH	TSH GH TSH	TSH	ACTH	ACTH	ACTH	GH
Pituitary and cerebral imaging	Normal	Normal APH + EPP Normal	EPP	Normal	APH+EPP+Stal hypoplasia	Normal	Normal

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ventilation during sleep. One had transient obstructive sleep apnea related to a viral upper airway tract infection, partially corrected by tonsillectomy. All patients had hypothalamic dysfunction: disorders of water balance were the most frequent manifestation (n: 10), followed by hyperprolactinemia (n: 7), central hypothyroidism (n: 5), GH deficiency (n: 5), adrenal insufficiency (n: 2), precocious puberty (n: 2) and hypogonagotrofic hypogonadism (n: 2). Autonomic dysregulation was identified in 10 patients, being strabism the main clinical sign (n: 6). Tumors of neural crest origin (ganglioneuromas) were found in 5 patients with a MAO of 5.42 years. The localization were adrenal gland (n: 2) and mediastinum (n: 3). Other clinical findings included thrombocytopenia, celiac disease, enuresis, type 1 and type 2 diabetes, seizures, hypo/hypertension and primary hypothyroidism. Three patients died.

Conclusion: A high clinical suspicion and an early recognition is essential for a prompt diagnosis to provide timely respiratory support and minimize morbidity and mortality. Better characterization and the availability of a large cohort of patients are needed to increase the knowledgement regarding this syndrome and its etiology.

P1-551

Impact of the COVID 19 pandemic on the incidence of precocious puberty

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The 1st lockdown from March to May 2020 probably led to an increase in the number of cases of idiopathic central precocious puberty in several European countries. Two Italian studies showed this, as well as a Spanish and a Turkish one.

We performed a retrospective study with all the children who came to our department for a 1st appointment or a check-up for pubertal signs between 01/04/2017 and 31/03/2021. We checked the data of 765 files and kept only the children with a diagnosis of idiopathic central precocious puberty (onset before or at 8 years of age for girls and 9.5 years for boys) confirmed by hormonal assays and ultrasound data (LHRH peak test LH>7, estradiol >15 pg/ml, inhibin B >20 pg/ml, uterus over 35 mm +/- signs of impregnation). We focused our statistical analysis on girls because there was no difference of incidence in our male patients.

During the lockdown period and a few months after, from 01/04/2020 to 31/03/2021, we diagnosed 49 girls with idiopathic central precocious puberty, versus 50 girls in total during the 3 years before the COVID 19 pandemic (from 01/04/2017 to 31/03/2020). We also performed statistical analysis on weight, BMI, birth parameters, historic of familial idiopathic central precocious puberty, adoption and biological parameters such as LH/FSH ratio over the LHRH test.

In addition, we noticed some patients had rapidly progressive puberty with 1st menstruation before 10 years, less than 18 months after breast development. We also reported, in the post-lockdown period, some cases of precocious central puberty confirmed by the dosages (estradiol, LHRH test), which would regress after a few months with return of the dosages in the prepubertal norm.

We therefore confirm the increase in the incidence (x3) of recourse to our center for idiopathic central precocious puberty among girls during the year following the 1st lockdown due to the COVID 19 pandemic. However, the mechanism is unknown for the moment.

P1-552

Final adult height in children with central precocious puberty – a retrospective study

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Background: Central precocious puberty (CPP) is a premature activation of the hypothalamic-pituitary-gonadal axis. One of its negative effects is lower final adult height (FAH) due to premature epiphyseal closure. GnRH analogues act by desensitizing GnRH receptors and stopping the progression of puberty and prolonging growth period.

Objectives: We aimed to evaluate the effect of the GnRH analogue on FAH and identify factors that predict FAH in children with CPP.

Population and Methods: A retrospective study included 93 children (12 boys and 81 girls) with CPP or menarche before 10 years, that reached their FAH (68 with idiopathic (iCPP) and 25 with an identified likely cause of CPP (nCPP)). Clinical characteristics including FAH between the two groups were compared. We also compared FAH between the children treated with triptorelin depo (n=71) and untreated children (n=22). Finally, to determine predicting factors for FAH, in 81 girls with CPP multiple regression analysis was conducted. Target height (TH) was calculated based on parental heights. Predicted adult height (PAH) was calculated based on bone age, chronological age, height at diagnosis and ethnicity with BoneXpert software.

Results: The children with iCPP reached significantly higher FAH than children with nCPP (p=0.002). Negative SDS of FAH in both groups indicated lower FAH in children with CPP as compared to the general population. There was no significant difference in the FAH between the treated and untreated children. However, the study was retrospective and the decision to initiate treatment was individualised and not randomised. Nonetheless, the treated group gained 31.2 cm since CPP diagnosis up to the FAH as compared to 23.7 cm in the untreated group, while at the diagnosis the treated group was younger (median 7.52 y [Q1= 6.59; Q3= 8.18] vs. 8.85 y [8.48;9.24]), had lower height and BMI SDS and less advanced bone age.

Predicting factors for FAH revealed by multiple linear regression analysis were bone age at diagnosis, height at the end of treatment, TH SDS, PAH SDS, height at diagnosis SDS, BMI at diagnosis SDS, LH peak, age at initiation and at the end of treatment, and height at the end of treatment SDS (R2=0,74).

Conclusion: Children with nCPP reached lower FAH as compared to the iCPP group despite similar baseline characteristics. From CPP diagnosis, the treated children gained 7.5 cm more than the untreated; yet, the FAH was not different. Factors that influence FAH are numerous, and should be considered at individualized decision-making.

P1-553

Evaluation of the Frequency of Multiple Hormone Deficiency and Long-Term Data in Patients with Craniopharyngioma

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Introduction: Craniopharyngiomas can lead to pituitary insufficiency and long-term endocrine complications due to the location, invasive character and risk of recurrence, besides they known as histologically benign.

Aim: In this study, we aimed to evaluate the demographic, clinical features, endocrinological problems and follow-up findings in patient with craniopharyngioma in childhood.

Method: Admission complaints, demographic and clinical features, laboratory and imaging results and follow-up findings of the 27 cases whose were followed up between 2000 and 2020 were evaluated.

Results: Eleven (40%) of the cases were female and 16 (60%) were male. The mean age at diagnosis of the cases was 8.52±3.28 years, the mean follow-up period of the cases was 5.03±4.61 years. Headache was the most frequent complaint, in 13 (48%) of the cases; 8 (30%) had visual symptoms such as double vision, nystagmus, sudden vision loss, and blurred vision, 5 (18%) had short stature, 1 (4%) had increased appetite and rapid weight gain.

Average weight SDS at application: -0.01±1.88; height SDS: -1.36±1.64; BMI SDS: 0.59±1.74. At the time of diagnosis, 9 (33%) GH (growth hormone) deficiency, 12 (44%) central hypothyroidism, 2 (7%) adrenal insufficiency due to ACTH deficiency, 5 (19%) gonadotropin deficiency, diabetes insipidus was detected in 3 (11%) of them.

There were 16 (%60) patients who were started on growth hormone (GH) treatment and continued to be followed up regularly, and the mean age of onset of GH was 39.38±26.72 months. L-thyroxine treatment was started in 20 of the cases (74%) due to the development of permanent central hypothyroidism. Hydrocortisone treatment was continued after the operation in 18 (66%) of the cases. Sex steroid replacement was performed in 12 (44%) of the cases.

Tumor diameter was 38,5±12,92 mm and there was a positive correlation between tumor diameter and obesity frequency in magnetic resonance imagine (r: 0,823; p:0,03). Recurrence was observed in 10 (37%) of 27 patients. Of the 10 cases with recurrence, 7 were operated for the second time, and the other 3 were treated with radiotherapy.

Conclusion: It is known that mortality and morbidity increase as tumor diameter increases in cases with craniopharyngioma. In our study, the correlation between the tumor diameter at the time of diagnosis and the development of obesity highlights the importance of frequent follow-up of children with increased tumor diameter in terms of obesity and other endocrine comorbidities that may develop in the follow-up.

P1-554

Oligogenic inheritance may explain the phenotypic variability and incomplete penetrance of deleterious *GLI2* variants in congenital hypopituitarism

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Background: *GLI2* encodes a zinc-finger transcription factor expressed in the developing hypothalamus and in Rathke's pouch, the embryonic precursor of the pituitary gland. Pathogenic *GLI2* variants have been implicated in the etiology of the broad clinical spectrum of congenital hypopituitarism (CHY): holoprosencephaly, midline facial abnormalities, Culler-Jones syndrome, combined pituitary hormone-deficiency (CPHD) and isolated GH-deficiency (IGHD) with hypothalamic-pituitary anatomical abnormalities. However, *GLI2* variants show a highly variable expressivity and incomplete penetrance, suggesting the possibility of a complex multifactorial genetic component.

Aims: Characterization of genotype-phenotype correlations in a cohort of patients with CHY and deleterious *GLI2* variants.

Subjects and Methods: 156 patients with CPHD (n=109), septo-optic dysplasia (SOD; n=35) or IGHD with pituitary abnormalities (n=12), were analyzed by targeted NGS with a custom gene panel, designed for the analysis of the coding sequences and intron/exon transitions (+/-50bp) of 310 genes implicated in the etiology of CHY and hypothalamic-pituitary development.

Results: Predicted deleterious *GLI2* variants were identified in 14/156 (9.0%) cases with a clinical diagnosis of CPHD. All (14/14) also presented with a burden of additional inherited, deleterious variants in multiple genes involved in the regulation of pituitary development signaling pathways (SHH, BMP/TGFb, FGF, WNT, NOTCH, NODAL). *GLI2* variants included 6 truncating [p.(Arg1226*), p.(Leu709Trpfs*15), p.(Ser267*),

p.(Ser859Profs*53), p.(Gln1224*), and p.(Leu182Profs*169)], all classified as pathogenic (ACMG), and 9 missense variants (ACMG: VUS). All patients with *GLI2* variants had pituitary hypoplasia, 75% had also ectopic neurohypophysis, and those with truncating variants had both conditions. These presented GH and TSH deficiency and 3/6 also ACTH deficiency. Among the 9 probands with non-truncating variants, 7/9 were GH and TSH deficient and 2/9 were also ACTH deficient. Other intra-familiar associated traits observed included postaxial polydactyly, ogival palate, bulbous nose, nephrourological abnormalities, and holoprosencephaly, with midfacial hypoplasia and hypotelorism being the most penetrant among the studied relatives (n=25) of the 14 probands.

Conclusions: All probands with *GLI2* variants presented with additional predicted deleterious variants in other genes involved in pituitary development signaling and function. This may explain the highly variable intra-familiar expressivity and incomplete penetrance observed, which may be determined by the combination with additional inherited variants in other relevant genes.

Pituitary hypoplasia and midline craniofacial abnormalities appear to segregate with complete penetrance and variable severity in patients with *GLI2* variants.

No *GLI2* variants were observed in SOD patients, suggesting that *GLI2* is not implicated in the etiology of SOD.

P1-555

Management Options for Adolescents with Abnormal Uterine Bleeding, according to their Demographic, Clinical and Laboratory Characteristics

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Background: Abnormal uterine bleeding is a common complaint among adolescents, however, there are no evidence-based guidelines for their treatment, and there is a paucity of outcome data available.

Objectives: To describe the characteristics of adolescents with menstrual abnormalities and to describe management protocol outcomes.

Methods: This is a retrospective study, based on information from medical records of patients aged 10-18 years, evaluated in the integrated adolescents gynecology-endocrinology clinic at the Shamir (Assaf Harofe) medical center in Israel for abnormal uterine bleeding from January 2007 to December 2020. Management protocols included cyclic oral progesterone (CyP), oral contraceptives (OCP), Metformin and Tranexamic acid (TA).

Results: One hundred and twenty-three teens were evaluated for abnormal menses, including heavy bleeding in 46.3%, oligomenorrhea in 32.5%, primary amenorrhea in 13.8%, and secondary amenorrhea in 7.3%. Following evaluation, 54 teens were diagnosed with polycystic ovary syndrome (PCOS), 34 with heavy menstrual bleeding (HMB), 7 with primary ovarian insufficiency (POI), and 7 with hypothalamic-pituitary insufficiency (HPI). Menstrual abnormalities resolved over time in 21 teens, diagnosed with an immature axis. Those with PCOS were older, presented more frequently with oligomenorrhea, had a higher body mass index (BMI), and a higher degree of hirsutism. A third of them needed to switch from CyP to OCP. Patients with HMB had significantly lower hemoglobin and were mainly treated with TA.

Conclusions: Management choices for adolescents with abnormal uterine bleeding should depend on age, blood count parameters, and etiology. Teens diagnosed with PCOS may be offered CyP or OCP, while oral TA should be offered to teens with HMB.

P1-556

Surprisingly high frequency of pituitary stalk thickening in pediatric patients during COVID-19 pandemic in Chile

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Introduction: Pituitary stalk thickening (PST) is a rare condition in pediatric patients. As there are few studies published in pediatric population, the definition has been difficult to establish. The etiologies involved in PST can be divided in neoplastic, congenital, inflammatory/infectious or autoimmune diseases. In children the most frequent causes are neoplastic, followed by congenital lesions. The inflammatory/infectious and autoimmune diseases are rare.

Methods: During the pandemic of COVID-19, we observed an increased incidence in the diagnosis of pediatric patients with PST in Chile, compared with previous years. A multicentric retrospective chart review of clinical, radiological and histological data was conducted on patients with confirmation of PST that presented during COVID-19 pandemic in Chile. The diagnosis of PST was made in patients with neuro-ophthalmic symptoms or pituitary dysfunction, who had a cerebral MRI with a pituitary stalk 3 mm or more at pituitary insertion or 4 mm or more at the optic chiasm, based on consensus guidelines.

Results: A total of 11 patients were diagnosed with PST during the pandemic period, most of them were girls (82%). The mean age at the onset of symptoms was 10.1 years (range 1.1-18). The most common causes were neoplasms. Germinal cell tumors (GCT) were diagnosed in 10 patients and Langerhans cell histiocytosis in 1 patient. Tumor markers for GCT were negative in serum and cerebrospinal fluid in all patients (alpha-fetoprotein and chorionic

gonadotropin). All patients presented with central diabetes insipidus and at least one anterior pituitary hormonal deficit. Thirty six percent had an abnormal campimetry. The diagnoses were confirmed by biopsy in all the patients and four patients required a second biopsy to confirm the diagnosis.

Discussion: A surprisingly high frequency of PST presented during the COVID-19 pandemic among Chilean pediatric patients. The most frequent diagnosis was GCT. All had negative tumor markers, with a greater incidence in girls, opposed to data previously reported.

The etiological diagnosis still remains challenging, and 36% of the patients required a second biopsy. It is important to establish new markers to assess patients with PST in order to make a prompt diagnosis.

Further research is needed to establish if there is a causative relationship between this high frequency of PST and the COVID-19 pandemic, especially among girls.

P1-557

Pituitary tuberculosis and hypothalamic obesity can be reversed by prolonged anti-tuberculosis treatment

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Background and Methods: Sellar and suprasellar tuberculomas are extremely rare in children and most often patients present with headache, vomiting, visual disturbances, and hypofunction of the pituitary gland. Here, we report a girl with hypothalamic obesity, that recovers after antituberculosis treatment.

Findings: An 11-year old girl presented with headache, fever and anorexia that progressively evolved into an encephalopathic status with cranial nerve paresis: ptosis on the right side and bilateral paresis of the abducens nerve. Brain MRI showed meningeal contrast capture along cranial nerves II (including optic chiasm), III, V and VI bilaterally and multiple contrast enhancing brain parenchyma lesions. Tuberculin skin test was negative but interferon-gamma release assay was positive. The clinical and radiological working diagnosis was consistent with tuberculous meningoencephalitis. Pulse corticosteroids for 3 days and quadruple antituberculosis therapy were started and the girl demonstrated obvious improvement of her neurological symptoms. However, after a few months of therapy she developed remarkable hypothalamic obesity and growth arrest. She gained 20 kg in one year. Her hormone profile revealed insulin resistance (homeostasis model assessment-estimated insulin resistance 6.8) and growth hormone deficiency (circulating insulin-like growth factor-I 104 μg/L (-2.4 SD)). Repeat brain MRI showed a decrease in basal meningitis, but increased parenchymal lesions in the hypothalamic region extending medially into the nucleus lentiformis, with now a voluminous tuberculoma at this site. Antituberculosis treatment was continued for a total of 18 months. The patient improved clinically, she regained her pre-illness BMI and her growth rate increased. On the hormonal side, the disappearance of insulin resistance (HOMA-IR 2.5) and of growth hormone deficiency (circulating IGF-I 175 μg/L (-1.4 SD)) was noted, and her last brain MRI showed a remarkable volume reduction of the suprasellar tuberculoma.

Conclusion: Pituitary tuberculosis can have a very dynamic presentation during the active stage of the disease, which can be reversed by prolonged anti-tuberculosis treatment. Previous studies showed that the tuberculous process can also cause long term and permanent changes in the hypothalamic-pituitary axis. Prospective studies are however needed in the pediatric population to know the exact incidence and type of endocrine dysfunction.

P1-558

Simultaneous quantification of 51 steroids in pediatric plasma and urine samples by LC–MS/MS

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Quantitative analysis of endogenous and exogenous steroid hormones is an important step for our understanding of the causes of endocrine disorders in pediatric. In this study, we developed a method to simultaneously quantify endogenous and exogenous steroids in pediatric urine and plasma. Ultra-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to simultaneously quantify steroid hormones in children plasma and urine. Under the optimum conditions, the method was achieved with a BEH RP18 column within 18 min. The method had excellent linearity (R2≥0.990) and a low quantification limit of 0.01~1 ng/mL. And the precision of most steroid hormones is less than 20%, and the recoveries range from 80% to 140%. The results

show that the method has good stability and sensitivity, and can be successfully used for the analysis of steroids in human plasma and urine. Compared with the control group, the endogenous steroids (corticosterone, cortisone, cortisol, etc.) in the experimental group significantly decreased and the fold change was 1.5-2.1-fold, while the exogenous steroids (prednisone acetate and triamcinolone diacetate) increased by 1.84 and 1.86-folds. The present findings demonstrate that the LC-MS/MS method enables rapid and robust quantification of multiple steroid hormones in plasma and urine samples.

P1-559

Circulating MKRN3 levels in 5 CPP girls with MKRN3 gene mutation

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Background: MKNR3 is a paternally expressed gene whose loss-of-function mutations cause Central precocious puberty (CPP). The precise molecular disruption produced by MKRN3 mutations remains unclear albeit protein structure suggests MKRN3 could play a role in proteasome ubiquitination. Circulating MKRN3 levels has been negatively associated to LH peak, estradiol and kisspeptin in idiopathic CPP and healthy controls. However, no literature data is available for plasma MKRN3 levels in CPP harbouring a MKRN3 mutation.

Our aim was to investigate for the first time a possible correlation between circulating levels of MKRN3 and different types of MKRN3 mutations.

Material and Methods: we selected five girls with familial CPP carrying different mutations in MKRN3 identified by direct sequencing of the coding region. CPP diagnosis was based on telarche onset before 8 years of age and LH-peak response to GnRH test >5mUI/mL. Circulating MKRN3 levels were measured by Biocompare ELISA assay kit (sensitivity 4.688 pg/mL and inferior detection limit of 7.8 pg/mL). Additionally, in two CPP patients we performed allelic expression analysis by expressed single-nucleotide polymorphism (SNP)-based approach. RNA was extracted from blood white cells samples of patients and their fathers, PCR analysis on RNA retro-transcripts was performed.

Results: Median age of our cohort at diagnosis was 7.6 years old. Two new mutations p.Gln352Arg and p.Ser165Cys, were identified previously described in literature. Subject 1 harbours a frameshift mutation (Pro160Cysfs*14) and an undetectable plasma MKRN3 level. Subjects 2, 3 and 4 carrying missense mutations, namely p.Ser165Cys, p.Arg328Cys and p.Gln352Arg, show divergent circulating plasma protein levels, respectively 27.32pg/mL, 40.56pg/mL and undetectable. Interestingly, patient with a non-sense mutation p.Cys410Ter reported low but measurable circulating levels (12.72 pg/mL). Allelic expression analysis was performed in patients 4, 5 and in their parents confirmed patients expressed MKRN3 paternal allele. Same analysis for other patients is ongoing.

Discussion and Conclusions: No correlation between circulating MKRN3 and type of mutation has been identified, remarkably circulating MKRN3 protein levels were detectable even in presence of a non-sense mutation, while missense mutation shown an unpredictable behaviour. Allelic expression analysis excluded that detected protein levels were due to reactivation of the maternal allele, consistent with the expression of wild-type protein in humans and mice. Unlike what has been proved for DLK1 mutations, these preliminary data demonstrate circulating MKRN3 could not be used as a potential screening tool for the diagnosis of familial CPP due to MKRN3 mutations.

P1-560

Craniopharyngiomas in children: Hormonal profile and regional complications

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Background: The craniopharyngioma is a non-endocrine tumor, developed along the infundibulo-pituitary axis, from the third ventricle to sphenoid, histologically benign but locally invasive. It is a tumor with serious complications because of its location, its considerable potential for extension, its tendency to recur, and its adhesions to neighbouring structures. Our aim is to assess hormonal profile, neuro-ophthalmological and metabolic complications at the diagnosis of craniopharyngiomas in children.

Patients and Methods: It is a multicentre Cross-sectional descriptive study in the town of Oran, with prospective and retrospective data collection. MRI, hormonal, biochemical and ocular tests, made the diagnosis. Data entry and analysis were performed with CDC Epi Info version 6 (USA), SPSS 20, Statistica10.

Results: In our study, we collected 35 non-adenomatous tumours in children (age ≤15 years), among them 13 craniopharyngiomas (37.1%), sex ratio boys/girls at 2.3, and average age at 7.5±3.2 years (2-13). Mean consultation time was 10.5±8.3 months. Circumstances of discovery: headaches - visual disturbances (76.9%), growth retardation (15.4%) and polyuropolydipsia syndrome (7.7%). Average dimensions (mm±SD): average height 35.1±15.4, transverse diameter 30.1±13.7, antero-post diameter 34.0±15.3, extremes 15-95 mm. Extensions (percentage): Supra sellar (85.5), Infra sellar (16.2), posterior (21.1), Multidirectional extensions (35.5). Signs of anterior pituitary insufficiency 89.2%, thyrotropic deficiency 59.2%, corticotropic deficiency 44.1 % and growth hormone deficiency 25%, Hyperprolactinémie (PRL >25 ng/ml) 23.0%. Complications: hypothalamic syndrome 30.8%, epilepsy 11.5%, diabetes insipidus 23%. Neuropsychiatric complications (55.1%), ophthalmological (79.8%), blindness 23%, hydrocephalus 68.7%.

Discussion: Significant pituitary, hypothalamic and neuro-visual morbidity accompanied craniopharyngiomas. The consequences of a delay in diagnosis increases the frequency and severity of complications, hence the need for early diagnosis in order to control this morbidity, the burden of which is considerable on the health system.

P1-561

A new DLK1 defect in a family with idiopathic CPP: elucidation of the male phenotype

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Introduction: Central precocious puberty (CPP) is due to premature activation of the hypothalamic-pituitary-gonadal axis. Mutations in the imprinted gene MKRN3 are the most common monogenic form of CPP. Recently, attention was directed to DLK1, another imprinted gene. Defects in this gene resulted to be a rare cause of CPP in girls and adult women with precocious menarche, obesity and metabolic derangement.

We aimed to investigate a cohort of female and male patients with idiopathic CPP, negative for MKRN3 defect, by molecular screening for DLK1 defects.

Material and Methods: This is a multicenter academic hospital center.

Gene sequencing of DLK1 gene was performed by Sanger sequencing. Circulating levels of DLK1 were measured in those with DLK1 defects.

Patients: We enrolled 14 girls with familial CPP and 13 boys with familial or sporadic CPP.

Main outcomes measures: description of clinical and biochemical characteristics of patients with DLK1 defect

Results: A novel heterozygous mutation in DLK1, c.288_289insC (p.Cys97Leufs*13), was identified in a male proband, in his sister and their father. Age at onset of puberty was in line with previous reports in the girl and 8 years in the boy. The father with reported untreated CPP showed short stature. No metabolic derangement was present in the father except hypercholesterolemia. Undetectable Dlk1 serum levels indicated the complete lack of protein production in the three affected patients.

Conclusion: A DLK1 defect has been identified for the first time in a boy, underscoring the importance of genetic testing in males with idiopathic or sporadic CPP. The short stature reported by his untreated father suggests the need for timely diagnosis and treatment of subjects with DLK1 defects

P1-562

DNA methylation status of MKRN3 in puberty: studies in Central Precocious Puberty girls and in pubertal mouse

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Background: Makorin RING finger protein 3 (MKRN3) is an important factor located on chromosome 15 in the imprinting Prader-Willi syndrome - associated region. Imprinted MKRN3 expressed in hypothalamic regions essential for puberty initiation and mutations have been found in patients with central precocious puberty (CPP). CPP caused by the early activation of pulsatile Gonadotropin releasing hormone (GnRH) secretion is clinically defined by the early maturation of the entire hypothalamic-pituitary gonadal axis and the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. DNA methylation is an epigenetic process associated with the control of expression of several genes. The aim of this study is to investigate the promoter methylation status of MKRN3 in CPP patients and in the hypothalamus of mouse prior, during and after puberty.

Methods: This study was performed on 26 girls with CPP tested negative for mutations in the coding region of MKRN3 and DLK1 compared to healthy controls. Genomic DNA was extracted from peripheral blood samples. Imprinting status was evaluated in all samples by multiplex ligation-dependent probe amplification (MLPA). In addition, promoter methylation was studied by bisulfite conversion followed by Sanger sequencing (bisulfite-sequencing). Also, promoter methylation status of Mkrn3 was examined by bisulfite-sequencing both in hypothalamus and peripheral blood collected from mice at three developmental stages; pre-pubertal, during puberty and post-pubertal.

Results and Conclusion: The imprinting status of the PWS locus in the 26 CPP patients was normal. In addition, the CpG sites of the promoter region of MKRN3 was hypermethylated both in CPP patients and healthy controls indicating that MKRN3 gene is silenced in peripheral blood cells. Hypermethylation of Mkrn3 promoter was also observed in mouse genomic DNA from peripheral blood samples in all three developmental stages; pre-pubertal, during puberty and post-pubertal confirming our observation in human peripheral blood samples. However, the methylation status of Mkrn3 promoter CpG sites in mouse hypothalamic samples was significantly differentiated when compared to peripheral blood samples as well between the three developmental stages. Our results suggested that Mkrn3 promoter methylation in hypothalamus may be considered as an important mechanism in the epigenetic regulation during puberty.

P1-563

Transient multiple pituitary hormone deficiency in critically ill pediatric patients

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Objective: Hospitalization in pediatric intensive care unit due to critical illness may be life threatening condition associated with severe acute physical stress and concomitant hormonal changes. Whether these changes represent an adaptive response or need to be treated is still not known.

Methods: Pituitary hormones evaluation in four patients who were hospitalized in pediatric intensive care unit due to different severe diseases accompanied by transient multiple pituitary hormone deficiency.

Results: The most common pituitary hormones alterations included deficiency of growth hormone axis, gonadotropins and thyroid stimulating hormone, but other pituitary hormones may be involved as well. Anterior pituitary hormonal function fully recovered within 10-14 days, without administration of hormonal replacement treatment. If posterior pituitary was also involved (i.e. transient deficiency or over secretion of anti-diuretic hormone), fluid restriction or a short treatment with desmopressin was indicated. Despite high cortisol and low insulin growth factor-1 levels, both predictors of poor intensive care unit outcome, all our patients recovered.

Conclusions: Hospitalization in pediatric intensive care unit due to severe critical illness may be accompanied by transient multiple pituitary hormone deficiency ("sick pituitary syndrome"). Whether this reflects compensatory mechanism to preserve energy sources and therefore should not be treated, or whether pituitary hormone replacement treatment should be initiated when hormonal deficiencies persists for prolonged period requires further research.

P1-564

Adenohypophyseal Hyperfuction in Childeren and Adolescents with McCune-Albright Syndrome

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Background: McCune-Albright Syndrome (MAS) is a rare disease caused by somatic gain-of-function mutations of the GNAS gene, presenting with fibrous dysplasia (FD), cafe-au-lait spots and gonadotropin-independent precocious puberty (PP). Adenohypophyseal hyperfunction syndromes is reported uncommon but potentially severe complication of MAS.

Method: A prospective study was performed to evaluate the prevalence of the pituitary hyperfunction syndromes in children and adolescents with MAS.

Result:

1. From 2002 to 2019, 175 girls who presented PP were diagnosed MAS. First visiting age was 4.00 (0.75-8.17) years. 15 girls (8.6%) had pituitary hyperfunction, in whom, 7 cases (46.6%) were typical types, 7 cases (46.6%) had cafe-au-lait spots accompanied with pp, and 1(6.8%) had PP only.
2. In the 15 cases, only 3 were confirmed pituitary adenomas by MRI scans,2 were macro-adenomas, another one was micro-adenomas. 5 cases had GH excessive accompanied with hyperlactinemia, while 8 had hyperlactinemia only, and 2 had isolated excessive GH secretion. In cases with excessive GH secretions, fasting GH levels were 1.02-22.28 ng/ml, and the standard deviation scores (SDS) of serum levels of IGF-1 were 2.17(-0.9-3.85SD). GH levels after oral glucose tolerance tests were 0.97-20.56ng/ml. Serum PRL levels in girls with hyperlactinemia ranged from 42.85-1036ng/ml. 7 patients also had other endocrinopathies: 4 hypercortisolism, 3 thyroid abnormalities.
3. In patients with hyperlactinemia, only 3 girls with typical traid occurred lactation. 1 had hyperlactinemia since 4.5 years old, but presented lactation, accompany with over growth and facial, extremities asymmetric at 14.33 years of age. Another one had normal pituitary functions at first visiting, but had hyperlactinemia and lactation 5 years later.
4. All accepted letrozole or tamoxifen treatment for the PP. In patients with lactation, Bromocriptine was combined. GH and PRL levels decreased in 2cases after treatment but still fluctuated. One had transsphenoidal pituitary tumor resection finally.

Conclusion:

1. Adenohypophyseal hyperfunctions is rare in children wiith MAS, and it is more common in patients with typical traid or combined with FD.
2. Although adenomas can be found, normal findings or adenohypophyseal hyperplasia can present in some children who have pituitary hyperfunctions. The status of adenohypophyseal hyperfunction can be variable from mild to severe along with age. Therefore, long-term follow up is recommended in the cases with high risks, even though no clinical manifestations presented or only negative findings by MRI scans.
3. Hyperlactinemiar can be corrected by bomocriptine in children with, however, in some cases other therapy may be needed.

P1-565

Adult Height is impaired in females with Medulloblastoma and hypogonadism: Impact of Pubertal Timing

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Introduction and Aim of the Study: girls with previous pediatric medulloblastoma (MB) are at risk of short stature and impairment of the hypothalamic pituitary gonadal function due to multiple risk factors; our aim was to assess the impact of hypergonadotropic hypogonadism (HH) on growth up to final height (FH) in females with or without growth hormone deficiency (GHD).

Methods: anthropometrics (height-Ht-SDS,BMI-SDS,Tanner stage,distance from target height- ΔTH) and biochemical data (LH,FSH, estradiol) of 30 females diagnosed with MB at the age of 6.7±3.3 years (at least 10 years old at last visit) were retrospectively collected at relevant time-points: first endocrine visit-T0 (9.2±3.9yrs); at suspected biochemical pubertal start-PS (defined as detectable serum LH/estradiol, n=16/30,8.1±1.4yrs); at Tanner B2 (n=25/30, 10.9±1.3yrs); at GHD diagnosis (n=21/30, 11.0±2.4yrs), six months after Tanner B2 (n=16/30,11.7±1.2yrs), at HH diagnosis (n=12/30,13.5±1.4yrs) and at FH (n=21/30, 15.4±1.6yrs; 16/21 with GHD). GHD patients were treated with rhGH therapy. Eleven girls underwent the standard risk, n=19 the high risk protocol and n=26 craniospinal-radiotherapy (CSRT 32.3±8.3 Gy). HH was defined as Tanner-B1 at 13 yrs (n=4) or as arrested pubertal progression for 12 months (n=8).

Results: There were no differences in cancer risk grading,RTCS dose and GHD (yes/no) between HH and non-HH females.HH and non-HH females presented a progressive height decline independently of GHD (T0 -0.9±1.2 vs -0.6±1.2 SDS;Tanner B2 -1.1±1.0 vs -0.7±1.0 SDS,respectively) with HH girls showing a steeper decrease of stature at HH diagnosis (-1.8±1.3 SDS), an absent catch-up after estrogen-replacement (ERT) compared to non-HH girls at FH (-1.8±1.0 vs -1.0±1.2 SDS) and a reduced final ΔTH (-1.6±0.7 vs -1.0±1.2 SDS);FSH values were elevated in HH compared to non-HH females at T0 (53.1±40.4 vs 11.4±16.0 IU/L,P=0.003),at Tanner B2 (54.9±47.1 vs 18.0±17.9 IU/L,P=0.02),after six months PS (73.9±38.7 range 33.7-114.1 vs 20.1±16.6 IU/L range 6.5-54.3,P=0.009).HH was predicted by FSH values at T0 in logistic regression analyses (R2 0.291,P=0.02),while FH by height (β 0.87,P<0.0001) and Tanner stage (β 0.32, P=0.02) at T0 in multiple regression analyses (R2 0.598).

Conclusions: the study shows that height is impaired in females with childhood-onset MB and HH; high FSH values are predictive of future HH before the age of 10 years even when spontaneous puberty occurs. ERT started an earlier age could improve height outcome.

P1-566

Cystic Giant Prolactinoma in Childhood

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Giant prolactinomas are rare tumours, with a prevalence of 0.5–4.4% among all pituitary tumours. In the literature, relatively few series describing their management and outcomes are available; moreover, only individual case reports of giant prolactinomas in children have been documented.

We report a 10-year-old boy presented with painless progressive vision loss, insidious in onset, and bitemporal headache of six mounths duration. On physical examination; height: 134.2cm (3-10p), weight: 34 kg (25-50p), BMI: 20kg/m2 (50-75p), prepubertal (Tanner stage 1) other system examinations were found to be normal. Magnetic resonance imaging showed supra-parasellar area, cavernous sinus, both internal carotid arteries, right temporal fossa and optic chiasm a mass with an extending cystic component was detected. The tumour had a maximum diameter of 42x40x46 mm. The laboratory investigations detected elevated prolactin levels (8730ng/ml), TSH: 2.83μιu/mL, fT4: 0.83 ng/dl, FSH: 0.41 ιu/l, LH: <0.2 ιu/l, ACTH: 17.9 pg/ml, Cortisol: 14.2 μg/dl, IGF-1: 141ng/ml(-2;-1SD), IGFBP-3: 4440ng/ml(0;-1SD). The patients were firstly partial reduction in size of the tumours and started on dopamine agonist therapy Histopathological and immunoisthochemical exams described prolactin-secreting adenoma features. Proliferation markers, Ki-67 expression:15 % (≥ 3% high) and mitotic count:8 (The number of mitoses observed is >2 per 10 high-power fields).

Nowadays, after nine months from diagnosis, dopamine agonist treatment leading to reductions in tumor sizeş (12x5 mm) and prolactin levels (13 ng/ml) in the normal range. After resection and dopamin agonist therapy visual function stabilized.

Conclusion: Giant cystic prolactinomas in childhood are extremely rare. Having very high prolactin levels, diffuse invasion of the mass and High KI-67 index that is expected to have a bad prognosis. Short-term therapy with cabergoline together with a pituitary surgery in our patient was the key for the successful management, achieving biochemical and clinical remission in our patients.

Keywords: Cystic Giant Prolactinoma, Hyperprolactinemia, KI-67 Index, Dopamine Agonist Treatment, Endoscopic Transsphenoidal Surgery.

Sex Differentiation, Gonads and Gynaecology, and Sex Endocrinology

P1-169

Analysis of the GHR gene polymorphism in a non-disgenetic 46,XY DSD cohort without molecular diagnosis

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Background: Being born small for gestational age (SGA) is an associated condition to nonspecific 46,XY DSD (without molecular diagnosis and with no specific disorders of undermasculinization). However, the underlying mechanism of the relationship between the presence of genital abnormalities and intrauterine growth restriction is unknown. The GH-IGF system is crucial for sex differentiation in mice and in humans, members of this system were detected in embryonic and fetal gonads. Furthermore, the GHR gene polimorfism (GHRd3) has been associated with decreased fetal growth and lower birth weight.

Aims: To analyze the genotypic frequency of GHRd3 gene polymorphism in undervirilized undiagnosed 46,XY DSD patients according to fetal restriction, and its relationship with gonadal function in minipuberty.

Methods: A cohort of 46,XY DSD patients follow in a single tertiary pediatric center was evaluated (n=187). Birth weight and length standard deviation were calculated according to gestational age (Intergrowth21). The identification of GHR genotypes GHRfl and GHRd3 were analyzed by multiplex PCR assay in nonspecific 46,XY DSD patients. Genotypic frequency of GHRd3 was evaluate according to fetal restriction and compared with the allelic frequency in control subjects (n=159). Serum LH, FSH, Testosterone, and AMH levels were analyzed according fetal restriction and the genotypic variants of the GHR gene.

Results: SGA was found in 25.4% of the 46,XY DSD cohort. Molecular diagnosis was achieved in 38%. The frequency of SGA was higher in non-disgenetic patients without molecular diagnosis and apparently normal testicular function ($p < 0.05$). In these patients no difference was found in the frequency of GHRd3 allele polymorphism among SGA and non-SGA, neither the control group (p=ns). In these subjects, the parameters of gonadal function during minipuberty were not different according the GHR genotypes or SGA condition.

Conclusions: The frequency of being born SGA in 46,XY DSD patients was higher in those patients with nonspecific 46,XY DSD. In this group, the allelic frequency of the GHRd3 gene polymorphism was similar to controls irrespectively of being born SGA. Furthermore, testicular function during minipuberty seems to be unrelated to the GHR genotype and fetal restriction. More patients and further studies are needed to evaluate these associations, and to clarify the role of other early factors involved in early embryonic growth and development, and in gonadal differentiation.

P1-170

Increased Circulating Levels of Myo-inositol in Girls with Polycystic Ovary Syndrome

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Background: Myo-inositol (MI) is a polyol involved in intracellular signaling pathways of insulin and MI has been used orally for therapeutic purposes in girls and adult women with polycystic ovary syndrome (PCOS) with variable success. As yet, serum MI levels have not been assessed in girls with PCOS.

Aim: Our primary goal was to compare serum MI levels in girls with PCOS with those in healthy peers. Secondary goal was to investigate the associations of serum MI with several gluco-insulinaemic variables, biochemical indices of hyperandrogenism, thyroid function tests and some metabolic variables.

Setting: Tertiary care centre.

Patients and Methods: Thirty-nine consecutive, treatment-naïve girls with PCOS (15.9±1.1 yr) and39healthy peers (16.0±1.1yr) were enrolled. Clinical examinations were performed using standard methods. Fasting blood samples were drawn from girls with PCOS for hormonal assessments to rule out other causes of oligomenorrhea and/or hirsutism and oral glucose tolerance test was performed to calculate insulin sensitivity index (ISI) (Matsuda index). Serum MI levels were measured using high performance liquid chromatography. Fasting blood samples were also drawn from healthy controls to measure serum MI and anti-mullerian hormone (AMH) levels.The girls with PCOS were stratified into subgroups according to **a**-abdominal obesity status, **b**-metabolic syndrome (MetS) status based on International Diabetes Federation criteria, **c**-having reduced ISI; i.e. Matsuda index less than2.5, **d**-having increased free androjen index(FAI); i.e.FAI>6.1.Serum MI levels were compared within the subgroups. Multivariable regression analysis was performed to investigate putatively influential variables associated with serum MI in the girls with PCOS. Signicance was granted for p≤0.05.

Results: Twenty-two (56.4%) girls with PCOS had abdominal obesity and nine (23%) had normal weight. Ten (25.6%) girls with PCOS had MetS. Reduced ISI was found in 16 (41%) and FAI was increased in 31 (80%) girls with PCOS. Serum MI levels were significantly higher in girls with PCOS than in controls (2.46ng/mL [25%-75%IQR 0.89-4.86]and0.88 ng/mL[25%-75%IQR 0.29-2.70]; respectively, p<0.001). Serum AMH was also higher in the PCOS group (p<0.001). Serum MI levels were not different within the subgroups in girls with PCOS (p>0.05 for all). In girls with PCOS, serum MI was associated with serum total testosterone (T) (β=+0.499), Matsuda index (β=-0.582) and serumTSH levels (β=-0.582) (Adjusted R2=0.319, p<0.001).

Conclusions: We found significantly increased serum MI levels in girls with PCOS and serum MI levels were associated positively with T and negatively with ISI. Our results might suggest the need for further studies to rectify the use of oral MI in PCOS.

P1-171

Predictors of surgical outcomes in boys with hypospadias

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Introduction: Complications are frequently reported post hypospadias repair and there is a need to understand the factors that influence their occurrence.

Aim: The aim of this study was to identify the occurrence of complications in boys with hypospadias that are in the I-DSD Registry.

Methods: Data from boys born with hypospadias between 2010-2020 were obtained from the I-DSD registry. Complications

were defined by abnormal function or cosmetic appearance of the penis, requiring surgical reintervention.

Results: Of the 469 eligible boys in the I-DSD Registry, data were available on 167 (36%) from 20 centres with an additional 27 patients included from one centre. The median age at the time of the study was 7.5 (3, 12) years. Of this total, 153 (92%) had hypospadias repair and of these 125 (82%) had proximal hypospadias. The overall complication rate was 56%. The most commonly reported complications were fistulae (n=28, 23%) and meatal shape or position (n=23, 18%) and the median age at time of hypospadias repair was 2 (0.8, 7) years. Genetic testing was undertaken in 118 (77%) of those undergoing repair, with variants reported in 50 (42%) of this group. Endocrine biochemistry was undertaken in 142 (94%) of those undergoing repair, with biochemical abnormalities reported in 80 (56%) of this group. Of those with proximal hypospadias, 86 (69%) had a clinical diagnosis of non-specific XY DSD; 15 (12%) had partial androgen insensitivity syndrome; 16 (13%) had disorders of androgen synthesis; 8 (6%) had partial gonadal dysgenesis. In these 4 groups of patients, complications were encountered in 48 (56%), 10 (67%), 10 (63%) and 7 (88%), respectively.

Conclusion: Complications post hypospadias repair are common in those with DSD. Complication rate may be affected by underlying diagnosis and affected patients should be counselled as such prior to surgery.

P1-172

Diabetes type 1 can induce testicular atrophy with Leydig cell hyperplasia and germ cell depletion and therefore prevents reproductive function and fertility in rats

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Research Aim: Diabetes type 1 can negatively influence testicular function and fertility but the pathomechanisms on the testicular level remain to be elucidated. Therefore, the aim of the study was to evaluate effects of diabetes mellitus type 1 disease on testicular function.

Material and Methods: BB/OKL rats developed type 1 diabetes during adolescence. Rats were treated with different Insulin implants to achieve sufficient and insufficient HbA1c levels. Leydig-, Sertoli-, and germ-cell function was analysed on RNA and protein level. Testosterone, androstendione and dihydrotestosterone were measured in serum samples and intratesticular with LCMSMS. Immunhistochemistry and functional analysis were performed, including the evaluation of apoptosis, inflammation and oxidative stress.

Results: After diabetes manifestation 25-33% of the rats developed testicular atrophy. In the atrophic testis, we found a strong reduction of elongated and round spermatids and spermatocytes by more than 80%. Leydig cells showed a hyperplasia with a strong and significant upregulation of steroidogenic enzymes on RNA and on protein level (Star by 106%/94%, 3Beta-HSD by 177%/203%, 17Beta-HSD by 276%/134%, CYP11A1 by 66%/65% and CYP17A1 by 1859%/2202%). Furthermore, we measured higher concentrations of androgens and INSL3 levels in the atrophic testis. In contrast, germ cells showed a depletion with a strong downregulation of DDX4 and Crem. In addition, we found a strong increase of oxidative stress, apoptosis and inflammation. SF-1 and DHH pathways were strongly upregulated in the atrophic testis and might me a possible pathomechanism.

Conclusion: Diabetes type 1 can induce testicular atrophy by germ cell depletion, apoptosis and increased inflammation. In parallel, Leydig cell hyperplasia develops with an upregulation of steroidogenic enzymes, and higher intratesticular testosterone levels. Therefore, diabetes type 1 can negatively influence reproductive function and fertility in male rats.

P1-173

Differences due to the variant type in the inheritance pattern of *BMP15* gene-related primary ovarian insufficiency: a girl with a homozygous null *BMP15* gene variant

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Background: Bone morphogenetic protein 15 (BMP15), is an oocyte-specific growth factor, that regulates folliculogenesis and ovulation rate. It is encoded by the *BMP15* gene (chromosome Xp11.2), in which heterozygous missense variants in the precursor or mature peptide cause primary ovarian insufficiency (POI) with the dominant-negative effect. BMP15-related ovarian dysgenesis (OD) constitutes 1.5-2.0% of POI. The underlying mechanism still remains elusive and a double dose of *BMP15* is required for adequate ovarian reserve. POI due to recently identified homozygous *BMP15* variants and the reports of physiological menopause in heterozygous mothers indicate that different mechanisms play a role in the etiology.

Case Report: A 17-year-old girl was admitted for the evaluation of amenorrhea. Her healthy parents were 1.5-degree cousins. She was born at term with a birth weight of 3,200 g. She had no history

of chronic disease or medication use. Her 42-year-old mother had regular menstrual cycles and her age at menarche was 12-years. Her weight, height, and body mass index at first evaluation were 76.6 kg (2.4 SDS), 164.5 cm (0.3 SDS) and 28.3 kg/m^2 (2.2 SDS), respectively. Physical examination was normal except for acanthosis nigricans and hemangioma on the 4 and 5th fingers of the left hand. Her breast was Tanner stage 4 and pubic hair was stage 5. Hypergonadotropic hypogonadism (LH 40.5 mIU/mL, FSH 88.7 mIU/mL, E2 <5.0 pg/mL) was detected in this girl with primary amenorrhea. Sizes of the uterus and left and ovaries on pelvic ultrasonography were, 17x34x55 mm, 10x18 mm, and 10x17 mm, respectively. Urinary ultrasonography revealed a duplicated collecting system. Steroid hormone profile (LCMS/MS) was normal and urinary reducing substance was negative. Echocardiography, audiology, and ophthalmologic examinations were also normal. Chromosome analysis was 46, XX (30 metaphases).

Clinical exome sequencing of the patient revealed a novel homozygous 'null' *BMP15* gene variant (NM_005448, c.610C>T; p.R204*). Segregation analysis confirmed that her mother was heterozygous and her father was hemizygous for this variant.

Conclusion: Our case supports the recent hypothesis that "null" *BMP15* gene variants cause POI only in the homozygous state, and this makes the role of isolated BMP15 haploinsufficiency in the etiology of OD controversial. Biallelic *BMP15* "null" variants have a recessive inheritance pattern with a "knockout-like" effect and this mechanism, which has been hypothesized recently, is supported by the present case.

P1-174

A rare case of male sex reversal syndrome (46,XX) with negative SRY gene: a disorder of sexual differentiation (DSD)

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Introduction: The 46,XX testicular disorder of sex development (DSD) is a rare genetic condition and clinical phenotype shows complete sex reversal from female to male. The sex-determining region Y (SRY) gene can be identified in most 46,XX testicular DSD patients, but approximately 20% of patients are SRY-negative. We report a 1.3 -year old SRY/negative 46,XX boy with complete sex reversal caused by SOX3 duplication.

Case Report: A 1.3-year-old boy was referred for clinical evaluation and additional diagnostic workup of cryptorchidism.

He was born from the mother's fifth pregnancy, in term, with elective cesarean section. His birth weight was 3770g, birth length 50cm. The absence of testicles in the scrotum was noticed at the first physical exam after the delivery, and on several occasions during the first year of life. The testicular tissue was not visualised by ultrasound neither intra-abdominal nor in the inguinoscrotal region.

On the first pediatric endocrinology evaluation, the boy had a body length of 75 cm (3.c, -1.8 SDS) and a body weight of 8.78 kg (weight for height 89%) without gross anomalies in clinical status. The external genitalia were male, penis size 2 cm, pubarche I Tanner stage, the distance from the root of the penis to the anus was 6.5 cm, and the scrotum was hypoplastic, empty, without palpable gonads in the inguinal canal.

Basic laboratory assessment included: LH (luteinizing hormone) <0.1 IU/L, FSH (follicle-stimulating hormone) 1.6 IU/L, testosterone <0.4 nmol/L, AMH (anti-Mullerian hormone)> 164 pmol/L, and cytogenetic analysis: 46,XX karyotype. The normal value of AMH confirmed testicular tissue, which had not been visualized until then. In order to assess the functional capacity of the testes, hCG test was performed after which testosterone levels rose to 8.4 nmol/L. Pelvic ultrasound did not reveal uterus, ovary and other Mullerian structures.

Additional cytogenetic analysis and in situ hybridization did not identify the SRY region. Chromosomal Microarray Analysis proved duplication in Xq27.1 region containing only SOX3 gene and confirmed the cause of the described phenotype in the patient.

Conclusion: This case emphasizes the need for additional genetic investigation in SRY-negative XX sex-reversed individuals and indicates that SOX3 is the evolutionary antecedent of sex-determining region Y. An accurate diagnosis is important for the provision of proper genetic counseling and for guiding patients in their long-term management.

P1-175

Primary Ovarian Failure as a Result of Homozygous Mutations in MCM10 Gene

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Background: Primary ovarian failure is (POF) characterised by primary amenorrhoea or early menopause in females. Minichromosome maintenance 10 (MCM10) is a gene involved in DNA damage repair, DNA replication and chromatin formation has received attention as a potential genetic etiology for neoplastic disease. Drosophila with mutated MCM10 have subfertility and dysfunction in female germline development. In humans, biallelic mutations of the MCM10 causes NK cell deficiency.

Objective and Clinical Phenotype: To elucidate the etiology of POF in an Ethiopian 17y old female, from a nonconsanguineous family presenting with absence of spontaneous pubertal development and primary amenorrhea. The Karyotype was 46,XX and gonadotrophins were elevated (LH – 22.7IU/l FSH – 53.7IU/l). Pelvic MRI detected a small uterus, but no ovaries could be seen.

Methods and Results: Whole exome sequencing, revealed the patient to have a novel homozygous mutation in the MCM10 gene: c.T1553C, p.F518S. The healthy parents and sister were heterozygous for this mutation. AA F518 is highly conserved among species. Structure analysis revealed that MCM10 works in a hexamer and that the mutation (F-S transition) destabilizes DNA binding and the secondary structure in its region. Chromosomal breakage assays on patient derived B-cells using DNA damage agent Mitomycin C (300mM) resulted with increased number of breaks per cell, (3.08±0.46 vs 1.90±0.35, P=0.005) when compared to unrelated control. DNA combing assays performed on patient derived fibroblasts showed slower progression of the replication fork when compared to control (2.55±0.06 vs. 2.09±0.04 Kbp/min, P=5X10-11).

Conclusions: The novel MCM10 p.F518S mutation cause increase rate of chromosomal breakage and slower progression of the replication fork, p.F518S thereby compromising meiosis and oocyte formation in humans resulting in ovarian dysgenesis. As such, MCM10 a component of the pre-replication complex, is crucial for gonadal development and maintenance in females. When mutated MCM10 is shown here to be a novel genetic etiology for ovarian dysgenesis. These findings re-emphasize the importance of meiosis, homologous recombination and normal DNA damage repair mechanism in ovariogenesis.

P1-176

Diagnostic and management practices of girls presenting with polycystic ovary syndrome (PCOS)-like symptoms to a tertiary paediatric endocrine clinic

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Background: Polycystic ovary syndrome (PCOS) continues to be a diagnostic challenge in adolescent girls. Symptoms like oligomenorrhea and acne, and polycystic ovarian morphology on ultrasound can be normal variants in adolescents. In addition to diagnostic difficulties, there is lack of randomized controlled trials for PCOS treatments specific to adolescents. Current guidelines for diagnosis and management of PCOS in adolescents have large variations and rely on extrapolation of adult data, leading to inconsistencies in endocrinologists' practice. The aim of this study was to map out current PCOS diagnostic and management practices at the paediatric endocrine clinic in the Royal London Children's Hospital.

Methods: Data of 46 adolescent girls presenting with PCOS-like symptoms to the paediatric endocrine clinic were collected from electronic records. A non-exhaustive list of patients was obtained to provide a snapshot of current practice. 6 patients were excluded as they ended up having an alternative diagnosis. Data on patient demographics, symptoms, investigations, management and outcomes was collected.

Results: The median age at first clinic visit was 15.3 years, and median age at menarche 11 years. The majority of girls presented with irregular periods (63%), others with secondary amenorrhea (25%),10% with primary amenorrhea and 1% with normal cycles. 65% of girls were Asian, 12% White, 3% Black, 5% Mixed, 10% Other and 5% Not Stated. 85% were overweight (BMI SDS >1), of which 85% were obese (BMI SDS > 2). 48% reported hirsutism, 38% acne, 23% mental health problems and 20% had a positive family history. 65% had acanthosis nigricans.

The most commonly performed investigations (>90%) were androstenedione, DHEAS, testosterone and LH/FSH. 60% had pelvic ultrasound (20% GP-initiated). 45% underwent oral glucose tolerance testing; 22% had impaired glucose tolerance and 78% had normal results.

Regarding management, 75% received lifestyle advice. Pharmacological management was given to 40% with progesterone only hormonal contraception in 10% and combined contraception in 12%. 13% of the girls received metformin as well as hormonal contraception and 2 patients received metformin only.

Menstruation outcomes were only documented for 35%, stating periods were more regular or had commenced. Changes in Body Mass Index (BMI) were available for 78% of patients with a median change in BMI SDS of –0.01.

Conclusion: This study can serve as a benchmark for comparison for other clinicians facing similar challenges as well as support the need for further research into diagnostic tools and treatment protocols.

P1-177

Empower-DSD: Development of a patient education programme for children, adolescents, and young adults with differences of sex development (DSD) and their parents

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Background: Differences in sexual development (DSD) are rare diagnoses, which affect the chromosomal, anatomical or gonadal sex differentiation. Although comprehensive counseling of patients and parents/carers is necessary to ensure a positive coping with the diagnosis and a well-informed decision-making, standardised programmes are lacking. Empower-DSD is a government-funded project, which developed an age-adapted multidisciplinary education programme to improve the diagnosis-specific knowledge, skills and empowerment of patients and their parents.

Methods: Within a consortium project of 5 university centers with DSD expertise in Germany, a new patient education programme was developed for children, adolescents and young adults with congenital adrenal hyperplasia (CAH), Turner syndrome, Klinefelter syndrome or XX-/or XY-DSD and their parents. The respective support groups (AGS Eltern- und Patienteninitiative e.V., Turner-Syndrom-Vereinigung Deutschland e.V., 47,xxy klinefelter syndrome e.V., Intergeschlechtliche Menschen e.V., Interfamilien) were involved in the entire developmental process.

Results: A modular structured patient education programme with four generic and three diagnosis-specific modules, based on the previously established ModuS concept for other chronic diseases, was developed. The trainings are conducted as a 2-day training with 4-8 participants in age-homogeneous groups. The first day starts with the welcoming and the participants introduce themselves to each other. The following are diagnosis-specific modules about medical information on diagnosis, treatment and prognosis and about competencies and motivation for basic therapy. A separate module about competencies for the prevention and management of acute crises is only necessary in the CAH-programme. On the second day, the focus is on psychosocial content and includes themes like coping with the diagnosis, empowerment and peer counseling. The 2-day home programmes end with a summary and recapitulation of key contents that participants want to take home.

The topics, learning objectives and recommended teaching methods are summarised in structured curricula, one for each diagnosis and age group. At five study centres, 56 trainers were qualified for the implementation of the training programmes. Children, youth and young adults with their parents can attend the Empower-DSD training programmes until August 2022.

Conclusion: Within the project Empower-DSD, modular training programmes for children and young adults aged 8-24 years with the diagnoses CAH, Turner-Syndrome, Klinefelter-Syndrome or XX-/XY-DSD and their parents were developed to improve diagnosis-specific knowledge, skills and empowerment. The effect of the training programmes will be investigated through a quantitative and qualitative evaluation. These results are still pending.

P1-178

Human chorionic gonadotropin (hCG)–secreting hepatoblastoma in a male infant with peripheral precocious puberty and 11-year follow-up

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Background: Hepatoblastoma is the most common malignant pediatric hepatic tumor virtually confined to infants and young children. Accompanied by raised levels of alpha-fetoprotein (AFP), rarely, the beta-human chorionic gonadotropin (β-hCG) levels may also be elevated, which can cause male peripheral precocious puberty (PPP).

Objective: To report a case of HB presented with PPP with elevated serum AFP, β-hCG, and testosterone levels, and suppression of follicle-stimulating and luteinizing hormone (FSH, LH) levels.

Methods: We described the clinical data of the infant and reviewed the relative literatures.

Results: An asymptomatic 23-month-old male infant presented with a history of rapid linear growth after birth and enlarged penile size and pubic hair and deepening of the voice for two months. On examination, he was tall with height 98.5 cm (+3SD). Abdominal examination revealed slightly protuberant abdomen, hepatomegaly (palpable 5 cm below the costal margin). Hair sparsely over the pubes, enlarged testes (volume 6 ml/6 ml), and enlarged penile size (7.2*2.7 cm) were noted on physical examination. Laboratory investigation revealed normal hemoglobin, white blood cell count and platelet count, normal transaminase levels, increased testosterone (>15 ng/ml), AFP 1892.7 μg/L, β-HCG 240.57 mIU/mL levels, DHEA 2.13 μmol/L, Δ4-A 20.3nmol/L, and 17(OH)P 6.38 ng/ml level. Serum FSH(<0.05IU/L) and LH(0.2IU/L) levels were suppressed. Bone age is 4 years. Ultrasonographic examination showed a heterogenic liver tissue. The diagnosis of hepatoblastoma was made by liver biopsy. Chemotherapy was administered for seven cycles accompanied

with serum AFP and β-HCG level reduction, and the patient was referred to surgery followed by 5 more cycles of Chemotherapy. Serum β-HCG and AFP level normalized 10 days and 3 months respectively after surgery. Meanwhile, linear growth slowed down, penile size and testicular volume reduced, and pubic hair disappeared 6 months later. The patient underwent five more operations for a biliary fistula at 1, 2, 4.5, 15 and 18 months, respectively, after surgery. The boy is still alive with a 11-year follow-up and no tumoral recurrence.

Conclusion: We report a male infant case of peripheral precocious puberty attributed to the elevated hCG secreted by hepatoblastoma and good outcome after chemotherapy and surgery.

P1-179

Loss of function of FIGNL1, a DNA damage response gene, is a novel cause of human ovarian dysgenesis

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Background: Severe Ovarian Dysgenesis (OD), a rare heterogeneous XX disorder of Sex Development presents clinically with primary amenorrhea, hypergonadotrophic hypogonadism and infertility. The genetic basis of OD remains unknown in 70% of cases. To identify novel causes of OD, we study patients in which known genes have been excluded.

Methods: Whole-exome-sequencing was performed in a 14.5y old Ashkenazi Jewish, non-consanguineous origin patient, with OD. DNA damage response (DDR) was tested using MitomycinC (MMC) in chromosomal breakage assay, and analysis of γH2AX and DYK-Fignl1 foci in response to MMC and Phleomycin.

Results: We identified compound heterozygous frameshift deletions in FIGNL1, a DDR pathway gene: c.189delT and c.1519delTCTCA. Segregation was consistent with recessive inheritance. Western blots of DYK-tagged-FIGNL1-constructs showed no protein is produced by c.189delT, and 64% of WT (P=0.003) is produced by c.1519delTCTCA. Chromosomal breakage assays revealed significantly higher number of DNA breaks in patient-derived fibroblasts compared to control. DNA breaks increasement occurred both spontaneously (22.82±1.66 vs. 10.61±0.98 P=6X10-9) and following DNA damage induction (MMC, 5.00±0.59 vs. 2.50±0.25 P=0.003). HeLa cells transfected with DYK-tagged-FIGNL1-mutant or wild-type constructs showed overall decrease in nuclear foci (c.1519delTCTCA 5.6±1.5 vs. 14.8±0.9) and in recruitment of FIGNL1 to the nucleus in response to phleomycin (0±1.3 vs. 5.8±0.8 P=0.02) in the mutant transfected cells.

Conclusions: The novel compound heterozygous mutations in FIGNL1 are accompanied by impaired DDR and suggest that FIGNL1 loss of function is a novel genetic etiology for ovarian dysgenesis in humans. This further expands the crucial role of DDR pathway in normal ovariogenesis.

P1-180

The lifetime cost of reproductive potential – who spends the most?

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Objectives: To determine who spends more energy over a lifetime on maintaining their reproductive potential: men or women?

Design: As a model and energetic equivalent, we set the mass of gametes supported over time from birth until exhaustion of fertility. We calculated gender-specific dynamics of gamete pool mass over time. To this purpose we collated data from existing literature, accounting for gamete volume over stages of development, time in each stage, mass density, and count. Our model generates the integral, or area under the curve (AUC) of the gamete pool mass over a lifetime as a proxy to energetic requirements.

Main Outcome Measure: The area under gamete mass curve over a lifetime in men and women.

Results: The number of gametes over a lifetime is 600,000 in women and close to 1 trillion in men. Accounting for mass and time, women invest approximately 100 gram*days in maintaining the female oocyte pool. Women reach 50% of lifetime AUC by age 10, and 90% by age 25. Men invest approximately 30 Kg*days over a lifetime (300-fold more), reaching 50% of lifetime AUC at age 37 and 90% at age 62 years old.

Conclusions: The study quantifies for the first time the area under gamete mass in men and women through a nuanced calculation accounting for all components of post-natal gamete dynamics. We found a 300-fold excess is supported male gamete mass over a lifetime (100g*days vs. 30 Kg*days in females vs. males, respectively). Our methodology offers a framework for assessing other components of the reproductive system in a similar quantitative manner.

P1-181

Monoallelic variants in Myelin Regulatory Factor (MYRF) associated with 46,XY DSD – two cases and first report of inheritance through parental mosaicism

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Background: Haplo-insufficiency of the Myelin-Regulatory Factor (MYRF) gene causes cardiac-urogenital syndrome (CUGS) and Differences in Sexual Development (DSD) in 46,XY and 46,XX (OMIM #618280). The gene product, a transcription factor, is involved in development of Coelomic epithelium derived cells, and likely causative for DSD. To date, only a few MYRF de novo variants are reported in children with DSD and associated CUGS symptoms.

Aims and Objectives: To report the clinical, hormonal and genetic findings in two infants with CUGS and DSD from a single centre.

Patients: Case 1 (46,XY) presented at term birth with diaphragmatic hernia and was commenced on extracorporeal membrane oxygenation due severe lung hypoplasia. The external genitalia were significantly under-masculinised (1 cm phallus, single opening, penoscrotal hypospadias, no gonads palpable) with non-detectable Mullerian structures but gonads identified in the iliac fossa on pelvic ultrasound. Gender was assigned female at birth. A rapid trio whole exome sequencing analysis identified a heterozygous frameshift variant in the MYRF gene [p.(Ser878Profs*20)]. Parental analysis detected the variant at a low-level mosaicism (estimated 10%) in mother. Sadly, the infant passed away at day 21 of life due to severe respiratory failure.

Case 2 (46,XY) presented at term birth with diaphragmatic eventration, Scimitar Syndrome and partial anomalous pulmonary venous drainage. The external genitalia were highly ambiguous with small phallus (2cm), single opening, penoscrotal hypospadias, underdeveloped scrotum and impalpable gonads. An ultrasound of the pelvis did not detect gonads or Mullerian structures. A testosterone level after birth was low (0.2 nmol/L), there were no other hormonal abnormalities with normal adrenal and thyroid function tests. Gender was assigned as male. Genetic analysis of the MYRF gene revealed a novel missense variant p.(Arg478Gln), which occurred de novo.

Discussion and Conclusions: Our cases expand the clinical and genetic spectrum of MYRF-associated CUGS and provides further evidence on its causative role in 46,XY DSD. We report the first case of MYRF haplo-insufficiency inherited through low-grad mosaicism from an asymptomatic mother, which has important implications for genetic counselling. We recommend genetic testing of the MYRF gene, in particular when cardiovascular and renal abnormalities are present in infants with DSD.

P1-182

Abstract Withdrawn

P1-183

Testicular sperm extraction in a patient with a new pathogenic *NR5A1* (SF-1) variant : p.Phe70Serfs*5

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Background: Steroidogenic Factor 1 (SF-1), encoded by *NR5A1* (Nuclear receptor subfamily 5 group A member 1) gene, is a transcriptional factor that is primordial for adrenal and gonadal organogenesis. Pathogenic variants of *NR5A1* are responsible for a wide spectrum of phenotypes with autosomal dominant inheritance, from adrenal insufficiency to gonadal dysgenesis and oligospermia-azoospermia in 46,XY patients.

Objective: Preservation of fertility in these patients remains challenging. The aim was to offer fertility preservation at the end of puberty in a patient with a new pathogenic *NR5A1* variant.

Case Report: The patient was born from non-consanguineous parents, with a disorder of sex differentiation: a small genital bud of 6x4mm, a perineal hypospadias, gonads in the left labrum and the right inguinal respectively. The morphological studies did not show any uterus or vagina. The karyotype was 46,XY. AMH levels were low at 58 pmol.L^{-1} the first day of life then 100 pmol.L^{-1} at the minipuberty. Testosterone level was low at 0.9 nmol.L^{-1} at 12-h of life, and Testosterone after hCG stimulation increased properly to 10.8 nmol.L^{-1}. The child was raised as a boy. During endocrine monitoring, he received androgen therapy (11 injections of

testosterone enanthate) for one year. He underwent a surgical treatment for his hypospadias at one year old and for testicular lowering at 7 years old. He was treated by triptorelin for central precocious puberty from 9.5 years old to 11 years old. From 13 to 15 years old, androgen therapy by testosterone enanthate was established to improve penis size prognosis.

Genetic study, performed at 15 years old, identified the new frameshift variant NM_004959.5(*NR5A1*):c.207del p.(Phe70Serfs*5) at an heterozygous state. Therefore, he was addressed for fertility preservation. At 16 years old, testicular volume was 6 ml bilaterally; AMH and inhibin B levels were low (2.6 $pmol.L^{-1}$ and 9.0 $ng.mL^{-1}$ respectively). No sperm cells could be retrieved from three semen collection between 16 and 17 years old. The patient accepted a testicular biopsy for testicular sperm extraction. The procedure was performed at 18 years old and no sperm cells were found. Histological analysis revealed a severe hypo-spermatogenesis with an aspect of histological mosaicism (seminiferous tubules either atrophic, either with Sertoli cells only or with arrest of spermatogenesis at the spermatocyte stage).

Conclusion: We report a case with a new *NR5A1* variant. The fertility preservation protocol proposed at the young age before parental project did not allow any sperm retrieval.

P1-184

Cerebello- Oculo- Fascio-Genital Syndrome and Scrotal Agenesis with MAB21L1 Mutation; Case Report

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Introduction: The most common congenital malformations of the scrotum are bifid scrotum, penoscrotal transposition, and ectopic scrotum. Scrotal agenesis is a very rare congenital anomaly characterized by the absence of scrotal rugae in the perineal tissue between the penis and anus. To date, 9 cases with complete scrotal agenesis have been described in the literature. Here, a case with complete scrotal agenesis with MAB21L1 homozygous mutation is presented to contribute to the literature.

Case: The patient, who was consulted to our department due to scrotal anomaly, was born with a C/S at 40+1 week, 2890 gr. In his family history, there was a first degree cousin marriage between her parents. It was learned that the patient, who applied to the pediatric neurology department due to inability to follow objects and nystagmus at the age of 2 months, was diagnosed with cerebellar hypoplasia and also had corneal dystrophy. A homozygous deletion was found in the MAB21L1 gene in the whole exon sequencing analysis of the patient, who also had syndromic facial appearance. It was learned that the same change was defined as heterozygous in the segregation analysis of the parents. The patient applied to us with these complaints when he was 13 months old. On examination, sparse and adjacent eyebrows, hypertrichosis, narrow forehead, nystagmus and hairy nipples were evident. PSB: 5 cm, pubic hair stage 1, hypospadia was present and scrotum was not observed. No hormone dysfunction was observed in the laboratory examination. In his abdominal USG, bilateral testicles were seen in the distal part of the inguinal canal. Testosterone response to the hCG test was obtained. The patient was operated in pediatric surgery and the testicles were lowered to the scrotal location between the penis and anus and fixed under the skin.

Conclusion: Scrotal agenesis is a very rare congenital anomaly. Here, we presented a case with MAB21L1 deletion, which is one of the causes of scrotal agenesis. In the literature, this mutation has been described in 10 individuals from 5 unrelated consanguineous families. Because the patients have similar clinical features, cases with MAB21L1 mutation were defined as cerebello-oculo- fasciogenital syndrome.

P1-185

Puberty induction in boys with CHARGE syndrome and hypogonadism: experiences of patients, parents and doctors

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CHARGE syndrome is a rare and complex disorder with an incidence of 1:15000 to 1:17000 live births. It is associated with a wide range of issues, including, but not limited to, coloboma of the eye, congenital heart disease, atresia of the choanae, retardation of growth and development, hypogonadotropic hypogonadism, ear abnormalities and hearing loss.

Hypogonadotropic hypogonadism is present in 60-88% of individuals with CHARGE syndrome. In these patients, hormone replacement therapy is necessary to induce pubertal development. Specifically in boys, the availability of two main treatment options, human chorionic gonadotropin (HCG) and testosterone supplementation, makes decision-making complex. There is little evidence about the optimal treatment in this group of boys. Differences in the course of treatment, expectations and beliefs about puberty as a phase of life in teenagers with a disability, concerns about possible side effects and doctors' experiences can all influence decision-making. In addition, parents are often concerned about behavioral problems.

We want to learn more about the experiences of patients, parents and doctors with the different treatment options, in order to make a tool to guide the decision-making process. We aim to achieve this by a mixed-methods approach which includes in-depth interviews, questionnaires and medical chart reviews.

We will present the results of the in-depth interviews with patients, parents and medical professionals. Treatment decisions were largely based on experiences and preferences of the treating pediatric endocrinologist and the focus was often on physical outcomes and feasibility of therapy. Doctors emphasized the importance of pubertal development for bone mineralization and the development of a healthy body. They stressed the importance of

starting puberty induction at the right age. However, there were differences in the type of therapy they preferred.

There was a large variation in the experiences of patients. All of them thought puberty was important, as well as having a similar development as their peers. However, where one participant explained that taking injections gave him a lot of anxiety, another participant explained that the development of his body, sexuality and his sexual orientation was very important to him.

This study shows that there are large differences in experiences with puberty induction, both in patients and professionals. These differences stress that there is a need for a broader conversation about puberty induction in boys with CHARGE syndrome.

P1-186

Inflammation and polycystic ovary syndrome (PCOS). Utilising proteomic analysis to unravel the link between inflammatory proteins and PCOS in adolescents

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Background and Methods: PCOS is common in adolescents and imparts a significant health and economic burden. Yet, our understanding of its complex pathogenesis is lacking. Proteomic analyses would be a valuable tool to deepen our knowledge of the biological pathways which underpin PCOS, and to identify novel biomarkers to diagnose and monitor this common condition. Therefore, we undertook a deep phenotyping discovery proteomic profiling (nano-2D-LC-QTOF MSe) on urine samples from 15 participants from a longitudinal adolescent PCOS cohort of 40 participants. We compared the urinary proteome of adolescents with PCOS, insulin resistance (IR), and controls. Subsequently, we validated these omic results in the entire adolescent cohort, and an adult PCOS cohort, by running an in-house, multiplexed, targeted proteomic panel of 89 known inflammatory-associated proteins.

Results: In the discovery urine proteomic analysis, we identified 3,793 proteins, of which, 66 were differentially expressed in the PCOS cohort in comparison to both IR and controls. As such these form a pool of potential biomarkers for PCOS. Bioinformatic analysis revealed that almost half of all biological pathways which significant proteins were involved in, were related to inflammatory/immunological responses and the thrombotic/fibrinolytic systems. The inflammatory response was the most significant biological process associated with PCOS ($p<0.001$). This association was validated using targeted proteomic analysis of inflammatory-associated proteins. Multivariate analysis demonstrated that there were differences between the inflammatory proteome of adolescent PCOS, IR, and control cohorts. Differences were identified at the proteome-level between adolescents and adults with PCOS. However, greater differences were identified between individual inflammatory-associated proteins.

In total, 11 inflammatory-associated proteins were upregulated in the adolescent PCOS cohort in comparison to either IR or control cohorts, and eight proteins were downregulated. Of these, four proteins were significantly different in the PCOS cohort in comparison to IR and control cohorts, making them potential candidate biomarkers for PCOS in adolescence. When comparing the proteome of adolescents and adults with PCOS, four proteins were identified as being similarly up- or downregulated in both PCOS cohorts in comparison to their age-matched controls. As such, these form a potential pool of PCOS biomarkers which may be clinically useful across the reproductive lifespan, from adolescence, into adulthood.

Conclusions: These analyses have provided vast data exploring the pathophysiology of PCOS, and strongly suggest that inflammatory processes play a crucial role. Several proteins of interest have been identified in urine, which have the potential for use as non-invasive biomarkers for PCOS.

P1-367

Evaluation of the relationship between the immune and endocrine system in children diagnosed with polycystic ovary syndrome

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Polycystic ovary syndrome is the most common endocrinological disease in women of reproductive age. Although it is thought that pathologies such as insulin resistance, chronic low-level inflammation and hyperandrogenism are central theme of the disease, the exact pathophysiology of the disease has not been fully understood. This study's aim is to reveal the relationship between routine endocrinological and immunological markers related to chronic inflammation, and to investigate the place of these values in the diagnosis, management and treatment of the disease. 32 PCOS patients who consulted to Gaziantep University Sahinbey Training and Research Hospital Pediatric Endocrinology and Metabolism clinic and 39 healthy girls who consulted to the General Pediatrics clinic were included in this study. Apart from anthropometric measurements, lymphocyte subsets were studied from both groups. The lipid profile, FSH, LH, testosterone, estrogen, glucose, insulin, HOMA score, ACTH, cortisol, AMH, DHEA-S and thyroid function tests results of the patient group were compared with reference values. Compared to the control group, PCOS patients had significantly decreased CD8+ and CD16/56+ percentages (p=0,037 ve p=0,001), and increased AMH and HOMA score. In the patient group, it was found that CD3+

percentage and estrogen hormone had positive correlation(p=0,023), while CD4+ percentage had negative correlation with LDL, triglyceride and AMH(p=0,01, p=0,038 ve p=0,005).In addition, a negative correlation was observed between 17-OH progesterone, DHEA-S and the percentage of HLA-DR+(p=0,008 ve p=0,023).As a result, PCOS is not only a disease with an endocrinological basis, but also a complex case that many different pathologies play a role, especially immune dysregulation, in its pathophysiology.

P1-368

Gender dimorphism in transgender youth – hormonal therapy and the balance between muscle, adipose tissue and cardiometabolic alterations

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Context: Given the importance of sex hormones in metabolic regulation, dynamics in body composition and cardiometabolic alterations may occur in transgender persons receiving gender-affirming hormone (GAH) therapy.

Objectives: Our aim was to explore the association between muscle-to-fat ratio (MFR) and the risk for metabolic syndrome components in transgender youth.

Methods: In 71 transgender female (birth-assigned male) and 149 transgender male (birth-assigned female) adolescents (mean age at first evaluation 15.9±2.5 years), generalized linear models with repeated measures (n=460) were applied for overweight/obesity, elevated blood pressure levels, glucose intolerance and dyslipidemia. Variables entered into the model were age, transgender female, socioeconomic position, family history of cardiovascular disease (CVD), psychiatric comorbidities, dietary pattern, physical activity, sleep, smoking status, alcohol consumption, hormone levels (estradiol and testosterone), GAH therapy duration and MFR z-scores. Body composition was measured by bioelectrical impedance analysis (Tanita MC-780MA and GMON Professional Software) according to birth-assigned sex and MFR z-scores were calculated.

Results: MFR z-score differed in a gender-specific manner; average for transgender females (*P=0.536*) and below average for transgender males (*P<0.001*). Transgender females (OR=0.06, 95%CI[0.02,0.23], *P<0.001*) and higher MFR z-scores (OR=0.02, 95%CI[0.01,0.06], *P<0.001*) were associated with lower odds of overweight/obesity; higher testosterone levels (OR=1.08, 95%CI[1.02,1.15], *P=0.007*) were associated with higher odds of overweight/obesity. Longer duration of GAH therapy (OR=1.39, 95%CI[1.03,1.86], *P=0.029*) and higher testosterone levels (OR=1.04, 95%CI[1.01,1.08], *P=0.011*) were associated with higher odds of elevated blood pressure levels. Higher MFR z-scores (OR=0.40, 95%CI[0.21,0.76], *P=0.005*) and favorable dietary pattern (OR=0.36, 95%CI[0.14,0.89], *P=0.028*) were associated with lower odds of elevated triglyceride (TG) levels. Transgender females (OR=0.01, 95%CI[0.003,0.040], *P<0.001*) and higher MFR z-scores (OR=0.59, 95%CI[0.42,0.81], *P=0.001*) were associated with lower odds of low HDL-c levels; higher testosterone levels (OR=1.11, 95%CI[1.05,1.18], *P<0.001*) were associated with higher odds of low HDL-c levels. Transgender females (OR=0.39, 95%CI[0.20,0.76], *P=0.006*) and higher MFR z-scores (OR=0.63, 95%CI[0.45,0.87], *P=0.005*) were associated with lower odds of elevated TG:HDL-c ratio.

Conclusions: Our findings support the notion that GAH-therapy in transgender youth affects the balance between muscle and adipose mass and cardiometabolic alterations in a sex-specific manner. Taking into consideration socioeconomic circumstances, family history of CVD, lifestyle-related factors and psychiatric comorbidities, transgender males remained at an increased risk for cardiometabolic disease. Our observations highlight the importance of targeted medical nutrition intervention in this group of youngsters in attempts to dampen potential detrimental outcomes of GAH-therapy.

P1-369

Prevalence of Overweight and Obesity in a Transgender Youth Cohort

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Background: Overweight as a predictor of adverse cardiovascular outcome is of particular interest in gender-affirming healthcare. Transgender populations are at a higher risk for obesity, possibly due to a combination of minority stress, psychiatric comorbidity, and lifestyle differences, such as reluctance to participate in group sports as a consequence of social withdrawal. However, robust auxological data in transgender adolescents is scarce.

Objectives: To evaluate differences in auxological parameters such as bodyweight, height and BMI between transgender and cisgender adolescents.

Methods: Retrospective analysis of auxological data of 186 transgender patients (75% trans male, 25% trans female) at the outpatient clinic for Pediatric Endocrinology at General Hospital Vienna (AKH Wien). All were treatment naïve at initial measurement. Height and weight data were compared to current WHO and Austrian growth standards, defining +1-2 standard deviations (SD) as overweight and >2 SD as obese. Additionally, we tested for confounders, specifically psychiatric comorbidities and medication, using univariate linear regression.

Results: In our untreated transgender population (mean age 15.7 years), 20% were overweight and a further 19% obese. Mean BMI was 0.71 SD above the WHO average (p<0.001). When split

by gender identity, this result was more pronounced in the trans male subgroup (+0.76 SD, p<0.001) than in the trans female group (+0.53 SD, p=0.03). While both groups were skewed towards overweight in a normal distribution, the trans female group showed a markedly higher variance in BMI as compared to both cisgender adolescents (p<0.001) and to the trans male group (p=0.03), due to a higher relative number of underweight observations. Transgender patients with a comorbid psychiatric diagnosis had, on average, BMI values which were 0.44 SD higher than those of trans patients without psychiatric comorbidity (p<0.001). However, in our linear regression model, when correcting for psychiatric diagnosis, transgender patients were still significantly overweight (p<0.001).

Conclusion: We observed significantly higher rates of overweight and obesity in our adolescent transgender cohort. The reasons for this are likely complex and multifactorial. In addition, the body dysphoria associated with transgender ideation may put patients at risk for manifest or subclinical eating disorders. Concealment of undesired secondary sex characteristics and decreased circulating sex steroids as a result of either obesity or extreme underweight could be potential secondary gains. This makes eating and exercise behavior a central topic in both transgender care and future research.

P1-370

An Investigation Of Androgen-responsive Non-coding RNAs In Boys With Atypical Genitalia Without Genetic Variants in the Androgen Receptor (AR)

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Introduction: Recent studies point to the existence of androgen-responsive non-coding (nc) RNAs in peripheral blood mononuclear cells (PBMC) RNA.

Aim: To quantify the androgen-responsive gene expression of SNORD5 and RNY5 and investigate their relationship to the testosterone (T) rise following hCG stimulation in boys with no genetic evidence of androgen insensitivity.

Methods: 19 boys with suspected DSD who were evaluated at RHC, Glasgow from 2018 to 2021 were included. Information on clinical, biochemical, and genetic assessment was obtained from clinical records. Of the 19 boys, 18 had undergone AR analysis to date and excluded AR variants. PBMC RNA was collected before and after hCG stimulation of the testes on day 4 (D4) and day 22 (D22), where appropriate, and gene expression was quantified using QuantStudioTM 3D Digital PCR.

Results: A median age at the time of hCG stimulation test was 0.8 yrs (0.5, 4). The median baseline and peak T levels were 0.5 nmol/l (0.5, 6.8) and 14.2 nmol/l (1.2,42.1), respectively. The median AMH was 752 pmol/l (13, 1588). Within this group, there was one patient who did not show a T response to hCG at all on D4 and a minimal response on D22 (1.2 nmol/l). The median fold change in SNORD5 and RNY5 on D4 in this patient was 0.09 and 0.05, respectively. The median fold change for the two ncRNAs on D22 was 0.14 and 0.04, respectively. In the rest of the cohort, the median post-hCG T on D4 and D22 was 13.6 nmol/l (2.5, 42.1) and 24.3 nmol/l (11.6, 37.3), respectively. In this group, the median fold change in SNORD5 expression on D4 and D22 was 1.93 (0.08, 13.9) and 1.4 (0.09,5.6), respectively. The median fold change in RNY5 expression on D4 and D22 was 0.8 (0.1, 37.5) and 0.7 (0.3, 7.7), respectively. Of the 19 boys, there were 3 boys who had a fold change in both ncRNAs that was below 25th centile at T peak. Of these 3, 1 was the aforementioned non-responder and the remaining 2 boys, although having a normal T response to hCG, also had variants in the CYP11B1 or HSD3B2 genes.

Conclusions: Expression levels of RNY5 and SNORD5 can be accurately quantified and show androgen dependency. Further research in poor hCG responders and genetically confirmed causes of DSD including androgen insensitivity is required to determine the diagnostic role of non-coding RNAs in XY DSD.

P1-371

Exome sequencing reveals a high proportion of causal and candidate gene variants in a large early-onset Primary Ovarian Insufficiency cohort

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Background: The presentation of early-onset Primary Ovarian Insufficiency (EO-POI), most often with primary amenorrhea, is at one end of a spectrum spanning 40 years. The aetiology of POI is frequently unclear but next generation sequencing of varied age groups has identified several associated genetic variants. Whether girls with EO-POI are more likely to have a genetic aetiology than those with later presentations remains unknown.

Methods: We performed exome sequencing (Nonacus) in a large cohort of young females with unexplained EO-POI and their unaffected family members where possible. Analysis was performed in QCI (Qiagen) following appropriate inheritance models. Variants were retained if rare/novel (minor allele frequency <0.01%), predicted pathogenic in silico, and enriched in the cohort compared to controls (gnomAD v3.1.2; Fisher's exact testing).

Hierarchical filtering considered genes associated with: A) POI with functional models (n=113); B) POI without functional models (n=315); C) animal models of ovarian insufficiency (n=120); D) differential expression during critical human fetal ovary developmental stages.

Results: A total of 147 women with EO-POI were recruited (29 familial POI (16 kindreds, 8 consanguineous); 118 sporadic POI). Of these, 81.6% (n=120) had primary amenorrhea and 61.9% (n=91) pubertal delay/arrest.

Pathogenic/likely pathogenic variants in POI-associated genes were found in 50.0% of familial POI kindred (n=8; 22 affected). These included variants in *STAG3, PSMC3IP, YTHDC2, PLEC, MCM9* (biallelic); *NLRP11, PRKD1, WRN* (heterozygous); *ANKRD31, POLR2C, PDE3A, POLR3H, CLPP, MSH6* (oligogenic). Variants in novel candidate genes (*MRPS14, PCHD15*) segregated with the phenotype in two further families.

Variants with established pathogenicity in POI were found in 22.9% of women with sporadic POI (27/118), likely explaining their diagnosis. These included variants in *GDF9, BUB1B, MCM9, MCM8, SETX, NBN, BMP15, NOBOX, AMH, ATG7, EIF4ENIF1, FOXO1, PRDM1,* and *BNC1*. A further 34.7% (41/118) had variants with recognised pathogenicity but which followed oligogenic inheritance or inheritance patterns not yet supported by functional models (e.g, digenic variants in DNA repair genes). Variants were biallelic in 13.2% (9/68), heterozygous in 54.4% (37/68), and oligogenic in 32.4% (22/68). Novel candidate genes were also identified (e.g., *FANCD2, C4orf33, TDRD9*).

Conclusion: Causal and possibly contributory variants within POI-associated genes were found in a high proportion of this EO-POI cohort. Frequent polygenic involvement and enrichment of rare heterozygous variants suggest possible haploinsufficiency/dominant-negative models, multiallelic interactions, or threshold effects of rare variants. POI is remarkably genetically heterogeneous and we demonstrate a categorical, hierarchical approach to exome analysis in this condition.

P1-372

Premature ovarian failure in a tall adolescent

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Introduction: Primary ovarian failure (POF) is traditionally defined as cessation of menstruation prior to 40 yr of age and diagnosis is confirmed by elevated serum FSH levels (often above 40 IU/L). It is known that 0.1% of the population is affected with POF before age 30 yr. Here, we report a case with POF, who presented wit tall stature due to structural abnormalities in X chromosome.

Case Report: A 13.5 year-old-adolescent girl was brought to medical attention because of secondary amenorrhea. She was born at term without any perinatal problems. The parents were second-degree cousins. Past medical history was unremarkable. She was 177 cm (2.9 SDS) tall. Her body mass index was 23.3kg/m2 (1.01SDS). Her midparental height was 171 cm (1.35 SDS). The physical examination revealed normal findings except for kyphoscoliosis. There were no other pathologic findings. Her Sexual Maturity Rating was consistent with Stage 3. Laboratory work up showed that serum LH and FSH levels were 25 mIU/mL and 43.7 mIU/mL, respectively. Serum estradiol level was 35.8 pg/ml and AMH level was <0.01 ng/mL. Serum androstenedione, dehydoepiandrosterone-sulfate, testosterone, 17-hydroxyprogesterone, prolactin levels and thyroid function tests were all normal. Due to tall stature, GH-IGF axis was evaluated; serum IGF-1 level was also normal, 304µg/L (SDS: -0.44). Pelvic ultrasonography showed uterine hypoplasia and streak ovaries. The karyotype was 46,XX. Due to coexistence of tall stature and POF, chrosomal microarray was performed. Partial Xq deletion and partial Xp duplication including SHOX gene was identified [(Xp22.33p11.21 (265492_57830778)x3, Xq22.2q28 (103534396_156003212)x1)]. She was placed on sex steroid replacement therapy with the diagnosis of POF.

Conclusion: Here, we report a case of POF who presented with tall stature due to SHOX overdosage. Gene dosage alterations in X chromosome that require molecular genetic tests should be considered in POF patients with tall stature that is unexplained by parental stature. A structurally abnormal X chromosome with Xp duplication concomitant with partial Xq deletion is a rare event. In the few cases reported to date, a very tall stature has been a frequent clinical finding. The enhancing effect of SHOX gene triplication in combination with estrogen deficiency has been proposed as a factor leading to tall stature.

P1-373

A novel Androgen Receptor mutation causes complete androgen receptor insensitivity syndrome with gender dysphoria and unusual postnatal androgen profile

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Background: Androgen Insensitivity syndrome (AIS), the most common cause of XY DSD, is an X-linked recessive allelic disorder caused by Androgen Receptor (AR) gene mutations. The complete form (CAIS) stems from abrogation of AR activity and is characterized by an external female phenotype and scarce pubic hair, as well as lack of Mullerian structures. Postnatal gonadotropin and testosterone levels are not increased, and the classical 'Mini-puberty' is absent. Gender dysphoria in CAIS is rare, probably due to absence of AR activity in the brain. Herein we describe the clinical and molecular characteristics in two siblings with a novel AR mutation.

Clinical Report: Two siblings presented postnatally 6 years apart with bilateral inguinal hernia and complete female external phenotype. Both had gonads in the inguinal canal, complete lack

of Mullerian structures on ultrasound, and XY karyotype. On third day of life endocrine workup showed normal cortisol and unexpectedly elevated testosterone (728 ng/dL, 468 ng/dL –normal neonatal male range 75-400 ng/dL) and LH (3.83, 2.75 IU/L) levels. They were both assigned female gender. The older sibling presented at the endocrinology clinic at the age of 6 years with consistent and extreme boy-like behavior, self-professed male identity and marked gender dysphoria.

Molecular Studies: Sequencing of the AR gene in both siblings revealed a novel hemizygous mutation c.1885G>A (p.Ala629Thr); The terminal nucleotide of exon 3 at the consensus splice site. The asymptomatic mother was found to be heterozygous to the mutation. The mutation was found to affect splicing; cDNA from peripheral leukocytes revealed an altered transcript, lacking entirely exon 3 (39 amino acids) without changing the reading frame in both affected siblings. The shorter transcript was also detected in maternal cDNA along with normal transcript.

Conclusion: The novel c.1885G>A (p.Ala629Thr) hemizygous mutation in the AR gene causes CAIS. This mutation alters AR transcription, skipping exon 3, which contains a D-box element crucial to AR dimerization. Interestingly, the postnatal (mini puberty) hormonal profile as well as the gender dysphoria observed in our cases are not expected in CAIS and possibly suggest that this mutant AR may have differential function in the brain versus the periphery. Further studies on the specific action of this novel mutation at different tissues are currently underway.

P1-374

Is testosterone supplementation required after induction of puberty in Duchenne muscular dystrophy? A follow-up study

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Introduction: Pharmacological doses of glucocorticoids (GC) reduce inflammation and preserve muscle function in boys with Duchenne muscular dystrophy (DMD) but cause almost universal pubertal delay. Long term consequences of GC on androgen status in young men who have received testosterone for pubertal induction remain unknown.

Objective: To determine the longer-term outcome after a 2-year pubertal induction regimen using 4-weekly testosterone injections on androgen status.

Design: 15 prepubertal GC-treated males with DMD, who were aged 12-17 years, were treated with an incremental testosterone regimen for 2 years (NCT02571205). They were evaluated at 6 months after last injection and subsequently attended a final follow-up visit, at a mean of 2.8 years (SD 0.44) after final injection. Data collected included testicular volume, testosterone, gonadotrophin and Inhibin B levels. Paired t-tests were used to assess differences pre and post-treatment.

Results: Participants were 18.7 years (SD 1.8) at final follow-up and had been on GC for 11.2 years (SD 2.2). Nine participants were on daily deflazacort, 6 on daily prednisolone. At the time of last injection, 7/15 participants were still ambulant, by final visit only 4 remained ambulant. Mean testosterone levels were similar at 6 months after the last injection and final follow-up (8.6nmol/l (SD 3.4) versus 11.0 nmol/l (SD 6.1). Two of the 15 patients had restarted testosterone supplementation during the follow-up period, based on clinical assessment during routine clinic visits. Testicular volume significantly increased from 2.8 mls (SD 0.9) at end of pubertal induction to 7.1 mls (SD 1.8) at 6-months after and 10.6 mls (SD 3.5) at final follow-up ($p<0.001$ for difference between end of regimen and final follow-up). In keeping with this, gonadotrophins remained suppressed at the end of pubertal induction but were measurable thereafter. A significant increase in Inhibin B levels occurred from initiation of testosterone treatment to final visit (55.6 pg/ml (SD 47.0) to 158.2 pg/ml (SD 87.6), $p=0.004$) but final levels remain lower than reference values of mean 305 pg/mL.

Conclusion: Inhibin B levels have been shown to positively correlate with spermatogenesis and the increase seen in this cohort is promising with respect to future fertility. Testosterone levels and testicular volumes, however, remain lower than adult reference values. Given the known additional advantages of testosterone on bone health, muscle and wellbeing, it will be important to continue monitoring testosterone levels in this population and supplement as required if levels become sub-optimal.

P1-375

Effects of long-term puberty suppression and gender-affirming hormones on body composition and metabolic profile in a preclinical mouse model and a cohort of transboys

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Background: The increasing number of transgender adolescents presenting in early puberty requires to investigate the effects of long-term puberty suppression and gender-affirming hormones (GAH) on body composition and metabolism. Clinical studies have ethical and practical limitations. A preclinical mouse model may be helpful to gain mechanistic insights.

Methods: Prepubertal (4week-old) female mice were treated with the gonadotropin-releasing hormone analogue (GnRHa) Degarelix (DGX), followed by testosterone administration started in early (6week-old) or late (8week-old) puberty. At adult age (16week-old), body composition (echoMRI), grip strength, glucose tolerance and hepatic lipids were assessed. The translational potential of our preclinical findings was verified in a cohort of 16 transboys who received GnRHa starting at Tanner stage 2-3,

followed by testosterone around 16years [mean GnRHa duration 40 (±7.6) months]. Body composition (DXA), grip strength and fasting blood sampling were assessed at start of GnRHa and at start of testosterone. Z-scores were calculated using reference values for cis-girls (Z-scoreAFAB) and cis-boys (Z-scoreAMAB).

Results: In the mouse model, DGX decreased lean mass% (-6.98%, p<0.001) and increased fat mass% (+7.51%, p<0.001) compared to female controls. The decreased lean mass was accompanied by diminished grip strength (-8.84% p=0.062). The increased body fat was paralleled by accumulation of subcutaneous (+106.52% p<0.001), gonadal (+121.88% p<0.001) and perirenal (+100.51% p<0.001) fat, and hepatic triglycerides (+66.09% p<0.001). DGX increased fasting glucose and HOMA-index, and decreased glucose tolerance. Testosterone reversed all DGX effects, irrespective of being started in early or late puberty. Effects on lean and fat mass% were most pronounced, both parameters reaching male control levels. Similar effects were observed in transboys on GnRHa: fat mass% increased significantly (+5%, p<0.001) while lean mass% decreased significantly (-3.46%, p<0.001). Grip strength Z-scoreAFAB increased non-significantly, Z-scoreAMAB decreased significantly [-1.36 (±0.64) to -2.28 (±0.44), p<0.001]. HOMA-index, tot-C, HDL-C, LDL-C and triglycerides did not change. Seven transboys were re-evaluated 31 (±2.6) months after start of testosterone. Fat mass% showed a decreasing trend, lean mass% an increasing trend. Muscle strength increased significantly [Z-scoreAFAB -0.87 (±0.28) to 1.36 (±0.15), p=0.002; Z-scoreAMAB -2.64 (±0.19) to -1.72 (±0.13), p=0.003]. HDL-C decreased significantly [68 (±22.01) to 45.2 (±11.65) mg/dL, p=0.025].

Conclusions: Prolonged puberty suppression in female mice decreases lean mass%, increases fat mass%, and causes metabolic alterations. Testosterone reverses these changes, earlier testosterone administration has no additional beneficial effect. Our clinical observations support the effects on body composition and muscle strength, however changes in metabolic profile were not observed.

P1-376

A virilizing ovarian tumour following previous rhabdomyosarcoma, masking ovarian failure

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An 11 year 8-month-old girl presented to her oncologist with recent voice change and increased leg hair growth. She had a past history of pelvic rhabdomyosarcoma in 2012, at age 2, with relapse and local metastasis at age 4. Prior to original tumour treatment, oophoropexy had been performed, aiming to prevent ovarian radiation exposure. At time of the new complaint, she was receiving a trial treatment.

Puberty was reported to have commenced at age 10, with 6-months of increased leg hair growth plus voice deepening, with a gravelly quality, causing her to remain quiet in class. MRI demonstrated a large (42x 36x 42mm) pelvic mass, abutting but not encasing the left external iliac vessels, uterine fundus and urinary bladder. Androgen excess was confirmed, with testosterone 10.4 nmol/L (0.1-1.9), FSH 4.7 IU/L (0-10), LH 4.5 IU/L (1-3), oestradiol 107 pmol/L. Endocrinology consult revealed Tanner stage 2-3 breast tissue bilaterally, stage 4 pubic hair and a deep voice. She was pre-menarchal. A family history of cancer in maternal grandparents (salivary/parotid, thyroid cancer, breast cancer) did not suggest a specific genetic link.

The pelvic mass was removed, histopathology consistent with stage 1 ovarian Sertoli-Leydig cell tumour (SLCT), with resolution of androgen excess (testosterone <0.4nmol/l/) but she had clear evidence of primary ovarian failure with FSH 60.7 IU/L (1-10), LH 32.1 IU/L (1-3.5) and Oestradiol 19 pmol/L, in the prepubertal range. Oestrogen will be commenced to continue normal feminization, remaining linear growth and bone mass accrual. Further genetic investigations to date have not demonstrated a DICER mutation.

This case demonstrates several important points. The enormous androgen levels due to SLCT completely masked past chemotherapy /radiotherapy related ovarian failure, only becoming evident after tumour removal and cessation of androgen excess. SLCT are rare sex-cord ovarian tumours, accounting for 1% of all childhood cancers and 10% of all ovarian tumours in paediatric patients, often adolescents (1, 2). Up to 85% have associated virilisation (1-3) with up to 63% reported to be due to a DICER 1 gene mutation (2, 3). Association between the rhabdomyosarcoma, the commonest soft tissue sarcoma of childhood (3) and later SCLT may be linked with DICER mutation, past possible radiation exposure or may be similar to a reported link between cervical sarcoma botryoides and ovarian SCLT in at least 19 patients, predominantly adults (3), where relapse within 3 years was common (1).

P1-377

Novel genomic variants, atypical phenotypes and evidence of a digenic/oligogenic contribution to Disorders/Difference of Sex Development in a large north African cohort

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The majority of individuals with disorders/differences of sex development (DSD) do not have a genetic etiology. However, recently new genes causing DSD have been reported and using the unbiased approach of whole exome sequencing (WES) the diagnostic yield should be improving. Here, we performed WES on a large cohort of 125 individuals all of Algerian origin, who presented with a wide range of DSD phenotypes. Parental consanguinity was reported in 36% of individuals. The genetic etiology was established in 49.6% (62/125) individuals of the total cohort, which includes 42.2% (35/83) of 46,XY non-syndromic DSD and

69.2% (27/39) of 46,XY syndromic DSD. Variants in the AR, HSD17B3, NR5A1 and SRD5A2 genes were the most common causes of DSD. Other variants were identified in genes associated with congenital hypogonadotropic hypogonadism (CHH), including the CHD7 and PROKR2. 30 previously unreported pathogenic/likely pathogenic variants involving a total of 25 different genes were identified in 22.4% of the cohort. Remarkably 11.5% of the 46,XY DSD group carried variants classified as pathogenic/likely pathogenic variant in more than one gene known to cause DSD. The data indicates that variants in PLXNA3, a candidate CHH gene, is unlikely to be involved in CHH. The data also suggest that NR2F2 variants may cause 46,XY DSD.

P1-378

Assessment Of External Genitalia Change Over Time In Boys With XY Disorder Of Sex Development (DSD)

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Introduction: The external masculinisation score (EMS) has been utilised as an objective numerical description of the external genitalia in undermasculinised patients with DSD in several studies. However, data on longitudinal change in EMS in the routine clinical setting are lacking.

Objectives: To determine the longitudinal change in EMS and its determinants in a cohort of boys with XY DSD in one specialist centre.

Methods: Boys with XY DSD between 2010 and 2020 were included. Clinical information on initial (EMS1) and most recent EMS (EMS2), results of endocrine and genetic investigations, as well as genital surgery and testosterone therapy were obtained from medical records.

Results: 205 boys with median age at initial and last assessment of 0.8 yrs (range, 0.0, 18) and 4.9 yrs (0.4, 19.3), respectively ($p<0.0001$), were identified. Median follow-up time was 3.4 yrs (0.2, 17.3). Median EMS, out of 12, at first and last assessment was 8 (2, 12) and 11 (1.5, 12), respectively ($p<0.0001$). Surgery was performed in 170 (83%) boys whereas testosterone therapy was recorded in 11 (5%). Boys with combined genital anomalies were more likely to show an increase in EMS but less likely to achieve an EMS2 of 12 whereas those with undescended testes were more likely to achieve the EMS2 of 12 but also had greater chance to have EMS2 decreased due to orchidectomy. Of the 40 boys who had endocrine abnormality and a gene variant (n, 20) or not (n, 20), the median change (Δ) in EMS was 1.5 (0, 9) and 0.5 (-2, 4.5), respectively ($p=0.045$). ΔEMS, duration of follow-up and the number of surgical procedures did not differ between those with normal endocrine investigations and with or without a gene variant. Testosterone therapy was not associated with an increase in EMS whereas those who had surgery showed a significant increase in EMS.

Conclusions: The EMS in boys with XY DSD improves over childhood and adolescence. The change in EMS in boys with DSD is poorer in those who have a combination of both endocrine and genetic abnormality and also in those who are hypogonadal and require testosterone therapy.

P1-379

The effect of timing of puberty suppression on breast development in trans girls; a cross-sectional study

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Context: For transgender women undergoing gender-affirming hormone therapy (HT), breast development is an important treatment outcome. Since earlier studies showed small breast volumes in trans women treated with HT, we hypothesized that testosterone exposure during puberty might negatively influence breast development and that early initiation of puberty suppression (PS) might have a positive effect on breast development.

Aim: To investigate the influence of timing of PS and subsequent HT on breast volume, satisfaction with breast size, and self-esteem.

Methods: Twenty-three trans women who started PS in early puberty (Tanner stage G2-3), and 19 who started in late puberty (Tanner stage G4-5) were included. Twelve individuals who had breast augmentation were excluded (early pubertal n=5, late pubertal n=7). 3D-scans of the breasts were used to calculate breast volume. Participants filled out questionnaires on breast satisfaction and self-esteem.

Results: Mean age at time of study was 19.4±1.9 years in the early group and 21.0±1.8 years in the late pubertal group. Both groups had used HT for 4.2±1.6 years. BMI was higher in the late group (median 21.6, IQR 19.1 to 30.3) compared to the early group (median 18.9, IQR 17.7 to 21.2). Mean breast volume was 114 cc (IQR 58 to 203), i.e. bra cup-size <A. Breast volume was 47 cc (95% CI -9 to 104) larger in the late group but this difference was only 20 cc (95% CI -43 to 83) after correction for BMI. In total, 64% of subjects were satisfied with their breast size (57% vs 74% in the early and late group, respectively). Participants had a self-esteem score of 19.0 ± 4.3; the early group scored 2.9 points higher (95% CI 0.3 to 5.4) than the late group.

Conclusion: In this study, early start of PS was not found to result in larger breast volume. There even was a trend towards larger breast volume in the late pubertal group, but this seems related to a higher BMI. These findings suggest that pubertal testosterone exposure does not affect breast development during HT.

However, exclusion of those who had undergone breast augmentation may have introduced bias. Despite a higher satisfaction with breast size, the late pubertal group had lower self-esteem scores. This might be explained by other physical differences due to longer testosterone exposure. The impact of timing of PS on other breast characteristics, such as breast shape and positioning, deserves further study.

P1-380

Effect of long acting gonadotropin releasing hormone agonists on height outcome in children

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Gonadotropin releasing hormone agonists (GnRHa) stops premature sexual maturation in young children and preserve the potential of achieving acceptable adult height.

Aim: To assess the efficacy of long acting GnRHa in suppressing early pubertal development and its impact on height outcome in our patient population.

Methods: Records of children treated with GnRHa since 2018 at Hull University Hospital; UK were reviewed. Predicted adult height was calculated using the GrowthXP Endo electronic toolkit.

Results: GnRHa were given to 18 children, 12(67%) for precocious puberty (Group A), and 6(33%) in an attempt to optimise target adult height potential. All children were females. Mean age (years) at start of treatment was 7.6 ±1.2, and 9.8 ±0.75 for group A and B respectively. Group A duration of treatment (years) was 1.8±0.79 compared to 1.37±0.87 in group B. Within group A, mean difference between bone and actual age was 1.4±0.8 years. In both groups, 11 (61%) of the children had initial low dose 11.25mg Triptorelin injection followed by 22.5 mg dose, while 39% started on the 22.5 mg dose. Before and after treatment height difference (cm) was 131.8±2.9 Vs 139.2±10.7 ($p< 0.001$) in group A and 132.6±3.2 Vs 137.5±4.7 ($p<0.001$) group B. Predicted adult height Difference (cm) was 170.8±2.5 Vs 171.4±8 in group A ($p<0.001$) and 157.6±4.7 Vs 158.7±5.2 ($p<0.001$) in group B. Predicted adult height (cm) was higher at the end of treatment (161.2±7.7 Vs 160.7±7.1 $p = 0.001$). The treatment was universally tolerated well by our patients.

Conclusion: When commenced before 10 years of age, long acting GnRHa treatment increased potential height growth for girls treated for precocious puberty in our population.

P1-381

Gynaecomastia And Its Management In Partial Androgen Insensitivity Syndrome (PAIS)

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Introduction: In adolescents and men with PAIS, gynaecomastia has been reported in the majority but its management remains challenging.

Objectives: To assess the current management of gynaecomastia as well as clinical characteristics in male PAIS.

Materials and Methods: Retrospective review in the I-DSD registry of 46, XY male PAIS who were over the age of 10 years.

Results: Of the 205 cases in the I-DSD Registry from 26 centres who were over 10 yrs of age, information was available in 64 cases from 13 centres with a median number of cases per centre of 4 (range 1,16). The median age at first presentation was 0.9yrs (0.1,41.0). The median external masculinisation score (EMS) at presentation was 6 (2,12). Of the 64 participants, atypical genitalia were the presenting feature in 40 (63%), an AR variant had been identified in 48 (75%) and gynaecomastia was reported in 49 (77%).

Of the 48 AR variant+ve cases, only 5 (10%) had no gynaecomastia at a median age at last presentation of 14.4 yrs (9.2,17.0). On the other hand, 6 of 13 (46%) cases in whom AR analysis had excluded a variant, had no gynaecomastia at a median age of 16.0yrs (13.0,20.0) (p=0.002). Median age at onset of puberty and at time of development of gynaecomastia were 12.0yrs (10.5,14.0) and 13.5yrs (11.0, 29.0), respectively. Median EMS at time of gynaecomastia development was 9 (3,12). In the cases with biochemistry available, serum testosterone was reported to be raised in 17/32 (53%) and LH and FSH were raised in 14/29 (48%) and 9/28 (32%), respectively. Of the 43 cases in whom information was available, 30 (70%) had either undergone surgery or were awaiting surgery (n,3) and 11 of these 30 had a poor response to a wide range of medical therapy. Median age at time of surgery was 16yrs (13,34). Median clinician score for therapy effectiveness was reported as 10 out of 10 (3,10) in those who had undergone surgery compared to 4.5 (1,9) in those who had medical therapy (p<0.001). Of 43 participants, 12 (28%) were reported to have received clinical psychology support and there was one report of gender dysphoria.

Conclusion: Gynaecomastia is common in PAIS but not necessary universal and may present without the typical biochemical signs of AIS. The current data suggest that surgical management may be more effective than medical therapy but there is a need for further systematic studies.

P1-382

Accidental transdermal estradiol exposure leading to gynecomastia and bone age acceleration in a 7 year old boy: a case presentation

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Case Presentation: A 7 year old boy was presented to us with height acceleration, symmetric breast development equivalent to Tanner stage B2 and sparse dark hair in the pubic region (PH2). Testicular volume equaled to 2ml, while external genitalia showed no clear signs of androgen effect.

The patient's biological father is a transgender woman who started a medical gender transition before the patient's birth. She has been continuously receiving transdermal hormone therapy using an estradiol gel at a high dose of 5 pump actuations per day (equaling to 3.75mg of estradiol). After application and drying of the gel, skin contact with the child occurred regularly.

Diagnostic Procedures and Results: Laboratory results showed a mild elevation in serum estradiol (9.6 ng/l), low gonadotropin and testosterone concentrations, as well as DHEAS and androstendione levels in the normal range. Serum estrone level was also normal at 22ng/l with no sign of increased aromatase activity. Inhibin B was decreased (<10ng/l). His karyotype was 46, XY. Skeletal maturation was significantly accelerated with a bone age of 11 years 3 months according to the standards of Greulich and Pyle.

Discussion: On the basis of clinical and laboratory findings we suspected exposure to exogenous estradiol as the primary cause for his symptoms. Although there are case reports in the literature of accidental testosterone exposure via skin-contact, to our knowledge this is the first case documenting accidental transdermal estradiol application. Of note, the manufacturer of the estradiol gel does not caution against the possibility of skin-skin-transfer.

We advised the parents on our findings and suggested an immediate change of treatment. The gender affirming hormone therapy was switched to estradiol patches. On follow-up, the boy showed reduction in breast gland swelling and pubic hair, and a significant reduction in growth velocity.

Conclusion: Even very small doses given continuously over years might be detrimental for growth and development in small children. As the patient's parent used an unusually high dose as off-label treatment the risk of estradiol transfer might have been augmented. Further observation of our patient is needed to evaluate potential long-term effects on growth, puberty and testicular development. The manufacturer has since been informed about our findings.

P1-383

Study of Quality of Life among Children with Congenital Adrenal Hyperplasia at Alexandria University Children's Hospital

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Introduction: Quality of life (QoL) is a complex concept with multiple aspects as cognitive and emotional functioning; psychological well-being; general health; physical functioning; and social well-being and functioning.

Stressors that appear with cases of Congenital adrenal Hyperplasia (CAH) vary and can present challenges to shared decision making with healthcare providers. Day-to-day care of a chronically ill child affects family finances and dynamics, as well as caregivers' levels of anxiety, stress, depression and QoL.

Aim of the Study: To assess the Quality of life in Children with CAH and to study the possible affecting factors.

Subjects and Methods: This study was conducted on 57 cases of CAH and 72 as control. The cases were recruited from Endocrinology Outpatient Clinic at Alexandria University Children's Hospital (AUCH), Egypt. Thorough history taking and clinical examination were done. We used the Arabic form of Pediatric Quality of Life Inventory™ 4.0 (PedsQL™) generic core scale (parent report) and (PedsQL™) generic core scale (Self-report) for children from (8-18) years to assess the child's physical, emotional, social, and school functioning in the past one month.

Results: The age of diagnosis of CAH ranged from one day and 3 years. The duration of illness ranged from 1.1 to 16 years. 45 patients (88.2%) had one stage operation while 6 patients (11.8%) had two stages operation. 42 patients were controlled and 15 were not controlled.

There was statistical significance as regard the physical function, emotional function, school function, psychosocial function and total score of quality of life (p<0.001) in which cases of CAH

had lower scores than controls while as regard the social function, cases of CAH had lower score than control without statistical significance (p=0.287).

Univariate analysis showed that older age, female, longer duration of illness and those been operated had a statistically significant poor impact on the quality of life.

Conclusion: Girls with CAH had significant lower physical, emotional, school function and total quality of life compared to control group. We recommend psychological counseling to all patients with CAH and their families.

P1-384

17 B-Hydroxysteroid Dehydrogenase Type 3 Deficiency Diagnosed in Early Childhood

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Introduction: 17 β-Hydroxysteroid Dehydrogenase Type 3 (17β-HSD3) enzyme provides the conversion of Δ4-Androstenedione (A) to testosterone (T) in testicles. 17β-HSD3 deficiency is a rare autosomal recessive cause of 46,XY disorders of sexual development (DSD) and is the most common form of testosterone biosynthesis defects. The external genitalia can vary from normal female appearance to atypical genitalia.

Case Report: A 2-month-old female patient presented with palpable swelling in both groins. There was no consanguinity between the parents of the patient, whose personal and family history was unremarkable. In her physical examination, the external genitalia was female, the phallus was 0.9 cm, the urethral and vaginal openings were separate, and the vaginal entrance was narrow. There were palpable gonads in both inguinal regions. In ultrasonography; there was an appearance compatible with testis in both inguinal canals and a hypoechoic area compatible with the root of the penis in the phallus root. Müllerian structures were not observed. The patient's karyotype was 46,XY, baseline FSH was 2.4 IU/ml; LH 1.32 IU/ml; ACTH 23 pg/ml; cortisol was 8.44 µg/ml. Basal androgen levels testosterone <0.1 ng/ml; androstenedione 0.3 ng/ml; DHEA-S 1.6 µg/ml; 17-Hydroxyprogesterone 0.22 ng/ml; 11-Deoxycorticosterone was 1.99 ng/ml. Inhibin B level was 187.8 pg/ml (90-400 pg/ml). The basal T/A ratio in mini puberty was <0.8 and the testosterone/dihydrotestosterone ratio in the hCG stimulation test was 10.2 (normal). In genetic analysis, a homozygous mutation of c.239 G>A (p.Arg 80 Gln) in the HSD17β3 gene was detected (mother and father are carriers for that mutation), and it was found to be compatible with 17 β-Hydroxysteroid Dehydrogenase Type 3 Deficiency.

Conclusion: 46,XY DSD due to 17β-HSD3 deficiency may present with inguinal swelling or mild cliteromegaly in infancy and early childhood, and virilization in adolescence. It can often be confused clinically with androgen insensitivity syndrome and 5α reductase type 2 deficiency. Although low T/A ratio supports 17β-HSD3 deficiency, the diagnosis should be confirmed by molecular genetic studies.As a result, this rare disease should be diagnosed in the early period and sex determination should be made, short and long-term treatment plans should be made, patients should be followed in terms of sexual function, fertility, malignancy risk, and appropriate psychiatric counseling should be provided.

P1-385

A Rare and Treatable Cause of Prepubertal Gynecomastia: Large Cell Calcifying Sertoli Cell Tumor

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Introduction: Gynecomastia is common in boys at early-mid puberty, while prepubertal gynecomastia is a rare condition. Sertoli cell tumors (SCTs) account for 2% of prepubertal testicular tumors. Most of the SCTs in prepubertal boys, which are generally bilateral and diffuse, are in the content of Peutz-Jeghers Syndrome (PJS) or other familial syndromes (Carney complex). Large cell calcifying Sertoli cell tumor (LCCSCT) is a variant of SCT and is seen in PJS. In LCCSCTs, aromatase enzyme expression is increased, which causes gynecomastia and advanced bone age.

Case: An eight-and-a-half-year-old male was referred with the complaint of stiffness in both breasts. He was born with a birth weight of 2800 g at term. When he was six months old, he was diagnosed with PJS as a consequence of the endoscopic examination. He was the first child of non-consanguineous parents. His grandmother and aunt had had colon cancer. His weight was at 1.7 SDS, height 3 SDS, and BMI 0 SDS. There were two dark pigmented lesions on the buccal mucosa. He had bilateral gynecomastia corresponding to Tanner stage 2. Pubic hair was at Tanner Stage 1 and testicular volumes were 4 mL bilaterally. Complete blood count, liver, renal, and thyroid functions tests were within normal ranges. Hormonal values were as follows: follicle-stimulating hormone:0.53mIU/L (N:1.3-19.3), luteinizing hormone: 0.05 mIU/L (N<0.3, prepubertal), total testosterone: 0.02 ng/mL (N:2.59–8.16), estradiol: 32 pg/mL (<20), estrone:24 pg/mL (N: 5-17), prolactin: 6.56 ng/mL (N: 3-14.7), 17-hydroxyprogesterone: 0.5 ng/mL (N: 0.5-2), androstenedione: <0.3 ng /mL (N: 0.6-3.1), dehydroepiandrosterone sulfate: 25.6 ug/dL (N: 2.5-145), human chorionic gonadotropin: <0.5 mIU/mL (N: <5.3). Bone age was 10.5 years. The annual growth velocity was determined to be 9 cm/year. Testicular ultrasound showed bilateral multifocal calcifications, the largest of which was 3 mm. Anastrozole (1 mg/day) treatment was initiated. During the follow-up, gynecomastia completely regressed. Growth velocity and pubertal development were convenient with their peers. There were no changes in the size, number, or characteristics of the calcifications. After four years of medication, anastrozole treatment was discontinued. However, anastrozole was restarted due to recurrence of gynecomastia after six months.

Conclusion: Testicular tumor should be investigated in a patient with PJS who presents with prepubertal gynecomastia. When findings are consistent with LCCSCT, biopsy may not be needed and aromatase inhibitors may be preferred in the treatment to reduce gynecomastia and delay skeletal maturation.

P1-567

Two Cases with Hypergonadotropic Hypogonadism Due to Derivative X Chromosome

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Introduction: A derivative chromosome (der) is a structurally rearranged chromosome generated either by a chromosome rearrangement involving two or more chromosomes or by multiple chromosome aberrations within a single chromosome. Balanced segmental anomalies such as inversion or translocation can lead to derivative chromosomes with partial duplication and deletion during meiosis. Here we present two patients with hypergonadotropic hypogonadism and various accompanying influences-related toderivative X chromosome.

Case 1: A 14-year-old girl was hospitalized with hyperglycemic ketosis. Appropriate fluid and insulin therapy was administered. Her body weight and height were at 25 percentile, pubertal examination was Tanner stage 5 and she had mild acanthosis nigricans. HbA1C:16%, Cpeptide:1.18 ng/ml, diabetic autoantibodies were negative. Insulin therapy was discontinued with the initiation of metformin.When evaluated for oligomenorrhea, FSH:49mIU/mL, LH:20mIU/mL, E2:23pg/mL; normal uterus and small right ovary consistent with puberty stage were detected, left ovary could not be visualized inpelvic sonography and MRI.Genetic analysis for ovarian failure and MODYrevealed 46,X,der(X)t(X;X)(q21;p21). Refinement of (der)X with microarraywas planned.

Case 2: A 10.3-year-old girl followed with epilepsy, cognitive retardation and iris coloboma was referred for obesity. She had a seizure at the age of 1, epileptic focus was detected in EEG and antiepileptic treatment was started. Her seizures did not recur afterwards but she continued treatment with valproic acid because of existingepileptic activity in EEG. Her obesity started after infancy and she used to have a high-calorie diet.Her body weight was +3SD, height was +1.67SD, body mass index was +2.6 SD,pubertal examination was Tanner Stage I. FSH:28 mIU/mL, LH:4 mIU/mL, E2:<11 pg/mL were consistent with hypergonadotropic hypogonadism.46,X,der(X)t(X;X)(p11.4;q21) was found inher microarray studied for copy number variation due to neurological findings.

Conclusion: Derivative X chromosomes with preserved X inactivation center (XIST) located at Xq13.2, as in both patients presented, are expected to be prone to inactivation. For this reason, serious clinical problems are not seen despite large segmental imbalances. However, problems such as long stature, ovarian failure, obesity, diabetes, global developmental delay and epilepsy can be seen in female individuals with a short arm duplication of the X chromosome containing PAR1 and a long arm deletion containing PAR2.

P1-568

Endocrine care for gender incongruent children and adolescents in The Czech Republic between 2011–2020

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Background: Gender incongruence (GI) is a topic of interest with major impacts on both the individual and society. In recent years, the small group of gender non-conforming children with an early GI history that persists through adolescence has been accompanied by a substantial rise in the proportion of adolescents reporting their gender doubts. The onset of gender dysphoria in this group is rapid. In the Czech Republic, multidisciplinary teams strive for high quality individual care to minimize overdiagnosis and the risk of detransitioning.

Methods: A systematic data review of four paediatric endocrinology centres within the years 2011 to 2021 was performed. We evaluated data including sex assigned at birth, age of onset of GI symptoms, mental health specialist care (MHS), endocrinology care, age of initiation of GnRH analogue and cross-hormonal therapy, the number of individuals with early termination or cessation of treatment, detransitioning and reasonings behind that.

Results: A total of 56, 132 and 484 individuals (2.4; 8.6-fold increase) younger the 18 years with gender dysphoria in 2011, 2016 and 2020 respectively received MHS care. During this period, the proportion of gender incongruent biological girls rose from 62.5 to 79.3 %. In 2011, 2016 and 2020, one, five and 39 (1.7; 3.7; 8 %) adolescents with GI respectively, underwent treatment at paediatric endocrinology outpatient clinics. Summing up to 133 adolescents within 10 years, 111 biological girls and 22 biological boys reported their first symptoms at median age (range) of 10.3 (3 - 14.5) years. MHS referred them for endocrinological care at 15 (11-18) years, i.e. 0.5 to 1.5 years after being diagnosed with GI. When used, GnRH analogue treatment was started at a mean of 14.5 (12-18) years, and cross hormonal therapy at 15.8 (14-18) years. Over the ten-years of follow-up, the drop out rate in our group was 3.7 % (5 biological girls with a complicated psychological history) and 1.5 % (2 biological girls) decided to detransition at the age of 19.5 years.

Conclusions: The growing incidence of gender dysphoria in adolescence and the larger proportion of GI biological girls in the Czech Republic conform with international trends. The age of Czech GI individuals at which MHS and endocrine care were initiated have been stable over the ten-year period. Based on our growing experience in this field, tailor-made individual care is crucial to reduce dropout rate and prevent the need to detransition.

P1-569

Abstract Withdrawn

P1-570

Does your daughter have a larger than usual clitoris"? Parental perception of CAH management outcome

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Background: Following the intense debates and controversies regarding all forms of genital surgeries on minors, particularly the appropriateness of clitoral surgeries, assessing all outcomes of clitoromegaly management is imperative in directing future management.

Methods: As part of a broader qualitative interview study involving 25 parents of patients with confirmed cases of clitoromegaly due to congenital adrenal hyperplasia, we asked 19 mothers and 6 fathers, the question, "Does your daughter have a larger than usual clitoris?" We also noted the parents' qualitative reflections on their responses. Each of the girls discussed had undergone one of the three management pathways in relation to clitoromegaly; (i) early childhood clitoral reduction surgery (ii) early childhood clitoral concealment surgery, or (iii) no surgery on or around the clitoris. Our measurement was of parental perception of size-normalcy as one element of clitoromegaly treatment outcome.

Results: We gained responses from 24 parents regarding 26 treated girls with CAH. The age range of the patients was 1-16 years with median age of 13 years old. Sixty-two percent (16) of the participants' daughters had undergone clitoral surgeries, the larger group being clitoral concealment (63%) with 37 % having undergone clitoral reduction surgery. However, 10 out of the 26 girls had not received any clitoral surgery. Our main finding was that at the time of interview; 73% (N= 19) of the parent participants perceived the clitoral size of their child/children to be larger than normal, while 27% (N=7) perceived the clitoral size to be normal. Perceived normalcy and of enduring large size were near equal in distribution across the three treatment groups. Qualitative comments provided additional information regarding parental acceptance of enduring genital difference.

Conclusion: Normalcy is an aim of early genital surgery, as part of the management of CAH. Most parent-participants in this study perceived their child's clitoral size to be larger than normal, irrespective of the treatment modality (surgery or no surgery). While parental perception of size-normalcy post treatment is only one outcome domain, it is useful in understanding the complexity of parental adaptation to CAH and its management. The low rate of parental perception of normalcy unrelated to different managements and our analysis of qualitative comments will demonstrate that most parents find enduring genital difference an acceptable outcome for their child.

P1-571

Detection of Copy Number Variations by Microarray in Disorders of Sex Development of Unexplained Molecular Etiology and Association with Clinical Findings

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Introduction: Microarray (SNP array) method offers a powerful full genome scanning opportunity in the diagnosis of disorders of sex development (DSD).

Aim and Method: We aimed to determine the copy number variations (CNVs) by using the microarray method to elucidate the molecular etiology in DSD patients. The variants found were scored according to the American College of Medical Genetics and Genomics criteria.

Results: Twenty-two cases with no molecular genetic etiology and no chromosomal anomaly were included in the study. Eighteen (81.8%) of the cases were classified as 46,XY, and 4 (18.1%) as 46,XX DSD. The age of admission was 7.44 months (4 days-15 years). In the 46,XX DSD patient group, 2 (%50) patients were followed up with a preliminary diagnosis of gonadal dysgenesis, 2 (%50) patients with androgen excess. In the 46,XY DSD group, 6 (33.3%), patients were followed up with a preliminary diagnosis of androgen effect defect, 10 (55.5%) patients were followed up with androgen synthesis defect and 2 (11.1%) patients were followed up with gonadal dysgenesis. External genitalia score (EGS) of the patients in the 46,XY DSD group at the time of admission in 4 (22.2%) between 0-5; in 10 (55.5%) patients between 5-10 and in 4 (22.2%) patients was evaluated as 10 and above. Of 46,XX DSDs, 2 (50%) admitted with suspicious external genitalia, one (25%) primary amenorrhea and one (25%) coincidentally found Müllerian agenesis. There were consanguinity between the parents in four (18.1%) cases.

While no variant was detected in 4 out of 22 cases with microarray analysis, a total of 142 copy number changes were detected in 18 cases. Of these, 114 (80.3%) were deletions and 28 (19.8%) were duplications. When variants of 18 cases with copy number

changes were evaluated 13 out of 5 cases were pathogenic; 19 out of 5 cases were classified as undetermined. While only 1 of the variants classified as pathogenic had a hypospadias-related phenotype previously recorded in databases, no genital anomalies were reported in other variants.

Conclusion: Microarray analysis should be included in selected cases within the diagnostic approach to elucidate the molecular etiology of DSD cases. In addition, microarray analysis can guide studies to find new genes responsible for DSD.

P1-572

Long-term GnRHa use and bone health in transgender adolescents: can a mouse model inform clinical practice?

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Background: Transgender individuals increasingly present at gender services in childhood. Consequently, to suppress pubertal development, more adolescents are long-term exposed to gonadotropin-releasing hormone analogues (GnRHa), from onset of puberty until start of gender-affirming hormones (GAH), around 16 years. Prolonged GnRHa may compromise bone health more than shorter-term treatment. If earlier start of GAH, when psychologically indicated, may partially restore bone health, is currently unknown. As clinical studies have ethical and practical limitations, a preclinical mouse model may provide mechanistic insight.

Methods: DXA [lumbar spine (LS), femoral neck (FN)] and pQCT (tibia 4%, 38%) were performed at start of GnRHa (Tanner stage 2-3), and at start of GAH in 16 transboys. Z-scores were calculated using references for cis-girls (Z-scoreAFAB) and cis-boys (Z-scoreAMAB). Similarly, we assessed the impact of long-term GnRHa on bone development in a mouse model and explored the effect of earlier start of GAH. Prepubertal (4week-old) female mice were treated with either the GnRHa Degarelix (DGX) alone, DGX at 4 weeks supplemented with testosterone at 6 weeks (early puberty), or DGX at 4 weeks supplemented with testosterone at 8 weeks (late puberty). Mice were sacrificed at adult age (16weeks) for bone phenotyping.

Results: In transboys, mean age was 12.4 (±0.93) years at start of GnRHa and 15.8 (±0.60) years at start of GAH; mean duration of GnRHa monotherapy was 40 (±7.6) months. All bone mineral apparent density (BMAD) Z-scores decreased significantly.

	Start of GnRHa	Start of GAH	P-value
BMAD-LS Z-scoreAFAB	-0.25 (1.76)	-1.34 (1.02)	0.001
BMAD-LS Z-scoreAMAB	0.57 (1.65)	-1.21 (0.83)	<0.001
BMAD-FN Z-scoreAFAB	0.26 (±0.94)	-0.37 (±0.86)	<0.001
BMAD-FN Z-scoreAMAB	-0.05 (±0.98)	-0.44 (±1.05)	0.033

In line, pQCT trabecular density at tibia 4% significantly decreased. Seven transboys were re-evaluated at gonadectomy, 31 (±2.6) months after addition of testosterone, showing partial restoration of trabecular bone.

In mice, DGX treatment significantly reduced femoral trabecular bone volume fraction (BV/TV) assessed by microCT from 4.03 ± 0.74% in female controls to 1.19 ± 0.34% in DGX-treated mice, $p<0.001$. Late testosterone restored BV/TV to 7.47 ± 2.07%, $p<0.001$. Early testosterone further increased BV/TV to 12.33 ± 1.46%, $p<0.001$, similar to male controls (11.81 ± 2.38%). Cortical bone loss in DGX-treated mice was less pronounced and completely reversed by testosterone in both early and late groups.

Conclusions: Prolonged GnRHa induce significant bone loss, mainly at the trabecular compartment. Early GAH start in a mouse model can restore bone volume up to male references.

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Long-term follow-up of *DHH* variant-caused 46, XY disorders of sex development with multiple complications in a Chinese Child

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Background: The Hedgehog (HH) family plays an important role in the development, proliferation and homeostasis in various tissues and organs. Desert hedgehog (DHH), as a member of this family, is mainly involved in the normal development of testis and the formation of nerve sheath. *DHH* variation mainly causes 46, XY disorders of sex development (DSD) with or without minifascicular neuropathy (MN). Up to date, only 22 affected patients in detail have been reported worldwide. Whether other organs are involved, rarely reported.

Case Presentation: We reported a Chinese female carrying a pathogenic variant (c.1027T>C, p. Cys343Arg) in *DHH* exon 3, the karyotype analysis was 46, XY and SRY gene was positive, which consistent with her phenotype 46, XY DSD with MN. With a female phenotype, she was admitted because of abnormal breast development, lack of menarche and "muscle spasms" occasionally. Slow motor and sensory conduction velocity were observed on electromyography. Surgical exploration revealed a blindly ending vagina, no uterus were found. The pathology of bilateral gonads was dysplastic testis tissue, which consistent with partial gonadal dysplasia (PGD). During our 6-year follow-up, she received estrogen replacement therapy and the breast development progressed without gender dysphoria. However, the MN became more obvious, before and after electromyography showed that sensory and motor conduction velocity was slowed down. In addition, the patient suffered multiple complications such as obesity, fatty liver,

hyperinsulinemia and gastric ulcer occurred, which were basically relieved after our comprehensive management.

Conclusion: We report a patient with 46, XY PGD and MN caused by *DHH* homozygous variant with a 6-year follow-up. For the first time in this type of patient, the comparison of before and after electromyography and the combination of obesity, fatty liver, hyperinsulinemia and gastric ulcer were shown.

P1-574

Phenotype-genotype characteristics of SRD5A2 with variation in gender choice among affected individuals: A single centre experience

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Background: 5α-reductase type 2 deficiency (SRD5A2) is a rare cause of 46,XY DSD. Consensus guidelines on sex of rearing assignment at birth favours male gender. Typically undervirilised genitalia at birth virilise variably at puberty, posing gender identity challenges.

Aim: We describe relevant data on clinical phenotype, hormonal and molecular workup and gender preference in patients with SRD5A2 deficiency from a single regional centre.

Materials and Methods: Retrospective patient data was collected from the medical records of SRD5A2 deficiency patients referred to the West Midlands-DSD-MDT clinic from 1993-2022. Clinical phenotype gender assignment, hormonal, molecular data including pathogenic variations in the SRD5A2 gene were analysed.

Results: 17 subjects were identified with genetic data available in 16. Age at presentation varied from birth in 9 (53%), mid-childhood in 5 (29%) and puberty in 3 (17%). Birth gender assignment was male in 8 (47%), with 9 (53%) assigned female gender, of which 2 were born outside the UK and underwent gonadectomies ages 2 and 11y. Female to male gender change at diagnosis occurred in 4 subjects; (2 < 1yrof age and 2 at puberty). One 3y old subject remains female gender assigned by parental choice, with the child to make a gender decision when older. Hypospadias (isolated or with microphallus, cryptorchidism or undervirilised genitalia with palpable gonads (100%)) was the most common birth presentation. The diagnostic sensitivity of stimulated T/DHT ratio was limited.

Clinical presentation at puberty in 4 subjects (23%), varied with clitoromegaly, primary amenorrhoea, absent breast development, palpable gonad, Hernia 2(11%) and change in voice; two teenage children changed gender to male after diagnosis; one had a gonadectomy at 16 years and choose to retain female gender identity. Gonadectomy was opted as parental choice of a severely autistic child diagnosed at 8yr of age.

Molecular analysis of (SRD5A2) gene identified homozygous recessive (n=12); compound heterozygous (n=3) and frame-shift (n=1) mutations. Most frequent pathogenic variants were p.Arg246Gln, p.Glu200Lys; p.Arg227ter and p.Ala192Thr homozygous mutations.

Management included orchidopexy (n=4), hypospadias repair (n=6), DHT gel for microphallus (n=8) and gonadectomy (n=4). Psychological issues (n=6) were more obvious during the teenage years where counselling was offered, concerns were mostly around patient dissatisfaction due to microphallus or undervirilised genitalia, despite corrective surgeries.

Conclusion: Our data supports the clinical-genotype heterogeneity of SRD5A2 demonstrating a spectrum of phenotypes and age at clinical presentation. We highlight the importance of open choice of gender in long-term follow up patients with SRD5A2 deficiency.

P1-575

A novel mutation in the BMP15 gene in a Palestinian family with primary amenorrhea revealing molecular genetics of premature ovarian insufficiency

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Background: Severe XX-DSD and ovarian dysgenesis (OD) are the extreme clinical phenotype of approximately 1% of women that are affected by primary ovarian insufficiency (POI). BMP15 and GDF9 are two members of transforming growth factor ß (TGF-β) superfamily; they share an oocyte-specific expression pattern and play a crucial role in early folliculogenesis. Only XX cases of mutations in BMP15 have been proved to cause human disease.

Here we describe a novel homozygous BMP15 mutation in 2 sisters from a consanguineous family presenting with primary amenorrhea.

Clinical Data: The 2 Palestinian sisters, presented with absence of spontaneous puberty, primary amenorrhea and hypergonadotropic hypogonadism (LH: 47 & 31.2, FSH: 130 & 31.2 respectively), Karyotype was 46, XX and pelvic MRI detected a small uterus but no ovaries in both affected sisters.

Molecular Data: next generation sequencing revealed a novel c.G959A:p.C320Y mutation in the BMP15 gene, both parents were heterozygous and two other sisters are prepubertal. As the Cysteine 320 is a highly conserved residue among species (8.006 in PhyloP100, 5.4 in GERP) the mutation is highly predicted to cause protein dysfunction (Revel, Polyphen, Sift) especially as it probably causes structural damage due to lack of cysteine S-S bond in an S-S bonds cluster at BMP15 mature protein chain.

Conclusion: The novel C320Y BMP15 mutation causes ovarian dysgenesis and primary amenorrhea in 2 sisters. The predicted change in S-S bonds may compromise protein function which is currently studied. To our knowledge, this is the first description of this disease in a Palestinian family with molecular confirmation, allowing accurate genetic counseling, early diagnosis of affected kindreds & early therapeutic interventions. Paving the way for genetic testing of primary ovarian insufficiency cases in Palestine.

P1-576

Relationship between environmental effects and metabolic characteristics of partial and central precocious puberty in girls: Understanding pathogenesis and identifying specific biomarkers

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Background: The differential diagnosis of partial precocious puberty (PPP) and central precocious puberty (CPP) is vital to the prompt intervention and administration, but their specific biomarkers are still unavailable. The potential harmful effects of environmental factors on children's growth and development attract great concern and require urgent investigation.

Objective: The metabolic differences and connection of PPP and CPP girls were investigated to elucidate their respective pathogenesis and screen the serum-specific biomarkers for early diagnosis. The relationship between serum perfluorinated compounds (PFCs), clinical indicators and specific biomarker was explored to reveal the environmental consequences on the occurrence of precocious puberty (PP).

Methods: A nuclear magnetic resonance (NMR)-based comparative metabolomic analysis was performed on serum from 146 PP girls. The metabolic characteristics of PPP and CPP were derived from the uni- and multi-variate statistic and metabolic network analyses. LC-MS/MS was used to measure the serum PFCs of PPP and CPP, and correlation analysis was performed to deeply explore the relationships between PFCs, clinical indicators and specific biomarkers in PPP and CPP girls.

Results: Eight and eleven serum-specific potential biomarkers were screened for PPP and CPP girls, respectively, and their sensitivity and specificity were investigated by random forest-based ROC curve. The disturbed pyruvate metabolism and butyrate metabolism were shared by PPP and CPP. PFHpA and PFHA were statistically different between PPP and CPP girls. The correlations between PFCs, clinical indicators and the specific biomarkers revealed the different pathogenesis of CPP and PPP girls and their differential responses to environmental effects.

Conclusions: Formate, ethanol, and 3-hydroxybutyrate probably can be used as early diagnostic indicators for PP girls. The serum-specific biomarkers could facilitate the differential diagnosis of CPP and PPP girls. PFCs may be involved in the occurrence and development of PP mainly by disturbing the endocrine homeostasis of girls.

P1-577

Pediatric transgender care from an endocrine perspective: experience over the past decade in a tertiary Swiss center

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Gender dysphoria indicates a psychological distress due to any incongruence between biological sex and gender identity, while transgender identity refers to an individual, whose gender identity is the opposite of the biological sex. The number of gender dysphoric youth seeking hormonal care seems to rise worldwide. Therefore, numerous bioethical and medical controversies are raising about possible side effects of hormonal therapies, including interference with brain development, growth, fertility and bone health.

In this retrospective observational study, we collected data between January 2012 and September 2021 of the gender dysphoric children and adolescent referred to our tertiary care center at the University Children's Hospital Bern, Switzerland. The aims of the study were to assess the number of the referred subjects, describing the persons' characteristics, the hormonal treatments and their effects.

Over the past 9 years, 57 subjects with gender dysphoria were referred to our center. Of these, 45 had a diagnosis of transgender, and among these 28 received a hormonal therapy in-house. Over all, we found a significant increase in the number of referred subjects ($p = 0.001$), aligned with the literature's results. However, for subjects with a confirmed diagnosis of transgender this increase was less significant ($p = 0.05$), and the number of hormonally-treated transgenders did not rise significantly ($p = 0.15$). The age at referral was mostly over 10 years and after puberty onset, however, 7 of the 57 children were referred earlier. Co-existing psychiatric comorbidities were diagnosed in 42% of the subjects.

Among the 28 in-house hormonally-treated transgenders, the median age at start of pubertal suppression therapy step 1 was 15.0 years (range 10.3-17.2y) and of the gender-affirming therapy ($n = 18$) was 16.4 years (range 14-17.6y). In our cohort, height, weight and BMI were within normal ranges for biological sex, with no significant changes after the hormonal therapies. There were two regrets after short course of step 1 therapy; none of them reported irreversible physical changed. Data about bone health and fertility preservation were scarce, with bone densitometry performed in only 15 individuals. However, there were no reported pathological fractures and no major side effects of the hormonal therapies. Four adolescents opted for an additional surgical therapy immediately after transitioning to adult care.

Longitudinal studies are still needed to investigate the possible long-term side effects of the hormonal therapies in transgender individuals in order to provide safe and standardized treatment.

P1-578

Results of Gonadotropin and Testosterone Treatments in Male Cases Diagnosed with Hypogonadotropic Hypogonadism: A Single Center Experience

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Purpose: Therapeutic goals in the adolescent male with hypogonadotropic hypogonadism (HH) are virilization, optimal adult height, normal bone mass, body composition, psychosocial development, and fertility. Until recently, only testosterone was used to treat adolescent males with HH. However, this treatment did not cover all treatment goals and adverse effects on fertility were reported. Therefore, gonadotropin therapy can be used in addition to testosterone in adolescent males with HH. However, there is no consensus on treatment protocols. In this study, we aimed to share the follow-up data of the cases who received recombinant follicle-stimulating hormone (rFSH), human chorionic gonadotropin (hCG) and testosterone treatment for HH.

Methods: Male patients who were followed-up with the diagnosis of HH and gonadotropin and testosterone replacement therapy were initiated between 2016-2021 were retrospectively analyzed. The treatment protocol was created based on the recommendations of Sato et al. (Sato et al., 2015). Treatment was started with 75 IU/day rFSH for 60 days. Then, weekly hCG, rFSH and monthly testosterone treatments were started. Treatments were continued with increasing doses every 6 months. Demographic data, complaints, physical examination, imaging and laboratory findings of the cases at admission and during the follow-up period were obtained from medical records

Results: The mean age of the 9 patients included in the study was 21.3 (16.5–25.3) years. In infancy, 5 cases were referred for bilateral undescended testis+micropenis and 1 case for isolated micropenis. Other cases presented with micropenis (15years), absence of ejaculation (17.5years), and short stature (16.5years). Kallman was detected in two of three cases with anosmia. In pituitary MRI, hypoplasia in three cases and empty sella in one case were detected. The mean age of starting rFSH, hCG and testosterone treatment was 17.6 years (14.2–19.8). Five cases had used testosterone treatment before. An increase in testicular volumes was observed in all cases with treatment, and measured similar to pubertal size in 6 cases. In three cases, the adult dose was reached in the third year of treatment. The patient who received treatment for 4.5 years, testicular volumes were found to be 15/12cc and 8 million/mL sperm concentration in the spermiogram.

Conclusions: Although gonadotropin therapy is quite costly compared to testosterone therapy alone, it allows testicular development and fertility by mimicking physiology. This study has given hope that gonadotropin therapy can have positive results on fertility. More data are needed to establish the most appropriate treatment protocol.

P1-579

MCM9 mutation in a case of premature ovarian insufficiency with vitiligo

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Introduction: Premature ovarian insufficiency (POI) is the loss of ovarian activity before the age of 40. POI presents with amenorrhea, hypergonadotropic hypogonadism and infertility. POI can be a part of a syndrome or in isolation and affects up to one in 100 females, including one in 1000 before the age of 30. Abnormalities of the X chromosome or autosomes, autoimmune, infectious, and environmental causes can lead to POI. POI is heritable in up to 30% of individuals. New causatives and proposed relevant candidates have been identified with recent approaches using next generation sequencing (NGS) and whole exome sequencing (WES). To date, more than 50 genes responsible for POI have been identified around the world. A meiotic gene *MCM9*, have been considered as responsible for Ovarian Dysgenesis 4; POF, short stature, chromosomal instability.

Case: A 14-year-old girl was presented with lack of breast development. She was a product of non-consanguineous marriage and was delivered at term (40-weeks) Her family history was unremarkable except her parents' consanguineous marriage. 4 years ago, PUVA therapy was applied to her whole body due to vitiligo. On physical examination, weight was 48 kg (-0.7 SDS), height was 153 cm (-1.3 SDS), blood pressure was 110/66 mmHg, and pubertal Tanner stage was compatible with stage 1 for breast development and stage 5 for pubic hair. No Turner stigmata, enlarged clitoris or palpable gonads visualized. She had macules of different sizes all over her body compatible with vitiligo. Other systemic physical examination features were unremarkable. Initial laboratory investigations had shown normal full blood count, electrolytes and renal, liver, thyroid functions. Hormone analysis revealed hypergonadotropic hypogonadism as FSH: 84 mIU/ml LH: 29 mIU/ml and estradiol <5 ng/dl. Bone age was compatible with 13 years and 6 months according to The Greulich and Pyle atlas. The ultrasonographic examination of the pelvis revealed atrophic uterus and streak gonads located in normal positions. Chromosome analysis from peripheral blood cells revealed 46, XX. A homozygous mutation in the *MCM9* gene associated with ovarian dysgenesis 4 was detected by Whole Exome Sequencing (WES) analysis. Estrogen replacement therapy was started.

Conclusion: In previous studies, mutations in the *MCM9* gene have been shown to be responsible for short stature, POI and chromosomal instability but it has not been reported that vitiligo accompanies in mutations of *MCM9* gene. Our findings enrich the *MCM9* clinical spectrum.

P1-580

A rare case of 46,XY difference of sexual development (DSD) due to combined homozygous CYP17A1 and heterozygous CYP21A2 mutations with a unique phenotype and hormone profile

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Background: 17a-hydroxylase/17,20-lyase deficiency is a rare cause of congenital adrenal hyperplasia (CAH). 46,XY infants may present with ambiguous genitalia. Adrenal crises are rare due to compensatory glucocorticoid action of the overproduced corticosterone.

Case: A 3-month-old boy underwent a complication-free externalization of concealed penis and circumcision by a paediatric surgeon. At the age of 2.5 years, the boy was first presented to pediatric endocrinology because of mild penile hypoplasia (2.3cm) and glandular hypospadias. The examination revealed non-familial tall stature, normal BMI and normally descended testes. A hypogonadotropic hypogonadism or testosterone synthesis defect were postulated due to normal basal LH and FSH and low testosterone 72 hours after 5000 IU/m2 HCG i.m. (3.72nmol/L). The stimulated testosterone/dihydrotestosterone ratio of 9 made 5a-reductase deficiency unlikely. Karyotype was 46,XY. Three testosterone enantate injections at 4-week-intervall resulted in penile growth up to 4.1cm.

At the age of 12 years, the buserelin test showed a normal LH rise and low stimulated testosterone at 24 hours (1.96nmol/L), possibly due to obesity. In the next two years, puberty progressed spontaneously (pubic hair stage IV, testes 12ml), but due to hypoplastic penis (6.5cm) and gynecomastia, testosterone synthesis defect was suspected and testosterone therapy initiated. In the presence of adynamia, ACTH testing (0.25mg/m2) confirmed partial adrenal insufficiency and hydrocortisone therapy was started. Blood pressure and electrolytes were always normal, as well as adrenal size in ultrasound, but ACTH was elevated (77pmol/L).

Plasma and urine steroid profiling (LC-MS, CG-MS) indicated metabolite changes of 17a -hydroxylase and 21-hydroxylase deficiency fitting to P450 oxidoreductase deficiency. However, genetic analysis detected a heterozygous CYP21A2 mutation in exon 7 [c.844G>T p.(Val282Leu)], a pathogenic variant reducing 21-hydroxylase activity to 30-60% in vitro, and a homozygous CYP17A1 mutation in exon 3 [c.529A>G p.(Asn177Asp)]. The consanguineous Turkish parents were both asymptomatic heterozygous carriers of the above CYP17A1 mutation, whereas the mother was also heterozygous carrier of the above CYP21A2 mutation. The CYP17A1 variant has been classified as likely pathogenic, encoding a protein with 10% 17a-hydroxylase and 17,20-lyase activities (Biason-Lauber 2000).

Conclusion: The referral to paediatric endocrinologists after mini puberty and the atypical presentation complicated the diagnosis of this rare form of 46,XY DSD with combined homozygote CYP17A1 and heterozygote CYP21A2 mutations. Enzyme activities appear to overlap, resulting in mixed clinical and hormone findings; this hypothesis is being tested in expression studies. In complex DSD patients with inconclusive findings, genetic analysis should be considered as early as possible.

P1-581

A case series of granulosa cell tumors of the ovary

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Introduction: Granulosa cell tumors (GSTs) of ovary are very rare, usually large gonadic neoplasms arising from the mesenchyme and sex cords. The main clinical appearance of the juvenile GCTs is represented of signs of excessive estrogen (precocious puberty - 75% of cases) or testosterone secretion (rare).

Aim: To present the different clinical presentation and outcome in a case series of a rare tumor patients.

Cases Presentation:

Case 1: 16 years-old-girl, with complete pubertal development, hirsutism and acne was admitted for secondary amenorrhea. Hormonal assessment confirms the mild hyperandrogenism, but also undetectable gonadotrophins with high estradiol (258 pg/mL) and high CA 125. Imagistic evaluation shows a heterogenous lesion of 11/8/4 cm, with a thin capsule and bridging vessel sign on the right ovary for which she undergone surgery. Histopathology (HP) and immunohistochemistry (IHC) confirm the diagnosis of a juvenile GST, and poorly differentiated Sertoli-Leydig tumor, inhibin positive, Ki67 40%. Postsurgical outcome was favorable, with normalized estrogen secretion and negative inhibin B, but she remains under observation.

Case 2: 5.7 years-old-girl, admitted for precocious telarche, with hyperestrogenism (31 pg/mL) and undetectable gonadotrophins, high inhibin B (372 pg/mL), negative beta-HCG and alfa-fetoprotein. Pelvic MRI appearance consists of a multi-cystic and multi-septal 3.7/1.8/2 cm mass, with a thin clear capsule, located on the right ovary. Right ovariectomy was performed and a sex cord tumor with annular tubules was diagnosed (inhibin positive; Ki67 8%). Postsurgical outcome was persistent favorable at 1.8 years – clinical and morphological regression of the puberty signs, along with prepubertal gonadal axis, undetectable inhibin B and no imagistic evidence of recurrence.

Case 3: 10.5 years-old-girl admitted for prolonged menometrorrhagia and abdominal pain, was diagnosed with a well-defined mass of 16.4/8 cm, with liquid and solid areas on the CT-scan, with positive tumoral markers (CA 125 88 U/mL). Right adnexectomy with tumoral excision, followed by HP and IHC examination established the diagnosis of a juvenile GST, pT1a/pNx/pMx, positive for inhibin; adjuvant chemotherapy was performed due to high values of inhibin B. 1.2 years after the initial diagnosis biochemical (inhibin B 243 pg/mL) and morphological (12.7/9.5/10.5 cm, similar to the initial tumor) recurrence occurred; surgical treatment is incoming.

Discussion: The low frequency, variable manifestations and the absence of a specific tumoral markers may delay the diagnosis in case of a GSTs. Surgical removal is mandatory, and the prognosis depends on the initial disease staging; still, periodic long-term evaluation in needed.

P1-582

An International Study of the Association between Local Health Care Resources and Acute Adrenal Insufficiency Events in Children with Congenital Adrenal Hyperplasia

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Introduction: The reported occurrence and management of acute adrenal insufficiency (AI) – related adverse events (AE) vary widely between centres and may depend on available resources.

Aim: To use the data within the I-CAH Registry to understand the association between the occurrence and management of AI related AE, their management and the availability of local resources.

Methods: Of the 32 I-CAH centres that reported on the occurrence of SDE (https://home.i-dsd.org/i-cah-registry-care-quality-report/), 24 completed a health care survey of local resources and clinical management with one point assigned for each resource. This included 16 centres from high income countries (HIC) and 8 from low/middle income countries (LMIC). Real world data from these 24 centres (420 children) were linked to the results of the health care survey from the centre.

Results: The median reported rate of sick day episodes (SDE, per patient year per centre) at HIC and LMIC centres was 0.75 (range, 0, 6) and 0.11 (0, 0.49), respectively, ($p<0.05$). Although, the availability of resources for management of AI – related AE was numerically greater at HIC centres vs LMIC centres with a median score of 5.5 (1,7) and 3.5 (2, 6), respectively, this did not reach statistical significance. The resources included written plans (100% of HIC vs 75% of LMIC), steroid emergency plans (87% of HIC vs 63% of LMIC, and family support events (38% of HIC vs 25% of LMIC). On the other hand, provision of contact details of medical and nursing team was reported more often in LMIC (75% of HIC vs 88% of LMIC). There was no relationship between the availability of resources and the rate of SDE in LMIC or HIC centres. The use of double dose hydrocortisone was reported more frequently in LMIC vs HIC centres (50% vs 31%). For management of adrenal crises, use of parenteral hydrocortisone was reported in 100% of HIC vs 63% of LMIC. On the other hand, the following were reported to be used more frequently in LMIC centres: prednisolone (LMIC:HIC - 38%:19%); glucagon (LMIC:HIC - 25%:13%); admission duration of 3 days (LMIC:HIC - 88%:25%).

Conclusions: Clear differences exist between the occurrence, prevention and management of acute AI–related AE in HIC and LMIC centres. The report of higher SDE rates in HIC than LMIC centres and the lack of a clear association at all centres between the level of resources available and the rate of SDE needs further study.

P1-583

Androgen receptor activity in genital skin fibroblasts in response to dihydrotestosterone, testosterone and androstenedione using the APOD assay

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Introduction: Androgens are essential for the development of male sex characteristics. Testosterone (T) production from androstenedione (A) by the Hydroxysteroid 17-Beta Dehydrogenase 3 (HSD17B3) in gonadal Leydig cells triggers the differentiation of the Wolffian ducts into epididymis, vas deferens, seminal vesicles and the prostate. Shortly after, the virilisation of the external male genitalia starts through the conversion of T into dihydrotestosterone (DHT) by the Steroid 5 Alpha-Reductase 2 (SRD5A2) outside the gonad leading to the differentiation of the outer male genitalia. However, pubertal virilization has been observed in individuals with 17-Beta Dehydrogenase- or 5 Alpha-Reductase-deficiency.

Objective: To investigate if T and its precursor A can activate the AR in genital skin fibroblasts (GF) of male controls and individuals with 5 Alpha-Reductase-deficiency.

Methods: Previous *in vitro* assays have shown a dose dependent activation of an androgen response element reporter construct in response to A, T and DHT. The APOD assay offers the opportunity to study AR activation endogenously in genital skin fibroblasts, the peripheral target tissue for external genital development, by measuring androgen-dependent induction of the AR target gene Apoliprotein D (APOD). AR activity was determined in five male control GF cell lines and in eight GF cell lines with SRD5A mutations or low 5 Alpha-Reductase expression after incubation with DHT, T and A for 48h.

Results: All three steroid hormones were able to activate the AR in GF, with DHT being the most potent activator, followed by T and A. GF with 5 Alpha-Reductase deficiency showed a similar induction profile as compared to control GF.

Conclusion: A, T can activate AR function in GF albeit to a lower level as compared to DHT. The T-activation is likely to be direct as GF with 5 Alpha-Reductase deficiency and hence no DHT production did not show a significant lower AR-activity as compared to control GF.

P1-584

A Late Reperfused Ovarian Torsion Diagnosed as Acute Appendicitis in a Prepubertal Case

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Introduction: Ovarian torsion (OT) occurs with partial or complete obstruction of blood flow as a result of rotation of the ovary around the infundibulopelvic ligament and/or utero-ovarian ligament. OT is very rare in the pediatric population. Although the most common form of presentation is abdominal pain, the unclear symptom profile in children can often result in missed diagnosis or late diagnosis. For the preservation of ovarian functions and future fertility; providing ovarian blood perfusion with early diagnosis is very important in terms of ischemia-reperfusion injury. Current surgical approach is detorsion±cystectomy±oophoropexy with ovarian incision. Here we present the follow-up of a case of ovarian torsion diagnosed with acute appendicitis in a prepubertal case.

Case: A 7 year-6-month old girl presented with the complaint of swelling in the left breast that had been going on for five months. From her medical history, it was learned that she was born 3250 g at term, was followed up due to scoliosis and her mother had a history of PCOS. In physical examination weight: 21.3kg (-0.84SDS), height: 123.7cm (-0.06SDS), breast development right Stage I/left Stage II, no axillary & pubic hair growth. Abnormal sweat odor, acne and cafe au lait spot were not detected. Bone age was 7 years 10 months. Serum gonadotropin and estrogen levels were prepubertal, both uterus and bilateral ovaries were pubertal in size on pelvic ultrasound, both ovaries were similar in size, and both had multiple millimetric follicles. LHRH test was prepubertal and tumor markers were negative. No treatment was required during puberty follow-up. The patient, who applied with the complaints of abdominal pain and vomiting in the second year of her follow-up, was operated with the suspicion of acute appendicitis. Appendectomy and right ovarian detorsion were performed when right ovarian torsion was detected with appendicitis in the diagnostic laparoscopy. Pathologically, it was confirmed that acute appendicitis was also present. In the postoperative 4th month doppler USG; while significant blood supply was observed in the left ovary, the color mode and spectral pattern of the right ovary could not be differentiated. AMH level was 4.68 (0.25-6.34)ng/ml. Intraovarian normal blood supply pattern in the right ovarian tissue was observed only in the 13th month postoperatively.

Conclusion: OT is a rare surgical emergency in premenarche girls and its association with acute appendicitis has been rarely reported in the literature. There is a need for experience regarding the duration and permanence of ischemia-reperfusion injury after detorsion. The damage may be temporary or permanent, as in our case.

P1-585

Long Term Follow-up of A Boy Who Had Suprasella Tumor Recurrence 4 Years After the First Diagnosis of Extracranial GCTs

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Background: In children with extracranial germ cell tumors (GCTs), brain metastases are rare and are classified as "poor prognosis". The longest interval to brain metastases was 36 months after diagnosis in children, however, it is still less understood.

Methods: We report a boy who had suprasella tumor recurrence 4 years after the first diagnosis of extracranial GCTs (thymus).

Results: A 6-year-6month old boy came to hospital due to penis enlargement and gynecomastia for 2 months. Laboratory data showed GnRH independent precocious puberty. Serum levels of β-hCG ranged from 56-193mIU/ml, while serum AFP levels were normal. hCG in CSF were normal (<1.2mIU/ml). MRI scans showed the tumor in the thymus (8mm*8mm). Sellar and cranial MRI found no abnormalities, except a cisterna magna arachnoid cyst. Pituitary functions were found normal. The boy accepted surgery therapy and the diagnosis of teratoma combine with malignant germ cell tumor was confirmed by pathology. After surgery, chemotherapy and radiotherapy was performed routinely. The serum levels of β-hCG decreased rapidly in the second day after surgery and could not be detected there after.

Three years later, the boy presented multiple pituitary hormone deficiency (growth hormone deficiency, central hypothyroidism, central adrenal insufficiency). Sellar MRI showed empty sella and disappearance of posterior pituitary gland, but the satlk was normal. The levels of serum and CSF β-hCG were normal. Hormone replacement therapy (HRT) has performed since then, and serum as well as CSF β-hCG was followed up every 3 months and remained normal. Four years after the first diagnosis (10 year and 9 month old), the boy again had penis enlargement and erection, and laboratory data showed elevated levels of serum β-hCG (181.4mIU/ml) and CSF β-hCG (14.1mIU/ml). MRI scans showed thickened pituitary stalk and suggested the suprasella region recurrence, but no other metastases were found (mediastinum, lungs, liver, pelvis, and spine were normal). Routine Chemotherapy+ radiotherapy was performed again and serum and CSF β-hCG levels returned normal very fast. After the relapse, the boy has been follow-up for more than 7 years. No second recurrence occur, but panhypopituitarism persistent and lifelong HRT needed.

Conclusion: The detection of serum levels of hCG combine with GSF hCG levels may be significant for the determination of the tumor locations and evaluation of tumor recurrence. The interval of relapse in children with extracranial GCTs can be 4 years, thus long term followed up is needed, and the prognosis is satisfied in our case.

Thyroid

P1-187

Analysis of miR-15a-5p, miR-126-3p, miR-142-5p and miR-150-5p levels in blood of children and adolescents with thyroid diseases

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Background: The pathogenesis of autoimmune thyroid diseases depends on many factors including genetic predisposition and environmental factors. Graves' disease and Hashimoto's thyroiditis are associated with an impaired immunological tolerance to antigen molecules in the thyroid gland. Abnormal immunotolerance results from impaired suppression involving regulatory T cells in peripheral immunocompetent tissues (Tregs). It is known that patients with autoimmune thyroid diseases are more likely to develop focal lesions in the thyroid tissue, and Hashimoto's thyroiditis and Graves' disease predispose to thyroid cancer. We would like to evaluate the levels of microRNA molecules (miR-15a-5p, miR-126-3p, miR-142-5p and miR-150-5p) in children with thyroid disorders, and their predisposition to cancer. MicroRNAs (miRNAs) are small non-coding RNA molecules, approximately 22 nucleotides long, that regulate gene translation by silencing or degrading target mRNAs. They are involved in many biological processes relevant to pathogenetic processes. Due to their important involvement in many processes, including proliferation, metabolism, haemostasis, apoptosis and inflammation, they are recognised as novel diagnostic and prognostic biomarkers for many diseases. There are no studies evaluating the concentration of these molecules in children.

Aim: The aim of this study is to analyse blood concentrations of miR-15a-5p, miR-126-3p, miR-142-5p and miR- 150-5p in pediatric patients with Graves' disease, Hashimoto's thyroiditis and nodular thyroid compared to a control group of healthy subjects.

Methods: The study includes a population of children and adolescents aged 10-18 years with autoimmune thyroid diseases and nodular thyroid. The study group was divided into 40 subjects with Graves' disease, 26 subjects with Hashimoto's thyroiditis, 21 subjects with nodular thyroid and a control group of 23 healthy subjects. The miR-15a-5p, miR-126-3p, miR-142-5p and miR-150-5p molecules will be determined by immunoassay using BioVendor reagents.

Results: In the group of patients with autoimmune thyroid diseases there are higher concentrations of miR-15a-5p molecule compared to the control group of healthy patients, while miR-126-3p and miR-142-5p, miR-150-5p molecules are lower in patients with nodular thyroid disease. The analysis of blood concentrations of these molecules in clinical practice will allow us to determine the predisposition to the development of autoimmune thyroid disease and nodular disease and possibly detect symptoms of thyroid gland dysfunction earlier and start treatment accordingly.

P1-188

A case report of Hirschsprung Disease and C Cell Hyperplasia: a new RET gene variant?

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We report and discuss a case of a girl who at birth underwent surgery for Hirschsprung Disease (HD). To closely investigate her condition, we used a Next Generation Sequencing (NGS) panel to carry out a study of some of the genes known as being associated with congenital megacolon (PHOX-2B, RET, EDN3, GDNF, ASCL1 and BDNF). This analysis showed a maternally inherited heterozygous variant in the RET protooncogene (c.734T>A, p.Val245Glu), which is not described in the scientific literature and can be identified as a variant with uncertain significance (VoUS).

At the age of 12.23 years, during a follow-up examination, the patient was subjected to a thyroid ultrasound that revealed the presence of a nodule of the left lobe (dimensions:12x4 mm). The nodule had a mixed ecostructure, with a transonic component and a more echogenic, apparently vascularized, solid part of 7x3 mm. We ran blood tests that showed normal values of TSH, FT4 and calcitonin.

After six months, the nodule's dimensions were doubled (24x11 mm), therefore we decided to perform a fine needle aspiration biopsy. This procedure suggested the presence of a benign nodule (TIR2).

After 12 months, the nodule presented additional growth (31x17 mm) and modified ecostructure; thus we decided to proceed with surgery. In particular, given the rapid expansion of the nodule, in agreement with surgeon's opinion, we chose total thyroidectomy rather than a hemithyroidectomy.

The anatomopathological examination indeed reported the existence of an encapsulated papillary thyroid carcinoma (pT2 pNx pMx, stadium I, AJCC TNM Staging System 2017), although in a context of bilateral multifocal C cell hyperplasia, a well-known pre-carcinogenesis stage correlated with RET gene mutation. Moreover, given the reported association between RET gene rearrangements and papillary thyroid carcinomas, an NGS analysis for the identification of fusion genes (including RET gene) was carried out. The NGS did not evidence any abnormalities.

RET gene mutations are usually associated with both susceptibility to HD and medullary thyroid carcinogenesis (C cell hyperplasia and medullary thyroid carcinoma). Hence, despite the detected variant is considered to be a VoUS, the patient's clinical

phenotype would highly suggest a pathogenetic RET gene variant. Accordingly, it would be worth conducting functional studies to demonstrate a potential genotype-phenotype association.

Additional studies should also be undertaken to explore the possible existence of a connection between RET gene point mutation and papillary thyroid oncogenesis, even in the absence of the already known RET gene rearrangements.

P1-189

Resistance to Thyroid Hormone β in an infant with a novel de novo mutation of the *THRB* gene

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Introduction: Resistance to Thyroid Hormone (RTH) is a clinical syndrome characterized by impaired end-organ responsiveness to Thyroid Hormone (TH). The cardinal features of this syndrome are elevated serum levels of free THs with normal or high TSH, often with goiter and no clear symptoms of thyrotoxicosis. Mutations in the Thyroid Hormone Receptor beta (*THRB*) gene constitute the most frequent cause of RTH, defined as RTHβ.

Patient and Methods: The patient was referred after neonatal screening for congenital hypothyroidism due to elevated TSH levels.

Thyroid function test revealed markedly elevated levels of TSH, T3, freeT4, while on physical examination tachycardia (140-170 beats/minute), increased head circumference and insufficient weight gain was observed. During hospitalization, impairment in hearing capacity, dilation of brain ventricles without the need for peritoneal drainage and a marked goiter were noted.

Molecular genetic analysis was carried out employing Whole Exome Sequencing (WES) on an Illumina NextSeq 500. After variant filtration patient's and his parents' DNA underwent Sanger sequencing of exon 10 of the *THRB* gene.

Results: WES revealed the presence of a novel heterozygous THRB gene variant, c.1301_1301delG, p.C434Sfs*9. The presence of this variant was verified by Sanger sequencing exon 10 of the *THRB* gene in the patient's DNA, but not in his parents, indicating that it is a de novo variant. The c.1301_1301delG results in a frameshift and a premature stop codon 9 amino acids further down rendering the THRB protein 20 amino acids shorter than the wild type. According to the ACMG criteria this variant is classified as pathogenic (PVS1, PM2, PP3).

A heterozygous variant in the same codon, the c.1302C>A [p.Cys434*] has been previously reported in a RTH patient who presented with both hypothyroid and hyperthyroid features, severe mental retardation (ID<50) and short stature.

During hospitalization the patient continued to show inadequate weight gain and non-response to auditory stimuli. Tachycardia was initially treated with β-blocker, but due to vagotonic symptoms, treatment was modified to α-blocker. Thyrostatic treatment, as expected, did not improve the symptoms, while the administration of high doses of T3 on every other day basis resulted in a decrease in TSH values and a slight remission of the goiter.

Conclusions: Early diagnosis of the rare thyroid hormone resistance syndrome as well as molecular confirmation of the clinical diagnosis allows both the timely investigation and treatment of the comorbidities of the syndrome and the appropriate genetic counseling.

P1-190

Genetic spectrum of 26 Korean patients with congenital hypothyroidism by targeted next-generation sequencing

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Introduction: Congenital hypothyroidism (CH) is caused by underdeveloped thyroid gland or defect of thyroid hormone synthesis. The prevalence of CH in Korea is 1 per 4,225 people, and DUOX2 mutations were previously known as the most prevalent mutation in Korean patients with CH. This study was performed to identify the correlation between etiology and genetic mutations in patients with CH in a single tertiary hospital.

Methods: This study enrolled 26 patients (12 males and 14 females) with CH (9 ectopic thyroid, 8 dyshormonogenesis, 6 hypoplastic thyroid, 3 athyrosis) between February 2020 and April 2021. All exons and exon-intron boundary sequences of the 23 causative genes were analyzed in 26 patients by targeted next-generation sequencing (NGS) panel.

Results: The median age of patients performed NGS was 10.4 years (range 3.3-22.6 years). Seventeen variants in 6 genes (DUOX2, TPO, TSHR, DUOXA2, SLC16A2 and SLC26A4) were identified in 13 patients (4 males and 9 females). DUOX2 mutations (23.5%), TPO mutations (23.5%) and TSHR mutations (23.5%) were most common detected variants in our patients. Among them, 5 patients (20%) carried biallelic mutations in DUOXA2, DUOX2, TPO and TSHR. Three compound heterozygotic mutations in DUOXA2, DUOX2, TPO and one homozygotic mutation in DUOXA2 were all found in patients with dyshormonogenesis. One compound heterozygotic mutation in TSHR was found in patient with hypoplasia. Biallelic mutations in DUOXA2 were most common (40%), which can be regarded as genetic diagnosis.

Conclusions: This study included 18 patients with thyroid gland dysgenesis and 8 patients with thyroid dyshormonogenesis. DUOX2, TPO and TSHR mutations were most common variants. The yield of genetic diagnosis using NGS panel was higher in patients with dyshormonogenesis (50%) than in patients with dysgenesis (5.6%), and DUOXA2 mutations were the most common biallelic mutations.

P1-191

Hyperthyroidism leading to Idiopathic Intracranial Hypertension in a Child – A Case Report

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Introduction: Idiopathic intracranial hypertension (IIH) is a rare neurological condition characterized by raised intracranial pressure (ICP) in the absence of hydrocephalus, brain parenchymal lesion, vascular malformation, or central nervous system (CNS) infection. Hyperthyroidism is a rare but known cause of raised ICP in children and adults, with only a few case reports in the paediatric population. We describe a 7-year-old boy with IIH associated with hyperthyroidism.

Case Report: A 7-year-old boy presented with 6 weeks history of headaches, which had increased in severity over the previous 2 weeks. His headaches were not associated with nausea, vomiting or visual disturbance. On physical examination there was no exophthalmos or goitre. He was slightly tachycardic for his age with normal blood pressure. His weight & height were between 50th – 75th centile, with head circumference at 12th centile. Ophthalmologic examination showed bilateral normal optic discs. Investigations revealed elevated free thyroxine 39.2 (normal 11.0 – 21.2 pmol/L), free T3 21.4 (normal 3.1 – 6.8 pmol/L) and suppressed Thyroid stimulating hormone (TSH) <0.01 (0.27 – 4.20 mIU/L). The anti-TPO antibodies 84 (normal <34U/ml) & TSH Receptor antibodies 2.3 (normal <1.75U/L) were elevated. His computed tomography (CT) scan of head showed craniosynostosis, copper beaten appearance with no intracranial mass or bleed. Blood investigations for etiology of IIH including serum parathyroid hormone, vitamin D and iron studies were normal. There was no history of prolonged use of antibiotics or vitamin A supplements. He was reported to wear minimal clothes during winter months and had been hyperactive since the age of 4 years. Magnetic resonance imaging (MRI) of brain confirmed CT head findings of raised ICP. Cerebrospinal fluid (CSF) opening pressure in recumbent and relaxed position (under general anaesthesia with PCO2 of 4.5kPa) was elevated to 38mmHg (normal < 15mmHg). Subsequently he was commenced on anti-thyroid therapy (Carbimazole) as well as acetazolamide. As his hyperthyroidism improved over next eight weeks, the headaches subsided.

Conclusion: Hyperthyroidism is a rare cause of IIH. It should be considered in children presenting with headache and features of hyperthyroidism. In some case reports increased cerebral blood flow due to hyperthyroidism has been postulated to cause increased ICP. In view of CT scan findings of craniosynostosis and copper beaten appearance which signify long standing raised ICP, another hypothesis is hyperthyroidism leading to early fusion of sutures and subsequent brain growth causing development of raised ICP. Successful treatment of hyperthyroidism is required to reduce the complications associated with IIH.

P1-192

Hashimoto's Encephalopathy in children: A case report

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We present the case of a 11-years-old girl who came to our attention for a first critical episode lasting a few minutes, with spontaneous resolution, described as a generalized clonic tonic crisis, which occurred in full well-being. An electroencephalogram (EEG) was performed which showed focal epileptiform anomalies in the right temporal center that spread evoked by hyperpnea and eye closure and an EEG after sleep deprivation that showed an accentuation of the anomalies in phase 2-3 of NREM sleep. Brain MRI was normal.

An anamnestic analysis revealed that since 1 month she was feeling "strange", as "if she were in a dream". No changes in her mood.

Her height and her weight were normal. The clinical examination revealed a palpable thyroid gland.

In consideration of the acute neurological symptomatology, in the suspicion of an encephalitis, a rachicentesis was performed which was negative for cellularity with negativity of the panel for autoimmune encephalitis on CSF and serum (NMDAR, anti GAD, LGI1, CASPr2, MOG, aquaporin). At the same time, EBV infection, neurological symptoms post-infection COVID-19, celiac disease, a model of encephalopathy with paraneoplastic aetiology and autoimmune encephalitis were excluded.

We found a hyperthyroidism with suppressed TSH (FT4 51.8 ng / L FT3 16.5 ng / L, TSH <0.005 mU/L) and positivity of anti-thyroid peroxidase antibodies (> 600 KU / L), anti-thyroglobulin (261 KU / L) and anti-TSH receptor (13.8 KU / L).

The diagnosis was Hashimoto's encephalopathy (HE). A therapy with methimazole at an initial dose of 0,5 mg/kg/day was started. In addition we gave intravenous methylprednisolone bolus therapy for 4 days followed by oral steroid therapy with gradual resolution of the symptoms and complete normalization of the EEG after one month of treatment, next to the normalization of thyroid function after 3 months.

Hashimoto's encephalopathy (HE) is a rare condition, especially in children.

It can present with neurological symptoms, psychiatric disorders or seizures. It is more frequently associated with hypothyroidism or euthyroidism, but it can occur, more rarely, even in hyperthyroidism.

The presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies is a criteria for the diagnosis HE.

The overall rarity of HE and the lack of knowledge of this condition often represent the main difficulty about diagnosis.

We underline that in the clinical suspicion it is a priority to perform the evaluation of thyroid function with autoimmunity to support the diagnosis, as the timely treatment of this condition represents an important prognostic element.

P1-193

Diagnostic Features and Risk Factors for Childhood Thyroid Cancers

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A worldwide increase in pediatric thyroid cancers incidence over the years has been observed. Although pediatric thyroid cancers tend to have a more aggressive course compared to adults, the survival rate is better.

In this study, we aimed to examine the demographic, clinical, pathological, and laboratory characteristics, prognostic and risk factors of children with thyroid cancer.

Methods: We retrospectively analyzed 39 children with thyroid cancer presented between 2008 and 2021. The study included 34 patients with differentiated thyroid cancer (DTC) (87.2%) including one follicular thyroid carcinoma and 5 patients with medullary thyroid cancer (MTC) (12.8%).

Results: The female-male ratio of the patients was 1.2:1 (Similar in pubertal and prepubertal groups). Among the patient with DTC, 11.8% of them had previously known thyroid disease (2 Hashimoto thyroiditis, one Graves disease, one radiation-induced hypothyroidism), and 11.8% had a prior malignancy. Radiation exposure was detected in 23.5% of DTCs. Hashimoto thyroiditis was revealed in 4 more patients at initial evaluation of thyroid nodule, increasing the frequency of autoimmune thyroid disease to 26.6 % in DTCs. Ultrasonographic characteristics of the nodules, including size <1 cm in 4, were solid in 81.6%, hypoechoic in 76.3% and, microcalcifications was detected in %57.9. Fine needle aspiration (FNA) revealed Bethesda V or VI in 66.6%, Bethesda IV in %18.2, Bethesda III in %6,1, and Bethesda I or II in 9.1%. of the patients. The lymph node and lung metastases were detected in 58.8% and 15.4% of the patients, respectively. Papillary microcarcinoma (PMC) was detected in 15,2% of patients diagnosed with PTC. Although no vascular and lymphatic invasion and, no lymph node or lung metastasis were detected in PMCs, 2 out of 5 patients did not receive RAI treatment and both had local recurrences. MEN2 syndrome was diagnosed in 80% of the patients with MTC. Among the patients who were followed for ≥ 2 years (n=29), no evidence of the disease was found in 69.2%, and recurrent or persistent disease was found in 28,2%. One patient who presented with primary lung involvement died due to disease at 7,5 years of diagnosis (2.6%).

Conclusions: Autoimmune thyroid disease and radiation exposure were the major risk factors for DTCs in our cohort. Pediatric thyroid cancers are aggressive and a nodule cut-off size of 1 cm is not applicable for children. RAI treatment should be given to all pediatric PTCs regardless of the tumor size and grade. Initial lung involvement is a poor prognostic sign.

P1-194

Response to initial treatment in a pediatric cohort of patients with papillary thyroid cancer (PTC): changes after 3 years of follow up

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Background: Childhood onset PTC has a more aggressive presentation but no overall increase in mortality compared to adults.

Objective: To characterize a pediatric cohort with PTC at diagnosis using the American Thyroid Association (ATA) Initial Risk Stratification (IRS) and to evaluate the response to initial treatment until 3 years based on the modified ATA Dynamic Risk Stratification (DRS) for adults.

Patients and Methods: Of a total cohort of 51 patients with PTC followed at our Institution between 2008 and 2019, 31 patients with complete data and a minimum follow-up of 3 years were included in this retrospective study. Clinicopathological data and outcomes were analyzed. Until 2015 patients were treated initially with total thyroidectomy and radioiodine ablation, while after 2015 following ATA Guidelines, low risk patients were excepted from radioiodine. IRS was classified in low (L), intermediate(I) and high (H) risk according to ATA Guidelines. Clinical outcome was assessed yearly by DRS into 4 response categories: excellent, indeterminate, biochemical incomplete and structural incomplete.

Results: Median (range) age at diagnosis was 13,7years (5,2-18), 74% were female and 80% pubertal. Median tumor size was 18mm (6-70). 49% were multifocal tumors. 16% were M1. 35% had thyroiditis. IRS was 16.1% (5) L, 22.6% (7) I and 61.3% (19) H risk. DRS at 3 years revealed 58% (18), 19.3% (6), 6.5% (2) and 16.2% (5) of patients with excellent, indeterminate, biochemical incomplete and structural incomplete response respectively. At 3 years all L risk patients, 86% I and 36% H risk were free of disease. Only 1 patient of the intermediate risk group presented at 2 years a cervical relapse.

Characteristics of initial H risk patients were analyzed showing that those with incomplete response at 3 years (7) were initially predominantly prepubertal (p 0.03) with a higher proportion of T4 stage (p 0.05) and M1(p <0.01) than those with excellent response (7).

Conclusions: Our data confirm the aggressiveness of pediatric PTC at presentation. Clinical outcome by DRS at 3 years showed a marked change in the cohort risk composition compared to admission.

L risk patients remained free of disease and I patients showed a trend to a better outcome. Half of H risk patients behaved promptly towards a more benign status while in the rest

improvement was slower or still incomplete. Yearly DRS assessment provided us useful information allowing a less aggressive approach to those that evolve to NED. These observations reassure the therapeutic intervention.

P1-195

Molecular characterisation of patients with thyroid dyshormonogenesis and variants in *DUOX2*

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Introduction: Thyroid dyshormonogenesis (TD) is a heterogeneous group of genetic diseases caused by the total or partial defect in the synthesis or secretion of thyroid hormones. It presents clinical heterogeneity, from subclinical hypothyroidism (SH) to goitre. The clearer understanding of the pathways and enzymatic activities involved in the synthesis of thyroid hormones has allowed us to identify an important number of causal genes. Defective organification of iodine is caused by abnormalities of thyroglobulin, TPO synthesis, or H_2O_2 production, in which DUOX2 oxidase (*DUOX2* gene, MIM:606759) is involved. Genetic variants in *DUOX2* can cause partial to total iodination defects.

Objectives: To undertake a molecular characterisation and genotype-phenotype correlation in patients with TD and candidate variants in the *DUOX2*.

Patients and Methods: 114 paediatric patients with congenital hypothyroidism from the Catalan Neonatal Screening Programme have been analysed using a high-throughput sequencing panel (Cell3 Target Custom Panel tier 2, NONACUS) including 14 genes.

Results: A total of 24 (21.1%) patients presented variants in the DUOX2 gene that could explain their phenotype. Eleven (45.8%) patients were heterozygous, six (25%) compound heterozygous, and four (16.7%) homozygous. In the remaining three patients, family segregation studies are required to confirm inheritance. In addition, seven (29.2%) of these patients presented variants in other genes, suggesting a possible digenic inheritance for TD: five patients presented variants in *TG*, one in *DUOX1*, and one in *TPO*. A total of 26 variants were described: 17 missense, 3 splicing, 3 frameshift, 2 nonsense, and 1 small deletion. Eleven (42.3%) of these variants have not been previously described in the literature. Sixteen (61.6%) were classified as variants of uncertain significance (VUS), seven (26.9%) as pathogenic, and three (11.5%) as probably pathogenic. The most frequent variant in our cohort has been c.2895_2898del/p.(Phe966SerfsTer29), classified as pathogenic according to reported functional studies. Ten of the 24 patients have been reevaluated, four were diagnosed with hyperthyrotropinemia, three had transient hypothyroidism, and four with permanent hypothyroidism (three mild and one severe). A clear genotype-phenotype correlation could not be identified; therefore, functional studies are being designed to analyse the H_2O_2 synthesis.

Conclusion: 22.8% of patients with congenital hypothyroidism in our cohort presented variants in *DUOX2*. A clear genotype-phenotype correlation could not be described; therefore, clinical reevaluation of these patients is advisable. Alternatively, *in vitro* functional studies could be a useful tool to confirm the pathogenicity of the described genotypes.

P1-196

Diffuse Sclerosing Variant of Papillary Thyroid Cancer in a boy with Goldenhar Syndrome

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A 16-year-old boy was admitted to the Emergency Department for a painless laterocervical swelling, dysphagia and an ultrasound suspect of thyroiditis. On examination he presented facial asymmetry due to maxillary bones hypoplasia and facial nerve palsy of recent onset. There was also a history of hearing loss, hypospadias, Arnold-Chiari malformation and vertebral defects according to a clinical phenotype of Goldenhar Syndrome (GHS).

Blood exams showed TSH 7.46 μU/ml (0.68-4.09), fT4 1.21 ng/dl (1.01-1.6), fT3 3.74 pg/ml (3.26-5.34), anti-TG antibodies 282 UI/ml (UI/ml<34), anti-TPO antibodies >4000 (UI/ml<115). A thyroid ultrasonography revealed an enlarged gland with irregular margins and a diffusely inhomogeneous echo-structure due to the presence of minute hyperechoic dots (snowstorm appearance), mixed with hypo-anechoic areoles, without signs of vascular overflow. Moreover, numerous lymph nodes with globose and polycyclic profiles and similar structure to thyroid parenchyma were noted. Initial diagnosis of Hashimoto's thyroiditis (HT) was made. However, similar ultrasound appearance was reported in literature associated with Diffuse Sclerosing Variant of Papillary Thyroid Cancer (DSV PTC). Due to lymph node enlargement a biopsy was carried out and the histological examination has confirmed this diagnosis.

DSV PTC represents a rare variant (0.7-6.6%) of PTC more common between 15 and 30 years of age. It typically involves one or both lobes. The relationship between HT and the risk of DSV PTC is still controversial. The coexistence of HT can make diagnosis of this tumor more challenging: in many cases described in the literature, the inhomogeneous echostructure have been misinterpreted as the micronodular pattern of thyroiditis.

GHS is a rare craniofacial disorder. The phenotype is clinically heterogeneous and can also include abnormalities of organs and/or skeleton. A multifactorial origin has been proposed, including environmental genetic and epigenetic mechanisms. Indeed,

several chromosomal abnormalities, many gene variants and DNA methylation of a multitude of genes have been associated with GHS.

To our knowledge this is the first case described of DSV PTC in a patients affected by GHS. Although the two conditions may be considered as two separate entities, it is possible that the altered formation of the I and II branchial arch may play a role in predisposing to thyroid tumor development.

Giving the severity of this tumor and the complexity of the syndrome, further studies are needed to try to identify a possible common origin of the two conditions.

P1-197

A familial case of PAX8 gene variant with incomplete penetrance

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Background: The PAX8 gene (paired box gene 8) is located on the long arm of chromosome 2 (2q12–q14), contains 12 exons and encodes a similarly named PAX8 protein. This protein is a transcription factor which in the thyroid gland is essential for the follicular cells formation and takes part in the expression of the thyroid-specific genes (TG, TPO, and SLC5A5). Variants in the gene have been previously associated with autosomal dominant thyroid dysgenesis with hypoplasia, and in rare cases with athyreosis and thyroid ectopy. Variants in PAX8 were also reported to cause urogenital tract defects.

Here we report two patients in the same family with congenital hypothyroidism (CH), attributed to the novel PAX8 gene mutation inherited from the healthy mother.

Case Report: Patient 1 (P1), a 2 year old boy and Patient 2 (P2), a 14-day old newborn girl were referred with CH. Patients were born at full-term with normal height and weight to unrelated parents and showed no abnormalities of the genitourinary tract.

P1. Screening TSH was 33 mU/L (reference ≤ 9 mU/L) with confirmation on day 11 (TSH 17 mU/L, T4L 14.7 pmol/l). Ultrasound examination at 2 years of age showed thyroid hypoplasia. Treatment started on the 11th day after birth.

P2. Screening TSH was 38 mU/L with confirmation on day 9 (TSH 73 mU/L, T4L 9 pmol/l). Ultrasound examination at 1 year of age also showed thyroid hypoplasia. Treatment started on the 9th day after birth.

According to the NGS-based genetic testing both children were showed to possess a previously unreported heterozygous variant in exon 4 of PAX8 gene (NM_003466.4:c.368C>G:p.P123R) which was classified as likely pathogenic according to the ACMG criteria. There were no other rare variants found in the gene, the coding regions and the adjacent intronic areas were completely covered. The parents were also subjected to the same genetic test which for the mother yielded two previously unreported heterozygous variants in the PAX8 gene: the one found in both children, and another one in exon 11 (NM_003466.4:c.1151G>A:p.G384D) which was classified as uncertain significance by ACMG.

Conclusion: Two children, both presented with congenital hypothyroidism associated with thyroid hypoplasia, and their healthy mother we shown to possess a previously unreported likely pathogenic heterozygous variant in the PAX8 gene. Differences in the clinical course can be attributed to the incomplete penetrance of the variant.

P1-198

FT3:FT4 ratio be used to predict relapse and remission? Single Centre Experience

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Introduction: Graves' Disease (GD) is autoimmune hyperthyroidism occurring mostly in adolescent girls. The main pathogenic role of the disease is attributed to TSH receptor antibodies (TRAb), which stimulate the thyroid gland to increase the production of the most active thyroid hormone- triiodothyronine (T3). High levels of TRAb and a large goitre size are commonly known as poor prognostic factors for the disease and are used to predict relapse.

The Aim: The purpose of our study was to check parameters that affect remission in GD.

Materials and Methods: 51 patients with GD were analyzed. The data were retrospectively retrieved from the hospital's records consisting of patients' sex, age, level of Anti- Thyroid peroxidase (TPO), TRAb, fT3, fT4 and thyroid volume on ultrasonography.

Results: The group was predominated by girls (25 % boys, 75 % girls). The mean age was 13.2 (min:4.1-max:17.3). Goitre was observed in 44 (%86) patients. Thyroid-associated orbitopathy (TAO) was observed in 56% of the participants. Twelve patients (23 %) are in remission and three relapsed (25%). Relapse occurred after a median of a 7 (±2.1 months) follow-up and remission time is shorter than no relapse ($p<0.05$).

Anti TPO was statistically significantly higher in those who were in remission ($p<0.05$).

Sex, age, level of TRAb, pubertal status, TAO, fT3, fT4, fT3:fT4 ratio, thyroid volume and T3-predominant GD concomitant use were not useful predictive factors for remission and relapse.

The time to remission in prepubertal children was found to be statistically significantly longer than in pubertal children.

Conclusions: Our remission rate of GD has substantially similar data and studies. Patients with GD exhibiting large thyroids, high TRAb levels and elevated FT3/FT4 ratios are related to poor prognostic factors. Furthermore, in patients with large thyroids, TAO is demonstrated higher rates of recurrence. Positive correlations between Anti-TPO levels (poor predictors of GD) may confirm a prognostic factor for GD severity. Remission in a short time (approximately in the first 7 months) is associated with relapse. The FT3/FT4 ratio is a new useful index for differential diagnosis of thyrotoxicosis but unreliable for predicting remission and relapse. The probability of remission in childhood Graves' disease is very low. It is still controversial what the most appropriate treatment method is in children and how long antithyroid drug treatment should be continued to achieve remission.

P1-199

Thyroid hormone receptor resistance alpha: Case report

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Introduction: Thyroid hormone resistance (THR) is a syndrome characterized by decreased response to thyroid hormones in target tissues. Thyroid hormone receptor resistance alpha (THRRα) is an autosomal dominant inherited disease that is characterized by near-normal thyroid function tests (TFT) and tissue-specific hypothyroidism, and is likely to be missed in practice.

Case: 10-month-old male patient was referred to us because of abnormality in TFT. It was learned from his history that he had been treated for constipation and anemia for a long time, and that his neurological development stages were lagging behind. On physical examination, he had a coarse facial appearance, flattened nasal root, and broad anterior fontanelle. TSH: 3.9 mI/IU (0.7-8.4), fT4: 0.89 ng/dl (0.9-2.2), fT3: 5.3 pg/ml (2.8-4.4), TG: 65.9 ng/ml (12-113), urinary iodine was 12.5 µg/dL. Thyroid USG was normal. The patient was diagnosed with central hypothyroidism and L-thyroxine treatment was started. Speech delay and motor coordination disorder were added to the findings in the follow-up, despite regular drug intake and normal fT4 levels, and he was diagnosed with specific learning disability by the child psychiatrist. Gross and fine motor coordination disorder partially regressed with LT4 treatment and special training. However, in the follow-ups, the patient's growth velocity was at the lower limit. His height was 3-10p, IGF-1 level was low, and his bone age was 1.5-2 years delay. When the chronological age was 11, growth hormone (GH) was started in the patient whose growth rate fell below 5 cm/year and there was no response to GH stimulation tests. Re-evaluation was requested from genetics with the findings of 'short stature, resistant anemia, hypothyroidism, learning disability, epiphyseal dysplasia'. Autosomal dominant inherited heterozygous c.1193C>G (p.PRO398Arg) variant in the THRA gene was detected in the patient. Since this result was consistent with clinical findings, patient was diagnosed with THRRα.

Conclusion: Because of the genetic and phenotypic heterogeneity of THRRα syndromes, the diagnosis and optimal treatment are unclear. While our patient was being followed up with central hypothyroidism, dysmorphic findings and prominent growth retardation made us suspect THR syndromes. In such cases, whole exome sequencing and diagnostic biomarkers may facilitate the diagnosis. L-thyroxine therapy may improve some metabolic abnormalities, constipation, and dyspraxia, especially in those with mild mutations or those diagnosed early. There are also patients receiving GH in the literature. Our case is being followed up with a combination of LT4 and GH treatment.

P1-200

Severe and non severe forms of autoimmune hypothyroidism in childhood: A retrospective analysis of 256 cases

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Introduction: Hashimoto's thyroiditis (HT) is one of the most common autoimmune diseases in childhood. Despite its frequency, there are still controversies concerning the spontaneous evolution and presentation in childhood.

Aim and Methods: this is a retrospective study aiming to evaluate clinical and hormonal features at diagnosis and auxological parameters after 3 years in subjects with Severe Autoimmune Hypothyroidism (SAH). We defined severe hypothyroidism as fT4 <5.5 pg/ml and TSH >30 mU/ml. Subjects' characteristics with SAH (group A) were compared to those with HT subdivided in group B if TSH 10-30 mU/ml and fT4 normal or fT4 <5.5 pg/ml, group C if TSH 4,5-10 mU/L and fT4 normal and group D if TSH <4,5 mU/L and fT4 normal.

Results: Mean features were reported in table.

Group (n.cases)	Group A (n.46)	Group B (n.26)	Group C (n.56)	Group D (n.128)
Mena Age at diagnosis (yrs±sds)	8,8±3,6*	10.46±3.0	11.36±2.6*	11.7±2.9*
Males (%)	21.7	34.6	33.9	21.1
Prepubertal stage (%)	63.4*	47.8	39.1	18.1*
TSH (mU/ml)	381.6±256.1*	16.1±6.6*	6.1±1.4*	3.0±1.0*
fT4 (pg/ml)	3.1±1.6*	8.1±1.9*	8.7±1.6*	8.9±1.9*
Ab Anti-TPO (%)	95.6	92.3	87.5	72.6
Ab anti-Tireoglobulin (%)	80.5	76.9	75	63.3

*=p<0.05

In group A 58.7% referred symptoms of hypothyroidsm (Asthenia the most common, 40% in A, 11.5% in B, 5.3% in C and 4.7% in D, p<0.05 A vs B-C-D). In Group A 80% showed clinical signs as Goiter 51.9% in A, 19.2% in B, 17.8% in C and 12.5% in D, p<0.05 A vs B-C-D; Growth Delay 30.7% in A, 0% in B and C and 1.5% in D, p<0.05 A vs B-C-D. 72.9% of group A had a familiy history for autoimmune diseases, 59.9% for group B+C+D. At SAH diagnosis, group A presented a difference between Height and Target Height of -1.21 SDS (0.04 for group B+C+D), -0.92 after 2 years (66.6% of subjects) (0.01 for group B+C+D) and -0.68 after 3 years (80% of subjects) (0.01 for group B+C+D).

Conclusions: The risk of developing SAH is greater in younger and prepubertal children, and they are more symptomatic. Family history for autoimmune diseases seems to be greater in subjects with SHA (pediatricians should be aware of it and follow carefully screening programs). We detected growth impairment at diagnosis in SAH compared to HT, progressively improving.

P1-386

Relationships of urinary bisphenol A in childhood on thyroid hormone function in adolescents

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Purpose: Bisphenol A (BPA) is endocrine disrupting chemicals used to manufacture plastics such as epoxy resins and polycarbonate polymers. BPA has weak estrogenic and strong anti-androgenic effects and has also been linked to disruption of thyroid function in previous studies. This study aims to investigate the relationship between urinary bisphenol A exposure in early childhood and thyroid hormone of pubertal children in Korea.

Methods: From the Ewha Birth and Growth Cohort Study, who visited Ewha Womens Mokdong Hospital between 2001 and 2005 were included. The concentration of urinary BPA measured repeatedly for the same subject at 3-5 years old and 7-9 years old. We measured serum free T3, free T4 and thyroid-stimulating hormone (TSH) levels at 10-12 years in 128 out of 164 subject who repeatedly measured BPA concentrations at ages 3-5 and 7-9 years old. Prospective associations of thyroid hormone function in adolescents with bisphenol A exposure levels in childhood were assessed using generalized linear model analysis and p-value for trend was obtained. We also investigated the interaction of thyroid hormone changes due to exposure to BPA in two period.

Result: We found that levels of urinary BPA in age 3-5 years was not significantly associated with levels of thyroid hormone in 10-12 years old adolescents. We found that levels of urinary BPA in age 7-9 years was to be significantly related with free T3 levels in 10-12 years old in girls. In boys, no significant differences in thyroid hormone levels were observed by exposure to BPA. The association between urinary BPA and levels of the other thyroid hormones (TSH, Free T4) were not statistically significant. Free T3 concentration was significantly decreased with increasing BPA concentration in girls (β:-0.15 95%CI:-0.28~ -0.03).

Conclusion: In conclusion, BPA exposure in childhood affects thyroid function in adolescent girls. It might be related to increasing of thyroid disorder in adolescents according to environmental effects.

P1-387

Pediatric Graves Disease (PGD): Presentation, treatment and follow up. A single center Argentine perspective

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Introduction: PGD is characterized by hyperthyroidism and antibodies against the TSH receptor (TSHRAB). Reported annual incidence is 4,58/100,000.

Objective: To describe an Argentinean cohort with PGD followed between 2006 and 2020 at the Ricardo Gutierrez Children's Hospital.

Material and Methods: Retrospective study of 69 patients, who were treated initially with antithyroid drugs (ATD) in a titration dose regimen with a median (range) time of follow up of 4,61 years (0,28-11,58).

Demographic, clinical, biochemical and treatment data were collected from clinical charts. Factors thought to predict outcome (age, sex, pubertal status, goiter, ophthalmopathy, family history of thyroid disease, free thyroxine (FT4) and TSHRAB) were analyzed with Student t-test for continuous variables, and the Fisher's exact test for categorical variables (significance: p< 0,05)

Results: At diagnosis median age was 12,3 years (1,7-17,2), 75% were girls, 65% pubertal. 71% had goiter ≥ 2 (OMS classification), 65% ophthalmopathy and 46% had a positive family history of thyroid disease. 85% had free thyroxine (FT4) > 50pmol/l (3,9 ng/dl) and 83% TSHRAB ≥ 3-folds upper normal limit of our assay. Goiter, ophthalmopathy and tachycardia were the main clinical signs observed.

Median methimazole (MMZ) starting dose was 0,84 mg/kg (0,4-1,3). 20% of the patients presented adverse effects (AEs) related to the drug, 79% in the first 5 weeks of treatment and 71% were severe enough to discontinue ATD.

The overall remission rate with a median of ATD of 3.29 years (1,3 -6,1) was 14% (n=10). 13% are still receiving ATD.

Older patients (p< 0,02) and patients with TSHRAB below 3 folds upper limit of our assay (p< 0,01) were more likely to respond to ATD.

Because of AEs, thyroid nodules, relapse, and flare-ups, 51% of patients underwent definite treatment: 54% radioiodine ablation, and 46% total thyroidectomy.

22% of the total cohort was lost to follow up, 9% in the first two years of ATD.

Conclusion: Our cohort presented severe cases of PGD. This approach implied long-term treatment and controls. Remission rate at approximately 3 years of treatment was low and 22% dropped out, unable to follow our recommendations and half of the cohort needed definite treatment. These results may lead us to reconsider our approach to severe PDG focusing on other factors associated with outcome such as compliance and social background and perhaps opting earlier for a definitive treatment as an alternative to ATD.

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Next Generation Sequencing Analysis of Congenital Hypothyroidism Patients in A Single Tertiary Center

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Background: Congenital hypothyroidism is the most common neonatal metabolic disorder and detected at a rate of 1 in 3000 to 4000 live births. Compared to congenital hypothyroidism caused by defects in thyroid development leading to thyroid dysgenesis, thyroid dyshormonogenesis has tendency to be detected at older age and its clinical manifestations are individually different. Thus, to evaluate exact causes and predict clinical course for congenital thyroid dyshormonogenesis and establish precise strategies for treatment, we conduct Next-Generation Sequencing (NGS) to patients who diagnosed congenital hypothyroidism with normal thyroid gland and analysis the results.

Methods: We conducted NGS to 33 patients who visited Department of pediatrics, Inha university hospital and diagnosed congenital hypothyroidism with normal contour of thyroid gland in ultrasonography from Jan. 2018 to Mar. 2021. We also analyzed their thyroid function test results, dose of levothyroxine and clinical manifestations.

Results: From NGS analysis, 33 CH patients revealed that 26 patients (24/31, 77.42%) were detected to have at least one potentially functional variant. 6 DUOX2 variants in 7 patients, 6 DUOXA2 variants in 5 patient, 5 TG variants in 3 patients, 5 TSHR variants in 7 patients, 2 TPO variants in 2 patients, 1 NKX2-1 variant in 1 patient, 1 THRB variant in 1 patient, 1 TRH variant in 1 patient, 1 SLC5A5 variant in 1 patient and 2 GLIS-3 variants in 2 patients as PV, LPV and VUS types were confirmed. Siblings and parents of the patients who agreed and were available underwent familial sequencing analysis. In most of cases, parents who had one heterozygote variant of the gene were symptomatic or had subclinical hypothyroidism.

Conclusions: In this study, we found DUOX2/DUOXA2, TSHR and TG variants were dominant in patients who diagnosed CH in a single center. And we cautiously recommend that using the NGS to strategize treatment plan for CH based on the clinical manifestations and genetic analysis of the family members of the index patients. To this, further additional studies are needed.

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Increasing incidence of Pediatric Graves' Disease

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Introduction: Graves' diseases is a rare autoimmune disease in children. Viral infections are considered as a trigger for autoimmune thyroid disorders. A temporal association between SARS-CoV-2 and a novel pediatric hyperinflammatory condition called Paediatric inflammatory multisystem syndrome has been reported in 2020, raising questions about the link between SARS-CoV-2 and autoimmune and autoinflammatory diseases. Over the last year (2021), we noticed an increase in the number of children presenting to our department with Graves' disease.

Our primary aim is to document the incidence of Graves' disease in our department since 2005, comparing our data with national data regarding thiamazol delivery. Our secondary aim is to compare the characteristics of the patients diagnosed before and during the SARS-CoV-2 outbreak.

Material and Methods: A retrospective study including all the pediatric patients diagnosed with Graves' disease seen in our department since 2005 was performed. Hyperthyroid newborns were excluded. Data collected were the date and the age at diagnosis, the thyroid hormone levels, TSI at diagnosis, data from the national health insurance regarding the number of delivered thyroid hormone synthesis inhibitor drugs, thiamazol, in children (<18 years)/year.

Results: A total of 48 patients with Graves' disease were diagnosed since 2005 in our department. Fifteen patients (1/3) were diagnosed since the SARS-CoV-2 outbreak, with the highest incidence in 2021 (11 patients). At the national level, an increase of thiamazol delivery is observed in 2020 and 2021 compared to the preceding years.

Similar results regarding the age of diagnosis, free T4 and T3 levels or the presence of auto-immune diseases in the personal or family history were observed between the patients diagnosed before and those diagnosed during the SARS-CoV-2 outbreak.

Conclusions: We observed a temporal association between SARS-CoV-2 outbreak and an increase in pediatric Graves' disease. The age and severity of the disease seems not to be influenced by the SARS-CoV-2 outbreak. SARS-CoV-2 could thus constitute a trigger for pediatric Graves' disease. Further studies are needed to confirm our findings.

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Does serum thyroglobulin predict thyroxine requirement during infancy in athyreosis and thyroid ectopia?

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Background: Thyroglobulin (Tg), a protein synthesized uniquely in the thyroid gland, may be elevated in primary congenital hypothyroidism (CH) due to increased TSH drive, absent in true athyreosis and Tg deficiency, and very elevated in some types of dyshormonogenesis.

Hypothesis: Serum Tg at the time of newborn screening may reflect the amount of thyroid tissue present in apparent athyreosis and thyroid ectopia, and hence provide a guide as to future levothyroxine (L-T4) requirement. This could be useful in avoiding overtreatment with L-T4.

Design: We studied the relationship between serum Tg at the time of referral in infants with CH due to athyreosis and ectopia, together with L-T4 dose (mcg/m2), plasma TSH and free T4 (fT4) at diagnosis, 6 and 12 months.

Results: Median (range) Tg at diagnosis in 26 infants with true (n= 9) and apparent (n= 17) athyreosis, and ectopia (n=56) was 10 (1.9-58) and 177 (84.7-3977) μg/L respectively (reference range 91.3-148 in 3-day infants). In patients with ectopia, median (range) L-T4 dose (mcg/m2) at 6 and 12 months was 102.4 (95.9-121.6) and 98 (83.9-114) respectively. There was a low negative correlation between serum Tg at diagnosis and L-T4 dose at 12 months (rho= -0.407, p=0.02), but no significant correlation at 6 months. In patients with athyreosis, median (range) L-T4 dose (mcg/m2) at 6 and 12 months was 97.9 (89.2-103.9) and 109.1 (98-117.6) respectively, with no correlation between serum thyroglobulin and LT4 dose at 6 and 12 months.

Conclusion: As well as being of diagnostic value in some forms of CH, serum Tg at birth may be of value in guiding LT4 dosage during the first year of life especially in patients with thyroid ectopia. However, larger patient numbers and prospective study are needed to offset confounding variables including L-T4 dosing protocols and adherence.

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Biochemical Indicators of Euthyroid Sick Syndrome in Critically Ill Children

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Purpose: This study aimed to determine the prevalence and predictors of Euthyroid Sick syndrome (ESS) in pediatric intensive care, and to establish a link between thyroid function tests and mortality.

Methods: Between January 2015 and March 2020, children admitted to our pediatric intensive care unit (PICU) and tested for free triiodothyronine (fT3), free thyroxine (fT4), and thyrotropin (TSH) levels were included. Patients with decreased fT3, normal or decreased fT4, and normal or decreased TSH levels were assigned to the ESS group. The association between biochemical indicators and ESS, as well as the relationship between fT3 and mortality, were examined.

Results: 141 (36%) of children were classified in the ESS group. The ESS group had a higher rate of 28-day mortality (12 [8.5%] vs 9 [3.7%]). Blood urea nitrogen (BUN), albumin, platelet, lactate, and pediatric index of mortality 3 [PIM3 (%)] were significantly associated with ESS (odds ratios in order: 1.024, 0.422, 0.729, 1.208, 1.013). Multivariate regression analysis showed that BUN, albumin, platelet, and lactate were independently associated with ESS progression. The area under curve (AUC [95%CI]) for fT3 was 0.644 (0.555–0.789) to detect mortality. Children with a fT3 level lower than 2.31 pg/ml had significantly higher 28-day mortality (log-rank test, p=0.001).

Conclusion: Our study identified BUN, albumin, lactate, and platelet count as independent risk factors for ESS progression in children. Furthermore, our findings indicated a correlation between fT3 and mortality, which makes fT3 an ideal candidate to be included in mortality indices.

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Clinical Features, Risk Classifications and Long-Term Follow Up Of Childhood Differentiated Thyroid Cancer (DTC): A Single Reference-Center Experience

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Background: Thyroid cancers are rare in childhood. ATA guideline (pediatric section) has been applied in daily practice since 2015. It is very significant to accurately predict the risk in the management of differentiated thyroid cancer (DTC). For this purpose, we shared our single center-20-year-experience about the follow-up features and management of childhood and adolescent thyroid cancer. We aimed to evaluate the dynamic risk stratification (DRS) and the other prognostic factors of DTC in childhood.

Methods: This retrospective study identified 41cases with DTC (F/M:35/6) followed for a median of an estimated five years (range:1–15 years) after total thyroidectomy. We classified patients according to the response to treatment and the course of the disease, according to both the ATA guideline and DRS, which was used for adults. Pretreatment risks, clinical features, treatment, and follow-up characteristics were retrieved.DTC status was evaluated after the initial therapy and at the last follow-up visit (Table).

Results: 41patients aged 5.9–19.6 years were evaluated. 25 had previous thyroid disease (4 congenital thyroid disease, 17 chronic lymphocytic thyroiditis,1 graves disease, 3 multinodular goiters). 33 had papillary thyroid carcinomas. Tumor size was 1.2cm (0.4-5), mostly localized on right lobe. 27 had cervical and one had distant metastasis at diagnosis. All underwent total thyroidectomy, 16 had radioactive iodine treatment (30-200mCi). Lymph node dissection was performed in 68% (29.3% central±lateral, 14.6% berry picking). One patient needed residual tumor excision. Risk factors were classified according to ATA and DRS (Table). 35 had in low risk according to ATA guideline, however they were classified as excellent response (n =32), indeterminate response (n = 4), biochemical incomplete response (n =4), structural incomplete response (n = 1) according to DRS.

Conclusion: Our study supported that the ATA staging was adequate for follow-up. In addition, DRS risk estimates contribute significantly to baseline and post-treatment follow-up.

Table.Pathological Features and Risk Classification of Patients	**%**
American Thyroid Association (ATA)	**%**
ATA initial risk classification, %	Benign: 4.9% Low: 34.2% Intermediate: 39.% High: 22%
Histology, %	Papillary: 80.5% Follicular: 19.5%
Lymph node metastasis, %	N0: 65.9% N1a: 24.4% N1b: 9.8%
Distant metastasis, %	2.4%
TNM AJCC Stage %	Stage-I: 97.5% Stage-II: 2.5%
ATA postoperative risk classification, %	Low: 85.4% Intermediate: 12.2% High: 2.4%
Dynamic Risk Stratification	**%**
Response to therapy classification, %	Excellent: 78.1% Acceptable: 17.1% Incomplete: 4.9%
Stimulated Tg done (first 2 years), %	Yes: 56.1% No: 43,9%
Clinical status after initial therapy, %	No evidence of disease: 73.2% Biochemical evidence of persistent disease: 14.6% Structural evidence of persistent disease: 9.8% Recurrent disease: 2.4%
Status at final follow-up, %	No evidence of disease: 95.1% Persistent/recurrent disease: 4.9% Death of disease: 0

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Urinary Iodine Concentration and Thyroid Function in Children by Age

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Background: There are few reports on age-related differences in urinary iodine concentrations, which reflect iodine intake.

Objective: We investigated the relationship between age-related differences in urinary iodine concentration and thyroid function.

Methods: The subjects were 749 children aged 1 year, 677 children aged 3 years (excluding 2 children aged 3 years whose urinary iodine concentration was less than sensitive), 559 children aged 6 years, 348 children aged 7 years, 211 children aged 8 years, 183 children aged 9 years and 26 children aged 10 years who participated in a cohort study at our hospital. Urinary iodine levels were measured, and age-specific values and changes were examined.

Results: The median (range) of urinary iodine (μg/L) at each age was 414 (25-79000) at age 1, 262 (25-6400) at age 3, 243 (29-22200) at age 6, 269 (40-11330) at age 7, 212 (49-25690) at age 8, 221 (29-46300) at age 9, 253. 5(96-2776) at age 10, with 3-10 year old age group being more than adequate according to WHO criteria and 1 year old being excessive.

The quartile ranges of urinary iodine (μg/L) were 205-1150 at age 1, 160-498 at age 3, 142-471 at age 6, 158-496 at age 7, 145-390 at age 8, 138-477 at age 9, and 150-434 at age 10, respectively.

Of the subjects whose urinary iodine was measured, the number of the subjects who also underwent blood tests showed TSH >5 μIU/mL was 13 at age 1, 12 at age 3, 2 at age 6, 2 at age 7, 4 at age 8, 1 at age 9, and 0 at age 10, but FT4 was within normal range in all cases, regardless of whether TSH was elevated or not.

Conclusion: Since most iodine is metabolized and excreted in urine, urinary iodine is a good indicator of iodine intake. This study suggests that Japanese children have excessive iodine intake, especially in infancy, and that there is no evidence of abnormal thyroid function in spite of high urinary iodine levels in all age groups.

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Analysis on the influencing factors of neonatal serum FT3, FT4 and TSH

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Background: With the increasing survival rate of extremely premature infants, neonatal thyroid dysfunction is more frequently observed clinically. Despite the guidelines, the timing of screening for neonatal thyroid function remains controversial, especially for premature infants. At present, there is no unified standard for serum FT3, FT4 and TSH levels of newborns of different gestational ages and postnatal days.

Objective: To analyze the change trend of thyroid function in neonates of different gestational age and postnatal day, and provide basis for the selection of screening and treatment time of neonatal thyroid dysfunction.

Methods: From June 1, 2020 to June 1, 2021, 359 neonates were selected as subjects, 23 possible related factors were collected to analyze the influencing factors of neonatal thyroid dysfunction statistically. FT3, FT4 and TSH levels were divided into groups 7±3 days, 14±3 days, 21±3 days and 28±3 days according to the day of postpartum examination, and divided into groups 28-31^{+6} weeks, 32-33^{+6} weeks, 34-36^{+6} weeks, ≥37 weeks according to the gestational age. Then analyzed the differences of neonatal FT3, FT4 and TSH in different gestational ages and postnatal days, and established the 25th, 50th and 75th percentile values of FT3, FT4 and TSH for newborns of different gestational ages and postnatal days.

Results: Neonatal FT3 and FT4 levels were positively correlated with gestational age. The main influencing factor of neonatal TSH level was birth weight, and the lower the birth weight, the greater the incidence of TSH elevation. In addition, compared with normal thyroid function group, the frequency of increased TSH was higher at 7±3 and 14±3 days of postpartum, the frequency of decreased FT3 and decreased FT3 with increased TSH was higher at 14±3 and 21±3 days of opostpartum. However, in most cases, the levels of FT3, FT4 and TSH of different gestational ages tend to be normal gradually with the increase of postnatal day.

Conclusion: Neonatal thyroid dysfunction is more common in premature infants. It is recommended a second screening test at 1, 2, 3, 4 weeks after birth for premature infants, babies with low birth weight and critically ill newborns. It is more reasonable to formulate the reference range of FT3, FT4 and TSH based on gestational age and postnatal day.

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Liquid formulations of Levothyroxine with and without ethanol in the treatment of congenital hypothyroidism: similar TSH and fT4 values in the first six months of follow up

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Background: There are two liquid formulations of Levothyroxine currently in use in Italy: one containing ethanol (Tirosint®) and the other ethanol-free (Tifactor®). The aim of our study is to compare the two liquid formulations of Levothyroxine in the first six months of treatment in newborns affected by Congenital Hypothyroidism (CH).

Methods: We retrospectively enrolled 156 patients treated with the ethanol-containing solution (Group A) and 49 treated with the ethanol-free solution (Group B) among patients in follow-up at our Institution. We collected data at diagnosis (gestational age, etiology, TSH, fT4, initial dose/kg) and data at 7-15 days, 1 month, 3 months and 6 months after the diagnosis (TSH, fT4, dose/kg); then, we compared median values in group A vs. group B.

Results: We observed lower TSH values at diagnosis in group B than in group A (p=0.0158), and lower dose/kg/day in group B than in group A at 7-15 days (p=0.0116), at 3 months (p=0.0194), and at 6 months (p=0.0014) after diagnosis in babies born at term. Moreover, fT4 concentration was significantly higher in group B at 3 months (p=0.0223), however being always in the correct range for age (median values 1.58 ng/dL in group A, 1.73 ng/dL in group B). We also calculated the percentage of patients with glands in situ and dysgenesis in both groups: we detected a significantly higher rate of glands in situ in group B (72% vs. 57%). Then, we conducted

the same analysis considering only patients with in situ gland: we obtained lower TSH levels at diagnosis in group B compared to group A (p= 0.0238), and dose/kg/day lower in group B than in group A (p= 0.0001) at diagnosis. During follow up, we observed significantly higher fT4 values in group B than in group A at 3 months (p= 0.0056), always in the correct range; also, the dose/kg/day at 7-15 days was significantly lower in group B than in group A (p= 0.0002).

Conclusions: Even though data on more patients and more extended follow-up periods are needed, our study confirms the efficacy of both therapeutic strategies in the treatment of CH. This allows us to personalize therapy depending on each patient's individual needs and on the characteristics of each of the two liquid formulations.

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A rare cause of acquired von Willebrand factor deficiency: Primary hypothyroidism due to autoimmune thyroiditis

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In children, autoimmune thyroiditis is often diagnosed with signs and symptoms such as goiter, short stature, and constipation. Delayed diagnosis of hypothyroidism may result in atypical signs and symptoms at presentation, depending on the severity of hypothyroidism. Von Willebrand disease (vWD) is the most common bleeding disorder caused by the quantitative or qualitative deficiency of von Willebrand factor (vWF). Acquired vWD (avWD) is a disorder characterized by low levels of vWF due to reduced production and/or enhanced removal of vWF from the circulation. It is distinguished from inherited vWD by a lack of prior history of bleeding diathesis in the index case and a negative family history of vWD. Herein, we report a case with acquired vWD due to delayed diagnosis of hypothyroidism due to autoimmune thyroiditis.

Case Report: A 9-year-old, prepubertal girl was referred to our pediatric hematology outpatient clinic owing to prolonged gingival bleeding after dental extraction. Past medical history was unremarkable. The physical examination revealed pallor, facial swelling, periorbital puffiness, dry skin and grade 1b guatr. She was 130 cm (-0.54 SDS) tall and body mass index was 21.8 kg/m2 (1.71SDS). The remaining systems' examination yielded normal findings. Coagulation profile revealed normal platelet count, prothrombin time, activated partial tromboplastin time (APTT), fibrinogen. Additional laboratory work-up revealed macrocytic anaemia (haemoglobin: 9.8 g/dL, MCV:93fL), and severe primary hypothyroidism (fT4: 0,79 ng/dL, TSH:697mU/L). Thyroid autoantibodies were positive and thyroid ultrasound confirmed thyroiditis. In literature, avWD due to hypothyroidism have been reported in children. Although APTT level was normal, we also found decreased levels of factor VIII (74% [N:60-150]), vWF antigen (56.6% [N:50-160) and vWF ristocetin cofactor activity (51% [N: 50-200]) in our case, suggestive of aVWD. Substitution therapy with levothyroxine was initiated. Prolonged bleeding did not recur after commencement of L-T4 treatment. The levels of factor VIII (107%), vWF antigen (132%) and vWF ristocetin cofactor activity (68%) were normalized and macrocytic anemia resolved at the fourth month of L-T4 treatment.

Conclusion: Delayed diagnosis of acquired primary hypothyroidism may lead to atypical signs and symptoms. Patients with bleeding diathesis of unknown origin should also be investigated for hypothyroidism. The pathophysiology of avWD in hypothyroidism is not clear, but it is hypothesized that there is a reduction in the synthesis of Factor VIII and vWF. The increase in levels of Factor VIII and vWF in our case in parallel with normalization of thyroid functions also support this hypothesis.

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Molecular diagnosis of non-autoinmune subclinical hypothyroidism in paediatrics

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Introduction: Subclinical hypothyroidism (SH) is a biochemical condition characterized by serum levels of TSH above the reference range upper limit (4,5µUI/mL), with normal concentrations of thyroid hormones. In cases of non-autoimmune subclinical hypothyroidism (NASHT), genetic defects have been described and can determine disorders in the biosynthesis process of thyroid

hormones, such as heterozygous mutations in the TSH receptor gene (*TSHR*) and in the gene encoding dual oxidase2 (*DUOX2*). In addition, it is suspected that other genes that regulate or participate in the biosynthesis of thyroid hormones could be involved in NASHT, although to date very few studies have evaluated its genetic basis.

Objective: To perform a molecular characterization and identify genotype-phenotype correlations in patients with SH

Patients and Methods: Descriptive, multicentre study in a cohort of 49 patients diagnosed with NASHT who presented in two separate determinations a TSH above 7μUI/mL. The molecular analysis was performed using a high-throughput sequencing panel (Cell3 Target Custom Panel tier 2, NONACUS) that includes 14 genes of which the most important were: *TG,TPO,DUOX2, DUOXA2,PAX8,TSHR,SLC5A5,SLC26A4*.

Results: A total of 49 patients with a mean age at diagnosis of 5.5±3.4years were studied. Eight centres from Catalonia participated. Twenty-seven patients (55%) were male. Twenty-eight (57%) patients received treatment with levothyroxine. The mean TSH at diagnosis was 9.2±2.0mU/L and the maximum TSH was 11.4±3.6mU/L. Thirty-one patients (63.3%) presented variants in the studied genes, of which twenty-five (80.6%) were heterozygous, five (16%) were digenic and one patient was compound heterozygous of *DUOX2* (Table 1). Of the heterozygous patients, sixteen (60%) presented a variant classified as pathogenic (PAT) or probably pathogenic (PPAT) and ten (40%) presented a variant of uncertain significance (VUS). Family segregation studies are being carried out to confirm the inheritance.

Conclusion: A significant percentage of patients (63.3%) with non-autoimmune subclinical hypothyroidism have variants in genes related to thyroid dyshormonogenesis and several have not been previously described. The functional studies of the undescribed variants have been designed to establish the genotype-phenotype relationship. These genetic findings can help to better characterize the patients to define the prognosis and the need for treatment.

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Unusually enlarged ovaries associated with severe hypothyroidism - Van wyk and grumbach syndrome case report

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Introduction: Since 1960, enlarged polycystic ovaries associated with hypothyroidism, delayed bone age and precocious puberty are recognized as Van Wyk and Grumbach syndrome. Although it is rare entity, it should be considered in differential diagnosis of the enlarged polycystic ovaries.

Case: An eleven-year-old girl was presented with sudden onset of abdominal pain and vomiting. A large mass with multiple cysts was seen on the abdominal ultrasound. MRI of the abdomen at the time revealed massive bilateral enlarged polycystic ovaries (right measuring 141x134x85 mm and left 85x96x71 mm). She was obese with BMI of 30.01 kg/m2, with height of 138.3 cm (-1SD). Tanner stage was B2, A2, P2. Her TSH levels were significantly elevated at 704 mIJ/L (normal values 0.35-4.94) and was accompanied by hyperprolactinemia over 4200 mIJ/L (normal values 110-562) and anemia (hemoglobin level of 84 g/l). Her FSH and LH levels were within normal range. Bone age was delayed almost 3 years behind her chronological age. Menarche presented two years before admission to the hospital, with irregular menstrual cycles afterwards. After thorough evaluation, she was diagnosed with Van Wyk and Grumbach syndrome due to unrecognized chronic lymphocytic thyroiditis. She was treated with thyroid hormone replacement. After one month of treatment, positive progress in the clinical response was observed. Her TSH levels in serum dropped 118 mIJ/L, while ovaries measurements evaluated via ultrasound were much smaller (72x38x42 mm and 67x38x35 mm on the right and left side respectively).

Table 1. Patient genotypes and variants detected

Compound heterozygote	1/31	*DUOX2*	PAT+VUS
Heterozygotes	25/31	*TG* (5patients)	1PAT,4VUS
		DUOX2 (4patients)	2PAT,1PPAT,1VUS
		PAX 8 (2patients)	1PAT,1PPAT
		TSHR (11patients)	5PAT,3PPAT,3VUS
		SLC5A5 (1patient)	VUS
		SLC26A4 (2patients)	1PPAT,1VUS
Digenic	5/31	*DUOX2*(VUS)-*DUOXA2*(PPAT)	
		DUOX2(VUS)-*TG*(VUS)	
		DUOX2(PPAT)-*TSHR*(VUS)	
		TG(PAT)-*TPO*(VUS)	
		DUOX2(PPAT)-*SLC5A5*(PPAT)	

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Conclusion: When evaluating girls with enlarged polycystic ovaries and precocious puberty, possibility of severe hypothyroidism should be considered, especially in the presence of delayed bone age.

P1-399

Evaluation of Childhood Thyroid Nodules: A Single Center Experience

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Introduction: Although thyroid nodule is seen less frequently in childhood than in adults, it is more likely to be malignant. The aim of this study was to examine the characteristics of the patients followed up for thyroid nodules and to define the patients with malignant potential by laboratory,radiological and cytological evaluations.

Method: 100 patients (F/M:63/37) with thyroid nodules followed up in Pediatric Endocrinology Clinic between 2010-2021 were retrospectively reviewed. Clinical, laboratory,imaging findings,cytology and histological results of the operated patients were recorded.

Results: The mean age at diagnosis was 12.9 ± 4.1 years.In the ultrasonographic (USG) evaluation,70% of the patients had a single nodule.The size of the nodules was ≥1 cm in 44% of the patients.48% of the nodules were solid,58% of them were hypoechoic.19%(n=9) of 48 patients who underwent fine needle aspiration biopsy (FNAB) had inadequate/non-diagnostic cytology,37.5%(n=18) were benign,12.5%(n=6) atypia/undetermined significance (AUS/FLUS),29%(n=14) suspected/malignant.22 patients underwent surgical treatment; total thyroidectomy was performed in 77%(n=17), lymph node dissection was performed in 68%(n=15) of the patients.The most common papillary carcinoma (68%,n=15) was detected, while the histology of 3 patients was benign. The histology of 4/6 patients whose cytology was AUS/FLUS was found to be malignant (Papillary carcinoma). Due to the suspicion of malignancy in the follow-up of 4 patients whose cytology was benign, surgery was performed and the histology of 2 of them was found to be compatible with malignancy.Lenf node metastasis was detected in 66%(n:10/15) patients.Nodules of 17 patients with malignancy were found to be single in 82%(n=14),94%(n=16) ≥1cm in size,76%(n=13) solid,58%(n=10) hypoechoic and 41%(n=7) of them had microcalcification. Age,gender,thyroid function tests,autoantibody positivity nodule size,number of nodules,increased blood supply were not found to be associated with malignancy,while the presence of microcalcification, solid structure and hypoechoic nodule were associated with malignancy ($p<0.005$).

Conclusion: Malignancy was detected in 17% of our patients followed up for thyroid nodules and 37% of those who underwent FNAB.Although the Bethesda classification of FNAB can be applied reliably in children,the malignancy rate was found to be higher in surgically removed nodules,especially in those with cytology of AUS/FLUS,compared to adults.In addition to the result of FNAB,it is important to make a careful evaluation in terms of malignancy in patient of sonographic findings such as microcalcification of the nodules,solid and hypoechoic structure.

P1-400

Total thyroidectomies for endocrinologic indication: Experience in a third level hospital

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Background: To evaluate the efficacy of thyroidectomy, it is necessary to know its complications; however, there is a great discrepancy in the literature regarding its incidence. A greater surgical aggressiveness achieves better control of the disease, but may be accompanied by more complications. Hypocalcemia is the most frequent potential complication after thyroidectomy, but its persistence can lead to serious systemic effects.

The objective of this study is to evaluate the indications for total thyroidectomy in our center, its treatment, and the incidence of complications in thyroidectomized patients.

Methods: In this cross-sectional study, patients who required total thyroidectomy from 2018 to 2022 were included. In these patients, loading doses of vitamin D were administered on days prior to surgery and preoperative and postoperative serum calcium levels were evaluated at 24, 48 and 72 hours. The indication, complications and treatment were recorded for all patients.

Results: 60% (3/5) of the patients underwent total thyroidectomy due to RET gene mutation, while 40% (2/5) suffered from pathological thyroid nodule (1/2 metastatic papillary carcinoma and 1/2 encapsulated follicular carcinoma). The mean age was 8.8 years (Range 5-13) and 80% (1/5) were male. Although 20% (1/5) had pre-surgical laboratory abnormalities (elevated calcitonin), no patient with RET mutation had a tumor in the surgical specimen. 40% (2/5) of the patients presented hypocalcemia in the first 24 hours after surgery, both men. Age and duration of surgery did not correlate significantly with hypocalcemia, $p > 0.05$. There were no other complications. Average length of stay was 5 days. 80% (4/5) required lower doses of levothyroxine than the theoretical dose which corresponds to them by age, $p<0.05$.

Conclusions: In our review, most surgeries were performed prophylactically due to RET mutation. The incidence of hypocalcemia is less than 50% in total thyroidectomy in our center. Our study did not report a significant correlation between hypocalcemia and duration of surgery or patients' age.

P1-586

Newborn screening for congenital hypothyroidism through dried blood spot in Low middle income country (LMIC): experience from a tertiary care center

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Background: Neonatal screening is a preventive strategy for various endocrine,metabolic and genetic conditions.Congenital hypothyroidism (CH) is one of the most common preventable and treatable causes of intellectual disability,and delayed diagnosis can lead to disastrous consequences.Incidence of CH is1:3000-1:4000 neonates worldwide but data varies globally.Pakistan lacks a national newborn screening programme for any inherited disease,but Aga Khan University Hospital (AKUH) is doing newborn screening for Congenital Hypothyroidism (CH).Since April 2019 CH screening is done through dried blood spot (DBS). Pakistan has a very scarce data regarding incidence of CH,indicating the importance of working in this direction.We present our data on CH screening through DBS over a period of two and a half year.

Objective: To determine the proportion of screen positive newborns(>33 weeks gestation) between April 2019 –October 2021,for Congenital Hypothyroidism as part of newborn screening programme done through DBS and also to identify confirmed CH cases on serum TSH testing.

Methods: Retrospective review of Laboratory data of DBS TSH levels of neonates >33 weeks of gestation from April 2019-October 2021.Screening is done between 48-72 hours of life and after 24 hours in case of early discharge.TSH is quantitatively determined and values ≥10 µIU/ml were taken screen positive,up to10 µIU/mL were taken normal,between 10-20µIU/mL were considered ambiguous, above 20 µIU/mL were labeled as presumptive positive. Ambiguous and presumptive positive babies were recalled to get TSH+/-FreeT4 tests.CH was confirmed on the basis of low FT4 and highTSH >10µIU/ml and treatment was started.

Results: 97%(14283 out of 14379)of the live born babies were screened for Congenital Hypothyroidism.To identify safe minimum recall criteria,babies were recalled if the DBS TSH level was more than 10 mU/l and if they were not preterm(<33 weeks).226 (96%) out of 235 screen positive babies were recalled,out of which serum TSH and/or FT4 was repeated in 158 babies(70%). Recall rate being 96%.15 newborns were diagnosed Congenital hypothyroidism through serum TSH testing and started on treatment within 2 weeks of life.Proportion of babies diagnosed with Congenital Hypothyroidism is 0.10% with average incidence rate being 1:1000 babies.

Conclusion: Due to high incidence rate of CH in our neonates,implementating a national screening program and also conducting further studies to determine the main risk factors for the high incidence of CH is essential.Overall coverage of CH screening programme at AKUH has been 97% which need to be further increased.

P1-587

Sensitivity to thyroid hormones and metabolic syndrome in pediatric patients with neuromotor disability

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Introduction: Thyroid hormones (THs) play a crucial role in growth, brain development and function and metabolic homeostasis. The sensitivity to TH indices seems to be associated with metabolic syndrome (MS), prediabetes and diabetes in adults. We evaluated the sensitivity to TH indices in a pediatric population with neuromotor disability in relationship with the MS presence, using a multivariate analysis (MVA).

Patients and Methods: We enrolled 55 children (36M/19F, median age 9 years) with neuromotor impairment (69.1% cerebral damage, 30.9% neuromuscular diseases). Clinical parameters, thyroid function with sensitivity to TH indices and the presence of metabolic syndrome (SM) were recorded. Thirty healthy subjects were included as controls. MVA was performed.

Results: SM was detected in 54.5% of children with neuromotor disability. Differences in metabolic parameters and the sensitivity of TH indices are evident for subjects with disability and MS compared to controls and patients without metabolic derangement. A decreased level of the sensitivity to TH indices was detected in subjects with MS. A difference in metabolic and sensitivity of TH indices (particularly thyrotroph T3 resistance index, TT3RI) were also noted in subjects with cerebral damage compared to neuromuscular diseases. At the multinomial logistic regression model, the probability to be in a condition of neuromotor impairment and metabolic derangement increases as the TSH-index values decrease.

Conclusions: Our clinical findings first contribute the clinical evidence the assessment of TH resistance on the crossroads of several evolving areas as treatment of disability, of metabolic disorders and prevention from diabetes and cardiovascular diseases. The interpretation of thyroid function cannot be based on simple diagnostic rules or laboratory tests. The altered sensitivity to TH indices may not only present a different sensitivity to hormone but also reflect an increased set-point of homeostasis. The role of thyroid status on the integrity of neural processes and a therapeutic role of THs could be also considered.

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P1-588

Thyrotoxicosis in children and adolescence in Iceland: A twenty-year retrospective study

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Introduction: Thyrotoxicosis is a clinical manifestation that arises due to excessive amounts of circulating thyroid hormone in the body with a subsequent hypermetabolic state. The condition has multiple aetiologies of which Graves' disease accounts for the most cases in children and adolescence. Symptoms in children are often more obscure than those seen in adults which may contribute to diagnostic delay of the condition. The aim of the study is to assess the incidence of thyrotoxicosis in children and adolescents in Iceland over the span of two decades (2001-2021), furthermore to investigate if the incidence rate has increased as well as to describe treatment options and disease recurrence.

Material/Methods: This retrospective descriptive study included all children and adolescents diagnosed with thyrotoxicosis in the years 2001-2021 in Iceland. Information was obtained from the Directorate of Health's drug database and from ICD-10 diagnoses at Landspítali – The National University Hospital.

Results: In total, 77 children and adolescents were diagnosed with thyrotoxicosis during the study period, with an overall incidence rate of 4.6/100,000 person-years for people younger than 18. Graves' disease accounted for 55 of the cases (77,5 %), Hashitoxicosis for 13 (18,3 %), two suffered from neonatal thyrotoxicosis at birth (2,8 %) and one developed post-operative thyrotoxicosis following a removal of ACTH producing pituitary adenoma (1,4 %). The gender ratio was 1:2.8 (male : female) and the mean age at diagnosis was 13.7 for boys and 14.2 for girls. Patients included in this study diagnosed with Graves' disease were the primary focus of therapeutic intervention, of which 8 individuals (14.5%) are currently receiving antithyroid drugs (ATD), 13 reached an euthyroid state with medication (23.7%), four relapsed and are currently receiving medication (7.3%), 25 received treatment with radioactive iodine (45.5%) and 5 underwent surgery (9.1%). Boys were more likely relapse and relapsed sooner following ATD although the difference was not significant. Disease relapse during the study period was 31.8%.

Conclusions: The incidence of both thyrotoxicosis and Graves' disease did not increase during the study period. The disease was more common in girls although gender ratio was lower than expected. ATD were the first choice in treatment. Recurrence of the disease was common and radioactive iodine treatment was the most common permanent treatment option. A possible relationship between the duration of ATD therapy and disease relapse should be investigated.

P1-589

Familial Dysalbuminemic Hyperthyroxinemia (FDH) in Asymptomatic Child with High Free T4 and Normal TSH

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Case Report: 6 yrs. old boy presented with high total T4, free T4, reverse T3, and normal total T3 and TSH. He has a history of tic disorder. Blood pressure, and heart rate were normal, no palpitations, no weight loss. Thyroid peroxidase and thyroglobulin antibodies were normal. Thyroid sonogram was normal. Family is of Hispanic origin. There was a family history of elevated T4 in the paternal uncle (half-brother of the father)

Methods: Blood was shipped for analysis to the Thyroid Study Unit at The University of Chicago. Written consents were obtained from all family members for evaluation of thyroid function and DNA sequencing. TSH levels were measured by direct method using automated immunoassay on the Siemens Centaur™ platform and by a direct equilibrium dialysis method. Free T4 was high when measured at Quest Diagnostics by direct method using the automated immunoassay (T4, Free, test code 866).

Results: Total T4 and rT3 were high, but not T3 suggested the presence of FDH. Father, paternal grandmother and paternal uncle have elevated total T4, normal TSH. The diagnosis of FDH was confirmed by sequencing the albumin gene which showed the rare variant (gnomAD MAF=0.00007) in exon 7 causing this condition. Using the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al 2015), this variant was classified pathogenic (PS3+PM2+PM5+PP1+PP5). It is a missense variant, a substitution of a guanidine (G) to adenine (A), resulting in the replacement of the normal arginine 218 with a histidine (R218H; rs75002628). Patient and his father inherited his mutation from paternal grandmother (PGM). Both patient and father, PGM, and paternal uncle have a double peak (black for G and green for A). Both are thus heterozygous in agreement with the dominant inheritance of a defect causing a gain-of-function (an increase in the binding affinity for T4).

Conclusion: Familial FDH is a familial autosomal dominant condition. It is caused by an abnormal albumin molecule with an increased affinity for thyroxine (T4). Genetic analysis in cases of elevated total and free T4 and normal TSH is important for proper diagnosis and avoiding potentially unnecessary treatment.

P1-590

Immunoglobulin Superfamily 1 (IGSF1) Deficiency: A Rare Cause of Isolated Congenital Hypothyroidism in Two Siblings

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Introduction: The Newborn Screening Programme (NBS) enables earlier diagnosis of congenital hypothyroidism (CH). However, cases of central congenital hypothyroidism (CCH) are missed in countries which use thyroid stimulating hormone (TSH) based screening strategy. Understanding the pathogenic aetiology of CCH is particularly important because many patients have additional pituitary hormone deficiencies. New genes have been implicated in CCH, including the recently discovered loss of function mutations in the IGSF-1 gene (1). We report, two siblings with CCH due to novel nonsense IGSF-1 mutation inherited from their mother.

Case Report: The proband (male infant) was born to non-consanguineous, Eastern European parents with no known medical issues. The postnatal course was uneventful; NBS did not detect any abnormalities. He presented with prolonged jaundice and investigations detected central hypothyroidism (FT4 8pmol/L, TSH 7mU/L). Further investigations including standard synacthen test and pituitary MRI were performed, which were normal. Serum prolactin level was borderline (100mIU/L; (100-410)). He was commenced on Levothyroxine and dose was titrated to keep his free T4 levels in the upper part of the normal range. Anticipating evolving hypopituitarism, he had close monitoring of growth and pituitary functions (repeat standard synacthen test, insulin-like growth factor 1 and prolactin). Prolactin deficiency was diagnosed upon repeat sampling (prolactin 40mIUL/L). Suspecting a genetic aetiology for CCH with prolactin deficiency, mutational analysis of IGSF1 gene was performed, which confirmed a hemizygous nonsense mutation (c.1829G>A, p.W610). Evaluation of his asymptomatic brother at age 1.4 years showed similar phenotype (TSH 1.76mU/L, FT4 8.2pmol/L, free T3 5.1pmol/L, serum prolactin <40mIU/L, normal standard synacthen test and IGF1) and identical IGSF1 mutation. He was also commenced on Levothyroxine. In addition, both boys have isolated speech delay. Their mother was noted to have a typical heterozygous profile with low normal FT4 and the family are closely monitored as per IGSF1 Care Group Recommendations (2).

Conclusion: IGSF-1 mutations are a rare but important cause for CCH for whom the risk of evolving endocrinopathy has implications for monitoring and surveillance(2). To our knowledge, there are only three such families with IGSF-1 deficiency related hypothyroidism, reported nationwide.

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P1-591

Evaluation of Permanent and Transient Congenital Hypothyroidism in Cases Referred from National Neonatal Screening Program

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Objective: The incidence of congenital hypothyroidism (CH) has increased worldwide. Lowering cut-off in screening programs has led to an increase in the rate of transient CH. We aimed to evaluate the rates of permanent and transient CH in cases referred from the screening program and to investigate the clinical and laboratory factors to predict the transient CH.

Methods: 109 cases referred from the screening program to our hospital, from September 2015 to April 2018, and 52 cases were diagnosed with CH. Those cases were prospectively evaluated and cases completed regular 3-years-follow up (n=44) were re-investigated to determine the rates of permanent and transient CH.

Results: Fifteen cases (34%) were diagnosed with permanent CH and 29 cases (66%) were diagnosed with transient CH. Gestational age in weeks (w) and birth weight were 38.2 ± 1.31 and 3021.3 ± 389.6 gram (g) in the transient CH group and both were significantly lower compared to permanent CH cases with the results of 39.06 ± 1.33 w and 3375,3 ± 425,3 g (P=0.025, p=0.007). Transient CH rate was found to be 50 % (all hypoplastic) in the dysgenesis group and 73.3% together in groups with the normal and hyperplasic thyroid gland. While fT4, thyroid-stimulating hormone, and thyroglobulin levels at diagnosis do not predict transient/permanent CH, levothyroxine (LT-4) dosage was significantly lower in the transient CH group in all years. The optimal cut-off value with highest sensitivity and specificity for LT-4 dosage as a predictive marker to differentiate transient CH from permanent CH was found 2.27 μg/kg/day (P=0.004; sensitivity: 71%, specificity: 83%) at 1st year, 1.85 μg /kg/day (P=0.013; sensitivity: 66%, specificity: 72%) at 2nd year and 1.69 μg /kg/day at 3rd year (P<0.0001; sensitivity: 90%, specificity: 83%).

Conclusion: Transient CH is more frequent than expected. Our results suggest that the LT-4 requirement may be a good marker for predicting transient CH. Therefore, infants with CH requiring LT-4 doses <2.27 μg/kg/day at 1st year, <1.85 μg /kg/day at 2nd year may be re-evaluated earlier to discriminate transient CH.

P1-592

Development of delayed thyrotropin elevation in small-for-gestational-age infants: Is a second screening needed?

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Purpose: Recent reports indicate that being small for gestational age could be a risk factor for delayed thyroid stimulating hormone (TSH) elevation (dTSH) in preterm infants. Very few studies have investigated the development of delayed thyroid stimulating hormone elevation in small-for-gestational-age late-preterm infants with a gestational age of 34–36 weeks.

Methods: We retrospectively included 70 small-for-gestational-age (SGA) infants and 86 sex- and gestational age-matched controls who presented with normal results on initial thyroid function testing.

Results: Small-for-gestational-age infants had a significantly higher prevalence of delayed thyroid stimulating hormone elevation (15.7% vs. 3.5%, P = 0.009) and increased likelihood of receiving levothyroxine treatment (11.9% vs. 2.3%, P = 0.008) compared to appropriate for gestational age infants. In SGA infants, the mean age at the time of dTSH was 24 days. Development of dTSH was associated with being SGA and medical treatment with dopamine or furosemide. After adjusting for confounding factors, multiple logistic regression analysis showed that being SGA was a significant risk factor for the development of delayed thyroid stimulating hormone elevation (odds ratio: 4.81, 95% confidence interval 1.1–21.7, P = 0.041).

Conclusion: SGA infants may be at risk for dTSH and may consider a second thyroid screening test around the age of 1 month.

P1-593

Genetic and functional studies of patients with thyroid dyshormonogenesis associated with defects in the TSH receptor (TSHR)

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Introduction: The thyrotropin receptor (TSHR) has a key role in the thyroid gland. It is involved in folliculogenesis, differentiation, organogenesis, and thyroid hormone synthesis and production. Its genetic defects can cause poor differentiation (thyroid dysgenesis) and/or thyroid malfunction (thyroid dyshormonogenesis, TD). Therefore, its phenotype spectrum is wide, ranging from severe congenital hypothyroidism (CH) to mild hyperthyrotropinemia. Some heterozygous genetic variants have been associated with non-autoimmune subclinical hypothyroidism (SH) and normal-sized or hypoplastic glands. In addition, *TSHR* variants with variable expressivity have been reported. More than 200 *TSHR* variants have been published, many of them still uncharacterized *in vitro*.

Objectives: (1) To genetically characterise patients diagnosed with TD or SH associated with *TSHR* defects; (2) to study the effect of the genetic candidate variants by *in vitro* functional studies in order to establish the genotype-phenotype relationship.

Patients and Methods: Paediatric patients with DT (N=114) and SH (N=47) were analyzed by high-throughput techniques using a panel of 14 genes related to thyroid development and function. The DT patients were diagnosed through the Catalan CH neonatal screening program (confirmation TSH range: 18.4-100 mIU/L). To determine the variant pathogenicity, *in vitro* functional studies were performed based specifically on measuring the TSH-dependent activation of the cAMP response element (CRE), using a CRE-reporter vector and a luciferase test. Studies of localization and expression in the membrane were undertaken.

Results: Twelve patients diagnosed with severe or mild TD (N=7, 6.1%) or HS (N=5, 10.6%) presented candidate variants in *TSHR*. Eleven different variants were detected in these patients, four of which had not been published. The patients had variable genotypes: 3 homozygous, 2 compound heterozygous, 1 double heterozygous and 6 heterozygous (most with SH). Five of these variants did not have associated functional studies. Our *in vitro* studies show a different functional profile for each variant (completely/partially deleterious, or non-deleterious). Furthermore, some variants have a mild or totally deleterious effect depending on if they are heterozygous or homozygous, respectively, whereas others show partial deficiency in both heterozygosis and homozygosis.

Conclusions: 7.4% of our patients -- diagnosed with subclinical, mild or severe HC -- present candidate variants in *TSHR*. Our design of the *in vitro* functional studies will contribute to the confirmation of the pathogenicity of the variants studied. In addition, our studies highlight the importance of studying the effect of the patient's genotype for a correct diagnostic confirmation.

P1-594

Unexpected fast growth velocity in a child with a thyroid hormone receptor beta mutation

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Resistance to thyroid hormone (RTH) is attributed to mutations in the thyroid receptor beta (RTH-β) gene. The syndrome is characterized by decreased sensitivity of target tissues to thyroid hormone (TH) action, leading to elevated TH levels, accompanied by normal or high thyroid-stimulating hormone (TSH) values, with variable clinical manifestations such as goiter, which is the

most common finding, reported in 66–95% of cases and delayed growth and bone maturation, learning disabilities, hyperactivity, and tachycardia.

Most of the affected children have attenuation in growth rate, leading in some cases to short stature as adults. Intriguingly, in this unique case, growth velocity was increased unexpectedly without a sign of precocious puberty or an increase in bone age.

Our patient, who is today a 11.5 years old boy, was born at 37 weeks of gestation with a weight of 2050 grams. He was referred at the age of 2 years for growth assessment due to failure to thrive and short stature.

Other than that, the child was a-symptomatic presenting without tachycardia and no goiter, had a normal echography and his cardiological assessment was normal. Over time, signs of hyperactivity developed as well as reduced attention span.

TSH was in the upper normal range and his thyroid hormone values were 2-3 folds higher than the upper limit. Between the ages of 2-5 years, the child was growing below the 3rd percentile. He underwent a growth hormone stimulation test that was normal. His bone age was 2 years younger than his chronological age and this gap still exists today. Thus, in the absence of overt clinical signs of hyperthyroidism, we decided not to treat him with antithyroid drugs.

Genomic DNA was extracted from peripheral blood leukocytes using the Flexi-Gene DNA Extraction Kit (Qiagen, Germany), and the p.Leu328SerExon 9 THRB gene de novo mutations were identified.

In the 9 years of follow-up, his growth velocity was increased unexpectedly, growing now in the 15th percentile without signs of precocious puberty or an increase in bone age. We propose that this is due to compensation by an adaptive increase of TH activity over time.

P1-595

Treatment of Graves' Disease in Children and adolecents with Long-Term Antithyroid Drugs: A 20-Year Single-Center Experience

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Background/Purpose: Graves' disease (GD) is an autoimmune disorder characterized by hyperthyroidism, diffuse goiter, and/or ophthalmopathy that is caused by the activation of the thyroid-stimulating hormone (TSH) receptor by thyrotropin receptor antibodies (TRAb). GD is the most common cause of thyrotoxicosis in children and adolescents, accounting for 10-15% of all thyroid illness in children and adolescents. The treatment of GD in children and adolescents differs by country and is influenced by local traditions and resources, patient age, patient and parent preferences, and illness severity. This is a study of 195 children and adolescents with GD who were treated in a single center in Korea.

Methods: This study included children and adolescents with GD diagnosed before 19 years of age for twenty years. The diagnosis of GD was based on the presence of typical clinical features (tachycardia, tremor, exophthalmos, goiter, etc.), high levels of free thyroxine (FT4), suppressed thyroid-stimulating hormone, and a positive titer of thyrotropin receptor antibodies. After ceasing antithyroid medication, remission was defined as maintaining euthyroid condition for more than six months

Results: A total of 195 patients with GD were included in this study. The mean age at diagnosis was 12.9 ± 3.2 years, and 162 patients (83.1%) were female and 33 (16.9%) were male. Among all 195 patients, eight (4.1%) underwent definite treatment. The mean duration of follow-up and ATD treatment were 5.9 ± 3.8 years and 4.7 ± 3.4 years, respectively. FT4 level at diagnosis was higher in the non-remission group than in the remission group (5.0 ± 1.9 vs. 3.9 ± 1.5 ng/dL, P = 0.002). FT4 level at diagnosis (P = 0.001) was predicting factors for remission. Methimazole (MMI)-related adverse events (AEs) occurred in 11.3% of patients. Of a total of 26 AEs, 22(84.6%) occurred within the first three months

Conclusions: In this study, the cumulative remission rate increased according to the ATD treatment duration. Even with long-term treatment, fatal side effects were uncommon. As a result, in children and adolescents with GD, long-term MMI therapy with careful monitoring of drug-related AEs is a beneficial treatment option before definitive treatment.

P1-596

Central and peripheral sensitivity to thyroid hormones and glucose metabolism in childhood obesity

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Objectives: Increased central and peripheral sensitivity to thyroid hormones seems to be associated with an increased risk of developing prediabetes in adulthood. The objective of this study was to evaluate the relationship between the severity of obesity, the presence of glyco-metabolic alterations, and tissue sensitivity to thyroid hormones in prepubertal euthyroid children with simple obesity.

Methods: Eighty prepubertal children with simple obesity (Group 1; mean age 7.60 ± 1.51 years) and 28 healthy normal-weight controls matched for sex and age (Group 2), underwent clinical (height, weight, BMI, waist circumference) and biochemical (TSH, FT4, FT3, reverse T3 (rT3), leptin) evaluation; in patients with obesity were also evaluated fasting and OGTT glycemia and

insulin, HbA1c, HOMA-IR, HOMA-β, insulinogenic index, Matsuda index, lipid profile. Insulin resistance (IR) was diagnosed in the presence of HOMA-IR values >2.5. In addition, indexes expressing peripheral sensitivity (FT3/FT4 ratio) and central sensitivity (TSH index, TSHI; TSH T4 resistance index, TT4RI; Thyroid Feedback Quantile-based Index, TFQI; Parametric Thyroid Feedback Quantile-based Index, PTFQI) to thyroid hormones were calculated.

Results: Patients in group 1 had significantly higher values of BMI (p=0.000) and leptin (p=0.000) than in group 2, but there were no significant differences for TSH, FT4, FT3, FT3/FT4. Patients had no alterations in fasting blood glucose or impaired glucose tolerance at OGTT. The FT3/FT4 ratio in group 1 correlated negatively with rT3 (r= -0.341; p=0.003), HOMA-β (r=-0.29; p=0.01) and was significantly associated with BMI (B=0.01; p= 0.03), presence of IR (B= 0.11; p=0.03) and fasting blood glucose (B=0.004; p=0.04). In group 1, rT3 correlated negatively with the presence of IR (r = -0.23; p=0.042) and was significantly associated with BMI (B=-0.010; p=0.01) and HOMA-IR (B = -0.19; p=0.042). TT4RI, TSHI, PTFQI correlated negatively with FT3/FT4 ratio (p=0.000; p=0.005; p=0.042, respectively) and were negatively affected by BMI (B= -13.6, p=0.04; B= -0.29, p= 0.035; B= -0.02, p=0.038, respectively) in group 1.

Conclusions: Central and peripheral sensitivity to thyroid hormones is significantly affected by the severity of obesity and the presence of IR. Altered tissue sensitivity to thyroid hormones in the obese prepubertal child could be implicated in the pathogenesis of changes in glucose metabolism and increased risk of prediabetes onset.

P1-597

Congenital hypothyroidism: outcome of a 26 year screening (1996-2021)

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Introduction: A natiowide screening for Congenital Hypothyroidism (CH) was introduced 1996 in Russian Federation and Saratov Region. Revelation of the incidence of CH is of great value at the background of moderate iodine deficiency existing in Saratov and Saratov Region. Neonatal screening is an effective method for early detection of congenital hypothyroidism, a disorder that requires the prompt initiation of the treatment, in order to prevent the subsequent neuropsychiatric disorders.

Objective: To evaluate the results of the screening program for CH in Saratov and Saratov Region population for 26 years 1996-2021. To determine the incidence of hypothyroidism at birth in 1996-2021.

Patients and Methods: Newborns underwent TSH (mU/l) determination from blood spots, taken at 24–72 h after birth using «DELFIA Neonatal hTSH» were measured. TSH levels were assessed by ELISA method in the regional medical genetic center. The diagnosis was confirmed by TSH, T4 and free-T4 levels in patient's serum. We analyzed data of the regional medical genetic center.

Results: In 1996-2000, the rate of incidences of CH among screened infants was 1:3700 newborns, in 2021 CH was diagnosed in 1 from 4506 newborns.

The CH prevalence in Saratov region of for 26 years of screening was 1:4679, a total of 145 children were identified with CH. In 1996-2000, the age of the Levothyroxine (L-T4) replacement therapy was 58-42 days of life, in 2012-2021 – 16-13 days of life. Early diagnosis and treatment with adequate doses of L-T4 have rescued affected children from a life of mental retardation. In 1996-2000, the rate of incidences of neonatal hyperthyreotropinemia (NHT) among screened infants was 37%, in 2001-2021 due to iodine support during pregnancy – 5%.

Conclusions: In summary, the incidence of congenital hypothyroidism in Saratov and Saratov region is within the limits reported in Europe.

The frequency of NHT has decreased by 7.8 times over 26 years: from 37% to 5%. However, this indicator remains higher than the WHO target criteria for iodine-rich regions (<3%), which indicates that currently mild iodine deficiency persists in pregnant women and newborns in the Saratov and Saratov region.

P1-598

Retrospective analysis and literature review of five cases of thyroid hormone resistance syndrome caused by THRB gene mutation

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Objective: To summarize the clinical characteristics, genetics and follow-up data of five children with thyroid hormone resistance syndrome (RTH) and review the related literatures.

Methods: The clinical data of the five children diagnosed with RTH in our hospital from 2018 to 2020 were retrospectively analyzed. Next-generation sequencing of the candidate genes related to thyroid diseases was performed using the blood collected from all the children and their parents who signed an informed consent. Then, relevant cases were retrieved on medical literature databases for analysis and summary.

Results: Among the five cases, four cases of goiter; two cases of tachycardia, throb, personality change, hyperactivity, weight loss; one case of academic performance decline, and no hearing and vision loss were observed. Laboratory thyroid function tests indicated a mild increase in free triiodothyronine(FT3) and with or without increased free thyroxine(FT4) levels. Thyroid-stimulating hormone (TSH) levels were normal or slightly elevated, but thyrotropin receptor autoantibodies were negative. Octreotide

inhibition test showed that the TSH levels of all the children decreased by more than 50% compared with the basal value (the genes of four cases were positive). However, magnetic resonance imaging of the pituitary gland showed no abnormalities. Related gene detection in the children and their families showed that four cases had THRB mutations: two proband mutations were from their fathers, and two cases had de novo mutations. One patient was negative for genetic testing.

Conclusions: The clinical manifestations of pediatric RTH vary, and the diagnosis mainly depends on thyroid function tests. With the development of gene sequencing technology, heterozygous mutations in THRB are common, but not all children with RTH have mutations. Furthermore, octreotide inhibition tests cannot be used as a diagnostic criterion to distinguish RTH from pituitary tumors in children.

P1-599

Twin pregnancy with a hydatiform mole and coexisting liveborn infant, with maternal hyperthyroidism and neonatal hypothyroidism

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Background: A twin pregnancy with a coexisting complete hydatiform mole and a healthy fetus is rare, with an incidence of 1 in 22.000-100.000 pregnancies. Associated with this condition are potencially serious maternal and fetal complications.

Case Report: A 32 year old pregnant woman presented with clinical features of hyperthyroidism, confirmed by laboratory. An ultrasound scan revealed a complete hydatiform mole (CHM) and a single structurally normal fetus. Her human chorionic gonadotropin (hcg) was > 112.5000 mUi/ml. She started treatment with methimazole.

At 26 weeks of gestation she developed preeclampsia, and delivered a healthy boy weighing 797 gr. After delivery she remained euthyroid, and methimazole was stopped. Hcg levels fell steadily after the removal of the hydatiform mole.

In the neonatal unit the baby required 12 days of mechanical ventilation. He had normal feeding and growth. There was no clinical evidence of hypothyroidism or goiter. His thyroid function studies performed at 72 hs showed a thyrotropin (TSH) 2.95uUi/ml, free thyroxine 0.49 ng/dl, total thyroxine 2.06 ug/dl, confirmed at day 5. With diagnosis of central hypothyroidism he started treatment with levothyroxine.

Conclusion: There are very few cases reported in the literature of gestational trophoblastic disease complicated with hyperthyroidism in which the infant's clinical and biochemical thyroid status is informed. These pregnancies should be monitored for hyperthyroidism and full clinical and biochemical evaluation should be performed on affected infants to further understand the mechanisms involved in thyroid dysfunction of the neonate.

P1-600

Response to Growth Hormone Therapy in Turner and Noonan Syndrome: First Year and Final Height

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Background: Despite different genetic backgrounds, Noonan syndrome (NS) shares similar phenotype features to Turner syndromes (TS) such as short stature, webbed neck and congenital heart defects. The primary cause of short stature in Turner syndrome and Noonan syndrome is GH resistance [1]. Recombinant human growth hormone (rhGH) is being used to promote linear growth in short children with Noonan syndrome. However, its efficacy is still controversial.

Aims: It was aimed to evaluate the effect of rhGH treatment on first-year response and adult height in children with Noonan and Turner syndrome.

Methods: Forty-eight patients (ten children diagnosed with NS (three patients diagnosed genetically), thirty-eight diagnosed with TS) data were retrospectively retrieved from the hospital's records consisting of patients' receiving growth hormone therapy.

Results: In Noonan Syndrome; the mean (SD) baseline age was 12.4 (± 2.4) years; HSDS, -3.6 (± 0.7), GH dose, 30 μg/kg/day. The mean (SD) HSDS increase from baseline (ΔHSDS) was 0.47 (±0.43) was. Six patients achieved NAH. The mean (SD) NAH SDS (NR) was -0.44 (± 3.7) (150.4 cm) in females and -2.96 (± 0.26) (158.1 cm) in males.

In Turner Syndrome; the mean (SD) baseline age was 9.9 (± 3.3) years ($p<0.05$); HSDS, -3.4 (± 0.8), GH dose, 44 μg/kg/day ($p<0.05$). The mean (SD) HSDS increase from baseline (ΔHSDS) was 0.43 (±0.94) was. Sixteen patients achieved NAH. The mean (SD) NAH SDS (NR) was -2.4(± 1.4) (148.8 cm).

The changes in height velocity or height SDS in the first year and Near-adult height were not related to the age, gender, height deficit or a delay in bone age maturation at the start of treatment, level of IGF-1 and IGFBP3 and IGF-1/IGFBP3 ratio.

Conclusion: We found children with NS to have a better growth response to treatment with rhGH than girls with TS. We had similar height velocity in NS with IGF-1 which increased less than TS. Effective treatment can be achieved with personalized doses.

Late Breaking

LB1

Amenorrhea in an Anorexia Nervosa patient as a presenting symptom of Cushing's disease

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Anorexia nervosa (AN) manifests in the restriction of energy intake relative to energy output. Atypical AN includes those who meet the criteria for AN but are not underweight.

Hypothalamic amenorrhea can be a presenting symptom in AN, and the return of menses is part of recovery. It can take more than a year for menses to return after weight restoration and nutritional rehabilitation.

Hypercortisolemia is common in AN, but usually does not cause cushingoid symptoms

We describe a 15 year old female with rapid 12 kg weight gain and anxiety at the age of 12 years that was attributed to environmental changes in her life (from 52 kg to 64 kg). A year later, she lost 20 kg in 8 months (44 kg) and was diagnosed with atypical restrictive AN and anxiety. She was treated in a multidisciplinary adolescent clinic with psychotherapy, dietitian counseling and sertraline up to 200 mg. Primary amenorrhea was attributed to her malnutrition.

At the age of 15, after successful treatment at the adolescent clinic, her weight was stable at 53 kg. Despite behavioral recovery she did not commence menses.

Since her breast tanner staging did not fit the amenorrhea, a combined ACTH and LHRH test was done. LH rose from 1.4 IU/L to 26.7 and FSH from 4.1 IU/L to 15.2, cortisol rose from 615 nmol/l to 1630.

Free urinary cortisol (235 ug/h), 1 mg dexamethasone suppression test (1897 nmol/l), salivary midnight cortisol (0.91 mg/100ml), 8 mg dexamethasone suppression test (780 nmol/l) and combined low dose dexamethasone suppression test with CRH all showed high levels of cortisol (1268 nmol/l) and ACTH (35 pmol/l). MRI showed a small hypodense nodule in the left side of the pituitary, slightly intense T2 signal. The stalk was in place. A 4-5 mm microadenoma was suspected.

She underwent a trans-sphenoidal resection of the tumor successfully. Pathology showed a sparsely granulated corticotroph adenoma.

Two months after resection she commenced menstruating and has regular periods. Her weight is stable and eating habits are within the norm.

Cushing's disease (CD) clinically overlaps with AN and anxiety. CD in children can manifest as growth failure, irregular menses, and depression.

CD is difficult to diagnose, diagnosing CD in AN patient is even more challenging. It is important to consider other potential etiologies for amenorrhea rather than malnutrition alone, such as CD.

LB2

Aromatase deficiency due to novel *CYP19A1* mutation: A rare cause of maternal virilization and atypical genitalia

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Background: Aromatase deficiency is a rare autosomal recessive condition due to mutation in *CYP19A1* encoding aromatase enzymes. This enzyme protects fetus and mother from excess of androgens by converting them into estrogen. Lack of its activity results in accumulation of androgens which in turn lead to maternal and fetal virilization.

We are reporting a neonate with atypical genitalia with severe maternal virilization due to a novel mutation in *CYP19A1*, c.575G>C p. (Arg192Pro).

Case Summary: A 10-day old neonate presented with concern of atypical genitalia. Baby was born full term with birth weight of 3.8 kg to consanguineous parents with one elder male sibling alive and healthy. Family history was insignificant for atypical genitalia. There was significant history of maternal virilization during pregnancy in the form of severe acne, hirsutism, and hoarseness of voice. Mother had taken only multivitamins during pregnancy and all antenatal scans were normal. On examination, baby was well looking with no signs of dehydration and pigmentation. Genital examination showed stretch phallus length of 2cm, partially fused labio-scrotal folds, single urogenital opening, and no gonads palpable.

On investigation Karyotype was 46, XX with ultrasound showing uterus and ovaries. Sodium and potassium were normal, 17-OH -progesterone 8.87 ng/ml, cortisol 21.18 ug/dl, LH 0.55 mIU/ml, FSH 44.21 mIU/ml, testosterone <2.50 ug/dl, AMH 0.055 ng/ml. Maternal workup revealed normal ACTH, 17-OH-progesterone, DHEA sulphate, and normal ultrasound. However, her testosterone was slightly raised.

Genetic assay revealed baby is carrying homozygous variant of *CYP19A1* gene c.575G>C p. (Arg192Pro) which is a novel mutation causing aromatase deficiency

Conclusion: We conclude that history of maternal virilization during pregnancy in infant born with atypical genitalia should alert physician to consider aromatase deficiency.

LB3

High Glycated Hemoglobin instead of High Body Mass Index Might Increase the Urine N-acetyl-β-D-glucosaminidase Concentration in Children and Adolescents with Diabetes Mellitus

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Children with diabetes, and particularly those with obesity, have poor glycemic control. They are thus at higher risk of early microvascular complications. Renal tubulointerstitial markers are integral to evaluating diabetic nephropathy. Various biomarkers have been proposed, but their role in the obese pediatric population is uncertain. We investigated renal injury markers in children with diabetes, according to obesity, and determined their role as early predictors of diabetic nephropathy. Fifty-three children and adolescents, diagnosed with either type 1 or 2 diabetes mellitus, and 43 control children, aged 7–18 years, were included. Clinical and laboratory characteristics, including six renal injury markers, were compared among subjects according to body mass index and presence of diabetes mellitus. Urine neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and N-acetyl-β-D-glucosaminidase (NAG) levels were higher in children as compared to those without diabetes. No renal injury markers differed significantly between obese and non-obese children. After adjusting for age, sex, body mass index, and urine albumin-to-creatinine ratio, HbA1c remained a significant risk factor for elevated urine NAG. Urine NAG could be a useful indicator of tubulointerstitial damage in children with diabetes in the pre-albuminuric state. Tighter glycemic control appears crucial for avoiding early progression to diabetic nephropathy.

LB4

The association between glycated albumin and HbA1c in pediatric acute leukemia patients

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Introduction: Traditionally, HbA1c has been used as a preferred glycemic index in diabetes patients. However, as many acute leukemia patients often present with anemia and/or pancytopenia, HbA1c may not accurately represent blood glucose level in this group. Glycated albumin represents the average level of blood glucose in recent 2-3 weeks, independent of red blood cell life. In this study, we aim to evaluate the usefulness of glycated albumin as glycemic monitoring index in pediatric patients diagnosed with acute leukemia.

Methods: We performed retrospective analysis of a total of 208 pediatric patients from The Seoul St. Mary's hospital, Catholic university of Korea. Medical records of 25 patients diagnosed with type 2 DM and 68 patients with acute leukemia were investigated for serum glycated albumin, HbA1c, fasting blood glucose level, and demographic data such as sex, age, height, weight and BMI z-scores. 115 children and adolescents who visited our outpatient center for routine child health examination were enrolled as the control group.

Results: The median serum glycated albumin levels were 12.6%, 19.1% for acute leukemia and T2DM patients. HbA1c and fasting blood glucose levels, 5.35% and 7.6%, 93.5mg/dl and 129mg/dl respectively, also differed in the two groups. All glycated albumin, HbA1c and fasting blood glucose level did not appear different in between the control and acute leukemia group.

In type 2 DM patients, glycated albumin and HbA1c showed positive correlations ($r=0.926$, $p<0.01$). Fasting blood glucose level was positively correlated to glycated albumin ($r=0.821$, $p<0.001$) and HbA1c ($r=0.773$, $p<0.001$). While glycated albumin did not appear related to HbA1c in the normal control group ($r=-0.02$, $p=0.831$), patients with acute leukemia also revealed a positive correlation between glycated albumin and HbA1c($r=0.275$, $p=0.023$). Glycated albumin was negatively related to BMI z-scores in the control group ($r=0.554$, $p<0.001$); however, the level showed no correlation to BMI z-scores in acute leukemia group and in T2DM patients ($r=-0.122$, $p=0.323$ and $r=-0.292$, $p=0.156$). HbA1c level was positively related to BMI z-scores in the control group ($r=0.249$, $p=0.007$) and showed no relations in the other two groups.

Multiple regression analysis found glycated albumin to be positively correlated to HbA1c both in acute leukemia pediatric patients and T2DM patients even when adjusted for age, sex and BMI z-score ($p=0.038$, $p<0.001$).

Conclusion: Glycated albumin showed positive relation to HbA1c in type 2 diabetic patients and acute leukemia patients, whereas it showed no correlation in the normal control group.

LB5

Incidence and Severity of Type 1 Diabetes Mellitus during COVID-19 Pandemic

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Background: The COVID-19 pandemic continues to impact healthcare overall particularly in relation to diabetes. Initial studies showed delays in emergent healthcare utilization, decreased preventative care visits, and more severe presentations of new onset diabetes. However, the pathophysiologic relationship between COVID-19 and type 1 diabetes is not yet well understood.

Objectives: Our primary objective was to compare the annual rates of new type 1 diabetes diagnoses between the pre-pandemic (1/2015-12/2019) and pandemic (1/2020-12/2021) periods. We hypothesized that the number of new-onset pediatric cases of type 1 diabetes increased during the COVID-19 pandemic compared to the preceding 5-year period.

Methods: We performed a retrospective review of EMR data from one pediatric tertiary care center from 1/1/2015 to 12/31/2021. Initial data were extracted based on ICD-10 codes (E08, E09, E10,

Table 1. Annual Number of T1DM Cases

Year	T1DM Cases	% Change
2015	120	
2016	147	22.5
2017	129	-12.24489796
2018	136	5.426356589
2019	145	6.617647059
2020	168	15.86206897
2021	197	17.26190476
Avg 2015-2019	135.4	
Avg 2020-2021	182.5	34.78581979

E11, E13). Data were validated and excluded according to the following criteria: age >21 years at diagnosis, diagnosis date outside of study period, confirmed other form of diabetes, complex disease without confirmed auto-antibodies, and inadequate data at time of diagnosis.

Results: Ultimately 1,057 patients met inclusion criteria. In the pre-pandemic period annual new onset cases ranged from 120-147 cases/year with a mean of 135.4 (Table 1). During the COVID-19 pandemic a mean of 182.5 cases/year were diagnosed (168 in 2020 and 197 in 2021). Cases increased 16% from 2019 to 2020 and further increased 17% from 2020 to 2021. Overall, cases increased 35% during the pandemic period (2020-2021) compared to the pre-pandemic period. Prior to the sharp rise in cases, new diagnoses declined in February-May 2020 (4 cases/ month in May 2020 compared to pre-pandemic average of 11.6 cases/month).

Discussion: Quantifying the increase in new diagnoses of type 1 diabetes during the COVID-19 pandemic is important to understand the true impact of the global health crisis on this population. The increase in cases during the pandemic is likely multifactorial and continuing to understand this relationship may have important implications for public health policy and understanding type 1 diabetes pathophysiology in the future.

LB6

A case series of two adolescent diabetic siblings due to novel mutation in *CFAP126*

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Background: *CFAP126* gene does play a role in the regulation of pancreatic beta cell. Literature suggests that *CFAP126* was significantly downregulated in human islet cells of pre-diabetic as compared to non-diabetic and further downregulated in type 2 diabetics. However, to date *CFAP126* has not been reported to cause clinical diabetes.

We are reporting 2 diabetic siblings, with strong family history of type 2 diabetes on maternal side, carrying a novel heterozygous variant of *CFAP126* gene.

Case summary: Two siblings (both females) from non-consanguineous parents presented with incidental hyperglycaemia at the age of 16 years (sibling 1) and 13 years (sibling 2). There was a strong history of type 2 diabetes on maternal side including mother, 2 maternal uncle, 4 maternal aunt, and maternal grandmother.

Siblings 1 and 2 had BMI of 16 kg/m2 and 23.07 kg/m2 respectively without any clinical evidence of insulin resistance. Investigation revealed that sibling 1 had HbA1C of 12.3%, insulin (6.6 IU/L) and C peptide 1.8 ng/ml. Sibling 2 had HbA1C of 12.6%, insulin level (7.3 IU/L) and C peptide 2.02 ng/ml. Both were negative for anti-GAD65 and anti-insulin antibodies and had normal celiac screen and thyroid profile. They were started on basal bolus insulin with total dose of 1 unit/kg/day (sibling 1) and 0.7 unit/kg/day (sibling 2) and genetic were sent for MODY.

On 3 month follow up both siblings 1 and 2 were having good control of diabetes with HbA1C of 6.6% and 6% respectively. However, their whole exome sequencing turned out to be negative for all variant of MODY gene, but a heterozygous mutation was identified in *CFAP126* gene with variant c.310A>T p. (Lys104*) in both siblings and mother.

After informed consent and counselling, glibenclamide was started in both sibling with written plan of gradual tapering of insulin if needed. Sibling 2 is on glibenclamide for last 3 months with obvious reduction of insulin requirement from 0.7 unit/kg/day to 0.2 unit/kg/day, recent HBA1C of 6.6%, and C peptide of 4.82 ng/ml. Sibling 1 was on glibenclamide for last one month with reduction of insulin requirement from 1 unit/kg/day to 0.5 unit/kg/day.

Conclusion: Mutation in *CFAP126* seems to be associated to cause diabetes which do respond to oral sulfonylurea. Further studies are needed to confirm the effect of this gene on insulin secretion at molecular level.

LB7

Abstract Withdrawn

LB8

Stretched Penile Length Nomogram in Prepubertal Egyptian Children Aged Five to Nine years

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Background: Penile length is used to assess the external genitalia and abnormalities in external genitalia, e.g. macro and micropenis. Early diagnosis of abnormal penile size is crucial, but proper assessment is mandatory to identify the normal population-specific, age-appropriate reference ranges.

Objective: Our study aimed at assessment of stretched penile length values for prepubertal Egyptian boys aged five to nine years in order to establish nomograms for penile length for this age group.

Subjects and Methods: Our cross-sectional study included 1500 boys aged five to nine years recruited from the Pediatric Department in Cairo University Children's Hospital, Faculty of Medicine. Children were divided into 5 groups (5-6 years, 6-7 years, 7-8 years, 8-9 years, 9-10 years; each group included 300 children). All children were subjected to weight, height, body mass index and stretched penile length measurements.

Results: The mean (SD) of the stretched penile length by age grouping were at five years = 5.31 (0.92) cm, at six years = 5.51 (1) cm, at seven years = 5.87 (0.85) cm, at eight years = 6.19 (0.93) cm and at nine years = 6.1 (0.92) cm.

Conclusion: This study provides novel reference values and percentiles for penile lengths for prepubertal Egyptian boys aged 5–9 years that can be used by physicians.

LB9

Prevalence and Factors Associated with Hypothyroidism in Children with Sickle Cell Anemia Aged 6 Months -17 Years Attending the Sickle Cell Clinic, Mulago Hospital, Uganda; A cross-sectional study

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Background: Sickle cell anemia (SCA) leads to chronic end organ damage including the thyroid gland. This is postulated to be due to recurrent hemolysis leading to iron overload, vaso-occlusive crises, micro-vasculature obstruction due to red cell entrapment and frequent transfusions. Some studies have demonstrated a relationship between hypothyroidism and SCA with a prevalence of 6% in children and adolescents. Hypothyroidism may affect brain and physical development.

Objective: This study aimed to determine the prevalence and factors associated with hypothyroidism among children with SCA attending the Sickle Cell Clinic (SCC), Mulago hospital.

Methods: A cross-sectional study of children aged 6 months - 17 years with a confirmed diagnosis of SCA, no prior diagnosis of hypothyroidism and in their steady state attending the SCC in Mulago hospital was conducted. Data was collected using a structured questionnaire and a blood sample obtained was used to measure thyroid stimulating hormone (TSH) and free thyroxine (FT4). Clinical Hypothyroidism was defined as TSH level >9 mIU/L and free T4 <0.6 ng/dL [primary hypothyroidism] or normal or low TSH level and free T4 < 0.6 ng/dL [central hypothyroidism], and sub-clinical hypothyroidism as TSH ranging between 4.5 and10 mIU/L with normal age appropriate free T4 levels that is: 6-11 months [0.9-2.0ng/dl]; 1-5years [1.0-1.8ng/dl];6-10 years [1.0-1.7ng/dl] and 11-17 years [1.0-1.6 ng/dl]. Multivariate logistic regression models were constructed to determine the factors associated with hypothyroidism. A p< 0.05 was considered as significant.

Results: Of the 332 children enrolled, 50.3% (167/332) were female; their median age (IQR) was 6 (3-10) years. Sixty (18.1%) participants had hypothyroidism (95% CI: 14.3 — 22.6) of whom all had sub-clinical hypothyroidism. The factors associated with hypothyroidism were constipation [aOR: 3.1, 95% CI:1.0 — 9.0, p=0.043] and male sex [aOR:2.0, 95% CI:1.1— 3.5, p= 0.025].

Conclusions: Approximately 1 in 5 children (18.1%) had hypothyroidism. Males and children who presented with constipation were more likely to have hypothyroidism. This suggests that clinicians should screen all children with SCA who present with constipation for hypothyroidism and those found with hypothyroidism should be treated appropriately to improve their growth and quality of life.

LB10

Novel *CUL3* Variant in Pseudohypoaldosteronism Type 2

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Introduction: Pseudohypoaldosteronism type II (PHA II) is an extremely rare disorder characterized by low plasma renin and aldosterone when a normal renal function with hypertension, hyperkalemia, and hyperchloremic metabolic acidosis. PHA II is also known as familial hyperkalemic hypertension or Gordon's syndrome and is an inherited autosomal dominant. PHA II could be caused by pathogenic variants of *WNK1*, *WNK4*, *KLHL3*, and *CUL3*.

Case: A 2-years-7-months-old boy had hyperkalemia, which was initially detected during the evaluation of elevated liver function tests. In our first evaluation, we detected hypertension, mild

hyperchloremic metabolic acidosis, and hyperkalemia under the fludrocortisone treatment. He was born small for gestational age. The fludrocortisone was discontinued and endocrinological evaluation showed low plasma aldosterone concentration of 0,7 pg/mL (40-480 pg/mL) and low PRA: >0,52 ng/mL/hr (1-6,0 ng/mL/hr). After thiazide treatment, the patient's aldosterone concentration, PRA, and electrolyte levels were normalized with normal growth and development. A Next-Generation Sequencing unveiled that patient was heterozygous for novel variant c.1207-2A>C in CUL3 (NM_003590.4). No variant was detected in *WNK1*, *WNK4*, and *KLHL3*. Segregation analysis showed that c.1207-2A>C was de nova

Conclusions: PHA II should be evaluated in children presented with hypertension, and hyperkalemia. We predicted that the novel splice acceptor variant disrupts splicing. The c.1207-2A>C in *CUL3* was not reported in the databases. De novo variant is classified as the "pathogenic", according to ACMG 2015 criteria with PVS1, PM2, and PS2. Aldosterone defects have a wide clinical and genetic spectrum and emergency treatment can be started without biochemical evaluation. Next-Generation Sequencing is effective in confirming the diagnosis.

LB11

Cortisol evaluation in 106 neonates born from mothers using corticosteroids during pregnancy. Proposal for practical approach in clinical practice

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Context: Supra-physiological exogenous corticosteroids used during the last months of pregnancy may lead to temporary neonatal adrenal suppression. Little is known about the outcome of neonates from mothers who used corticosteroids during pregnancy.

Objective: The evaluation of clinical symptoms and biochemical findings of adrenal suppression in neonates from mothers using corticosteroids during pregnancy.

Methods: We retrospectively investigated files from neonates of mothers who used corticosteroids for at least the last three weeks of the third trimester between 2010-2016. In the first days after birth, random serum cortisol levels were determined in neonates of 29-41 weeks of gestational age. If cortisol levels were <550 nmol/L, ACTH-stimulated cortisol levels were measured within 4 weeks after birth. Adrenal suppression was defined as maximum cortisol <550 nmol/l after ACTH stimulation.

Results: Neonates (n=106) had a median gestational age of 38 weeks (IQR 36-39 weeks) and a median birthweight of 2963 gram (IQR 2400-3331 gram). The majority of the mothers used prednisone (n=96), the median dose of prednisone was 18 mg/day (IQR 7.5-30 mg). We found no clinical signs of adrenal suppression nor Addisonian crises in the neonates. Seventy-nine % of the available highest cortisol levels of the neonates was < 550 ; 55% < 300; 37% < 200 nmol/l. There was no association between low random cortisol levels and hypoglycemia. Furthermore, the outcome of a ACTH stimulation test was normal in the vast majority of the group who underwent the test.

Conclusion: This is the first study in a large group of neonates after maternal corticosteroid use during pregnancy. No clinical adrenal problems were seen. In addition, random serum cortisol levels in these neonates do not seem to identify the cases that will have a higher chance of an Addisonian crisis. We propose a protocol in which no standard serum cortisol levels will be measured after birth, but in which parents are educated when and how to seek help in the very small chance of Addisonian crisis in the first months after birth.

LB12

Sleep Quality in Caregivers of Type 1 Diabetes Mellitus Pediatric Patients - The Impact of isCGM Alarms

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Background: Type 1 diabetes mellitus (T1DM) is one of the most frequent chronic diseases in the pediatric age and demands constant and rigorous glycemic control. Intermittently scanned continuous glucose monitoring (isCGM) systems are a helpful tool in diabetes management. Second-generation isCGM contain alarms to assist in the detection of hyper or hypoglycemia. We aimed to compare the sleep quality of principal caregivers of T1DM pediatric patients who use isCGM with and without alarms and assess its impact on metabolic control.

Methods: An observational and cross-sectional study was carried out in March 2021, including T1DM patients who used an isCGM and a continuous subcutaneous insulin infusion device. The principal caregiver's sleep quality was assessed through the Pittsburgh Sleep Quality Index (PSQI), and metabolic control was evaluated through the ambulatory glucose profile and HbA1c level.

Results: Forty-two children and adolescents with T1DM and their caregivers were included, 14 patients using isCGM with alarms and 28 controls. The PSQI score showed no significant differences in parental sleep quality between groups: a median of 6.5 in the alarm group (IQR 7) and 9.0 in the control group (IQR 5), p=0.348. The assessment of metabolic control (adjusted to children's age and the caregivers' educational qualifications) revealed HbA1c mean of 7.93 vs 7.59 (p=0.393), time in range (TIR) 52.17% vs 42.60 % (p=0.134), time below range (TBR) 1.56% vs 5.59%

(p= 0.014) and glucose coefficient of variation 35.4 vs 41.6 (p=0.004) in the groups with and without alarms, respectively. There was no significant correlation between the PSQI score and HbA1c or TIR.

Conclusions: The use of isCGM alarms did not lead to a worse sleep quality or more frequent nocturnal awakenings in caregivers of T1DM children and adolescents. However, the alarms improved metabolic control by reducing TBR and glucose CV. Thus, our results support the use of isCGM alarms in diabetes management without prejudice to the caregivers' sleep quality.

LB13

Residual C-peptide secretion and glycemic control in pediatric patients with Diabetes Mellitus type 1

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Introduction: Residual C-peptide secretion has been associated with less hypoglycemic events and lower glycemic variability in patients with Diabetes Mellitus type 1 (DM1), primarily in adults.

The authors sought to evaluate the association between residual C-peptide secretion in pediatric patients with DM1 and glycemic control variables.

Methods: Cross-sectional study conducted in a level II hospital, in DM1 patients younger than 18 years old, treated with continuous subcutaneous insulin infusion, with a C-peptide value available between August 2021 and April 2022. Glycemic control variables were obtained through the insulin pumps, and were compared between individuals with undetectable C-peptide (<0.02ng/ml) and with residual secretion (≥0.02ng/ml).

Results: The sample included 36 participants, with a mean age of 12 years. Individuals with detectable C-peptide had an older age at diagnosis (9.8 years [3.6] vs 4.4 years [2.0], p<0,001) and shorter disease duration (42.5 months [22.4] vs 81.8 [37.3], p=0,001), compared with those with no c-peptide secretion, but no differences were found regarding sex or current age. C-peptide secretion was associated with less time below range (<70mg/dl) (3.9% [3.6] vs 7.2% [4.6], p=0.021), maintaining statistical significance after adjusting for potential confounding variables (disease duration and glycated hemoglobin) through logistic regression (p=0.024). Individuals with detectable C-peptide had less hypoglycemic events per week (1.4 [1.6] vs 2.8 [2.2], p=0.03), and less glycemic variability but without statistical significance (45.8% [6.2] vs 49.1% [5.1], p=0.130). No differences were found in glycated hemoglobin values, time in range and above range, mean glycemia or insulin doses.

Conclusion: Residual C-peptide secretion in pediatric DM1 patients seems to be associated with less time in hypoglycemia, suggesting that this might be a relevant marker regarding glycemic control. It also suggests that more intensive goals might be proposed more safely in these patients, with lower hypoglycemic risk. More studies are needed to evaluate potential c-peptide secretion preservation therapies.

LB14

A formula to simplify the screening fot impaired glucose tolerance in youths with overweight or obesity

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Aim: To develop a low cost formula as screening tool for identifying youths with overweight/obesity (OW/OB) at risk for impaired glucose tolerance (IGT).

Methods and Results: A retrospective observational study was performed in 1189 Caucasian youths with OW/OB aged 5-17 years, in whom information about family history for diabetes (FD), fasting glucose (FG), 2-hour glucose levels post-oral glucose tolerance test, alanine aminotransferase (ALT), and lipids were available at their first visit. Youths with impaired fasting glucose and high HbA1c were excluded from the study. Prevalence of isolated IGT was 6.6% (n =78). Youths with IGT were older, showed higher prevalence of FD, higher levels of FG and post-load glucose, ALT, triglycerides, and low HDL-Cholesterol compared to youths without IGT. The sample was divided into training set (TS) (n = 883) and validation set (VS) (n =306). The formula predicting IGT was obtained by logistic regression analysis in the TS, as it follows: 0.043*ALT+0.064*FG+0.87*FD-0.06*HDL. The cut-off of 5.7 showed sensitivity 0.29, specificity 0.95, and overall accuracy 0.91 (0.89-0.93) for detecting IGT. Similar results were found in the VS.

Conclusions: Using low cost variables, this simple formula can help pediatricians to select young people with OW/OB who should perform the OGTT for the screening of IGT.

LB15

Examining Sedentary and Activity Status Predictors in Adolescents and Their Implications for Diabetes Prevention

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Background: Physical activity (PA) has been conclusively shown to reduce the incidence of diabetes in prior research. A 2,000 steps/day increment yielded hazard ratio (HR) 0.88 for incidence of diabetes 95% CI 0.78–1.00; p = 0.046 (Garduno, 2022). Despite this, the role of different factors associated with higher adolescent after-school PA is understudied after the coronavirus pandemic, during which a greater proportion of parents worked remotely. This study aimed to evaluate statistically significant factors that are associated with higher adolescent PA versus sedentary behavior with the goal of identifying effective diabetes prevention interventions.

Methods: Study participants from Florida, U.S., aged 13-19 were enrolled and categorized into three groups based on the number of days of after-school exercise completed each week: 0 days of after-school exercise (No PA, n=214), 1-4 days of after-school exercise (moderate PA, n=245), and 5-7 days of after-school exercise (high PA, n=252). The statistical significance of the study factors associated with each PA group was assessed using two-tailed t-tests with a 95% confidence level.

Results: The participants' mean age was 15.6±1.2 years. Among participants with high PA, moderate PA, and no PA, 19.4%, 26.4%, and 30.9% were affected by overweight or obesity respectively ($p<0.05$). PA was influenced by gender (81.7% of males had high PA, versus 59.5% of females, $p<0.01$). The incidence of high PA levels was greater among those participants whose parents were married (77.7% vs 58,8%, $p<0.05$) or those who were the oldest children in the family (85.1% vs 58.1%, $p<0.05$). In terms of modifiable factors, possibly due to a role-modeling parenting effect, high PA levels were more among participants who exercised together with parents (94.2% vs 49.1%, $p<0.01$), and if one of the parents had a healthy diet (74.1% vs 55.9%, $p<0.05$). High PA levels were also more prevalent in adolescents who read nutrition labels (86.6% vs 54.6%, $p<0.01$), who were concerned about protein content in food choices (90.5% vs 56.1%, $p<0.05$), who considered fiber (95.8% vs 64.4%, $p<0.05$), sugar (85.1% vs 62.8%, $p<0.05$), or whole food content (80.1% vs 65.8%, $p<0.05$).

Conclusion: A deeper understanding of the factors associated with physical activity can help design more effective interventions. Study findings provide insight into environmental and behavioral factors associated with physical activity and provide the rationale for family-level interventions aimed at improving modifiable variables that will assist in the reduction of diabetes burden.

LB16

Glucose variability in 6–12-month-old healthy infants

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Background: Continuous glucose monitoring (CGM) devices are novel tools to measure the impact of dietary intake on glucose rhythms/metabolism in children. There is a significant gap in the literature on glycemic response in healthy, term infants and young children up to 2 years of age.

Objective: To investigate glucose excursions in response to infant feeding, using CGM in healthy 6–12-month-old infants.

Methods: An observational, non-intervention exploratory study was conducted in healthy, full-term 6–12 month-old infants. Continuous glucose measurement with the "FreeStyle Libre® Pro" (Abbott® Diabetes Care, Witney, Oxon, UK) device was performed over 5 days. We analyzed key glycemic parameters including incremental area under the curve, (iAUC), incremental maximal glucose value (iCmax), time to reach this value (Tmax)) as well as the correlation between macronutrient consumption and interstitial glucose fluctuations.

Results: Out of 54 infants screened, 10 infants were recruited (50% females). Mean age was 10.2 ± 1.5 months, weight (mean z-score 0.26 ± 1.08) and height (mean z-score 0.97 ± 1.27) were all within normal ranges. No serious adverse events were observed while on CGM. In total, 70% of glucose values were within the normal range (3.5 – 5.5 mmol/L) while 10% measured 5.5 – 10 mmol/L and no values were >10 mmol/L. Notably, 20% were <3.5 mmol/L with 11% falling below 3.0 mmol/L. Feeding occasions containing >30g carbohydrate (mid-day, afternoon and evening) induced higher 2h-iAUC (respectively 3.42, 3.41 and 3.50 mmol/L*h) than the two morning feeds that contained <25g carbohydrates (with iAUC respectively 2.72 and 2.81 mmol/L*h) ($p<0.05$). Feeding occasions including high fat content induced larger Tmax values. The difference between glucose values before each excursion and the fasting glucose value (3.34 ± 0.55 mM) increased significantly during the day: from 0.24 ± 0.39 mM in the early morning to 1.07 ± 0.57 mM in the evening ($p<0.05$).

Conclusions: Our proof-of-concept study demonstrates the feasibility of using CGM in infants aged 6–12 months old. The observed circadian rhythm and range of glucose values identified may highlight the need for a deeper understanding of metabolic adaptations to nutritional intake in early life.

LB17

Mapping of the current transition of care practice for patients with pituitary disease at Endo-ERN reference centers

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Rare endocrine conditions present specific diagnostic and management challenges to healthcare providers, especially regarding transition. Despite the need for practical guidance on this subject, consensus on structured approaches to transition are lacking.

The aim was to map the current clinical practice, and identify the unmet needs regarding transition of care for patients with pituitary disease in the reference centers (RCs) of the European Reference Network on Rare Endocrine Conditions (Endo-ERN). A survey-based, cross-sectional study using the EU Survey tool was performed, and completed by 46 physicians (n) from 30 RCs (N). The respondents were pediatric and adult endocrinologists, representatives for Main thematic group 6 (MTG6) for their respective centers.

The survey demonstrated that transition is a common practice among Endo-ERN centers (n=44/46), usually accomplished by a multidisciplinary team meeting (N=20/30). Criteria for start and end of transition were defined in half of the RCs (N=15/30), with 20% (N=5/30) of centers providing conflicting answers. Another aspect – the transition readiness was assessed in more than 75% of the RCs (N=26/30). That was done primarily by unvalidated tools such as subjective opinions and informal consultations. Pituitary-specific transition assessment tool was applied in one center only. Transition protocol was present in 9% of RC. Decisions about transition management were taken at combined meetings, or based on clinicians' personal judgment in 91% RCs. A minority of physicians evaluated the effectiveness of transition-related interventions (n=11/46), or medical outcomes (n=8/46). Patient-reported outcome measures were least often used (n=4/46). Unmet needs included development of guidelines (n=5/46), and EU-wide approach (n=2/46).

This study exemplifies the unmet needs for a structured approach to transition of patients with rare hypothalamic and pituitary conditions from healthcare providers and patients' perspective. It also demonstrates the need for further research on the definitions of successful transition of care and factors facilitating the successful transition.

LB18

Efficacy of liquid-chromatography and radioimmunoassay in false-positives' drop-off in CAH newborn screening

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The high rate of false-positive (FP) results in congenital adrenal hyperplasia newborn screening (CAH-NBS) worldwide challenges NBS-programs and reinforces the need of high specificity subsequent tests. Few studies assessed the efficacy of different serum steroids by the available methodologies. Serum 21-deoxycortisol-21DF demonstrated a high diagnostic accuracy in CAH children/adults but was not evaluated in the NBS context.

Objective: to evaluate the efficacy of confirmatory tests using different serum steroids by radioimmunossay and liquid chromatography methodologies in the CAH-NBS.

Patients: data of 708,437 newborns (NBs) were retrospectively evaluated.

Methods: newborns with neonatal-17OHP (N17OHP) results ≥ 2x99.5th percentile were recalled for serum dosages [RIA (17OHP) and LC-MS/MS (17OHP, 21-deoxycortisol-21DF, androstenedione-Δ4, cortisol)]. Hormonal data were validated by CYP21A2 genotyping. Non-parametric tests and ROC-curves were used.

Results: the recall rate was 0.045% and, in the serum confirmatory tests, 17OHP remained altered in 26% of newborns by RIA (PPV=30%) and in 11% by LC-MS/MS (PPV=49%); fifty-eight classical NBs were diagnosed and 32 asymptomatic-NBs persisted with increased serum 17OHP levels. In the ROC-curves between false and true-positives, 17OHP/LC-MS/MS had the highest accuracy as a single steroid (cutoff 48.3 ng/ml=100% of sensitivity for classical forms); surprisingly, serum 21DF was not superior than 17OHP/LC-MS/MS. Among the steroid ratios, the [(17OHP+Δ4)/cortisol] presented the highest accuracy (cutoff 24.9 = 100% of PPV to detect salt-wasting form).

Conclusions: 17OHP and [(17OHP+Δ4)/cortisol] ratio analyzed by LC-MS/MS presented the highest accuracy in the serum NBS tests. Differently that observed in older CAH patients, 21-DF was not superior than 17OHP in newborns as a diagnostic tool to optimize the CAH-NBS.

LB19

Early adrenal activation in boys with Cystic Fibrosis may explain impaired final height

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Background: Rapid BMI increase in early childhood was found to be a contributing factor for impaired final height in boys with Cystic Fibrosis (CF). This may be explained by early adrenarche triggering an accelerated bone maturation resulting in a compromised growth spurt during puberty, comparable to children with SGA. In healthy Dutch boys, adrenarche starts from the age of 9 years with DHEAS ≥ 1 µmol/L. In Dutch girls, the onset of adrenarche is from age 8 onwards.

Aim: We aimed to analyse the timing of adrenarche in boys with CF and associate early rapid BMI increase to timing of adrenarche. Also, we aimed to analyse differences in DHEAS-levels between boys and girls with CF.

Methods: Boys and girls with CF, aged 8-9 years, visiting the CF expertise center UMCU were included. Since 2018, anthropomorphic, pubertal and endocrine data were collected. Early adrenal activation in boys was defined as a DHEAS ≥ 1 µmol/L before the age of 9 years.

Results: Thirteen boys (mean age 8.55 ± 0.27 yrs) and 13 girls (mean age 8.52 ± 0.31 yrs) were enrolled until June 2022. The median (range) DHEAS level was 1.3 µmol/L (0.40 – 6.30) and 0.96 µmol/L (0.25 – 1.80) in boys and girls respectively (p = 0.199). Eight boys (61.5%) had an early rise in DHEAS-levels ≥ 1 µmol/L (i.e. before the age of 9 years).

Five out of 11 boys (45.5%) and 4 out of 8 girls (50%) had a mean accelerated bone-age of 1.55 ± 0.97 and 0.75 ± 0.96 yrs respectively.

The mean difference between chronological age and bone-age was more pronounced in boys and girls with DHEAS-levels ≥1 µmol/L (Δ0.65 ± 1.47 (n=8) and Δ0.75 ± 0.72 yrs (n=4)) in comparison to boys and girls with DHEAS-level <1 µmol/L (Δ-0.91 ± 0.29 (n=3) and Δ-0.25 ± 0.21 respectively) (p = 0.11 and p = 0.036).

A moderate, significant correlation was found between the ΔBMI-SDS and DHEAS-levels between 1-6 years (r=0.653, p = 0.029) in boys. This relationship was absent in girls.

Conclusion: In this small cohort, 61.5 % of boys with CF between 8-9 years had an early rise of DHEAS, which could be correlated to ΔBMI-SDS between 1-6 years. In comparison to girls, boys had higher DHEAS levels. Early adrenal activation may be one of the factors contributing to early and suboptimal growth during puberty and impaired final height in boys with CF.

LB20

A Structured Education Program on Hormonal Control and Quality of Life in Congenital Adrenal Hyperplasia: a study in Indonesia

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Background: Classic Congenital Adrenal Hyperplasia (CAH) needs life-long treatment of glucocorticoids. Compliance with long-term medication is still challenging, particularly in developing countries. However, there has been no prospective study about the strategy to improve compliance in CAH and its relationship with hormonal control and quality of life (QoL) in CAH, especially in underprivileged countries such as Indonesia. This study aimed to determine the relationship between compliance and hormonal treatment, QoL, and parental stress of CAH patients.

Methods: This study is a randomized pretest-posttest control group study to evaluate the compliance and quality of life in a one-year CAH structured education program. Both groups received the same education program every three months. Additionally, the intervention group received medication diaries with reminder messages using phone calls and short text messages at regular intervals (every month). We assessed treatment compliance by counting pills and the questionnaires; the QoL using PedsQL, and the parental stress using the Parental Stress Scale (PSS). We measured salivary 17-hydroxyprogesterone and androstenedione using LCMSMS to evaluate hormonal control every 3 months. The differences between the two groups in hormonal profile, quality of life, and PSS scores were analyzed by Mann-Whitney U Test and Paired T-test.

Results: Fifty patients with CAH (age range 0-20 years) were included in the intervention group of the study (n=23) and the control group (n=27). A good compliance increased from 30.4% at the baseline to 42.9% at the end of the visit in the diary group. Based on androstenedione levels, the undertreatment status decreased from 67.3% in the first visit to 50% at the end, whereas

the overtreatment status increased from 12.2% at the However, the difference between undertreatment vs. adequate and overtreatment before and after a year of education program showed no statistical difference (p=0.564). The PSS of the mother decreased, and the median PSS score of the father declined gradually from the first until the last visit. The median score of physical health subscale of PedQL was significantly improved after the education program in mother proxy reports (p=0.022), but not in the father proxy report.

Conclusions: The structured education program improved the hormonal control in CAH as well as dimensions of physical health in the quality of life and reduced parental stress. These results are a strong encouragement to improve CAH education in resource limited settings.

LB21

Glucose levels are not the same for everyone: A real-world big data study evaluating glucose levels by sex and age among children

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Purpose: Understanding the normal range of laboratory values as pertained to different age groups and males or females is paramount in health care delivery. We aimed to assess the distribution of glucose levels by age and sex in the general population of children using a large-scale population-based cohort.

Methods: A retrospective study with real-world de-identified data from a large, state mandated health fund in Israel among children aged 2 to 18 years old between 2006 and 2019. Age, sex, and BMI differences in mean glucose levels were evaluated using 3-way Anova.

Results: Study included 130,170 blood samples from 117,411 children, 53.3% were female. After adjusting for age boys had higher glucose levels than girls, with a mean of 89.21 ±8.66 mg/dL vs. 87.59 ±8.35 (p<0.001).

Compared to the 15 to 18 year-olds (88.49 mg/dl ±7.63), 2 to 5 year-olds had lower glucose levels (84.19 ±10.65, (p<0.001)), 11 to 14 year-olds had higher glucose (90.40 ±7.42 (p<0.001)) and 6 to 10 year-olds showed no difference (88.45 ±8.25). Among our cohort, 33.0% (n=42,991) had a BMI percentile record the same year as their glucose test result. There was a weak yet significant positive association between blood glucose levels and BMI (Pearson coefficient <0.1).

Conclusions: Our large cohort indicates that boys have higher glucose levels than girls, as do adolescents compared to younger children. This finding is important for the delivery of adequate health care, screening for illness and avoiding unnecessary investigations and tests.

LB22

Maternal and Cord Blood Metabolites Associations with Childhood Glucose Outcomes in the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study

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Background: Maternal triglycerides, fatty acids, and their metabolites together with sugars and metabolic intermediates may play a role in newborn outcomes. Furthermore, maternal amino acids, acylcarnitines, lipids and fatty acids and their metabolites are associated with cord C-peptide independent of maternal BMI and glycemia, highlighting the potential contribution of maternal metabolites to offspring outcomes. This study examined the associations of maternal metabolites during pregnancy with childhood glucose outcomes. Associations between cord blood metabolites and childhood glucose outcomes were also assessed in a subset of offspring.

Methods: Phenotype data from the multi-ethnic Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study and HAPO Follow Up Study (FUS) were used together with targeted and non-targeted metabolomics data obtained fasting and 1-hr after a glucose load at ~28 weeks gestation. Maternal metabolite association analyses included 2,145 mother offspring pairs while cord blood association analyses included 808 offspring. Multiple logistic and linear regression were used to examine associations between primary predictors, maternal metabolites and cord blood metabolites, and child glucose outcomes. Model 1 included field center, child age, sex, and pubertal status with sex by Tanner stage interaction term, maternal variables at pregnancy OGTT (age, height, mean arterial pressure, parity, smoking, alcohol, and gestational age), and child's family history of diabetes in first-degree relatives. Model 2 included Model 1 + maternal BMI at pregnancy OGTT, Model 3 included Model 1 + maternal glucose z score sum at pregnancy OGTT, and Model 4 included Model 1 + maternal BMI and glucose z score sum at pregnancy OGTT.

Results: In the fully adjusted model (Model 4), no associations of fasting maternal metabolites and childhood glucose outcomes were identified. 1-hr maternal methionine, acetylcarnitine (C2), and hypoxanthine were positively associated with child HbA1c (b =0.02, 95%CI: 0.01-0.04, p<0.001), 2-hr glucose (b=1.69, 95%CI: 0-8-2.58, p<0.001), and insulinogenic index (b=0.02, 95%CI: 0.01-0.03, p<0.001) respectively. Multiple maternal fasting and 1-hr metabolites were significantly associated with childhood adiposity outcomes in Model 1 but were not significant after adjusting for maternal BMI and/or maternal glycemia. There were no significant associations between cord blood metabolites and childhood glucose outcomes.

Conclusions: Only maternal methionine, acetylcarnitine (C2), and hypoxanthine were associated with childhood glucose outcomes after adjusting for maternal BMI and glucose. Additional metabolites were significantly associated with child glucose outcomes after adjusting for maternal BMI but not maternal glucose, suggesting that maternal glucose accounts for these associations.

LB23

Ten years of growth hormone treatment in children born small for gestational age with persistent short stature- results of a Portuguese multicenter study

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Background: Growth hormone (GH) treatment is indicated for children who are born small for gestational age (SGA) and fail to achieve sufficient catch-up growth during infancy and remain short throughout childhood.

Aims: To evaluate the effect of GH treatment in a large, multicentric, Portuguese SGA children cohort and to analyze for correlation between GH treatment response and clinical factors.

Methods: A retrospective, multicentric study was conducted from 2011 to 2020. The study group included children born small for gestational age (birth weight and/or length at least 2 SDS below the mean for sex and gestational age) with persistent short stature after 4 years of age, who underwent GH treatment for at least one year.

Results: A total of 111 children were enrolled. The mean gestational age was 37.50±4,2 weeks. Birth weight and length standard deviation score (SDS) were -1,85±0,9 and -2,52 ±0,78 respectively. At the start of GH treatment, the mean chronological age was 7,26±2,76 years, bone age (BA) was 4.64±2,91 years, and the mean height SDS was -3,19±0.78. The mean initial GH dose was 32,34 ± 5,34 mcg/kg/dia. The mean height SDS change (ΔHt SDS) was 0,59±0,58 after the first year of treatment (n=111) and 0,27±0,33 after the second year (n=94). Up to a 27% of patients showed a poor response in the first year (ΔHt SDS < 0,3). The first year growth response was positively correlated with younger age (p=0,033) and lower BA (p=0,037) at the start of treatment; GH dose was not correlated with height SDS change (p=0,288). Nineteen patients (17% of the sample) had attained final height; their mean initial height SDS was -3,04±0,77 and they achieved a mean height SDS of -1,84± 0,94.

Conclusions: In the first year, there was a good response to GH treatment in the majority (73%) of patients (ΔHt SDS > 0,3). In this sample, GH doses were very similar and GH dose was not an important predictor of growth response. Early initiation of GH treatment improved growth outcomes so monitoring growth of SGA children is crucial for an earlier GH treatment.

LB24

"PRECOCIOUS PUBERTY AND RAPIDLY PROGRESSIVE PUBERTY DURING THE COVID-19 PANDEMIC"

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Introduction: During the COVID-19 pandemic, we have seen an increase in consultations for Precocious puberty (PP) and accelerated puberty.

Aim: To assess the frequency of PP and its progression before and during the pandemic.

Materials and Methods: We retrospectively evaluated the patients's medical records referred to a Paediatric Endocrinolgy Unit between April 2018-March 2021. Patients who consulted for suspected PP during the pandemic were analyzed (Period 3: April 2020-March 2021) and compared with two years previous (Period 1: April 2018-March 2019 and Period 2: April 2019-March 2020). We collected clinical and complementary studies. The initial evaluation and evolution were recorded. Study according to the declaration of Helsinki II and approved by Ethics Committee. Stata software was used for the analysis. Qualitative variables were described using frequency and percentage and quantitative variables with mean and standard deviation. The association between qualitative variables was evaluated with Chi-square test and Fisher's exact test, and quantitative variables with Student's t-test.

Results: 5151 consultations were recorded. An increase in the percentage of consultations due to suspected PP was observed during Period 3 (21% vs.10% and 11%.p<0.001). The number of patients who consulted for suspected PP in Period 3 increased 2.3 times (80 vs.29 and 31.p<0,001). 95% were girls, this population was analyzed. 132 patients were included. Age was similar in the 3 groups (8±1,1; 8,2±0,6 and 8,2±0,9.p:0,912) as well as the risk factors for PP. The patients were similar in Weight (1,6±1,4 vs. 1,2±1,2 vs. 0,9±1,5; p:0,104), Height (1,5±1,2 vs. 1,5±1,2 vs. 1,2±1;p:0,925) and Δ Height-target genetic height (0,9±1,3 vs. 0,9±1,4 vs. 0,8±0,9;p:0,925). Lower BMI was observed in Period 3 (0,7±1,2 vs1,3±1 and 1±0,9;p:0,033). A higher percentage of breast stage Tanner 3-4 (78% vs.64% vs.51%;p:0,02) and larger uterine size (36,2±9,9 vs.29,6±9,2 and 34,6±6,7mm;p:0,012) were found in Period 3. Bone age was similar in the 3 groups (8,9±2 vs. 9,5±1,6 vs. 9,3±1,7 years;p:0,506) as well as hormonal determinations. 106 patients completed the initial evaluation. Treatment was indicated in 26%. In the rest, evolution was controlled for an average of 13 months. 49% presented a rapidly progressive evolution, during Period 3 in 87%.

Conclusions: It's the first study in our country to evaluate PP during the pandemic. An increase of 2.3 times in consultations for suspected PP and accelerated evolution were observed in girls.

LB25

Challenges of Gender Assignment in Disorder of Sex Development (DSD) in Developing Countries

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Background: Gender assignment in children with disorder of sex development (DSD) is a key step in their management and needs detailed assessment. In developing countries, children with DSD are often presented late, due to lack of awareness and social stigmatization, which makes management more challenging.

Methodology: Retrospective review of complex DSD cases (karyotyping different from current sex of rearing), presented in DSD clinic of a tertiary care hospital over last 2 years.

Results: Sixteen cases with complex DSD were reported with mean age of presentation 11.6 (3.4 – 16) year. 46, XY DSD was the most common disorder (n=9), followed by 46, XY DSD (n=6) and sex chromosome (n=1).

All 46, XX DSD were the late presentation of congenital adrenal hyperplasia (CAH) with mean age of presentation 11.6 (9 – 16) year and current sex of rearing as male. 5/6 cases were salt-wasting CAH and born with atypical genitalia, but living as male due to social and family pressure. However, there was one case of non-salt-wasting CAH, presented at 9 years of age with bilateral undescended testis along with precocious puberty (Prader scoring 5). After considering the child and family decision, gender identity assessment, androgenization of brain and advanced Prader scoring it was decided to keep them as male and they underwent hysterectomy, oophorectomy with male genitoplasty.

Among 46, XY DSD, partial androgen insensitivity was the most common (n=3), followed by 5-alpha reductase deficiency (n=2), severe gonadal dysgenesis (n=2), complete androgen insensitivity (n=2). Mean age of presentation was 12.5 (9-15.8) year, and all were having female sex of rearing at presentation. Virilization at puberty (n=5) was the most common presentation, followed by inguinal swelling (n=2), and primary amenorrhea (n=2). Both cases of 5-alpha reductase were re-assigned a male gender and underwent orchidopexy with male genitoplasty. Cases with complete androgen insensitivity and severe gonadal dysgenesis were reared up as female and had bilateral gonadectomy followed by female hormone replacement therapy. 2 cases of partial androgen insensitivity were reared up as male and 1 as females.

One case of Sex chromosomal DSD (45, XO, 47, XXY) with mixed gonadal dysgenesis, presented with atypical genitalia at birth with Prader scoring of 3/5. She was reared up as female with plan of bilateral gonadectomy.

Conclusion: There is a need to establish a system for early identification and referral of DSD in developing countries. It will help in improving their clinical outcome and quality of life.

Poster Category 2

Adrenals and HPA Axis

P2-1

An adrenal enigma: adrenal crises following an acquired CMV infection in an immunocompetent infant

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Here we describe a 10 week old previously healthy infant that underwent several severe adrenal crises marked by electrolyte disturbances (K=7.8 Na=128), and cardiorespiratory resuscitation (intubation and pressors). The adrenal insufficiency developed while admitted after developing a short febrile illness, and severe prolonged watery diarrhea, accompanied by development mild hypertransaminasemia and rash.

Crises were characterized by elevated Renin 119 mU/l [Ref: 3.4-64], inappropriately normal or moderately elevated aldosterone (10,000, 2,536 pmol/l), that was low between crises (159 pmol/l). Severe crises were preceded by exacerbation of watery diarrhea and moderate to severe dehydration. Of note, one crisis occurred following diarrhea-associated dehydration while on hydrocortisone 50mg/m^2/day and fludrocortisone 0.2mg/day.

An extensive metabolic work-up was negative, leading to utilizing expedited whole exome sequencing (WES). The WES was negative. Adrenal imaging by U/S and MRI has revealed normal appearance.

Work-up for acquired causes of hypoaldosteronism has revealed an active CMV infection (viremia 239,000 copies/ml). Work up for congenital CMV including PCR of blood sample on Guthrie paper collected perinatally, retinal exam, BERA and brain MRI confirmed that her CMV infection was acquired. Work-up for immunodeficiency including HIV serology was negative.

CMV-associated adrenal injury is well described in cohorts of patients with HIV. Cytomegalovirus has specific affinity to the adrenal cortex and medulla, however a clinical phenotype will be evident if over 90% of the relevant cell population is impaired. Four cases of neonates/infants with adrenal insufficiency associated with CMV infection were described so far, of which one was in a likely acquired rather than congenital CMV.

The patient's partial ability to raise aldosterone has led to assessment for component of aldosterone resistance. Renal U/S revealing no signs of urinary tract obstruction, as well as negative blood and urine cultures have ruled out common acquired causes. A recent case series describes aldosterone resistance in infants with excessive GI losses, thus we suggest that this mechanism may have contributed to the clinical course.

Following initiation of Ganciclovir adrenal crises stopped and diarrhea subsided. We therefore discuss the first case of acquired CMV infection in an immunocompetent infant leading to adrenal injury combined with CMV-associated diarrhea associated partial aldosterone resistance.

P2-2

Retrospective cross-sectional study reviewing local practice in assessment of adrenal axis at a tertiary children's hospital

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Introduction: There is considerable variation in practice when assessing adrenal function in adrenal insufficiency; duration of glucocorticoid defined to confer risk, early morning cortisol assay (EMC), Synacthen test (ST) - both low dose (LDST) (1microgram) or standard dose (SDST) (36microgram/kg [maximum 250micrograms]) and symptomatology.

At our tertiary children's hospital, even between departments, there is variation in those identified as being at risk of adrenal insufficiency and in their assessment.

Aims: To perform a cross-sectional review, establishing how and when our two Synacthen test protocols (LDST and SDST) and EMC are being used.

Overall, aiming to standardise practice, improve patient care and service delivery.

Methods: Patients identified through inpatient and day case lists over a six-month period, June to December 2021. Data was collected from electronic records.

Results: 54 patients were identified as being at risk of impaired adrenal function. Of the 54, 66.6% (n=36/54) had their ST during the review period. The assessments were carried out by 11 different subspecialties.

80.5% had an EMC (n=29/36). Mean EMC was 244nmol/l (lower quartile [LQ]113.5nmol/l and upper quartile [UQ] 359.5nmol/l). Two patients had an EMC >450nmol/l and proceeded to have a ST which they passed. 41.6% (n=15/26) had an EMC <150nmol/l and proceeded to have ST, peak cortisol >450nmol/l in 40% (n=6/15), of those most had a baseline <150nmol/l (n=4/6).

77.8% had a LDST (n=28/36). Those who underwent LDST compared with SDST had a mean lighter weight and younger age (14.5kg lighter and 4.6 years younger). There was minimal observed difference in peak cortisol for LDST (569nmol/l LQ 384nmol/l, UQ 722nmol/l) versus SDST (578nmol/l LQ 559nmol/l, UQ 700nmol/l).

Conclusion: The review highlights the need for a pathway, to identify and assess patients at risk of adrenal insufficiency, in order to standardise and improve patient care; prior to proceeding to ST protocol.

Although the numbers are small, decision for LDST included younger and lighter patients. There was minimal observed difference LDST and SDST peak cortisol. Whilst further studies are needed, in this cohort, it suggests SDST did not result in false positives.

EMC can be used to triage patients. Locally, those with an EMC >450nmol/l can be assumed as being adrenally sufficient and the majority of those with EMC <150nmol/l can be assumed as being adrenally insufficient, without the need for further assessment with ST. A pathway utilising EMC as first line, would enable us to rationalise resources locally and standardise our care.

P2-3

A Rare Cause of Peripheral Precocious Puberty

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Introduction: Peripheral precocious puberty is a non-gonadotropin-dependent early pubertal development. Exogenous intake of sex steroids, gonadal or adrenal pathologies, ectopic hCG-secreting lesions play a role in the etiology. Adrenal tumors is a rare cause of heterosexual precocious puberty.

Case: An eight-year-old female patient was admitted with the complaints of genital hair growth and breast enlargement. The patient's history and family history were unremarkable. On physical examination, body weight was 34.5 kg (+1.28 sds), height was 137.2 cm (+1.41 sds), puberty Tanner stage3, hyperpigmentation in the areola and cliteromegaly were detected.

In the laboratory tests of the patient, FSH 0.8 U/L, LH < 0.07 U/L, Estradiol 470 ng/L, Total Testosterone 389 ng/ml, DHEA-S 262.02 µg/dL, Androstenedione 30.2 nmol/L, DHEA 6.60 ug/L, 11 deoxycortisol 4.32 ng/ml, 17-OH progesterone 6.29 nmol/L, ACTH <5.00 pg/mL Cortisol 18, 5 µg/dL,24-hour urinary cortisol 539 ug/m2 detected.

Result of the one mg dexamethasone suppression test is ACTH<5.00 pg/mL Cortisol 16.2. Bone age is 12 years old, and in the pelvic ultrasonography the uterus 35x24x26mm, endometrium 5 mm, right ovary 5.7 mm, left ovary 3.3 ml was found. At the same time in the abdominal ultrasonography, a heterogeneous hypoechoic mass with 43x34 mm calcifications was observed in the right adrenal.

With advanced imaging methods, it was seen that the mass was localized in the adrenal gland. The patient underwent mass excision. In the laboratory examinations of the patient one week after the operation, Estradiol 11.0 ng/L, Total Testosterone <0.07 ug/L, DHEA-S 6.74 µg/dL, Androstenedione <1.05 nmol/L, DHEA 0.88 ug/ L, DHEA-S 6.74 µg/dL, 11 deoxycortisol 0.0943 ng/ml. The pathology result was compatible with adrenocortical carcinoma and genetic analysis was sent from the patient in terms of p53 mutation. The patient is under follow-up by our endocrinology and oncology department.

Conclusion: Adrenocortical tumors are a very rare cause of childhood malignant tumors. Weiss criteria are the most preferred method in the differentiation of malignant/benign tumor. The clinical course of a case with extremely rare seen malignant adrenocortical carcinoma in the etiology of peripheral precocious puberty, is shared.

P2-4

The utility of random cortisol in identifying neonatal primary adrenal insufficiency

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While it has been established that within the first 4 months of life there is an absence of the circadian rhythm guiding cortisol secretion, it remains unclear if a random serum cortisol (rSC) level is useful in diagnosing neonatal primary adrenal insufficiency (PAI). The objective of this study is to determine the utility of rSC in determining PAI within the first 4 months of life.

This is a retrospective chart review of subjects who had rSC collection and high dose cosyntropin stimulation test (HDT) prior to 4 months of life. Indications for performing HDT were: genital ambiguity, hypoglycemia, hypotension and other, which included abnormal newborn screen for congenital adrenal hyperplasia (CAH). Subjects who were deceased, received medications such as opioids, ketoconazole, or steroids (inhaled or oral within 48 hrs of obtaining rSC), or had missing data points were excluded from analysis. Baseline laboratory measurements, including rSC levels, were recorded and the cohort was divided into 2 groups: those with PAI, defined as peak stimulated cortisol levels < 15.5 mcg/dL and a clinical diagnosis associated with this such as CAH or adrenal hemorrhage, and a non-PAI group of subjects with normal peak cortisol levels (≥15.5 mcg/dl). rSC levels were compared between the groups using unpaired, two-tailed t-test. P-values < 0.05 were considered significant. Receiver operator curve (ROC) analysis was used to identify the area under the curve (AUC) for the diagnosis of PAI.

The study included 92 infants. Mean age and weight (±SDs) were 35.8±30.8 days and 3128.1 ± 1188.8 g, respectively, 41 (45%) preterm, 27 (29 %) females, and 7 (7.6%) had PAI. The most common indications for rSC testing were to assess for CAH (56%) and hypoglycemia (22%). During the first 4 months of life mean, rSC levels were for the PAI group (4.94 ± 4.39 mcg/dL) vs non-PAI (6.13 ± 5.07 mcg/dL) groups, p=0.55. ROC analysis for rSC in diagnosing PAI during the first 4 months vs first 28 days of life, showed AUC 0.5504 vs 0.6420, respectively.

While rSC can be collected within the first 4 months of life, and there is marginal improvement in the AUC during the first 28 days of life when compared to the first 4 months of life, its diagnostic utility in determining PAI is quite limited. Based on this data if there's a high index of suspicion for PAI, a stimulated cortisol level derived from HDT should be obtained.

P2-5

Prevalence and genotype of 21-hydroxylase deficiency in Croatian Romani population

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Objective: Clustering of rare diseases and private founder mutations is a common phenomenon in many founder populations such as Romani. Congenital adrenal hyperplasia (CAH) owing to 21-hydroxylase deficiency (21-OHD) is a rare autosomal recessive disorder caused by mutations in the CYP21A2 gene.

The aim of the study was to estimate the prevalence of 21-OHD and the frequency of particular CYP21A2 gene mutations in the Croatian Romani population.

Methods: Data from the Croatian 21-OHD genetic database was reviewed, and only Romani patients were included in the study.

Results: According to a survey conducted in 2017, Croatia had 22 500 Romani people and six of them had salt-wasting (SW) form of 21-OHD. All were homozygous for Intron 2 (I2G) mutation and descended from consanguineous families belonging to different Romani tribes (Bayashi, Kalderash and Ashkalia). The calculated prevalence of 21-OHD in Croatian Romani is 1:3750, while in the Croatian general population it is 1:18 000. Three of the six Romani patients originated from two neighboring villages in Northwestern Croatia (Slavonia County), as well as the seventh patient is of mixed Romani/Croatian descent and heterozygous for I2G mutation (not included in prevalence calculation).

Conclusion: The Romani population in Croatia has a high prevalence of SW 21-OHD. Six Romani patients from consanguineous families belonging to different Romani tribes are homozygous for I2G mutation.

P2-6

High carrier frequency of a nonsense p.W230X variant in HSD3B2 gene among Ossetians

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Background: Congenital adrenal hyperplasia (CAH) caused by 3ß-HSD deficiency is a rare form of congenital adrenal deficiency with an autosomal recessive type of inheritance. We have previously demonstrated that a single nucleotide variant NM_000198.3:c.690G>A (p.W230X) in the homozygous state is a frequent cause of CAH among the indigenous population of North Ossetia-Alania represented by Ossetians.

Aims: To study carrier frequency of the p.W230X variant in HSD3B2 gene in North Ossetia-Alania.

Methods: Genotyping of the nucleotide variant NM_000198.3:c.690G>A (p.W230X) was performed by Real-time PCR. 339 individuals of Ossetian origin were included in the study. Allele frequencies, Fisher's confidence intervals (CI) were calculated using the WinPepi v. 11.65 software. Comparizon of allele frequencies was performed with the z-score test for two proportions.

Results: Among 339 samples investigated nucleotide variant c.690G>A was detected in 8 cases of heterozygous carriage. The total allele frequency of the studied variant was 0.0118 (n=8/678, 95% CI=0.0051-0.0231). Accordingly, the frequency of heterozygous carrier was 0.0236 (n=8/339). The frequency of CAH caused by nucleotide variant c.690G>A in HSD3B2 among Ossetians was 1:7183 or 13.9 per 100,000 (95% CI: 1:1874-1:38447 or 3-53 per 100,000).

We performed a haplotype study using genotyping with Affymetrix high-density SNP Array in two patients with homozygous c.690G>A variant. As a result, we detected autozygosity regions at chr1:119425396-152538358 and chr1:117767918-145829474 encompassing the HSD3B2 locus and overlapping the centromere of the chromosome. Using Rutgers Map v.2 the physical boundaries of autozygosity regions determined by the SNP array were converted into 6.06 and 3.44 cM (Kosambi) sex-averaged genetic distances, which corresponds to a common ancestor of 8.25–14.53 generations ago.

Conclusions: The results demonstrate high frequency of NM_000198.3:c.690G>A variant among Ossetians, which is most likely attributed to a founder effect.

P2-7

Suboptimal cortisol response on ITT and subsequent adrenal insufficiency

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Background: Insulin Tolerance tests (ITT) have long been considered the gold standard for dynamic function testing of the hypothalamo-pituitary-adrenal (HPA) axis. Sub-optimal cortisol responses during an ITT in children may be found in children during ITT without a previous clinical suspicion of Adrenal insufficiency (AI). It is not clear what the clinical significance of this is and whether all of these children require formal synacthen testing.

Methods: A 9-year retrospective case review of cortisol responses to insulin during ITT was conducted for children and young people at a tertiary paediatric endocrine centre in the United Kingdom (UK). The primary objective was to establish the outcome of patients who attended for an ITT with a sub-optimal cortisol (<430nmol/L) response and how many had further testing with a standard synacthen test (SST). An optimal cortisol response was considered to be any result greater than 430nmol/L on both ITT and on SST.

Results: 223 patients (72.5% male, 27.5% female) were identified from 2013-2022. The median age was 13.74 (5.74-20.1) years. 204 (91.5%) were included, 19 (8.5%) were excluded due to missing data. 87/204 (42.6%) patients had a sub-optimal (cortisol <430nmol/L) cortisol response to ITT. Of those with a sub-optimal response to ITT, 55/87 (63.2%) proceeded to SST. Only 2/55 (3.6%) patients that underwent an SST had a sub-optimal response. Of those who did not have a SST, 2/32 (6.3%) were commenced on hydrocortisone, 7/32 (21.9%) had a previous normal response to SST, 2/32 (6.3%) had an acceptable early morning cortisol, 8/32 (25%) it was deemed not medically required, there was no documentation for 7/32 (21.9%) patients and 6/32 (18.7%) patients were already on hydrocortisone. Thus, only 4/204 (2%) new patients were diagnosed with AI following initial referral for ITT. Six patients that had a sub-optimal response to ITT were already known to have AI. Therefore, in total, ITT identified 10/204 (5%) patients as having AI despite 87/204 (42.6%) patients having a sub-optimal cortisol response to Insulin.

Conclusion: Low cortisol levels during ITT were identified in nearly half of children undergoing ITT, however these children are rarely confirmed as having AI on synacthen testing. Additional synacthen testing, results in further hospital visits, cannulations, use of resources and parental concerns for a large number of patients. Data on the long-term outcome of cases that have sub-optimal cortisols on ITT, but adequate levels on synacthen testing are lacking.

P2-8

An Unusual Case of Histiocytosis Presenting as Bilateral Adrenal Masses

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Objectives: We describe an unusual presentation of Histiocytosis in a 17 year old female with a large lung mass, and bilateral adrenal masses.

Methods: Case report

Results: A 17-year-old female presented with chest pain, as well as several weeks history of fatigue, decreased appetite, a dry cough and unintentional weight loss. No history of fevers or night sweats. Her vital signs and physical exam were normal; no virilization or cushingoid features. CBC showed normocytic anemia. She had normal electrolytes. CT-A Chest revealed a 9.2 x 8 x 7.4 cm heterogeneous hypervascular mass in the right lower lung; a similar-appearing 7.1 x 5.4 x 6.9 cm heterogeneous mass in the left adrenal gland and a 3.4 cm hypodense mass in the right adrenal gland.

Tumor markers showed normal CA 19-9, AFP, Beta-Hcg, CA 125, and CEA. Dopamine, Epinephrine and Norepinephrine levels were normal. Urine metanephrine to creatinine ratio was normal at 226 ug/g. HVA and VMA were in normal ranges at 3.9 and 3.6 mg/g respectively. Free metanephrines and normetanephrines were both normal at less than 0.2 nmol/L. Testing for echinococcus, tuberculosis and coccidioides was negative. Endocrine workup was normal with 17-OHP at 81 ng/mL, Aldosterone 2.0 ng/dL, Renin 1.5 ng/mL/h, DHEAS 37 ug/dL, Testosterone 14 ng/dL, Progesterone less than 10 ng/dL, ACTH 29 pg/mL and AM Cortisol 18.2 mcg/dL. She underwent IR-guided biopsy of the left adrenal mass and was discharged.

She was readmitted for chemotherapy after preliminary pathology from the adrenal mass returned ALK-positive. MRI spine showed evidence of spinal metastasis, so she received a short course of palliative radiation therapy. She was started on Crizotinib, an ALK/ROS1 inhibitor. Final pathology report returned as ALK-positive Histiocytosis. Follow up CT after starting Crizotinib showed decrease in size of lung and adrenal masses.

Conclusions: The differential diagnosis for bilateral adrenal masses includes metastatic diseases (renal, lung cancer, melanoma), lymphoma, pheochromocytoma, ACTH–dependent Cushing's, congenital adrenal hyperplasia, primary aldosteronism, bilateral macronodular adrenal hyperplasia and infections such as tuberculosis or fungal. This case was unique in that Histiocytosis presented as bilateral adrenal masses along with a large lung mass. We hope that by reporting this interesting case we can increase physician awareness of this condition, and help expand the differential diagnosis for bilateral adrenal masses.

P2-9

Thrombocytosis as a Rare Manifestation in Salt Wasting Congenital Adrenal Hyperplasia: A Case Report

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Introduction: Congenital adrenal hyperplasia (CAH) has an incidence of 1:14 000 to 1:18 000 worldwide. It is caused by autosomal recessive gene mutations. Neonates typically present with virilization at birth, or in shock, 'salt-losing crisis', around days 10–14 of life. Some children present later with simple virilizing CAH, often with milder compound heterozygous mutations. Reactive thrombocytosis is a rare manifestation in CAH. Gasparini et al, reported 1 case of CAH with thrombocytosis in 1996. Pathophysiology of thrombocytosis in CAH is still unknown. But might occur due to the metabolic stress and resolved after adequate treatment.

Case Report: Two months old girl came to emergency room with profuse vomiting 4 days before admission. She vomits about 2-5 times a day. The patient looked thirsty, fatigue and decreasing of body weight. Patient is the third child from P3A0 mother, born at 39 weeks gestational age.

Anthropometrics examination showed body weight was 3,75 gr, body length was 52 cm and head circumference 37 cm. The body weight for age was -2,28 SD, height for age was -2,49 SD, body weight for length was 0,03 SD and head circumference for age was -1,04 SD based on WHO Growth Chat Standards. Physical examination showed sign of mild dehydration. Genital examination showed clitoromegaly, vagina, hyperpigmentation of labia majora with Prader stage III. There is no testis palpable.

Laboratory examinations showed thrombocytosis (811.000/mm3), hyponatremia (102 mEq/L), hyperkalemia (7,5 mEq/L), normal blood glucose, normal urinalysis, and elevated 17-OH-Progesterone (134,55 ng/mL). Other hematologic tests are within normal limit. Chromosome analysis is 46 XX. Electrocardiogram result is within normal limit. The cause of thrombocytosis in this case cannot be explained aside from CAH condition. During hospitalization, the patient was given rehydration with natrium chloride 0,9% solution, hydrocortisone and fludrocortisone orally. The patient shown improvement after 4 days hospitalization but thrombocytosis still persists. The patient recovered uneventfully and discharged on day 4.

Conclusion: Thrombocytosis is typically transient, but duration depends on the etiology. Severe and extreme thrombocytosis rarely persists, often declining within 3 days of discovery and are more common in young patients. In CAH thrombocytosis happened due to the dehydration and metabolic disorder condition. As a pediatrician, first we should exclude infection since it is the most common etiology of thrombocytosis in children. According to literature thrombocytosis in CAH resolves after the metabolic disorder improve.

P2-10

Long-term Outcomes for Ninety-four Boys with Central Precocious Puberty or Early and Fast Puberty in Chinese Boys

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Objective: To assess the efficacy and influential factors of GnRHa treatment for Chinese CPP/EFP boys.

Methods: From April, 1994 to June, 2020, 94 boys diagnosed with CPP or EFP who had reached the final adult height were retrospectively included. Among these patients, 41 patients received no treatment, 43 patients received GnRHa treatment alone and 10 patients received GnRHa + GH treatment. The final adult height and the demographic data during the treatment were obtained.

Results: The bone age on the initial of the treatment was relatively old (>12y) compared with girls, only 1/43 patients in the GnRHa group, 1/10 patients in the GnRHa+GH group and 1/41 patients in the no treatment group was younger than 12 years. Higher PAH was observed after treatment in both GnRHa group and the GnRHa+GH group (PAH2 - PAH1 = 4.03 ± 5.36 cm vs. 7.61 ± 4.60 cm). The FAH (170.41 ± 5.78cm in GnRHa group, 168.80 ± 7.69cm in GnRHa+GH group and 170.19 ± 6.28cm in no treatment group, $P > 0.05$) showed no significant difference among three groups. GnRHa+GH group showed significant larger height gain (FAH-PAH1) in comparison with GnRHa and no treatment groups (GnRHa+GH 4.3 ± 2.60 cm vs. GnRHa 1.21 ± 4.47 cm, post hoc $P < 0.05$, GnRHa+GH vs. no treatment 1.03 ± 4.50 cm, post hoc $P < 0.05$), while there was no significant difference between GnRHa group and no treatment group. In the 7th-12th months, both of the GnRHa group and GnRHa+GH group GV< 5 cm/y, but the height gain of GnRHa group showed no significance compared to the no treatment group. ΔBA/ΔCA during treatment was significantly negatively correlated with height gain. If ΔBA/ΔCA<0.624, the height gain probably < 0 cm.

Conclusion: GnRHa treatment could significantly inhibit the gonadal axis and bone maturation. But For Chinese CPP/EFP boys with relatively old bone age (> 12 y), GnRHa alone could not benefit for the height gain compared with the no treatment group, especially when PAH > THt, ΔBA/ΔCA > 0.624 and GV< 5 cm/y during treatment, while the GnRHa+GH treatment significantly improve the height gain.

P2-11

Differences in the management of classic childhood congenital adrenal hyperplasia in Spain according to a patients association

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Objective: Despite published guidelines, there is no single approach to management in congenital adrenal hyperplasia (CAH). The objective of the study was to explore the variations in treatment for CAH in Spain.

Material and Methods: A retrospective study in a single center was done analyzing the data provided by patients and relatives through the Spanish Association of CAH from a online survey of 25 questions. It was diffused from December 2021 to February 2022 using the google-docs format. A descriptive statistical analysis was performed. Data from patients aged 0-18 years with classical-CAH were collected. The type of treatment, formulation, dose, administration schedule, as well as the action in case of stress/decompensation were analyzed. Patients were subdivided into 4 age groups (<2 years, 2-8 years, 8-12 years, 12-18 years). The study was approved by the hospital ethics committee.

Results: 51 valid responses were received. The mean age of the patients was 6.2 years (2 months-18 years), 53,5% women. 11 belonged to Group 1, 23 to Group 2, 7 to Group 3 and 10 to Group 4. All used Hydrocortisone (HC) (except two, with a night dose with dexamethasone) and 21% administered it in solution form. The mean dose was 12.1mg/m2/day (7-24mg/m2/day), with Group 3 having the lowest dose (13.6; 12.4; 11.4 and 13.1mg/m2/day, respectively). 67% of patients administer 3doses/day, the rest 4doses/day. The timing of HC administration was highly variable, 29 patients (55%) administered a dose past 11pm (13.4% even at dawn); 42% administered a higher dose first thing in the morning. In case of stress/decompensation, most doubled or tripled the dose, 7 of them had administered HC IM at home, most due to lack of oral tolerance. Regarding the fludrocortisone replacement, the average dose prescribed was 0.08mg/day, administered in 2 doses in 71% of the patients without changes in age but with a wide variety of schedule.

Conclusions:

- This study shows a global vision of the management of CAH in our country. The doses follow the international recommendations, being lower in periods of greatest growth.
- The diversity in HC dosage draws attention, specially the distribution and schedule, a fact that would indicate the need for a more physiological dosage or to carry out personalized cortisol secretion studies.
- Regarding situations of decompensation, it would be necessary to consider whether to have home access to parenteral HC.

P2-12

Trends in diagnostics and treatment of congenital adrenal hyperplasia

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Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive diseases caused by a deficiency of enzymes responsible for the steroidogenesis. The most common cause is 21-hydroxylase deficiency. There are three forms of CAH due to 21-hydroxylase deficiency: the classic form with salt loss, the classic virilizing and the non-classical form. In pediatric age, CAH is most often manifested by masculinization of the genitals of female newborns, adrenal crisis or premature puberty. Therapy is based on hormone replacement with hydrocortisone and fludrocortisone.

The aim of present study was to analyse changes in the diagnosis and treatment of children with CAH in our centre during previous 15 years. This retrospective cohort study included patients who were diagnosed with congenital adrenal hyperplasia due to 21-hydroxylase deficiency in the period from 2007-2021 in endocrinology service of the Mother and Child Health Care Institute of Serbia "Dr Vukan Čupić". Specifics about disease diagnosis, hormone treatment and genital surgery were collected. Subjects were divided into a group whose diagnosis was made in period from 2007-2014 and another group of those whose diagnosis was made from 2015-2021. Statistical analysis using Hi-square and Mann Whitney U test was conducted using software "IBM SPSS ver. 22", and p values <0.05 were considered significant.

Of a total of 55 patients included in the study, 46 patients (83.6%) had 46XX karyotype. The diagnosis was made in all patients on the base of corticotropin stimulation test. In the second group diagnosis was confirmed by genetic analysis in statistically significantly higher number of children compared to children from the first group who underwent genetic analysis. 49 patients (89.1%) received hydrocortisone therapy and 16 patients received fludrocortisone therapy. In the second group all of the patients with classic form of CAH received fludrocortisone with hydrocortisone, which is statistically significant result. In the second group of patients, genital surgery was performed at later age compared to the first group. In the first group of patients, the mean age at which genital surgery was performed was 9.6 months, while in the second group, the mean age at the time of first genital surgery was 2.2 years.

The presented study findings revealed significant changes regarding the diagnosis and treatment of children with CAH in our tertiary center during the previous 15 years, highlighting the need for constant improvement of care for children with congenital adrenal hyperplasia.

P2-13

Failure to thrive as a manifestation of neonatal cushing

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Failure to thrive is a term used to describe inadequate growth or the inability to maintain growth, which usually occurs in early childhood.

Case Report: female patient, 7 months old, referred to the pediatric clinic of Hospital de Clínicas de Porto Alegre due to a possible syndromic condition. He had no diagnosed comorbidity to date and was using only prophylactic ferrous sulfate and vitamin D. No family history of similar illness. Physical examination showed hypertrichosis on the forehead, cushingoid facies, anthropometry below p1 in the weight and length curve for age and sex, café au lait spots on the face, back, trunk and limbs without crossing the midline, in addition to neuropsychomotor developmental delay. After a suspected diagnosis of McCune-Albright Syndrome (MAS), laboratory tests were performed that showed hypercortisolism (morning serum cortisol 32.8 mcg/dL; overnight serum cortisol 16.8 mcg/dL; overnight salivary cortisol 25.2 mcg/dL; cortisol after dexamethasone 23 mcg/dL; but cortisoluria were negative, as urine collection is difficult in pediatrics). After confirmation of hypercortisolism, a tomography of the abdomen with adrenal protocol was performed, which showed bilateral macronodular hyperplasia of the adrenals. Among the screening exams, bone scintigraphy and echocardiogram were within the normal range and whole body radiography with diffuse osteopenia. Due to the findings, the patient met the criteria for MAS and the treatment performed was laparoscopic bilateral total adrenalectomy, with good postoperative recovery. The patient is currently under regular follow-up at the Pediatric Endocrinology Service, with progressive improvement in development, but still no catch up in growth.

Conclusion: MAS is a rare disease that results from the postzygotic mutation of the alpha subunit of the GNAS gene, which encodes the Gs protein, continuously stimulating the endocrine system. It has a broad clinical spectrum, as it depends on which tissue was affected by the mutation. The diagnosis is clinical and made with the combination of bone fibrous dysplasia and one or more extraskeletal features or the presence of two or more extraskeletal features. These are: café au lait spots with irregular edges and that respect the midline of the body, gonadotropin-independent production of sex steroids which may result in precocious puberty, thyroid lesions with or without non-autoimmune hyperthyroidism, excess growth hormone, hyperphosphaturic hypophosphatemia and neonatal hypercortisolism. Diagnosis is essential for proper treatment and monitoring of other changes that may arise throughout life.

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P2-14

The first case of pediatric Cushing disease in Serbia

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Background: The definition of Cushing disease (CD) is hypercortisolism caused by excess adrenocorticotropic hormone (ACTH) secretion by a pituitary corticotrope adenoma. It is extremely rare in the pediatric population and requires rapid diagnosis and early management.

Case Presentation: A 14-year old boy was hospitalized because of sudden onset of chest pain, loss of consciousness, elevated cardio-specific enzymes, and suspected cardiomyopathy. On admission, he was short stature (-3 SD), obese (BMI 32,9 kg/m2, at +3 SD), with wide and long purple stretch marks on the abdomen and in the axillary region, hypertrichosis of the back, round face, buffalo hump neck, hypertensive (95-99th percentile), tachycardic (HR 109/min) with systolic murmur 3/6, Tanner stage A3, P4, testicles volume 2-3 ml. In the last few years, he has started to gain weight abruptly. His mother noticed that he is shorter than his peers. Easier got bruises and stretch marks on the abdomen have been noticed during the last 6-12 months. Also, the last two years, he withdrew and distanced himself from society, felt depressed, and took antidepressants for a while. In blood analyses, he had metabolic alkalosis, severe hypokalemia, hypophosphatemia, low level of serum immunoglobulins, high blood sugar, and hypercortisolism without circa dial variation. Ultrasound of the heart showed hypertrophic cardiomyopathy with obstruction in LVOT and mild mitral regurgitation. CT and ultrasound of the abdomen displayed hyperplasia of both adrenal glands without pathological masses. We did dexamethasone suppression tests-overnight and prolonged. We didn't obtain suppression of cortisol. After all, we got the result of elevated ACTH. Pituitary MRI described microadenoma of the right half of the adenohypophysis. We consulted an adult endocrinologist and start metyrapone (11β hydroxylase inhibitor). After 2 days of metyrapone therapy, the boy had clinical deterioration due to sepsis caused by Coagulase negative staphylococcus followed by pulmonary edema. We started therapy immediately in the intensive care unit (antibiotics, diuretics, intravenous immunoglobulins, fraxiparine, aminophylline, oxygen therapy) and after 9 days he got recovered. In a month transsphenoidal surgery of the pituitary gland was performed. The tumor was completely removed. The morphological finding, supplemented by immunohistochemistry, corresponds to a neuroendocrine pituitary tumor of corticotropic adenoma type, densely granulated subtype.

Conclusion: CD is a serious disorder, which could be life-threatening, where pediatric endocrinologists have limited experience. A multidisciplinary approach is a key to success in timely diagnosis and therapy.

P2-15

Congenital hyperreninemic hypoaldosteronism due to aldosterone synthase deficiency

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Introduction: The aldosterone synthesis is dependent on aldosterone synthase (AS), an enzyme encoded by the CYP11B2gene, one of the cytochrome P450 enzymes (P450c11Aldo). It catalysis the final steps of adosterone biosynthesis.

Case: A 10 days old boy is presented with poor feeding, jaundice and weight lost. He was born from a 35 years old mother, as 4 th children, from consanguineous parents. One sister and one brother of the mother were died during early infancy from unknown causes. On physical examination his weight was 2600 gr, heart rate 170 /min, blood pressure 72/ 42 mmHg and dehydrated. On laboratory examination, sodium 123 mmol/L, K: 8.66 mmol/L, pH: 7.15 HC03: 13mmol/L. He was hospitalized in intensive care unit and prompt treatment with fludrocotisone 0.2 mg and NaCL was started (8 mEq/kg). First hormonal work up revealed Renin> 150 ng/mL/h, aldosterone < 0,5 ng/dL (5-99), cortisol 24.95 ug/dL, ACTH 2.10 pg/mL and 17-hydroxy progesterone: 0,84 ng/mL. He was diagnosed as aldosterone synthehase deficiency and discharged with NaCL (4*0,5 gr) and fludrocortisone (0,2 mg). Genetic analysis was performed with direct DNA sequence analysis of the entire coding regions of the CYP11B2, c.1382T>C (p.L1461p) homozygote mutation was detected. This mutation was detected in a Turkish patient with CMO I deficiency, the mutation involved a putative heme binding site. In vitro functional expression studies showed that the L461P substutition totally abolished the 18-hydroxylase activity required for conversion of 11-deoxycorticosterone to aldosterone, even though the mutant product was detected in the mitochondrial fraction of transfected cells.

Conclusion: Mineralocorticoid deficiency can be presented with severe salt-wasting with important signs and symptoms of dehydration, feeding difficulties and failure to thrive in the neonatal period. Clinical presentation with typical biochemical profile with hyponatremia, hyperkalemia, normal cortisol and sex steroids, high plasma renin levels and unappropriated normal or low aldosterone levels must suggest the disease. The urgent treatment was life saving and clinical severity decrease with age. Adults are frequently asymptomatic despite no mineralocorticoid therapy. This fact can be associated with a gradual declining dependency on aldosterone during lifetime for normal ionic imbalance due to possible extra-adrenal compensatory mechanisms and alternative ACTH-dependent pathways for mineralocorticoid biosynthesis.

P2-16

Adrenocortical tumor: a rare tumor in children. Report of 2 infants presented with precocious pubarche and rapid growth

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Adrenocortical carcinoma is very rare in children, with annual incidence of 0.21 case per million patient younger than 20 years. At this article I reported two patients. First case was A 16-month-old girl presented with 3 months history of increased appetite and rapid weight gaining, appearance of hair at pubic area for 2 months and acne on face for one-month duration. Parents are non-consanguineous, had no endocrine disorders or tumors. On examination: chubby baby, cushingoid faces, three acne on the forehead, not dysmorphic. Weight and height were above 97th centile. Tanner stage: B1PH3. Enlarged clitoris, length: 2 cm. Investigations: elevated serum cortisol level: 789 nmol/l, low ACTH: < 1 pg/ml, elevated DHEAS: 927 mC/dl (Normal: 16-96 mC/dl) and high testosterone: 5.46 nmol/l. Renal profile and electrolytes: normal. Bone age: advanced= 2 years +8 months. CT abdomen: large left sided suprarenal mass with dimensions of 2.4 x 3.5 x 3.2 cm with no signs of calcifications, infiltration and no metastasis to liver or lungs. Multiple paraaortic lymph nodes were noted. Due to financial concerns of parents, the patient was referred to other hospital, at which left adrenalectomy done. Clinicopathological classification was corresponding with a malignant adrenocortical carcinoma. Adrenolytic therapy was given using mitotane. Father refused to do genetic study to rule out P53 germline mutation. Currently, the patient is on replacement dose of hydrocortisone.

The second case is a 26-month-old boy brought by parents concerned of hair appearance at pubic area associated with smell of adult sweat for 2 months duration. Parents are non-consanguineous. Mother had total thyroidectomy 13 years ago for ??Papillary thyroid carcinoma followed by radioactive Iodine therapy. On examination: chubby baby with cushingoid faces. Both weight and height were above 97th centile. No acne, not dysmorphic. Tanner stage: T1PH3, Stretch penile length: 7 cm, width: 1.2 cm. Investigations: elevated serum cortisol: 650 nmol/l, low ACTH : < 1 pg/ml, high DHEAS : 221 mC/dl (Normal: 11-120 mC/dl) and elevated testosterone: 22.4 nmol/l. Renal profile and electrolytes: normal. Bone age: advanced = 4 years. CT abdomen : well defined mass at Right Adrenal gland measuring 2.5 x 2.7 x 2 cm. Due to financial concerns of parents, the patient was referred to other hospital, at which right adrenalectomy done. Clinicopathological classification was corresponding with a benign adrenocortical adenoma. The patient was on replacement hydrocortisone therapy, weaned later gradually. Currently patient is off treatment.

P2-17

Adrenal Dysfunction in Omani Children Live with Transfusion Dependent Beta-Thalassemia: A Routine Assessment is Recommended

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Introduction: Thalassemia is an autosomal recessive inherited disease that requires frequent blood transfusion. The life expectancy of thalassaemic children improved with regular blood transfusion and chelating agents. Hemosiderin precipitation in endocrine glands of patient with Transfusion Dependant Thalassaemia (TDT) leads to progressive gland dysfunction. The adrenal insufficiency is one of the complications that results from iron deposition either in the pituitary or adrenal glands. It is defined as impaired synthesis and release of cortisol when it is required

Objectives: To detect the prevalence of adrenal insufficiency in Omani Children and young people live with TDT, cared by Sultan Qaboos University Hospital, a tertiary centre in Oman.

Methods: A prospective cross sectional study targeted all patients with TDT who are currently under age of 20 years old. They were evaluated clinically for symptoms and signs of adrenal insufficiency. They had basic laboratory workup including CBC, ferritin level, basal cortisol, and ACTH levels followed by low dose Synacthen test (LDSST) [(dose of 500ng/1.73m^2, equivalent to 0.5 mcg/1.73m^2) x Body surface area (m^2)] to identify patients with secondary or partial adrenal insufficiency. Normal response of the LDSST is considered when the peak cortisol exceeds 550 nmol/L. Inadequate response if the peak cortisol is between 350 to 550nmol/L, and adrenal insufficiency if less than 350 nmol/L, for which patients require regular doses of hydrocortisone replacement therapy and strict follow up.

Results: 90 patients were recruited and 76 (38M: 38F) of them have completed the study. Their mean age was 9.30±4.9 years. The prevalence of adrenal insufficiency is 13.2%, secondary in nature. Majority of the studied patients 57.9% had inadequate response to LDSST (peak cortisol between 350-550nmol/L), indicating partial adrenal insufficiency, for which they require steroid cover only during sick days. Mean serum ferritin level was high among all patients, but highest values were unexpectedly mainly in patients with normal adrenal response to LDSST. Saying that, there was no significant statistical difference for the ferritin level of patients with different adrenal responses ($p < 0.398$). Interestingly, the serum phosphate level was significantly higher in adrenal insufficiency group compared to others ($p < 0.008$), however it remained within the normal range.

Conclusion: Routine assessment of TDT patients for adrenal insufficiency is highly recommended, as early detection of adrenal insufficient patients and implementing an appropriate treatment plan may results into saving lives and reducing the possibility of unexpected adrenal crisis for TDT patients during intercurrent infection or illnesses.

P2-18

Bilateral adrenal hemorrhage as a cause of pediatric acute abdominal pain

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Introduction: Bilateral adrenal hemorrhage is a rare pathology, contrary to what happens with unilateral ones. It is more common in newborns and associated with situations of perinatal hypoxia, sepsis, traumatic births, or coagulation abnormalities. The classic triad includes jaundice, anemia, and a flank mass, which can lead to severe shock. Extensive bilateral hemorrhage is required to produce a situation of adrenal insufficiency. The diagnosis is made by imaging techniques (ultrasound or CT) and requires ruling out the different causes mentioned. Treatment is usually supportive (fluid therapy, phototherapy, transfusions and replacement therapy).

Case Report: Two pediatric patients with acute abdominal pain are presented. Both required admission to the Pediatric Intensive Care Unit (PICU). The diagnosis was adrenal insufficiency with bilateral adrenal mass was noted on imaging test.

Patient. 1. A 10-year-old girl with no important medical history. She started with symptoms of high fever, abdominal pain, weakness and vomiting. On physical examination general condition was affected and she showed signs of peritoneal irritation. A blood test was performed showing signs of infection. Abdominal ultrasound and CT showed image of mesenteric infarction and bilateral adrenal mass. She was admitted to Intensive Care Unit with arterial hypotension and hyponatremia. Due to the suspicion of adrenal insufficiency, blood tests were taken with data of primary adrenal insufficiency. Therapy with stress-dose hydrocortisone was started. She does not require surgical intervention. Coagulation study and infectious screening were normal. Currently, after one year, she maintains hydrocortisone at a replacement dose due to primary adrenal insufficiency.

Patient 2. A-10-year-old boy with a medical history of primary autoimmune thrombocytopenia. Clinic of 2 weeks of evolution of weakness, abdominal pain, headache and vomiting. He shows signs of dehydration and peritoneal irritation. With the suspicion of acute abdominal pain, blood test were performed with no signs of infection and showed hyponatremia, thrombocytopenia and coagulopathy. Abdominal ultrasound and CT showed image of mesenteric ischemia and bilateral adrenal mass. He was admitted to the Intensive Care Unit, blood tests were extracted showing data of primary adrenal insufficiency, and treatment with stress-dose hydrocortisone was started. Anticoagulant lupus in coagulation study. Good evolution with replacement dose of hydrocortisone and anticoagulation.

Conclusion: In the presence of abdominal pain of unknown etiology, clinical suspicion is important to detect adrenal insufficiency in patient with risk factors or suggestive data in imaging test.

P2-19

A case series on Adrenal Cortical Tumors in Children, Experience from Colombo, Sri Lanka

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Introduction: Paediatric adrenocortical tumors (ACT) include both benign adenomas and highly virulent malignant tumors. However, it is very rare among children. The aim of this study is to evaluate the clinicopathological data of children presented with ACT and to assess the survival.

Methods: This is a retrospective cohort study which includes patients diagnosed with ACT from August 2020 to July 2021 and followed up at Lady Ridgeway Hospital, Colombo.

Results: 5 children were diagnosed with adrenal cortical tumors during the study period. The age of them ranged from 10 months to 6 and half years. 4 of them were boys and the oldest one was a girl. All of them were presented with features of gonadotrophin independent precocious puberty; boys with increased stretched penile length, increased body hair and voice changes, and the girl with clitromegaly. One boy phenotypically had features of Beckwith-wiedemann syndrome but not genetically confirmed. The median time duration of diagnosis since the onset of symptoms was 4 months. 3 out of 5 children had rapid height and weight gain. 3 of them had hypertension requiring anti-hypertensives. The preoperative diagnosis was made through clinical manifestations, elevated DHEAS levels and enlarged supra renal masses in CT. All 4 boys had right side supra renal masses while the girl had it on the left side. All underwent surgery for tumor resection. The diagnosis was confirmed based on the histopathology of the adrenal specimens. None of them were malignant tumors. The youngest developed adrenal insufficiency following surgery requiring corticosteroid replacement. To date, all 5 of them are doing well without any disease recurrence.

Discussion: Even though these tumors are rare, an increased number of cases are detected in Brazilian children due to specific gene mutations. There are two peak times for presentation, during the 1st 2 years of life and peripubertally. Girls are more predominant to develop ACT though we have a different sex predominance in our study. Most of the ACT are functional in children and 80-90% of them have endocrine manifestations at the diagnosis. Viralization is the commonest presentation but 10-15% will present with Cushing's syndrome. Histopathology is essential to distinguish adenomas from carcinomas.

Conclusion: It is important to consider adrenal tumor as a possibility when children present with precocious puberty. To ensure early diagnosis, we need to raise awareness about the signs of viralization among parents and the general-public.

P2-20

Autoimmune polyglandular syndrome type 2: Two different applications

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Autoimmune polyglandular syndrome (APS), on the other hand, is a cluster of endocrine disorders resulting from immune dysregulation, often accompanied by damage to non-endocrine organs. There are 2 types of APS: type 1 and type 2 (APS-1 and APS-2). Type 2 APS is characterized by the development of organ- and tissue-specific antibodies. In those with Addison's disease, antibodies to the 21-hydroxylase enzyme found in the adrenal cortex are present in more than 90% of patients. It should be known that autoantibodies will be found positive before clinical disease development.

Our first case, a 16-year-old male patient, applied to the emergency service with the complaints of drinking a lot of water for 3 weeks, urinating a lot, rapid weight loss, weakness, dizziness and nausea in the last week. The fact that the patient's autoimmune adrenalitis findings appeared at a relatively late age and was associated with type 1 diabetes suggest APS type 2, and 21 hydroxylase antibodies in our case were found to be 42.20 U/ml. Our patient is being followed up in our outpatient clinic. Our second case was admitted to our emergency department at the age of 7 years and 10 months with the complaint of abdominal pain. As the laboratory tests revealed glucose: 84 mg/dl, Na: 108 mmol/L, F: 4.03 mmol/L, HGB: 8.8 g/dl, Na-increasing fluid therapy was started and ACTH and cortisol were studied with a preliminary diagnosis of adrenal insufficiency. ACTH: We started hydrocortisone and fludricortisone treatments for our patient with cortisol renin aldosterone. Since our patient had congenital hypothyroidism with follow-up and the addition of primary adrenal insufficiency, we ran 21 hydroxylase antibodies and it was found to be 46.70 U/ml positive. Our patient is currently 16 years old and is still being followed up in our outpatient clinic. It is noteworthy that our first case presented as diabetic ketosis, but there were signs of adrenal insufficiency after laboratory and physical examination. It is noteworthy that autoimmune adrenalitis was present at the time of initial diagnosis, newly diagnosed Type 1 diabetes, and there was no such case described in the literature. In our second case, both the presence of autoimmune adrenalitis and the presence of thyroiditis support APS type 2, and the development of thyroiditis first and then adrenalitis is both important and important to keep in mind.

P2-21

Abstract Withdrawn

P2-22

Two Familial Cases of Congenital Adrenal Hyperplasia Combined or Complicated with Central Precocious Puberty

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Central precocious puberty (CPP) may be secondary to congenital adrenal hyperplasia (CAH), due to 21-hydroxylase deficiency. CPP in CAH may be associated with elevated sex-steroid levels and possibly a decline in negative sex-steroid feedback after treatment initiation.

We experienced the two family cases of the salt-wasting form of the CAH, complicated by CPP with early maturation of the hypothalamic-pituitary-gonadal axis in all patients from two families.

Family 1: Patient 1. The diagnosis of the salt-wasting form of CAH was established at the age of 4. Replacement therapy with glucocorticoids and mineralocorticoids was assigned. At the age of 6, the growth velocity was 9 cm/y, sexual development matched 3 stage by Tanner's classification. CPP was diagnosed and therapy with prolonged analogs of gonadotropin-releasing hormone has been assigned. Patient 2. Diagnosis CAH, salt-wasting form, was established at the age of 2. Replacement therapy with glucocorticoids and mineralocorticoids was assigned. After 6 months, both clinical and laboratory investigations were done. By the time, there was also noticed the presence of central precocious puberty, and a gonadotropin-releasing hormone stimulation test was carried out, which showed a pubertal response. The molecular genetic examination of the gene CYP21A2 to common mutations determined mutation I2spl in homozygote form in two brothers.

Family 2: Patient 1. At the age of 2 salt-wasting form of CAH was diagnosed treat form within glucocorticoid and mineralocorticoid was started. Acceleration of bone age continued. After 1 year of CAH treatment, CPP was established and treatment was started. The brother of this girl also has CAH and the diagnosis was made at birth. Treatment was started immediately. But at the age of 4 diagnoses of CPP was established and treatment of CPP was initiated. CAH was confirmed by genetic analysis, mutation of V281L in homozygote form in sister and brother was found.

Conclusion: CPP can be a complication of CAH due the to late age of diagnosis, especially in countries where a routine neonatal screening program for this condition is missing. Regarding our first family, the diagnosis of two brothers also was delayed. But in the second family diagnosis of brother was established at birth and treatment was started immediately. Despite it, CPP started. Further studies are needed to examine the possible contribution of genetic factors.

P2-23

Primary pigmented nodular adrenocortical disease in a young boy associated with a rare somatic mutation of the PRKACA: Case report and literature review

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Introduction: Cushing's syndrome(CS) is rare in the pediatric population, and the cause vary with age. Primary pigmented nodular adrenocortical disease (PPNAD) is one of the causes of CS, though it is a rare disorder. It has been proposed that in children with CS, PPNAD should be suspected. Here we report a young boy with CS due to PPNAD associated with a somatic mutation of the PRKACA.

Case Presentation: The child was marked by growth arrest and weight gain for 6 months. No family history or chronic diseases in the past. Physical examination showed: height 112.6cm (-2.2SD), wight 39.1kg(+2.9SD), moon face and obesity, hirsutism but no abdominal striae. BP 90/69 mmHg. 8 Am cor 20.10 ug/dL, 0Am Cor 18.50 ug/dL, 8Am ACTH <0.22 pmol/L. A 2 days sequential Liddle's test revealed the paradoxically increased urinary cortisol levels from baseline(576.60 ug/24h to 1423.36 ug/24h). Magnetic resonance imaging (MRI) showed bilateral adrenal enlargement, mainly on the left side. Thyroid fuction was normal. Thyroid nodular(TR2) was found by thyroid ultrasound. Laparoscopic unilateral adrenalectomy was performed. CS remission was achieved after operation. And the Histological examination showed nodules in the adrenal cortex. Lipofuscin pigment in the cytoplasm was found in some cells. DNA analysis revealed a copy number duplication mutation in the PRKACA in the adrenal. However, genetic testing including the PRKACA and carney complex was negative of the boy and his parents. So a somatic mutation chimera was speculated. According to literature search, the most common PPNAD-related gene mutations reported are PRKAR1A, PDE11A, PDE8B in peripheral blood. Recently, a case of somatic mutation of PRKAR1A leading to PPNAD was reported, which suggested that somatic mutation may be the genetic background of sporadic PPNAD. PRKACA mutation is a rare cause of PPNAD. So far, only several cases of germline mutation have been reported, while somatic mutation has not been reported.

Conclusion: PPNAD should be considered as one of the reasons of CS in young children, though it is rare. This article is the first to report a rare case of PPNAD in children caused by somatic mutation of PRKACA, which enriches the datas on the relationship between clinical phenotype and genotype in such rare diseases, having guiding significance for the diagnosis and treatment of PPNAD.

Keywords: Non ACTH dependent Cushing's syndrome; primary pigmented nodular adrenocortical disease; PRKACA; protein kinase A(PKA).

P2-24

Long-Term Follow-Up of a Case with Clinical Image Syndrome

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Introduction: IMAGE Syndrome (#614732) is an autosomal dominant inherited syndrome as a result of CDKN1C mutation characterized by the association of intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies. Here, long-term follow-up of a case with clinical IMAGE syndrome, no genetic mutation was detected, will be presented.

Case: A three-month-old baby boy was brought with the complaint of respiratory distress. He was born at 33 weeks and 950 grams due to oligohydramnios, TSH: 16 μIU/mL, fT4: 7.6 ng/L was found at the 28th day, and L-T4 treatment was started in an external center. His parents were third-degree relatives. When his corrected age was one-month, his weight was 2.2 kg (-3.25 SDS), height was 45.7cm (-3.07 SDS), head circumference was 35 cm (-2.07 SDS) with syndromic facial appearance. His testicles were not palpated, but were observed in the inguinal canal on ultrasonography. ACTH: 766 pg/mL (0-46) and cortisol: 3.36 μg/dL (4.9-16.8) were measured due to hyperpigmentation. Causes of primary adrenal insufficiency were screened and excluded. Adrenal glands were normal on ultrasonography. Hydrocortisone was started. Since plasma sodium was 134 mEq/L (135-143) and urine sodium was 128 mmol/L, fludrocortisone was added in the follow-up. The patient had recurrent lower respiratory and urinary tract infections in the follow-up.

Growth hormone (GH) stimulation tests were performed due to decreased growth rate and inadequate responses (4.91/5.3 ng/mL) were obtained. GH treatment was started when he was $5^{9/12}$-years-old, with a bone age of 2-years and a height of 93.5 cm (-4.56 SDS). When he was 8-years-old, GH treatment was discontinued because his family did not want to continue the treatment (height: 106.2 cm, -3.87 SDS).

In the nephrology follow-up due to recurrent urinary tract infection, renal calculi was detected at the age of 6.5 years, and a double-J-stent was inserted when he was 8-years-old due to bilateral hydroureteronephrosis.

The patient, who was 10-years-old at the last control, weight: 18.2 kg (-3.91 SDS), height: 120 cm (-3.07 SDS), and he was prepubertal. The karyotype was 46,XY and CDKN1C mutation was negative. Since there is no renal calculi in MIRAGE syndrome, it was not planned to examine SAMD9 mutation.

Conclusion: We present the long-term follow-up of our case, whose clinical features are compatible with IMAGE syndrome, in terms of phenotype&genotype relationship, but no mutation was found in the CDKN1C gene, and whose advanced genetic examination continues.

P2-25

Premature adrenarche: A common disease with a novel presentation

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Introduction: Premature adrenarche refers to appearance of pubic hair and sometimes axillary hair before eight and nine years in girls and boys respectively. The most constant sign is the appearance of pubic/axillary hair. Furthermore, other signs of androgen effect (adult type body odor, acne, greasy hair, accelerated statural growth) are valuable to complete the diagnosis. However, it is important to be mentioned that no virilization signs are associated with this disorder. Its diagnosis is settled after exclusion of the causes of androgen excess such as simple virilizing congenital adrenal hyperplasia, adrenal and gonadal androgen producing tumors and exogenous androgens.

Case Presentation: A 7-year-old girl was referred with a six months history of itching in the peri-anal area. The mother noticed presence of hair in this area. Thus, she sought medical advice. No history of any local treatment for this area. Her height was on the 50th centile, while her weight was on the 75th centile. Examination revealed normal female genitalia with no ambiguity or hyperpigmentation. Using Tanner staging for pubertal development assessment, breast was T1 (no breast development), no pubic hair or axillary hair. There were long, dark and coarse hairs noted in the perianal area. Hormonal assessment revealed normal basal and post ACTH stimulation cortisol and 17-OH progesterone levels. Furthermore, she had normal androstenedione, testosterone. Although, DHEA-s was slightly elevated than normal for age and sex. Bone age was within average for chronological age (not advanced). Ultrasound on adrenal glands and internal female genitalia was unremarkable. Thus, she was diagnosed as premature adrenarche and no treatment was given for the girl. After two months, she developed fine hair on labia majora. So, adrenal protocol CT was done and was unremarkable. After six months of follow up, the course was stationary with no new clinical signs.

Conclusion: Peri-anal area examination should be put into consideration during examination for assessing pubertal development. Furthermore, peri-anal hair may be an early sign for premature adrenarche.

P2-26

3 β-Hydroxysteroid Dehydrogenase Deficiency, Rare in the Diagnosis of Congenital Adrenal Hyperplasia: A Case Report

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A defect in one of the 5 enzymes related to the cortisol biosynthesis pathway (cholesterol side chain degradation enzyme, 3-beta-hydroxysteroid dehydrogenase, 17-hydroxylase, 21-hydroxylase and 11-hydroxylase) is responsible for the formation of KAH. Congenital Adrenal Hyperplasia (CAH) is seen in newborn babies with a frequency of 1/10,000-16,000. The most common 21 hydroxylase enzyme deficiency. 3-β-hydroxysteroid dehydrogenase (3βHSD) deficiency is a rare form of KAH caused by defects in the HSD3B2 gene located on chromosome 1p12, which is primarily expressed in the adrenal glands and gonads. Normally, 3βHSD catalyzes the conversion of pregnenolone to aldosterone, 17-hydroxypregnenolone (17OHPreg) to cortisol, and dehydroepiandrosterone (DHEA) to androstenedione. Defects in HSD3B2 block the conversion of precursor hormones leading to the accumulation of metabolites. We present here a 6-year-old female patient with a rare and previously unidentified 3-β-hydroxysteroid dehydrogenase (3βHSD) deficiency.

A 6-year-old girl who was diagnosed with KAH at the age of 2 months in another center applied to the pediatric endocrinology outpatient clinic for follow-up and treatment. The patient, who was followed up for dehydration and vomiting, was investigated because of the large size and hyperpigmentation in the labium majus in the physical examination, and she was diagnosed with KAH. Karyotype examination was reported as 46.XX. 21 hydroxylase enzyme deficiency, which is the most common cause of KAH, was examined but found to be normal. In the examinations performed when she applied to us, she was reported as homozygous for Aldosterone: 1.31 pg/ml, 17OHP: T(p.Arg335*) mutation. The patient is currently 14 years old and is being followed up in our outpatient clinic.

Although 21 hydroxylase enzyme deficiency is the most common type, 3βHSD deficiency should also be considered in the differential diagnosis since it can cause adrenal crises. Although 3βHSD deficiency can occur with adrenal crisis like classical CAH, it is particularly interesting that the mutation could not be detected early. Considering the relationship between genotype and degree of enzymatic activity when we examine similar cases, a small but insufficient residue that provides some protection in early life is thought to have activity. However, future functional studies or identification of this mutation in other cases will help clarify this point. In conclusion, 3βHSD deficiency has a variable phenotypic presentation and early diagnosis is crucial. Newborn screening is unlikely to detect 3βHSD deficiency. Genetic investigation of affected individuals in terms of 3βHSD deficiency should be kept in mind in undiagnosed patients.

P2-27

It is not always a piece of cake!!

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Introduction: Congenital lipoid adrenal hyperplasia (lipoid CAH),is a rare subtypes of adrenal hyperplasia yet the most fatal form, which seriously disrupts adrenal and gonadal steroidogenesis by a defect in the conversion of cholesterol to pregnenolone. Affected patients show salt loss from impaired mineralocorticoid and glucocorticoid synthesis. The defect in lipoid CAH is mainly in the steroidogenic acute regulatory protein (StAR), which

promotes entry of cholesterol into mitochondria, where it becomes the substrate for the cholesterol side-chain cleavage enzyme, P450scc1. Most patients have female external genitalia regardless of chromosomal sex and have evidence of salt loss in the first year of life and usually within the first 2 months.

Case Presentation: A 7-day-old 46,XX neonate presented with severe adrenal insufficiency; hyponatremia, hyperkalemia, hypovolemic shock and hyperpigmentation. Congenital lipoid adrenal hyperplasia was diagnosed after detection of steroidogenic acute regulatory gene mutations.

Conclusion: Lipoid CAH is the most fatal form of CAH. Most cases of lipoid CAH are caused by recessive mutations in the StAR gene. Gene sequencing is the only definitive diagnostic method.

Bone, Growth Plate and Mineral Metabolism

P2-28

Longitudinal assessment of bone health index (BHI) as a measure of bone health in short-statured children before and during treatment with recombinant growth hormone

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Introduction: Bone Health Index (BHI) determined by measurement of cortical thickness of metacarpalia II-IV in x-rays of the left hand represents a method to estimate bone health in children. Aim of this study was to investigate changes of BHI SDS in the course of growth hormone (GH) treatment.

Method: 256 consecutive children with short stature (isolated GH deficiency (IGHD) n = 121, multiple pituitary hormone deficiency (MPHD) n = 49, intrauterine growth retardation (small for gestational age (SGA)) n = 52, SHOX (short stature homeobox gene) deficiency n = 9, Ullrich Turner syndrome (UTS) n = 25) and start of treatment with GH between 2010 – 2018 were included. Repetitive BHI SDS were analysed retrospectively by BoneXpert software in X-rays of the left hand routinely taken for bone age determinations (Greulich & Pyle). Relevant clinical data (anthropometry, IGF1 concentrations) were extracted from the electronic patient charts. Results are presented as median (25%/75% interquartile ranges).

Results: Before the start of GH therapy, the BHI SDS was decreased and similar in all patients regardless their diagnoses(-0.97; -1.8/-0.3); bone age according to Greulich and Pyle was retarded (-1.6 years; -2.31/-0.97) compared to chronological age; height velocity SDS (-1.68; -2.52/-1.01) as well as serum IGF1 (SDS -1.90; -2.68/-1.20) were decreased; BHI SDS were not correlated with retarded bone ages (r=0.02; p=0.753) or height SDS (r =-0.088; p=0.171).

BHI SDS increased to -0.17 (-1/0.58) after 1.5 years (0.5-1.49; p=<0,01) of GH treatment. Thereafter BHI SDS (-0.2; -1.00/0.50) remained unchanged and similar in all patients throughout the study period (5.3 years; 3.45/7.25). BHI SDS correlated with height velocity SDS and serum IGF-I SDS in the course of GH treatment.

Retardation of bone age did not change significantly after 1.5 years (-1.64; -2.40/-1.05; p=0,49) but improved after (-0.66 (-1.52/0.14; p=<0,01 at the end of study). Catch-up growth was most pronounced in the first year of treatment (height velocity SDS 2.12 vs. SDS 0.31 at the end of study). Serum IGF 1 levels normalized within 1.5 years (SDS 0.10; -0.70/0.70) and remained unchanged thereafter (SDS 0.2; -1.00/0.90).

Conclusion: BHI SDS are reduced in GH naive children with short stature regardless of the etiology, increase initially after GH start with plateauing thereafter indicating sustained bone health and correlate with height velocities and serum IGF-I during GH treatment. Thus, bone health as estimated by BHI represents a relevant target of GH therapy in children.

P2-29

Benign family hypercalcemia: A case report

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The calcium-sensing receptor (CaSR) is a member of the G protein coupled receptor family. It is mostly found in the parathyroid gland and renal tubule. CaSR disorders occur with inherited or acquired mutations. Familial hypocalciuric hypercalcemia syndromes are associated with inactivating mutations in CaSR. The heterozygous form is "benign familial hypercalcemia" and the homozygous form is "neonatal hyperparathyroidism". In this article, "benign familial hypercalcemia" cases are presented and it is emphasized that asymptomatic cases can be encountered incidentally.

A 10 year old male patient was referred to our outpatient clinic due to high calcium levels. In the evaluation; there was no consanguinity between the mother and father of the patient, whose height was 142.3 cm (50-75p), and weight was 41.9kg (75-90p). His general condition was good, and system examinations were normal. Systolic and diastolic blood pressures were within normal limits for age. In the blood tests of the patient, Ca: 11.31 mg/dL, ALP: 306 U/L, Mg: 2.15 mg/dL, P: 3.65 mg/dL, PTH: 73.6 ng/L, 25(OH) vitamin D: 11.4 ng/mL, fT4: 1.13 pg/mL, TSH: 3.27 mU/L and urinary calcium/creatine: 0.01 mg/dL. After detailed evaluations and DNA sequence analysis, CASR gene c.2532_2539delCAGCTTT (p.Ser845fs*133) mutation was detected as heterozygous. This variant was evaluated as a 'probably pathogenic variant' explaining the patient's clinical findings. After the patient's detailed family history, detailed physical examination and laboratory tests were performed on his sister, who was older than her age. Ca: 11.7 mg/dL, ALP: 325 U/L, Mg: 2.1 mg/dL, P: 5.4 mg/dL, PTH: 12.3 ng/L, 25(OH) vitamin D: 29, urinary calcium/creatine: 0.01 mg/dL.

Genetic analysis was performed and the same mutation was found in his sister. Genetic analysis was performed in the mother and grandmother in the family with familial benign hypocalciuric hypercalcemia, and the same CASR mutation was found.

After the patients were hydrated, no additional problems were encountered. The follow-up of the patients continues in our outpatient clinic.

Considering the diagnosis of familial benign hypocalciuric hypercalcemia in a patient with hypercalcemia after evaluating all the factors that may affect calcium metabolism, the familial history of these cases and similar clinical findings will often distract the physician from misdiagnosis. In the diagnostic approach of hypercalcemia, it will be beneficial to keep the diagnosis of familial benign hypocalciuric hypercalcemia in mind.

P2-30

Long QT revealing hypoparathyroidism in a B thalassemic major

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Introduction: Beta thalassemia major (BTM), a hereditary haemoglobinopathy due to a deficiency in the synthesis of beta-globin, leads in the homozygous state to severe anemia requiring regular transfusions associated with chelator treatment.

The endocrine complications encountered in BTM, secondary to martial overload by direct damage to the glandular parenchyma, continue to be observed in our consultations, although early and well-managed chelation can reduce their frequency and delay their appearance. Among these complications, hypoparathyroidism (HPT) is rarely found.

Case Report: A 20 year old female patient presented with BTM since the age of 6 months, under regular transfusion regime without adequate chelation therapy due to its unavailability. She presented in consultation for repeated malaise with lipothymia where a prolongation of the QT space was found on the ECG. The etiological diagnosis revealed severe hypocalcemia (corrected calcinemia 45mg/l) with low PTH. Further investigations revealed hypogonadotrophic hypogonadism, primary hypothyroidism, vitamin D deficiency and osteoporosis. Martial overload was confirmed with a ferritin level of 5044 ng/dl.

The patient was put on vitamin-calcium treatment, thyroid and gonadal replacement therapy. Bisphosphonates were proposed after normalization of the phosphocalcic balance.

Conclusion: Hypoparathyroidism manifests itself beyond the 2nd decade in BTM patients, often asymptomatic, but sometimes reveals itself by a decompensated cardiomyopathy. The seriousness of such consequences underlines the importance of monitoring the phosphocalcic balance once a year from the age of 10 years in all BTMs.

P2-31

Short stature and single central incisor of the upper maxillar: Pathogenic variant in the SHH gene

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Introduction: The Sonic Hedgehog (SHH) gene is involved in the development of midline structures. Pathogenic variantd in this gene have been associated to holoprosencenphaly 3; Microphthalmia with coloboma 5; Schizencephaly; and Single median maxillary central incisor syndrome (SMMCIS). All of them are inherited in an autosomal dominant pattern and exhibit incomplete penetrance as well as variable expressivity.

Case Report: A 6-year-old girl in follow-up in our clinics for postnatal short stature and congenital microcephaly. Neonatal anthropometry was normal (weight -1.81 SD, length -1.5 SD) except for the presence of microcephaly (HC -2.56 SD). At birth, she required admission to neonatology due to generalized cyanosis coinciding with infancy, a CT scan of the paranasal sinuses was performed and anterior mucosal thickening of the nostrils was diagnosed. In addition, he has required follow-up in Nephrology due to unilateral pyeloureteral stenosis, in Cardiology due to interventricular communication and in Neurology due to ADHD. Physical examination revealed a weight -2.26 SD, height -2.17 SD, WC -5.89 SD, sitting height -0.77 SD and normal fathom, as well as a single upper central incisor (Image 1) and a deviation of the nasal septum without other dysmorphic features. On the other hand, the mother presents a similar phenotype without single central incisor but a height of -3.13 SD.

It was requested a karyotype and cerebral MRI, without anormal findings. We performed a skeletal dysplasias panel using Next Generation Sequencing (NGS). A pathogenic variant in the SHH gene (NM_000193.3:c.449C>T; p.(Thr150Met)) was found. It is not previously described in the literature. Segregation study has been requested from the parents and sister.

Discussion: Phenotypic spectrum of SHH gene include the presence of holoprosencephaly, microcephaly (33%), facial dysmorphisms (midfacial hypoplasia, hypotelorism, flat nasal root, cleft lip/palate and a single upper central incisor), congenital obstruction of the nasal airway (90%), hypopituitarism (15%), short stature and intellectual disability (50%). It also has being associated cardiac or genitourinary malformations with less frequency.

Conclusions: The non-pathological brain imaging and the presence of single upper central incisor, short stature, microcephaly, alterations of the nasal airway, cardiac malformations and genitourinary malformations makes SMMCI the most plausible diagnosis.

P2-32

A novel pathogenic variant in PLS3 causing severe osteoporosis and vertebral fractures in an adolescent

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Introduction: Bone fragility or predisposition to fractures with low-impact energy is a rare but potentially limiting condition. Variations in PLS3 gene are a cause of monogenic osteoporosis due to the alteration of osteoclast and osteocyte function and bone mineralization. It is characterized by early-onset osteoporosis, peripheral fractures, vertebral compression fractures and thoracic kyphosis. Due to its X-linked inheritance, the phenotype is more severe in males.

We report an adolescent with severe multiple vertebral fractures associated with a novel pathogenic variant in the PLS3 gene.

Case Report: A 11-years old male consulting due to chronic lumbar pain (last six months), which limited normal life activity. He had a history of five previous non-simultaneous long bone fractures. He denied high energy impacts. He was born at 36-week gestational age with a normal birth length (+1.41 DS) and weight (+2.2 DS). He received Vitamin D prophylaxis the first year of life. Psichomotor development was normal and had no chronic treatment. His father and mother were both healthy with heights of 186 cm and 168,5 cm respectively and denied consanguineity. Non familiar history of fractures, joint or vertebral column problems. Our patient´s height and weight were normal, but he presented a wide arm-span (103%) and a reduced trunk height to standing height ratio (-0.27 DE). He had hypoplastic tooth enamel and hyperkiphosis. On the contrary, he had white sclarae, and no dismorphic features or joint hyperlaxity.

X-ray and magnetic resonance (MR) revealed dorsolumbar shortened biconcave vertebrae and multiple fractured vertebrae. The lumbar and neck bone mineral density (BMD) was under normal values for sex, age and height. Calcium, phosphate, magnesium, 25-hydroxyvitamin D, intact parathiroid hormone, phosphatase alkaline and urinary phosphoethanolamine levels were in normal range by sex and age. Only procollagen type I N-terminal propeptide, osteocalcin and urinary calcium/creatinine were increased at diagnosis (1100 ng/dl, 85.8 ng/dl and 400 mg/g respectively).

The bone fragility NGS panel identified a hemizygous variant (c.1761-1G>T) at intron 15 of PLS3 gene. It is located in a canonical splice acceptor of intron 15 and could predict an abnormal RNA processing and an aberrant protein and was classified as pathogenic. Segregation study showed that same variant in his mother.

Comments: Patients with multiple fractures or chronic bone pain need to be assessed for bone fragility entities. A shortened trunk, increased arm-span or low sitting height/standing height ratio are alarming signs of vertebral problems.

P2-33

Maternal Vitamin D deficiency leading to Rickets, Cardiomegaly and Unusual Metabolic Acidosis in a Term Infant: A Case Report

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Introduction: We describe a 4 month old term infant of a vitamin D deficient mother who presented with bronchopneumonia and cardiomegaly needed respiratory support. Despite resolution of bronchopneumonia he had persistent normal anion gap metabolic acidosis. In the process of investigating into symptomatic hypocalcaemia revealed rickets with 25-hydroxy-vitamin D (Vit D) deficiency and high parathyroid hormone (PTH) which led to distal renal tubular acidosis. Biochemical, radiological resolution and disappearance of cardiomegaly were demonstrated with adequate vitamin D treatment.

Case Report: A 4month old previously well baby boy presented with a 3 day history of cough, fever and tachypnea. He was diagnosed to have bronchopneumonia and cardiomegaly needed ventilation. Echocardiogram revealed left ventricular dilatation. He had normal growth with exclusively breasting. Despite the settlement of respiratory infection his tachypnea persisted. He developed carpopedal spasms.

His blood gases revealed normal anion gap metabolic acidosis. Chest x-ray revealed osteopenia and rachitic rosary. Serum ionized calcium was 1.37 mmol/l (normal range 2.2-2.7mmol/L) with low phosphate levels 0.57mmol/L (1.45-2.16) and high alkaline phosphate (ALP) level of 1230IU/L. From the same serum sample PTH level was very high 891.4pg/ml (7.5-53.5) and Vit D level came as 28nmol/l (<30nmol/l deficient). He was acutely managed with IV 10% Calcium gluconate followed by oral calcitriol 250 ng twice daily and titrated according to corrected calcium. The baby was started on Vit -D3, 2000IU/day with calcium carbonate 250mg twice daily.

Further clinical evaluation large anterior fontanel, widening of wrists were noted. X-ray of wrist showed classical metaphysical widening, fraying, splaying and cupping. The diagnosis of vitamin D deficient rickets was made. However normal anion gap

metabolic acidosis persisted (PH-7.223, HCO3-12 mmol/l, CO2-21 mmHg). urinary PH was 6.5 and urine electrolytes were normal. USS KUB didn't show evidence of nephrocalcinosis. Mother's Vit D level was 48nmol/l, which was insufficient with normal calcium and alkaline phosphatase levels and started on Calcium and vitamin D supplements.

After 3 months of therapy, treatment response has been demonstrated with normalization of biochemical markers, blood gas and normal cardiac status, with vitamin D3 treatment and calcium supplementation.

Conclusion: This is a rare manifestation of nutritional rickets in an infant due to maternal vitamin D deficiency with cardiomegaly and PTH induced distal renal tubular acidosis. Vitamin D deficiency is possible as a result of poor maternal stores. Prompt management with Vit D and calcium supplementation will help to achieve quick clinical recovery.

P2-34

Optimal 25-OH-Vitamin D level in children derived from metabolic parameters

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Context: Optimal levels of 25-OH-Vitamin D (25OHD) for children are unknown. Prevalent population levels of 25OHD are likely to be sub-optimal since sun exposure is reduced in modern living.

Objective: To deduce recommended levels of 25OHD by testing, in children, the level at which 25OHD optimally effects calcium, phosphate and parathyroid hormone levels in a population-based data.

Design: An observational retrospective "big-data" study.

Methods: We analyzed 49,935 25OHD tests from children sampled in Clalit Health Services, Jerusalem district between 2009 and 2019. Associated data were available in the following number of samples: corrected calcium – 18,869, phosphorus – 1,241, calciumXphosphorus product – 698, and PTH - 449. We tested correlations between each parameter and 25OHD.

Results: There was a positive correlation between 25OHD levels and each of the parameters tested. The level at which increase in 25OHD continued to cause significant alteration in the corresponding parameter was: 1. For calcium – beyond 100 nmol/l (40 ng/ml), 2. For phosphorus up to 100 nmol/l (40 ng/ml), beyond this there was no further increase, 3. PTH there was a significant negative correlation up to 100 nmol/l. Beyond this, the trend continued the numbers were too small to reach significance.

Conclusion: 25OHD levels above 100 nmol/l are associated with improvement in parameters known to be associated with increased bone mineralization. Therefore, one should aim for a 25OHD level of 100 nmol/l or above.

P2-35

Parathyroid Hormone and Its Relationship to Calcium, Magnesium, and Phosphate in Children age 2 – 5 years old with Abnormal Levels of Vitamin D

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Background: Parathyroid Hormone (PTH), a key regulator of calcium and phosphorus homeostasis through its effect on bone, kidney, and intestine. The serum concentration of PTH is derived both from the release of PTH stored in secretory granules and from de novo synthesis of PTH in response to alterations in the serum levels of calcium, phosphorus, and vitamin D. Magnesium has a potent role in secretion of PTH, while alkaline phosphatase appears to be important biochemical marker of bone formation and involving in PTH disorders.

Method: A cross-sectional study was conducted in 80 children aged 2 – 5 years old with level of vitamin 25(OH)D < 30 ng/mL. Anthropometric and laboratory test including magnesium (Mg), calcium (Ca), phosphorus (Ph) and alkaline phosphatase (ALP) level were assessed. The reference values of vitamin 25(OH)D used in the present study were as follows: <20 ng/mL (deficiency), 20-29 ng/mL (insufficiency), 30-100 ng/mL (sufficiency), and > 100 ng/mL (increased). Anthropometrics were evaluated using WHO child growth standards.

Results: From 80 children included, the age means value 3,53 ± 0,90 years with minimal age in 2 years and maximal age in 5 years, consist of 37 (46,3%) boys and 43 (53,8%) girls. According to WHOCGS: 32 (40%) were stunted (height/age < -2SD), 31 (38.8%) were severely stunted and 17 (21.3%) were normal with mean BMI (body mass index) value 15,23±1,25. There are no signs and symptoms of mineral bone disorders found in all subjects. Children with insufficient vitamin D had PTH level was inversely associated with vitamin D and level of minerals as follow: vitamin 25(OH)D ($r = 0.877$; $p<0.05$), Mg ($r = 0.890$; $p<0.05$), Ca ($r = 0.972$; $p<0.05$), Ph ($r = 0.897$; $p<0.05$). PTH level was positively correlated with ALP ($r = 0,965$; $p<0,05$).

Conclusion: In children with Vitamin D insufficiency may not exhibit obvious symptoms and signs except various stature including normal and short stature. Nevertheless, levels of PTH, magnesium, calcium, phosphate and alkaline phosphatase were shifted.

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P2-36

A Novel Variant of PHEX in a Korean Family with X-linked Hypophosphatemic Rickets

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X-linked dominant hypophosphatemic rickets (XLH) are the most common form of familial hypophosphatemic rickets resulting from hypophosphatemia caused by renal phosphate wasting, which in turn is a result of loss-of-function mutations in PHEX. Herein, we report a 39-year-old female with short stature and skeletal deformities and 12-month-old asymptomatic daughter. The woman has a history of multiple surgical treatments because of lower limb deformities. Through additional questions about the family, we found that her mother was also short stature. Her biochemical findings revealed low serum phosphorus levels with elevated serum alkaline phosphatase activity and normal serum calcium levels, suggesting presence of hypophosphatemic rickets. To identify the molecular causes, we used a multigene testing panel and found a mutation, c.667dup (p.Asp223GlyfsTer15), in PHEX gene. To the best of our knowledge, this is a novel mutation. A heterozygous form of the same variant was detected in her daughter. She presented no typical symptoms such as bow legs, frontal bossing, or waddling gate. But her biochemical findings suggested hypophosphatemic rickets like mothers and radiological findings showed early signs of impaired mineralization including widening, fraying, and cupping of the proximal tibial metaphysis and distal radial and ulnar metaphysis. The daughter was initiated onto early medical treatment with oral phosphate supplementation and an active vitamin D analog. Because the daughter was genetically diagnosed based on a family history before the onset of symptoms, appropriate medical management was possible from early infancy.

P2-37

A rare case of childhood hypophosphatasia presenting with fibrous dysplasia

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Objectives: Hypophosphatasia (HP) is a rare inherited disorder characterized by defective bone and teeth mineralization, and deficiency of serum and bone alkaline phosphatase activity. The symptoms are highly variable in their clinical expression, which ranges from stillbirth without a mineralized bone to early loss of teeth without bone symptoms. We aimed to report a patient with HP presenting with fibrous dysplasia.

Methods: For genetic analysis, written consent was obtained from the family. Targeted exome sequencing (TES) was carried out using the NextSeq 500 sequencing platform and TruSight One Sequencing panel (Depth 94X) (Illumina, San Diego, CA, USA).

Results: The patient was an 8-year-old boy who was referred to our clinic due to fibrous dysplasia. He was born at full-term by vaginal delivery and weighed 3140 g. There was no perinatal problem. He had suffered from intermittent dizziness and pain in both legs and lower back. His height was 131 cm (50th percentile) and his weight was 26 kg (25-50th percentile). There were no skin lesions such as café-au-lait macules. On laboratory findings, bone ALP was 36.9 μg/L (range: <20.1 μg/L); total calcium was 9.9 mg/dL (range: 8.8 – 10.8 mg/dL); inorganic phosphorus was 5.0 mg/dL (range: 3.7 – 5.6 mg/dL). He was initially suspected of having a monostotic fibrous dysplasia because brain MRI showed fibrous dysplasia involving the left greater wing and body of the sphenoidal bone. TES identified ALPL gene mutation, c.668G>A (p.Arg223Gln), in the patient. The patient was finally diagnosed with HP accompanied by decreased level of ALP (145 IU/L, range: 172 – 437 IU/L) and elevated pyridoxal-5'-phosphate (69.9 μg/L, range: 5.0 – 50.0 μg/L).

Conclusions: This is the first report of HP presenting with fibrous dysplasia. It is necessary to check biochemical findings such as pyridoxal-5'-phosphate and ALP in patients with fibrous dysplasia.

P2-38

Is Platinum-Based Chemotherapy resulted Hypomagnesemia in a Girl with Osteosarcoma? A Case Report

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Introduction: Magnesium is the second most abundant intracellular cation, and its low level causes several side effects related to hypoparathyroidism, hypocalcaemia, and vitamin D deficiency. Furthermore, some of the cases of hypomagnesemia are linked to platinum-based chemotherapy, resulting in neurotoxicity and nephrotoxicity. Dorsal root ganglion is the main target of platinum drugs, whereby its signs and symptoms can be detected months after chemotherapy. There are some researches involving hypomagnesemia in patients receiving cisplatin-based chemotherapy.

Case Report: A 5-year-old girl visited the Emergency Room (ER) with a chief complaint of decreased consciousness that began one day before admission. She also had a generalized seizure in the past two days before admission, which occurred more than five times a day and lasted less than one minute each. No complaint of

fever, vomiting, or diarrhoea. Previously she was diagnosed with osteosarcoma and had completed eight cycles of chemotherapy. Magnesium level was checked after the first dose of cisplatin, and the result was within normal limit. Furthermore, after the fifth cycle of chemotherapy, the patient had limb salvage with cryosurgery and internal fixation with plate and screw. After the sixth cycle of chemotherapy, spasticity was developed on all extremities. There is no family history of seizure, epilepsy, or other abnormality in neurology system. The most active agents used in chemotherapy are cisplatin, doxorubicin, etoposide, and ifosfamide. No mineral supplementation was given routinely. Physical examination in ER showed tachycardia with normal blood pressure. She had normal stature with severe malnutrition, decreased motoric strength and physiological reflex on all limbs, stiffness, and carpopedal spasm. The laboratory results was notable for severe hypomagnesemia (0.4 mg/dL) and decreased level of sodium, potassium, calcium, phosphate, insufficient 25 (OH)D and normal PTH. Furthermore, a head CT scan with contrast showed no bleeding, ischemic lesion, neoplasm, and vascularization malformation. There was no epileptiform signal on electroencephalography. Electromyography and conductive neuron velocity showed mixed polyneuropathy (motoric and sensory polyneuropathy). This patient was diagnosed with hypomagnesemia due to drug-induced chemotherapy (cisplatin). MgSO4 intravenously continued with magnesium per oral, Calcitriol, Vitamin D3 and Calcium was given and improvement was observed. The patient was discharged from the hospital and continued the treatment at outpatient clinic.

Conclusion: Measurement of magnesium level periodically is recommended in all patient receiving cisplatin and magnesium supplementation must be included in cisplatin-based chemotherapy planning.

P2-39

An anomalous gait

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A 5-year-old Moroccan patient comes to our attention due to impaired gait with pain in the lower limbs, easy fatigue and poor gain in weight and stature. In the previous months he had some episodes of abdominal pain.

During our first physical examination he was pale, with diffuse muscular hypotrophy, uncertain gait with an enlarged base, dubious hypertrophy of the calves and Gowers' sign. No varus / valgus of the lower limbs. Symmetrical and normo-evocable osteotendinous reflexes. No stenic deficits.

After the physical examination we hypothesized gastroenterological (celiac disease, gastroenteritis), orthopedic (transient hip synovitis, epiphysiolysis, Perthes disease) and neurological problems (Duchenne muscular dystrophy, polyneuropathy). First-level blood tests were performed, with the evidence of an iron-deficiency microcytic anemia (Hb 9.4 g / dL), associated with reduced levels of folate and vitamin B12. Normal CPK and transaminases. Serum calcium values below the normal range (7.4 mg/dL, normal values 8.8-10.8), elevated PTH (279 pg/mL, n.v. 15-65), phosphorus at lower limits (3.3 mg/dL, v.n. 2.85-5.25) and hypovitaminosis D (25OH 11.7 ng/mL, n.v. 20-68) as seen in vitamin D deficiency rickets. Radiological images of the lower limbs confirmed the diagnosis of rickets, highlighting irregularities in the distal metaphyseal-epiphyseal area of the femurs and tibiae, with modest cup-like enlargement, also associated with reduced bone mineralization.

For diagnostic completion, he was screened for celiac disease: we found a frankly pathological result with positivity of anti-transglutaminase (21770 U.A.) and anti-endomysium antibodies.

All the symptoms presented by the patient (impaired gait, poor gain in weight and stature, paleness, fatigue) could therefore be explained by an intestinal malabsorption in celiac disease, with consequent vitamin D deficiency rickets.

The therapy consisted of a gluten-free diet and a supplementation of calcium (2000 mg/day), cholecalciferol (4000 U/day), iron and folate. After three months of therapy we observed a complete remission of the clinical and laboratory findings, with the patient successfully showing a physiological gait.

P2-40

Overlooking hypoparatahyroidism in an 11-year-old boy patient with CHARGE syndrome

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Introduction: CHARGE syndrome is characterized with coloboma, heart defects, atresia of choanae, retardation of growth and development, genital hypoplasia and ear abnomalities. Recently, symptoms of CHARGE syndrome and 22q11.2 deletion syndrome were known to overlap.we describe a case of CHARGE syndrome that has variation in the CHD7 gene with hypoparathyroidism.

Case Report: The patient is an 11-year-old boy who was born at 39 weeks and 4 days gestational age and 2700 g birth weight. Cardiac malformation was noticed during fetus. Immediately after birth, he was intubated and respiratory management was started. He showed hypocalcemia during the neonatal period and was started with alfacalcidol for a while. At 17 days of age, aortic transection and ventricular septal defect were oparated. Tracheostomy was performed due to the difficulty of extubation at one month of age. The CHD7 variat was identified as c.934C>T at 2 years of age and he was referred to our hospital thereafter due to moving. At 5 years of age, we performed blood tests for short stature. Calcium was 8.2 mg/dL, Phosphorus was 6.7 mg/dL, alkaline phosphatase (IFCC) was 222 U/L, intact–PTH was 9 pg/mL (reference range: 10–65 pg/mL) and albumin was 4.3 mg/dL. Blood tests including calcium were not performed in previous hospital. He was diagnosed with primary hypoparathyroidism and were stateted with alfacalcidol (0.02 μg/kg/day) was started. Thereafter, calcium remains stable between 7.2 and 9.4 mg/dL, and intact–PTH also remains at lower levels. Fortunately, no hypocalmica-induced convulsions were observed. There was no 22q11.2 deletion in the FISH assay.

Discussion: Both alleles of CHD7, the gene responsible for CHARGE syndrome, and TBX1, the gene responsible for 22q11.2

deletion syndrome, are required for normal development of the fourth gill artery. These genetic dysfunctions are known to induce following hypoparathyroidism and hypocalcemia. There has been a high degree of overlap in the clinical presentation of CHARGE syndrome and 22q11.2 syndrome. Hypoparathyroidism has been reported to occur in 72% of patients with CHARGE syndrome, more frequently than with 22q11.2 deletion syndrome. In contrast, hypoparathyroidism has been reported to occur in 37.5% of patients with CHARGE syndrome and 60% of patients with 22q11.2 deletion syndrome. Both pediatric endocrinologists and pediatrician/neonatologists involved in CHARGE syndrome need to be aware of complications of hypoparathyroidism.

Conclusion: Caution is warranted that hypoparathyroidism may occur in CHARGE syndrome.

P2-41

A Case Of Pseudohypoparathyoidism with an Unusual Presentation

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Pseudohypoparathyroidism (PHP) is a disorder caused by PTH resistance due to a genetic defect in imprinted GNAS cluster. It is characterized by high phosphorus, low to normal calcium and elevated PTH. It is classified into types 1a, 1b, 1c, pseudopseudohypoparathyroidism and type 2. Type 1a is often associated with Albright Hereditary Osteodystrophy (AHO) which is characterized by short stature, round facies, obesity, brachydactyly, ectopic calcifications and developmental delay.

A 1-year-old boy presented to our clinic with obesity. Weight was 18 kg (+4.7 SD), length was 80 cm (1.2 SD). TSH was found to be 13.8 uIU/ml (normal: 0.7-6.4) and T4 was 5.9 ug/dl (normal 7.3-15). He was diagnosed as primary hypothyroidism and started Levothyroxine and diet plann.

At 4 years old, subcutaneous calcifications were noticed on the dorsum of left foot, left side of neck and skull. Height was 107.0cm (+1.0 SD), US/LS: 1.4, weight 30 kg (+3.9 SD) and BMI 33.2 (+5.6 SD). Patient had a notably round face and neurodevelopmental delay with IQ 80%.

Lab studies revealed highly elevated PTH 307 pg/ml (normal: 15-65). Ca 8.9 mg/dl (N: 8.6-10.3), iCa 5.04mg/dl (N. 4.4 -5.4), Ph 5.5 mg/dl (N 4-7.0), ALP 138 U/L (N up to 644) and 25(OH)vit D 20ng/ml. Vitamin D and calcium supplementation were added till 25(OH) was normalized. However, PTH remained persistently elevated on repeated testing reaching 473 pg/dl despite of normalization of vit D.

Plain Xray and soft tissue Ultrasound confirmed the presence of subcutaneous calcification in multiple locations. MRI brain and sella tursica revealed a diffusely thickened calvarium, multiple cutaneous & subcutaneous calcific spots.

Our clinical diagnosis of pseudohypoparathyoidism was supported by the abundance of characteristic features as early onset obesity, hypothyroidism (TSH receptor resistance), stocky build, round face, neurodevelopmental delay, tissue calcifications and elevated PTH. However, the absence of hypocalcemia, hyperphosphatemia, normal urinary ca/creatinine ratio with high PTH and unusual normal height (+1 SD) were pointing us towards normocalcemic primary hyperparathyroidism.

Confirmation was done via Whole Exome Sequencing. A heterozygous pathogenic variant was identified in GNAS associated with autosomal dominant Pseudohypoparathyroidism Ia (OMIM: 103580)

Insufficient phenotypic features and lack of classical biochemical abnormalities should not exclude pseudohypoparathyroidism especially with metastatic calcification. Genetic testing should be considered to prevent false diagnosis.

P2-42

Decreased vitamin D Levels in the pediatric population after COVID-19 lockdown

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Background: SarsCov2 infection began to spread worldwide since December 2019 and, on March 2020, the World Health Organization characterized its related disease, named COVID-19, as a pandemic. In Italy, to contain the spread of infection a severe lockdown from March 10th, 2020 to May 4th, 2020 was instituted. Other less severe restrictions were imposed in the winter 2020-2021 and in the spring 2021. The containment measures caused a series of consequences for the population and, in particular, for children and adolescents that presented several psychophysical problems.

Aim: This study aims to investigate the serum levels of vitamin D in children and adolescent before, during and after the lockdown consequent to COVID-19 pandemic.

Materials and Methods: This is a retrospective cross-sectional study, including all children and adolescents between 1 to 18 years referring to the Pediatric Endocrinology Service of the University Hospital of Verona, Italy, between January 2019 and December 2021. All patients affected by clinical conditions that involve vitamin D metabolism or assuming vitamin D supplementation were excluded.

Results: In total, 490 children (36.7% males and 63.3% females) were enrolled in this study. The vitamin D levels decreased over time: 28.2 ± 10.2 ng/mL in 2019; 28.2 ± 11.4 ng/mL in 2020 and 24.9 ± 10.1 ng/mL in 2021 ($p<0.05$). The vitamin D levels are significant higher in summer and in autumn in comparison with the levels of winter and spring, regardless of the examined years.

Conclusions: Our data showed that the measures adopted to contain the covid-19 pandemic led to a reduction of serum levels of vitamin D in pediatric population, probably due to the reduced solar exposure. This may have severe consequences on the bone metabolism of those children who did not present optimal vitamin D levels even before the lockdown. Therefore, an adequate supplementation of vitamin D is necessary at least during the winter period in children living in Northern Italy.

P2-43

Clinical-molecular assistance pathway for primary bone fragility: a pediatric monocentric experience

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Bone fragility is a more typical condition of old age, linked to physiological aging. In pediatric age, on the contrary, it represents a rare problem, but more often has an underlying primary cause.

This condition manifests itself in most cases with recurrent or abnormal fractures and bone deformities, with a limitation of mobility, bone pain and consequent reduction in the quality of life of the child.

The great difficulty for the clinician consists in reaching a correct diagnostic classification by moving in a heterogeneous context of possible causes which includes primitive congenital and secondary causes of different nature. Among the primary forms osteogenesis imperfecta has a prevalence of 1:15000 pediatric patients.

In this context, an observational study was conducted at Calcium-Phosphorus Clinic of our Pediatric Endocrinology Department, studying a cohort of 22 pediatric patients (0-18 years) referred for a condition of suspected bone primary fragility, from 2019 to 2021.

The study aims to identify a possible diagnostic-assistance pathway that can be proposed to pediatric patients with suspected bone fragility, directing them to clinical and instrumental investigations that allow rapid identification of the underlying pathology and subsequent correct treatment and follow-up to improve their quality of life.

Through this investigation it was possible to highlight the central role played by the clinical-anamnestic framework of the Pediatrician Endocrinologist, who allows to identify patients deserving of further investigations, in particular bone metabolism assessment, densitometry, and in selected cases molecular analysis via NGS panel for analysis of genes selected for bone fragility [COL1A1, COL1A2, IFITM5, TMEM38B, CREB3L1, BMP1 CRTAP, LEPRE1, PPIB, FKBP10, SERPINH1, SPERPINF1, WNT1, MBTPS2, P3H1, MESD, SP7, SPARC, TENT5A, FAM64A, PLOD2, PLS3].

The analysis of this case series also focuses attention on the peculiar aspects of the natural history of osteogenesis imperfecta, which represents the main primary chronic condition of bone fragility in childhood In particular, what are the differences in clinical presentation that allow to hypothesize a congenital defect of the bone matrix, reserving to these subjects a program of instrumental (detection rate 27-45%) and genetic tests (detection rate 64%) that are part of the so-called "precision medicine" (over all detection rate of program 70%), with subsequent personalized follow-up in order to be able to intercept early and reduce the complications of patients natural history.

Despite the case series limitation, this analysis lays the foundations for further multicentric studies and to standardize clinical and molecular aspects in diagnostic-therapeutic-assistance multicentric pathways.

P2-44

The changes of body composition in children with obesity

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Background: in our days the case of reduction of bone mineral density becomes more common. This pathology can be detected in children and adolescents with obesity with the help of densitometry.

Aim: to reveal the dynamics of body composition indicators in obese children.

Methods: we examined 32 children with obesity in the University Hospital (Minsk) in 2020-2022 yrs. Their anthropometric parameters (height, weight, body mass index (BMI)) were determined. Body composition with evaluating of mineral component were made by dual energy X-ray absorptiometry with calculation of total fat mass (TFM) (kg, %), free fat mass (FFM) (kg), bone mineral density (BMD) (g/cm2), abdominal (A) and gynoid (G) distribution, A/G coefficient. In the biochemical blood test, the parameters of Ca2+, Mg2+, P were evaluated.

All children were divided into 2 groups: group 1 - children with obesity early (stage 2-3 according to Tanner) (11 boys(B)/9 girls(G)) 13,7±0,9 years and 10,6±0,2 years accordingly) and late (stage 4-5 according to Tanner) (7 B/5 G 15,8±0,2 years and 13,8±0,6 years accordingly) groups of puberty.

Results: an increase in BMI indicators was revealed with the development of puberty: in group 1 it made up to B 31,8±0,6 kg/m2 and G 32,5±0,4 kg/m2, in group 2 B 34,9±0,3 kg/m2 and G 35,8±1,2 kg/m2. Body weight in group 1 was B 84,9±5,2 kg and G 67,2±3,5 kg, in group 2 it was B 110,1±1,7 kg and G 89,2±6,3 kg ($p<0,001$).

A decrease in the level of ionized calcium 1,03±0,02 mmol/l and ionized magnesium 0,52±0,09 mmol/l relative to the norm for boys in group 1, phosphorus values were within the normal range 1,2±0,08 mmol/l.

Indicators of bone mineral density (BMD) in group 1 were B 1,42±0,05 g/cm2 and G 1,07±0,04 g/cm2, in group 2 the indicators were B 1,59±0,02 g/cm2 and G 0,96±0,08 g/cm2 ($p<0,001$).

An increase in BMD indicators was revealed with the development of puberty for boys and decrease in indicators for girls. There were no age and gender differences. With the development of puberty boys showed a percentage decrease in fat depot with SM increase, in girls - an increase in the indicators of TFM and FFM ($p<0,001$).

Conclusions: There was a decrease in the level of Ca2+, Mg2+ in obese boys with BMI>30.0 kg/m2 without changes in BMD.

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P2-45

Adult weight and BMI associate with higher bone mineral density in the lumbar spine and femoral neck in young adults born preterm in the surfactant era

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Background: Vitamin D is a steroid hormone which contributes to the maintenance of calcium homeostasis and bone mineralization. As bone mineral accretion occurs mostly during the third trimester of pregnancy, mineral storages are deficient especially in the extremely low birth weight (ELBW <1000g) preterm infants at birth. Recent studies suggest that ELBW is a risk factor for compromised bone mineral density at adulthood, but the role of neonatal morbidity and vitamin D is controversial.

Methods: 38 adults born <34 gestation weeks, with a mean birth weight of 1397g (SD 301g), were recruited for the study at the mean age of 23.6 (SD 0.74) years. Vitamin D concentration (S-25OHD) was measured at the entry, mid-point, and end of the study. A dual energy X-ray absorptiometry for bone mineral density (BMD) was performed on 37/38 participants at the start and 35/38 at the end of the study. Vitamin D supplementation for one year was started to participants whose S-25OHD was under 80 nmol/l at the entry or mid-point evaluations (n = 35).

Results: The lowest lumbar spine BMD Z-score (mean -0.489, 95% CI -0.782 to -0.196), was significantly lower in the preterm born participants compared to age- and sex-specific reference values. BMD Z-scores were lower in the femoral neck (mean -0.332), but this finding was not statistically significant. During the intervention, S-25OHD levels increased from 60.3 nmol/l (SD 18.7 nmol/l) to 82.9 nmol/l (SD 25.8 nmol/l), with no association with BMD Z-scores.

Lumbar spine or femoral neck BMD had no correlation with gestational age, birth weight or length, respiratory distress syndrome (RDS), surfactant treatment or antenatal steroids. Instead, postnatal dexamethasone treatment for RDS associated positively with lumbar spine BMD Z-Score (mean difference 0.93, 95% CI 0.27 – 1.59, p = 0.007). Postnatal dexamethasone had no effect on adult weight, height, or BMI. Adult weight and BMI associated positively with lumbar spine (r = 0.337, p = 0.041, r = 0.395, p = 0.015) and femoral neck (rs = 0.457, p = 0.004, rs = 0.451, p = 0.005) BMD.

Conclusions: Bone mineral densities, especially in the lumbar spine, appear to be lower in the preterm born population. Adult weight and BMI associate with higher BMD both in the lumbar spine and femoral neck. Postnatal dexamethasone treatment associated with higher lumbar spine BMD, but the mechanism remains unclear and requires further research.

P2-46

Successful treatment with zoledronic acid of a 13-year-old boy with corticosteroid-induced osteoporosis after hematopoietic stem cell transplantation

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) has emerged as an increasingly successful option to cure a variety of malignant disorders in children. Children benefit from improved survival; however, HSCT is associated with numerous acute and long-term toxicities. Osteoporosis is a well described, late effect of allogeneic HSCT, associated with corticosteroid treatment and patients exposed to cumulative doses >9000 mg/m2 of prednisone equivalent are more likely be affected. Bisphosphonates are standard treatment of osteoporosis in adults, but their use in children remains off label and is reserved for selected cases.

Case Presentation: A 12-year-old boy with myelodysplastic syndrome (MDS-EB) was treated with myeloablative chemotherapy followed by allogeneic HSCT from a matched sibling. The boy had neutrophil engraftment on day +20 and platelet engraftment on day +28. Unfortunately, on day +4, he developed acute graft-versus-host disease of the gut and was started on methylprednisolone 2 mg/kg. The patient was discharged on day +56 on the same dose of methylprednisolone and was supplemented with calcium and vitamin D for prevention of bone loss. He was tapered off glucocorticoid therapy five months post-transplantation. Eight months post-transplantation, the boy developed severe back pain, needing regular pain killers. Radiographs of the spine revealed lumbar and thoracic vertebral compression fractures and dual-energy x-ray absorptiometry (DXA) showed low bone mineral density (BMD) for age and sex, with a lumbar BMD Z-score of -2,3 (osteoporosis). At the age of 13.2 years, he was commenced on bisphosphonate treatment with zoledronate at a dose of 0.025 mg/kg, administered every three months (annual dose 0.1 mg/kg). Five doses of zoledronate were administered over 15 months, with no significant adverse events. Acetaminophen was administered for the first 2 days after infusion to reduce the incidence of acute-phase reaction symptoms and post-infusion hypocalcemia was managed with administration of elemental calcium (2-3 gr/day). On review at 14.1 years, his spine BMD showed considerable improvement (Z-score -0,1) and he had entered puberty with 10 ml testes bilaterally. One year later, at the age of 15.1 years, his spine BMD Z-score was -0,7, and puberty was progressing with 14 ml testes bilaterally. Spine BMD remained normal at the age of 16.5 years. Most importantly, he is no longer in pain.

Conclusion: A high index of suspicion for osteoporosis in patients receiving HSCT is required, to allow prompt treatment with bisphosphonates and improve quality of life, with no skeletal malformations or bone pain.

P2-47

Severe hypophosphatemia in a girl with vitamin D-dependent rickets type I: A case report

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Introduction: Vitamin D-dependent rickets type I (OMIM # 264700) is a rare autosomical recessive disorder that affects vitamin-D metabolism characterized by severe hypocalcaemia with moderate hypophosphatemia. The most common form is type IA, caused by the mutation of gene coding for 1-alpha-hydroxylase (CYP27B1OMIM* 609506. 12q14) that converts the 25-OH-vitaminD in 1,25-OH-vitaminD.

Case Report: A 2.3 years female with an isolated and unvestigated history of severe symptomatic neonatal hypocalcaemia come to our attention for suspected hypophosphatemic rickets and a regression of psychomotor development with difficulties in keeping orthostatic position because of a severe hypotonia. At physical examination the child presented rachitic rosary, widening of wrist, deformity of legs with varus knees and an accentuated kyphosis in sitting position. X-ray showed typical alterations of rickets. Blood tests showed moderate hypocalcaemia (8.7 mg/dl), severe hypophosphatemia (1.8 mg/dl), unexpected and very high parathyroid hormone (924 pg/ml) and alkaline phosphatase (3936 IU/L) levels, normal 25-hydroxyvitaminD (48 ng/mL) and inappropriately normal 1,25-dihydroxyvitamin D (31.8 pg/mL). Because the severe hypophosphatemia, a possible vitamin D resistant rickets was hypothesized and FGF23 was requested, as well as 24-hour urinary calcium and phosphorus. So, we started a treatment with Joulie's oral solution, calcium and calcitriol, discovering a significant reduction in serum phosphate (1.2 mg/dl), and calcium (6.9 mg/dl) levels and a significant increase of parathyroid hormone level (1028 pg/ml) and unmodified alkaline phosphatase level (3599 IU/L). Meanwhile, FGF23, 24-hour urinary calcium and phosphorus were normal. So, in relation to the clinical and laboratoristic course, a Vitamin D dependent rickets type I was hypothesized; we stopped Joulie's oral solution adjusting appropriately the dosage of calcium and calcitriol, with a progressive normalization of the bone metabolism parameters and significative amelioration of clinical features.

Conclusion: Severe Hypophosphatemia, associated to mild hypocalcaemia are typical of hypophospatemic rickets but could be present also in other forms of rickets, as well as vitamin D-dependent type I rickets. For this reason, waiting for the dosage of FGF23, some parameters of the bone metabolism, such as unexpected parathyroid hormone, alkaline phosphatase and 1,25-dihydroxyvitamin D levels, may be useful markers in suspecting a form of calcipenic rather than phosphopenic rickets.

P2-48

An unusual case of rickets and anemia due to severe nutritional deficiency in a child of non-caucasian ethnicity

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Background: Rickets is a disease due to a reduced mineralization of the rapidly growing bones (skull, ribs, wrists, knees, ankles) with consequent accumulation of non-mineralized bone matrix, called osteoid tissue. The most frequent cause of rickets is vitamin D and/or calcium deficiency caused by reduced sun exposure, inadequate dietary intake or malabsorption (nutritional rickets).

Clinical History: R., a 1 year and 6 month-old female child of Moroccan ethnicity, comes to our observation for pallor, anserine gait and skeletal deformities. Nutritional anamnesis highlighted the intake of a predominantly milky diet with low amount of carbohydrates, meat and vegetables. Auxological examination: weight and height at the 50th percentile for age and gender. Physical examination: pallor, marked varism of the knees, delayed dental eruption, costal deformities, abnormalities of wrists and ankles.

Blood tests showed iron deficiency anemia (Hb 10.1 g/dl, MCV 58.41 fl, ferritin levels 3 ng/ml), normocalcemia, normophosphoremia with increased urinary phosphate excretion (TmPO4/GFR 1 mmol/L), marked elevation of serum alkaline phosphatase (ALP 1250 U/L) and of bone isoenzyme of alkaline phosphatase (BAP 173.7 ug/L), and severe vitamin D deficiency (25 OH vitamin D: 4 ng/ml) resulting in secondary hyperparathyroidism (PTH 310 pg/ml).

Radiographs of the wrist and left hand and lower limbs showed an enlarged cupped appearance of the distal epiphyses of the wrists, knees and ankles that had blunt and jagged metaphyseal edges with trabecular appearance and initial concavity (Thacher grade 6-7).

Diagnosis and Therapy: The clinical, biochemical and radiological findings were consistent with the diagnosis of nutritional rickets associated with iron deficiency anemia. The diagnosis was supported not only by the nutritional history, but also by the genetic predisposition due to the non-Caucasian ethnicity and by the reduced vitamin D absorption due to the concomitant iron deficiency. Therefore, oral iron (3 mg/kg/day) treatment and cholecalciferol (4.000 IU/day) supplementation were started. After 6 months of follow up, normalization of biochemical parameters was observed, and after 12 months the imaging demonstrated an improvement of rickets lesions consistently with a progressive walking recovery.

Conclusion: The peculiarity of this case report lies in the coexistence of two comorbidities, rickets and anemia, both secondary to a severe nutritional deficiency in a Moroccan child whose ethnicity is a genetic predictor for nutritional rickets per se.

Diabetes and Insulin

P2-49

A case of diabetes and deafness with heteroplasmic mutations in the mitochondrial DNT1 gene

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Introduction: Diabetes mellitus can develop as a result different etiology. Mitochondrial diseases may also cause diabetes mellitus. However, mitochondrial mutations are generally thought to be accompanied by a severe clinical finding. We present a patient who is determined 80% heteroplasmic deletion in the MT-DNT1 gene, with hearing loss and mitochondrial diabetes, which is quite different from the classical phenotype.

Case: A 10-year-old male patient, who was diagnosed with diabetes mellitus in another medical center 6 months ago, was started on insulin therapy and applied to our outpatient clinic for follow-up. In his history; He was born 3700 grams as a term birth by spontaneous vaginal delivery, was operated at the age of 1 due to an undescended testis. When he was ten months old, he started using a hearing device. In his development assessment, he started walking at the age of 15 months, and his language development was later than that of his peers. In the family history; there was a 3-degree cousin marriage between his parents, the father was diagnosed as type 2 diabetes. The mother had not any type of diabetes mellitus.

Anthropometric measurements; his height, weight and body mass index were 159 cm (SDS:2,25), 58,1 kg (SDS:2,053) and 23 kg/m2 (1,63 SDS) respectively. In his examination; he had hearing aid. Testicular volume was 3 ml on the right, left testis was non-palpable. Neurologic and other systemic examinations were normal. Laboratory examinations revealed; hemogram, kidney and liver function tests, vitamin and mineral levels, thyroid function tests and tissue transglutaminase antibodies were normal. HbA1C: 10.9, C peptide 0.6 (1.1-4.4 g/L), anti-GAD: 10.91 IU/ml (0-17IU/ml), anti-insulin antibody 6.95U/ ml (<20 U/ml), Islet Cell Antibody: 23.56U/ml (0-28 U/ml). As diabetes autoantibodies were negative, genetic analyzes were performed in the patient who also accompanied by hearing loss. Heteroplasmic deletion was detected in 80% of the patient's MT-DNT1 gene. The patient whose genetics were compatible with MELAS syndrome was accepted as mitochondrial diabetes. Other parameters of MELAS mutation were examined, lactic acid level was normal. The patient's EMG was normal, and there was no finding in favor of stroke in the cranial imaging. Genetic studies of the family members were normal.

Conclusions: Mitochondrial disorders should be kept in mind in diabetic patients with hearing loss and negative result of autoantibody, and genetic studies should be performed. In this way, early intervention will be possible for other accompanying system disorders.

P2-50

Inhaled glucagon, a new well-accepted therapeutic tool in pediatrics

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On 01/14/2021, the European Commission authorized the marketing of Baqsimi® 3 mg (nasal glucagon), a powder medicine, ready to be used, in the treatment of severe hypoglycemia in adults, adolescents and children over four years of age with diabetes mellitus. Baqsimi® is the first and only nasal glucagon treatment available approved in the European Union (EU), and has been designed as a rescue treatment in cases of severe hypoglycemia, being absorbed passively into the nasal mucosa after its administration. The safety data obtained from these studies demonstrated that nasal glucagon is well tolerated as an emergency treatment of severe hypoglycaemia in adult and pediatric patients with diabetes 4 years of age and older.

The most frequently reported adverse reactions in the adult population associated with its use were increased lacrimation (36%), irritation of the upper respiratory tract (34%), nausea (27%), headache (21%) and vomiting (16 %).

Objective: To evaluate the clinical experience in incorporating BAQSIMI into routine clinical practice.

Methods: DM1 patients over 4 years old, enrolled in school, from the start of follow-up in specialty consultations at our center. Previous use of GLUCAGEN hipoKIT. Assessment of age, sex, weight, height, BMI (Carrascosa 20210), age of debut, HbA1c. Descriptive study IBM SPSS Stastistics 19.0.

Results: 68 children older than 4 years (35♂), mean age 9.5 to [4-17]. HbA1c (DCA): 7.7% [6.8-9.2], time to debut 3.8a [0.8-10.1], mean weight -0.32 SDS [-1.2, + 0.8], mean BMI - 0.28 SDS [-1.4, + 0.9]. 93% use of MDI, 5 pumps. 100% correct use of inhaled glucagon. There was no impediment due to medical inspection except in 1 case (belonging to another health area). Previous severe hypoglycemia with previous loss of consciousness in <5% of cases (0.03 patient / year cases). Number of recipes made 70. (67 unique + 3 multiples).

3 episodes of severe hypoglycemia (loss of consciousness, crisis) (2 in the same patient) associated with exercise + incomplete intake and / or incorrect bolus calculation. The 3 cases in MDI. Use of Baqsimi in all 3 cases. Recovery from the episode WITHOUT sequelae and almost immediately. Symptoms manifested: tearing (33%), irritation of the upper respiratory tract (33%), nausea (33%), headache (66%) and vomiting (33%). Paternal evaluation: excellent (3/3).

Conclusion: We assume that this study may have some shortcomings due to the size of the sample, but our study demonstrates the efficacy of inhaled glucagon in emergency situations in real life, its good tolerance and its excellent reception by families.

P2-51

Effect of combined hormonal contraceptives use in telomere length and metabolic profile in young women with T1D

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Introduction: The metabolic effects of oral hormonal contraception (OC) on telomere length (RTL) in young women with T1D are unknown.

Objective: To determine the effect of using an OC on glycemic control, inflammatory profile, and RTL in young women with T1D and healthy women without diabetes (C).

Methodology: T1D (n:20, age: 20.6 ± 3.3 years) and C (n:22, age 20.2 ± 3 years) used OC (150 ug desogestrel and 30 ug ethinyl estradiol) for 18 months. HbA1c, C-reactive protein measured by an ultrasensitive assay (usCRP), and RTL were evaluated at baseline, 12, and 18 months. RTL was determined using the MMq-PCR technique. DNA was obtained from blood mononuclear cells. Non-parametric statistics and linear regression were used.

Results: RTL was similar in the T1D and C groups at baseline, 12, and 18 months. In C, the RTL decreased by 0.2 ± 0.4 at 18 months (p=0.044). The decrease in RLT in the T1D group did not reach statistical significance (p=0.096).

In the T1D group, increasing BMI (Spearman's coefficient of -0.446; p=0.049) and increasing usCPR (Spearman's coefficient of -0.541; p=0.037) correlated with decreasing RTL. Changes in HbA1c did not correlate with changes in RTL (p>0.05).

Conclusion: The use of OC for eighteen months did not deteriorate glycemic control in young women with T1D. However, subclinical inflammation was observed in both groups. These results suggest that despite the lack of an adverse effect of the OC on glycemic control in women with T1D, attention should be given to other pro-inflammatory risk factors such as higher BMI and usCRP, which are associated with decreasing telomere length in young women.

P2-52

Bone and mineral turnover in newly diagnosed children and adolescents with type 1 diabetes mellitus

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Introduction: There is still controversy about the levels of bone turnover markers at type 1 diabetes (T1D) onset and their dynamics at follow-up. Bonfanti et al. did not find any differences at onset, while few months afterwards beta cross laps level was significantly lower. Pater et al. found lower levels of osteocalcin and Log beta cross laps at onset which normalized after 3 and 12 months.

Possible mechanisms are metabolic acidosis, decreased activity of insulin-IGF-1 system, hyperglycemia.

The ability to reach peak bone mass is impaired early in the course of the disease and puts them at a higher fracture risk.

Objectives: To determine if newly diagnosed T1D patients have alterations in bone and mineral metabolism (osteocalcin, beta cross laps, bone-specific alkaline phosphatase, PTH, IGF-1, 25(OH)vitamin, Ca, Phosphorus, Mg) compared to healthy controls and to look for correlations with disease-specific parameters – HbA1c, pH and insulin dose.

Methods and Materials: A cross-sectional study of 35 patients with newly diagnosed (within one week of diagnosis) T1D (15 females) aged 10.55years ±4.58 and 52 (25 females) controls aged 9.86 years±4.60, p>0.05. Mean HbA1c 102 mmol/mol (11.57%±1.90). Statistical methods used were correlation analysis and t-test.

Results: We found significantly lower levels of serum osteocalcin -49,51 ng/ml ±41,47 in patients vs 79,21 ng/ml±40,5 in controls, p<0,001. Beta cross laps, bone specific ALP, IGF-1, their SDS and PTH tended to be lower in patients, p>0,05.

25(OH)D in both groups was in the recommended range -64,13±28,9 vs 76,87±32,34, p>0,05. No patients had vitamin D

Table 1. Glycemic and inflammatory parameters and telomere length

	T1D			Controls		
	Basal (n:20)	**12 months (n:20)**	**18 months (n:15)**	**Basal (n:21)**	**12 months (n:21)**	**18 months (n:18)**
HbA1c, %	7.9 (6.9 – 8.6)	8 (6.9 – 8.4)	7.5 (6.8 – 8.3)			
HbA1c, nmol/mol	63 (52 – 70)	64 (52 – 68)	58 (51 – 67)			
usCRP, ng/ml	2.73# (1.04 – 4.35)	5.86#* (2.55 – 13.87)	8.16* (2.42 – 12.13)	1 (0.33 – 2.39)	3.1* (1.19 – 5.56)	7.5* (5.01 – 12.4)
RTL	1.61 ± 0.49	1.39 ± 0.41	1.35 ± 0.41	1.54 ± 0.33	1.49 ± 0.43	1.43 ± 0.28*

Data are shown as median (interquartile range) or mean ± standard deviation. # p<0.05 between T1D and C. *p<0.05 compared to baseline.

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deficiency but five (28%) had insufficiency -35,56 nmol/l±28,9. Among controls there were seven (14%) with vitamin D alterations - three had vitamin D deficiency(13,58nmol/l±3,22) and four had insufficiency (43,94nmol/l±1,47), p<0,001.

Patients had significantly lower levels of serum Ca - 2,30±0,1 vs 2,40±0,1 in controls, p<0,001 but higher levels of serum Mg – 0,86±0,004 (0,78-0,91) vs 0,85±0,003 (0,75-0,96), p<0,001.No significant differences in ionized Ca and serum phosphorus.

Significant negative correlation between osteocalcin and insulin dose was found, r=-0,430, p<0,05. No correlations with pH or HbA1c level.

Conclusions: Patients with newly diagnosed T1D seem to have significantly depressed bone formation. We confirm the stimulatory effect of osteocalcin on insulin secretion. No significant correlations with HbA1c and pH were found. Further studies, including imaging are needed to elucidate the exact mechanisms and evolution of the observed alterations.

P2-53

Clinical and immunological characteristics of new-onset type 1 diabetes in children during the COVID-19 pandemic

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Background: Type 1 Diabetes (T1D) is a chronic disease resulting from autoimmune destruction of insulin-secreting pancreatic β cells. Viruses are known to play a role in the pathogenesis of T1D. There is no consistent evidence that SARS-CoV-2 induces T1D in children or adults. Nevertheless, evidence suggests that the SARS-CoV-2 affects β cell function, suggesting a role for the virus in the pathogenesis of the disease. It is thus plausible that the effects of the SARS-CoV-2 on β cells and the environmental alterations caused by the COVID-19 pandemic affected the clinical and immunological characteristics of new-onset T1D.

Objective: To find the clinical and immunological signatures of the COVID-19 pandemic on children diagnosed with T1D.

Methods: A single-center, retrospective observational study comparing the clinical and immunological characteristics of children diagnosed with T1D at our clinic the year before and during the first two years of the COVID-19 pandemic. Data were extracted from the medical records of the children at the time of diabetes diagnosis, including clinical and demographic parameters, COVID-19 PCR results, and the presence of anti-islet, thyroid, and celiac-related autoantibodies. Also obtained from the medical records were a family history of T1D, celiac disease, and autoimmune thyroid disease in a first-degree family member.

Results: 376 children were diagnosed with T1D at our diabetes clinic during the study period. 132, 121, and 123 children were diagnosed during the pre-COVID-19 era, the first and second pandemic years, respectively. The rate of diabetic ketoacidosis at presentation was slightly higher during the COVID-19 era than in the pre-COVID-19 era (not reaching statistical significance) and comparable between the first and second pandemic years. Multiple antibodies were significantly higher among patients diagnosed in the pre-COVID-19 era than those diagnosed in the first two years of the pandemic (72% vs.61%, p=0.03). Islet-cell autoantibodies (ICA) levels were higher among children diagnosed during the COVID-19 era compared to pre-COVID-19 era (1341.34+1786.36U/ml vs.968.02+1495.66U/ml, p=0.042). GAD-antibodies levels were higher in children diagnosed with COVID-19 before the diagnosis of T1D than in children without COVID-19 (614.86+793.90U/ml vs.317.08+611.45U/ml, p=0.027). Tissue Transglutaminase antibodies were more common among children diagnosed during the COVID-19 era compared to the pre-COVID-19 era (17% vs. 8%, p=0.024).

Conclusions: Our findings suggest that SARS-CoV-2 and the environmental alterations caused by the pandemic affected the immunological profile of children diagnosed with T1D. Thus, it appears that the virus plays a role in the autoimmune process causing T1D.

P2-54

Abstract Withdrawn

P2-55

A case of *de novo* ABCC8 gene mutation resulting in Transient Neonatal Diabetes

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Neonatal diabetes is characterised by hyperglycaemia in the first 6 months of life. Transient neonatal diabetes (TND) is differentiated from permanent neonatal diabetes by its remission in infancy/early childhood, with possible relapse during adolescence in 50% of the cases. Incidence of neonatal diabetes is thought to range from 1:90,000 to 1:160,000. A gene mutation affecting pancreatic beta cells synthesis/secretion of insulin is present in more than 80% of the cases. Overexpression of genes on the 6q24 locus is the most common cause of TND followed by mutations of the ABCC8 or KCNJ11 genes coding for the ATP-dependent potassium channel (KATP) in the pancreatic beta cell. Activating mutations in either of the two genes result in inappropriately open KATP channel despite hyperglycaemia leading to inability of the cell membrane to depolarise and release insulin.

Female infant born at 31 weeks' gestation to non-consanguineous parents, via C-section, after rupture of membrane and breech, weighing 1.440 Kg (50th centile). Uneventful initial course.

Incidental finding of hyperglycaemia at day 9 of age on a capillary gas, glucose of 18.2 mmol/L (true glucose 14.4 mmol/L) and highest glucose measurement of 22.2 mmol/L. No ketonaemia/acidosis and no stress factors present. Treatment with Actrapid 0.025 IU/Kg/hour was started. Insulin was titrated accordingly to a maximum of 0.06 IU/Kg/hour and discontinued on day 29 of age. A glycaemic control and study of pancreatic reserve (when hyperglycaemia detected and when insulin discontinued) were assessed.

Glibenclamide was due to be started at 0.05 mg/Kg/day in two divided doses, however, infant's blood glucose levels stabilised at 4-7 mmol/L, decision was made to hold off sulfonylurea treatment.

Genetic testing: heterozygous mutation in the ABCC8 gene, leading to a missense mutation in the SUR1 protein. There is no relevant family history, and parents did not show any related mutation.

Neonatal hyperglycaemia is a common finding however a genetic mutation should be considered in the absence of contributing factors, with normal birth weight and a later hyperglycaemia (after day 3-5 of age).

Genetic testing is important as a specific genetic mutation can significantly alter the treatment and outcome. Patients with activating mutations of either ABCC8 or KCNJ11 respond well to oral sulfonylurea therapy.

Despite remission, close glucose monitoring and education of caregivers about diabetes is essential. Long term monitoring is planned (to puberty) with a focus on possible diabetes relapse.

P2-56

Monogenic Diabetes (MODY) in Adolescents and Personalized Treatment.

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Background: MODY can be mistaken for Diabetes type 1 or type 2.

Objective: To evaluate genetic background in 22 patients presented with diabetes, negative islet cell antibodies, normal C-peptide and positive family history of diabetes. Genetic testing was done at Invitae laboratory and evaluated 28 genes for diagnosis of MODY.

Results: Patients were divided into 2 groups: Group 1 with a positive genetic test for MODY and Group 2 with a negative.

In Group 1 there were 15 patients (21.9 ± 15.3 yrs, 6 females and 6 males, from 5 families and in addition 1 female and 2 males), (4 Caucasians, 3 Hispanics, 8 Asians).

In Group 2 there were 7 patients (17.4 ± 4.5 yrs, 4 females, 3 males, 5 Hispanic, 2 Asians)

In Group 2 BMI (40 ±8.3), C- peptide (3.8 ± 0.7), SBP 134 ± 15.3, DBP 80.3 ± 7 were higher comparing to Group 1: BMI (29 ± 10.2), C- peptide (1.8 ± 1), SBP 115 ± 15.3, DBP (71.6 ± 9.7).

There were no differences in Age, Hb A1c, Cholesterol, Triglycerides, HDL, LDL, ALT, AST between groups.

In Group 1, after confirmation of genetic test Insulin treatment was discontinued in 3 cases. 3 patients with HNF4A were treated only with Gluburide 1.25 mg twice a day, 8 patients with Glyburide 20 mg twice a day, Metfromin 850 mg twice a day, and 6 patients with additional Victoza, 1 patient with IER3IP1gene was treated with Insulin and Metformin, 3 patients with GCK MODY 2, didn't require any treatment.

In Group 2, 4 patients were treated with Gluburide 20 mg twice a day, Metfromin 850 mg twice a day and Victoza, and 3 patients with Metfromin and Insulin.

In Group 1 Hb A1c significantly improved after treatment from 9.9 ± 2.4 % to 6.8 ± 0.8 ($p < 0.001$). In Group 2 - no improvement in Hb A1c from 7.5 ±1.9 to 7.6 ± 1.7 %.

Heterozygous polymorphism in ABCC8 gene was found in 3 cases from 15 (20%) (Mother, daughter c.2473C>T (p.Arg825Trp)) and 1 boy (c.4280A>T (p.Asp1427Val)), in GCK gene in 4 cases 27 % (father, 2 sons (c.452C>A (p.Ser151Tyr)) and 1 girl (c.1033C>G (p.Arg345Gly)), in GLIS3 gene in 2 cases 13% (mother and son (c.951G>T (p.Glu317Asp)), in HNF1A gene in 2 cases 13% (brother, sister (c.775G>ApV2591)), 3 in HNF4A 20% (2 sisters and father c.224+2T>C in intron 2), 1 in IER3IP1 gene 7 % (c.69C>G (p.His23Gln).

Conclusion: Genetic testing in case of suspected MODY is important because of different responses to treatment.

P2-57

Outcome of positive adrenal antibodies identified on screening in children with T1DM

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Background: Primary adrenal insufficiency (PAI) is characterised by the immune destruction of the adrenal cortex and leads to impaired production of the adrenal hormones. It is a potentially life-threatening condition that can be managed if identified early. The onset is insidious and often difficult to diagnose. Screening for adrenal autoantibodies is routinely performed in autoimmune conditions such as type 1 diabetes mellitus (T1DM). The guidance around the management of patients with T1DM following a positive adrenal antibody result is limited.

Objectives: To evaluate our current practice and investigate the outcome of patients with T1DM who have a positive adrenal antibody result.

Design: We identified patients by looking at all adrenal antibody tests performed on paediatric patients at our large tertiary centre between January 2014 and July 2021. We reviewed the electronic record of all patients with a positive result to explore the indication for each test and clinical outcome. We looked retrospectively at all results available for each patient.

Results: There were 2451 adrenal antibody tests performed over this period on 1334 patients. Of these results, 27/2451 (1.1%) were positive, 22/2451 (0.9%) were equivocal, 4/2451 (0.2%) were

reported as weak positive and 23/2451 (0.9%) were not processed due to sampling or lab issues.

The 27 positive tests identified 22 patients. In 8/22 (36%) the investigations were performed due to clinical suspicion of primary adrenal insufficiency. Conversely, in 14/22 (64%) they were performed as part of a screening process. Thirteen (93%) of these were for routine screening for diabetes and 1/14 (7%) was for monitoring of an autoimmune polyendocrine syndrome.

The follow up period from initial positive result for the diabetic patients ranged from 0.69-10.56 years (mean 6.15). Only 1/13 (7.69%) diabetic patient developed primary adrenal insufficiency over this period. The interval between the first positive adrenal antibody result and diagnosis of PAI was 0.22 years.

The practice of repeating adrenal autoantibodies and performing short synacthen tests varied between patients.

Conclusion: Our study showed that less than 1% of all adrenal antibody tests reported positive results in paediatric patients undergoing routine screening for diabetes. Of these, only one patient developed PAI and this was after a short interval of less than 3 months. Whilst guidelines for screening for adrenal antibodies exist, there is limited guidance for follow up of those with positive antibodies, especially in T1DM. A standardised approach for these patients would be useful.

P2-58

Real-world use of continuous glucose monitoring and its effect on glycemic control among Korean children, adolescents, and young adults with type 1 diabetes

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Background: The Korean National Health Insurance Service has started reimbursing the cost of continuous glucose monitoring (CGM) in type 1 diabetes (T1D) in 2019. We investigated the effect of CGM use on glycemic control among Korean children, adolescents, and young adults with T1D in a real-world setting.

Method: We retrospectively reviewed the medical records of childhood-onset T1D patients aged < 30 years (n = 448) at the last follow-up at Seoul National University Children's Hospital between January 2020 and June 2021. Among 297 patients who had received CGM prescription, 187 patients used CGM for more than 3 months. After excluding 21 patients with missing glycosylated hemoglobin (HbA1c) values, 166 patients (56 males and 110 females) were included in the final analysis. Glycemic control was assessed by HbA1c and CGM metrics, including the time CGM is active (tCGM).

Results: Greater than 70% use of CGM over 3 months (≥70% tCGM group) was more frequently achieved in patients with a diabetes duration < 1 year than those with a duration ≥ 1 year (100% vs. 65.9%, p = 0.001). When we analyzed 129 patients with a diabetes duration ≥ 1 year (17.4 ± 5.9 years of age; 8.4 ± 5.7 years of diabetes duration; 82 real-time CGM and 47 intermittently scanned CGM users), ≥70% tCGM group (n = 85) showed significantly higher time in range (54.8% vs 44.7%, p =0.003), and lower HbA1c (7.5% vs 8.2%, p =0.004) and time above 250mg/dL (15.1% vs 24.8%, p=0.003) compared to <70% tCGM group (n = 44) at 3 months after CGM initiation. When we further investigated ≥70% tCGM group, HbA1c was significantly decreased from 8.1% to 7.5% at 12 months (p =0.006). HbA1c lowering effect was evident at the first 3 months of CGM use and maintained throughout 1 year (p <0.001). Time in range (from 52% to 59.6%, p =0.002), time below 54mg/dL (2.2% to 1.3%, p = 0.028), time above 250mg/dL (17.3% to 12.4%, p = 0.021) significantly changed from baseline to 12 months of CGM use.

Conclusion: Appropriate and continuous CGM use resulted in significant improvement in glycemic control in youth with T1D. Educating patients to keep the recommended "time CGM is active (≥70% use of CGM)" is important for better glycemic outcomes.

P2-59

First case of Diabetes Mellitus Caused by compound heterozygous changes in the WFS1 and PTF1A Genes from Kazakhstan

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Background: We report the first case of Wolfram syndrome with heterozygous polymorphisms of WFS1 and PTF1A genes.

Case Description: 16 years-old girl presented with diabetes mellitus at 12 years of age with HbA1c of 8.4 %. The IA-2, Islet cell, Insulin antibodies (Ab) were negative. GAD Ab were positive 26 U/ml (nl< 4). C-peptide level was normal 1.33 ng/ml (1.1-4.4 ng/ml) even after 4 years of diagnosis. She was initially treated with Metformin 500 mg twice a day and HbA1c increased to 12.1 %. Metformin was increased to 850 mg twice a day and Glibenclamid 3.5 mg once a day was added and HbA1c improved to 6.7%. Right side sensorineural hearing loss was diagnosed at 14 yrs. She has mild ataxia diagnosed at 16 yrs. and learning disability diagnosed at 12 yrs. MRI the brain and pancreas were normal. MGF and PGM had diagnosis of diabetes type 2.

Results: DNA analysis revealed a heterozygous polymorphism c.47C>T or p.Pro16Leu (rs34653805) in exon 2 of WFS1 gene. This sequence change replaces proline with leucine at codon 16 of the WFS1 protein.

Another heterozygous polymorphism c.172C>T or p.His58Tyr (rs759962056) was identified in the PTF1A gene. The PTF1A gene is associated with pancreatic and cerebellar agenesis. This sequence change replaces histidine with tyrosine at codon 58 of the PTF1A protein. In our case it is of uncertain significance. No evidence of cerebellar or pancreatic hypoplasia.

Discussion: It is remarkable that heterozygous polymorphism in WFS1 presented with sensorineural hearing loss, learning disability, mild ataxia and progressing diabetes not yet requiring insulin.

Rare heterozygous variants in WFS1 were described before in cases of hearing impairment, diabetes, impaired vision. C-peptide

level was normal after 4 yrs. of diabetes, despite positive Gad Ab. Positive GAD Ab are uncommon in Wolfram syndrome but described in rare cases.

Conclusion: The genetic investigation of diabetes in case of negative islet cell AB, normal C-peptide results in a personalized treatment. In our case identification of heterozygous polymorphism in WFS1 helped in clincial investigation of hearing, neurological evaluation and understanding of diabetes.

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P2-60

Pediatric Diabetic Ketoacidosis with Hyperosmolarity in Korea: Clinical implications and Outcomes

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Objectives: Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are potential life-threatening emergencies of diabetes mellitus (DM). DKA and HHS may coexist, making the treatment difficult. With increasing rates of childhood obesity and pediatric type 2 DM, cases of mixed HHS and DKA are expected to occur more frequently than before. But the frequency and implications of combined DKA/HHS in children/adolescents are not yet well known. We aimed to investigate the frequency and clinical outcomes of children/adolescents with combined DKA/HHS.

Methods: We reviewed all cases admitted between 2009-2021 with diagnosis of DKA or HHS. We determined 1) the frequency of HHS, DKA, and combined DKA/HHS (DKA criteria plus elevated effective osmolality) 2) severity of illness and clinical comorbidities in each group.

Results: There were 199 patients with type 1DM and 149 patients with type 2 DM, of which a total of 86 patients were hospitalized with hyperglycemic crises [type 1DM (n=79) and type 2 DM (n=7)]. Significant portion of patients diagnosed as DKA had combined features of HHS; Eleven (14%) patients with type 1DM and 2 (29%) patients with type2 DM had combined DKA/HHS features. Severe complications in patients with DKA/HHS included acute kidney injury, rhabdomyolysis, thrombocytopenia associated multi-organ failure (TAMOF), and diabetic amyotrophy. In type 1DM patients, combined DKA patients had higher creatinine level (1.20±0.25 vs 0.83±0.30 mg/dL, P<0.001) and longer hospital day (12.5±64.8 vs 8.9±3.5 days, P=0.004) than isolated DKA group.

Conclusions: Combined DKA/HHS can accompany severe complications, and is associated with longer hospital stay compared with isolated DKA. Adequate acute phase management and monitoring of complications are required for these patients.

P2-61

Ketoacidosis and age distribution in new-onset type 1 Diabetes during COVID-19 Pandemic

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Background: There are numerous reports indicating increased risk of diabetic ketoacidosis (DKA) in new-onset type 1 diabetes (T1D) in childhood during COVID-19 pandemic. Delayed diagnosis, reduced access to immediate health care and psychological effects of pandemic have been suggested as possible reasons.

Methods: We conducted cross sectional, single-center study at Department of Pediatrics, University Hospital Center Zagreb, Croatia, evaluating severity of DKA in patients diagnosed during COVID-19 pandemic as compared to pre-pandemic period. Besides COVID-19 pandemic, Croatia suffered two severe earthquakes, adding psychological burden and difficulties to health care organization. The data collected for the period March 2012 - March 2022 included: age, sex, laboratory parameters at presentation (pH, HCO3, HbA1c), association of celiac and autoimmune thyroid disease and frequency of positive pancreatic antibodies. The pandemic group (PG) included patients diagnosed form March 2020 to March 2022 while previously diagnosed patients comprised control group (CG).

Results: There were 107 patients in pandemic group (57M/50F) as compared to 337 controls (191M/146F). No significant difference was found between PG and CG regarding age (9.2/ 8.9 years), sex, DKA frequency (44.9/40.4%) or severity (mild: 15.2/13.8%; moderate 15.2/13.5%; severe: 13.3/12.3%), HbA1c at diagnosis (11.5/ 11.2%) and frequency of admission to intensive care unit. There was no difference regarding frequency of celiac (5.6/ 3.0%) and autoimmune thyroid disease (15.0/22.0%) at presentation, or negative pancreatic antibodies (6.8%/4.5%).

We found significantly higher frequency of new-onset diabetes in children < 5 years during pandemic (32.7% vs. 20.5%, p=0.009). Particularly increased frequency during pandemic was noted in children < 2 years (12.1% vs. 6.2%, p=0.045). The age distribution was as following in PG/CG: <2 yrs 12.1/6.2%, 2-5 yrs 20.6/14.2%, 5-11 yrs 26.2/41.8%, 11-18 yrs 41.1/37.7%. No difference in DKA frequency or severity between PG and CG was noted among age groups.

When comparing 1st and 2nd pandemic year, there was no difference regarding age, sex, frequency and severity of DKA.

Conclusion: Despite adversities experienced during COVID-19 pandemic and post-earthquake recovery, we did not find increased frequency or severity of DKA in new-diagnosed T1D. However, we found increased percentage of new-onset T1D among patients <5 years during pandemic, particularly < 2 years, but we did not find increased DKA presentation in any age group. Further studies are necessary to elucidate the effect of COVID-19 pandemic on presentation and related complications of T1D and to determine if the shift toward the younger age at presentation will be abiding.

P2-62

Time Trend and Potential Risk Factors for Celiac Disease Development in Children with Type 1 Diabetes Mellitus-10-year Single Center experience

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Background: Celiac disease (CD) is an important association with type 1 diabetes (T1DM) with a significant impact on growth and glycaemic control. The frequency of coexistence of T1DM and CD is widely described, ranging from 2.5 to 16.4% in 23 studies worldwide, much greater than the general population risk of 1%. The risk of CD is higher among younger children (less than 4 years), females and during the first few years of T1DM diagnosis.

Objectives: We aimed to describe the demographic and clinical characteristics of children with CD with an underlying diagnosis of T1DM. Also, we estimate the incidence and time trend of CD diagnosis among our cohort. We also investigate potential factors that might increase the risk of development of CD among this cohort.

Method: A retrospective chart review of EMR of children (age 1-18 years) with T1DM who attended the paediatric endocrine clinic during the period 2010-2021.

Results: 898 patients with T1DM were identified during the study period. 93 of them developed CD during the study period, with an incidence of CD among our study cohort of 10.4%. The female gender represents 52.7% of them. The mean age at CD diagnosis was 8 ± 3.5 years, with the average duration of diabetes of 2.9 years ± (2.8) before CD diagnosis. The majority (64.5%) were asymptomatic for CD and were identified through routine screening. Among T1DM with CD majority (83%) developed CD over the first 5 years of T1DM diagnosis. All children with the coexistence of CD and T1DM had positive serology for CD, 79.5% underwent endoscopic duodenal biopsy, and 90.5 % of them showed villous atrophy. In our cohort, we were able to identify risk factors for developing celiac disease which includes: Age ≤ 8 years at the time of T1DM diagnosis (P=0.003) and positive family history of CD (P=0.001). The coexistence of autoimmune thyroid disorder (AIDs) and gender were not significant predictors of developing CD in our cohort (P=0.056) and (P=0.92) respectively.

Conclusion: The incidence of CD among children with T1DM in our setting is 10.4%; comparable to the regional & international studies. The estimated cumulative risk of CD is significantly higher in younger children and those with a positive family history of CD. The majority (64%) were asymptomatic for CD and identified through routine screening. More than two third of children with CD were diagnosed during the first 5 years of T1DM diagnosis. These findings support the importance of implementing routine CD screening among children with T1DM to reduce the risk of potential health-related consequences of undiagnosed CD.

P2-63

Atypical diabetes with spontaneous remission associated with systemic lupus erythematosus in an adolescent girl with African ancestry

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Background: New-onset diabetes in youth can classically fall into three categories: type 1 diabetes (T1D), type 2 diabetes (T2D), or monogenic diabetes (MD). This classification is based on the underlying disease mechanisms, dictates treatment, and predicts outcome. Type B insulin resistance syndrome (TBIR) and ketosis-prone diabetes (KPD) are described in the African population, but their incidence in the pediatric population is very low.

Case Presentation: We present the case of an adolescent girl of African descent recently diagnosed with systemic lupus erythematosus (SLE). She was admitted to the emergency room with ketoacidosis, positive anti-insulin antibodies, a hemoglobin A1c (HbA1c) of 12.1% (109 mmol/mol) and was diagnosed with T1D and managed accordingly with intravenous insulin. Metformin was added due to obesity and signs of insulin resistance. She also received treatment with hydroxychloroquine, mycophenolate mofetil, and prednisone in the context of SLE. After discharge from the hospital, the family slowly discontinued insulin injections and metformin without informing the treating physicians. Five months after the diabetes diagnosis, the HbA1c values and glycemia had normalized without any anti-diabetic treatment, despite continuous glucocorticoid therapy accompanied by an increase in body weight. Exome analysis did not reveal any variants involved in MD. Type 1 genetic risk score (GRS), to assess type 1 diabetes susceptibility, was below the 1st centile.

Conclusion: We illustrate a complex form of a reversible diabetes subtype. Several features, such as the anti-insulin antibodies, an additional autoimmune disease, SLE, point towards an autoimmune origin. The overlapping HLA risk haplotypes for T1D and SLE supports this idea. Further, we hypothesize that a decrease in SLE disease activity, supported by the drop of SLE antibodies, could have favorably influenced the remission of diabetes in this case. In addition, the current immunomodulating treatment for SLE could have helped to abort the developing T1D. The GRS does not support this hypothesis, but does not rule out T1D entirely, because it was not developed for people of African ancestry. Ketosis-prone diabetes, classified as idiopathic but not an HLA-associated form of T1D, could be another differential diagnosis. We rather rule out T2D because remission should not have occurred during weight gain and while on glucocorticoid therapy. The clinical phenotype does not quite fit with the diagnosis of TBIR. In the near future, the recently developed ancestry-tailored GRS will improve the prediction of T1D across ancestries and lead to a better understanding of the different underlying disease mechanisms.

P2-64

Diabetes Secondary to Glucokinase Gene Polymorphism with Obesity and Fluctuating Severity of Diabetes

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Case Report: 14 yrs. old Hispanic girl was referred for evaluation of diabetes (Hb A1c 9.8 %) and morbid obesity BMI 36 kg/m2.

She developed acanthosis nigricans, elevated triglycerides (TG) 1162 mg/dl, low HDL 34 mg/dl, fatty liver with elevated AST 84 U/L, ALT 103 U/L. The abdominal sonogram revealed significant hepatomegaly with moderate steatosis.

Her islet cell AB were negative, C-peptide 3.11 ng/ml was normal. She has a strong family history of diabetes: mother, maternal aunt, uncle and maternal grandmother.

She was treated with Glyburide 10 mg twice a day, metformin 1000 mg twice a day, Victoza 1.8 mg daily, Gemfibrozil 600 mg twice a day, Omega 3 1000 mg daily.

After 1 year of treatment BMI decreased to 31.6 3 kg/m2, Hb A1c improved to 6.7 %, TG decreased to 144 mg/dl, HDL 34 mg/dl, LDL 115 mg/d, ALT18 U/L, AST 14 U/L. All medications were discontinued except Metformin. Dexcom sensor readings confirmed glucose level in the normal range on Metformin treatment.

Results: Genetic analysis identified heterozygous polymorphism in Glucokinase gene GCK c.1033C> G (p.Arg345Gly). This sequence change replaces arginine with glycine at codon 345 of the GCK protein (p.Arg345Gly). The arginine residue is highly conserved and there is a moderate physicochemical difference between arginine and glycine. This variant is not present in population databases (ExAC no frequency). This variant has not been reported in the literature in individuals with GCK-related conditions. ClinVar contains an entry for this variant (Variation ID: 987827).

Discussion: Glucokinase MODY 2 is usually suspected in non-obese patients without signs of insulin resistance, with mild fasting hyperglycemia, normal C-peptide, negative β-cell antibodies, and associated with a positive family history of diabetes. In our case after BMI improved from 36 to 31.6 kg/m2, the severity of diabetes improved and only Metformin was enough to keep glucose level in the normal range.

MODY 2 with obesity was described before. But this is the first case when obesity with MODY 2 was complicated with severe diabetes, with dramatic improvement in HB a1c after moderate weight loss.

Conclusion: Genetic analysis in cases of diabetes is important for individualized treatment and understanding of the natural history of diabetes.

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P2-65

Effect of carbohydrate counting education in Korean patients with type 1 diabetes

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Background: The achievement and maintenance of normoglycemia is one of the most important goals to prevent both short and long-term complications in type 1 diabetes mellitus (T1DM). As carbohydrate acts as the primary macronutrient affecting postprandial glycemic response, carbohydrate counting is crucial in adjusting prandial insulin doses to preserve postprandial blood glucose within normal limits. The purpose of this study is to examine the effect for carbohydrate counting education on glycemic management in patients with T1DM in South Korea and further discuss its important and future directions.

Method: A retrospective chart review of 128 diagnosed T1DM patients who underwent carbohydrate counting education was conducted. All subjects were diagnosed with T1DM before December 2019, and were educated carbohydrate counting before December 2020 in pediatric endocrinology, Severance Children's Hospital, Seoul, Korea. We analyzed the effect of education on the basis of changes in HbA1c levels. In addition, the differences in educational effects according to various variables such as sex, age, diabetes duration, presence of complications, degree of disease control, and device use were identified.

Results: In 128 T1DM subjects educated, 48 (38%) were male. Their mean age at diagnosis was 8.6 ± 4.0 (years) and mean age at the time of education was 22.6 ± 7.8 (years). Overall, HbA1c levels at 3, 6, and 12 months after education showed a significant decrease compared to the baseline. The mean ±SD (standard deviation) HbA1c level, which was 8.8 ±1.9 (%) at the baseline, decreased to 8.3 ±1.7 at 3 months, 8.3 ±1.7 at 6 months, and 8.3 ±1.7 at 12 months after education. In multivariate linear regression analysis, only the value of baseline HbA1c ($P<0.001$) as an indicator of disease control was significantly correlated with decrease in HbA1c.

Conclusions: In our study, carbohydrate counting education seems effective in glycemic control in patients with type 1 diabetes mellitus, but the decrease in HbA1c seems not enough. The effect of education differed between poorly managed and well managed patients. For patients with poor management, providing proper education of carbohydrate counting, itself can make improvement in glycemic control. For well-managed patients, more advanced approach beyond traditional education appears to be required. With proper education, better blood glucose control can be expected to reduce complications and improve quality of life in T1DM patients.

P2-66

A Novel Mutation in the Hepatocyte Nuclear Factor 1-Alpha Detected in Case of a 13-Year-Old Female with Maturity Onset Diabetes of the Young (MODY)

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Maturity onset diabetes of the young (MODY) is a rare type of non-autoimmune diabetes mellitus which usually present in young adulthood. An estimated prevalence was 1.2% within the pediatric diabetic population. To date it has been proposed that pathogenic variants in at least 14 genes cause MODY. Among these genes, most cases result from mutations in HNF1A (MODY3), GCK (MODY2), HNF4A (MODY1) and HNF1B (MODY5). The patient is a 13-year-old, previously healthy, nonobese female with no past medical history without weight loss, polydipsia, nocturia, and polyphagia. However, strong family history of diabetes was reported with mother, grandfather in mother. Her height and weight were 155.3 cm and 44.8 kg, respectively, and her body mass index was 18.7kg/m² at the 25th percentile for age and sex. Her vital signs were within normal limits, her blood pressure was not elevated, and she was well-appearing. Her screening lipid panel was within normal limits (cholesterol 190 mg/dL, high-density lipoprotein 70mg/dL, low-density lipoprotein 107 mg/dL, and triglycerides 73 mg/dL). HbA1c was significant for a value of 9.5% and all islet cell autoantibody screen and all other screening labs returned as negative. Urinalysis showed no evidence of acidosis or urine ketones except glycosuria. In the setting of new-onset diabetes, a negative islet cell autoantibody screen and a family history of autosomal dominant diabetes, a diagnosis of MODY was suspected. Next generation sequencing was sent and revealed a heterozygous mutation in HNF1A gene designated c.788G>A (p.Arg263His) consistent with MODY3 which was not reported previously. In silico predictions (SIFT, PolyPhen, and MutationTaster) were predicted to be deleterious. The patient's glycemic control has been started with intensive insulin therapy, and plan to change to sulfonylurea to reduce microvascular comorbidities and maintain the glycemic control successfully. We present a case of a 13-year-old previously healthy female with a multigenerational family history of diabetes diagnosed with MODY due to a mutation in HNF1A. In families with 2 or more generations of diabetes, there should be a low threshold for asymptomatic screening with a serum HbA1c. Early diagnosis and appropriate management can aid in preventing potentially irreversible consequences of undiagnosed, persistent hyperglycemia.

P2-67

Impact on metabolic control in pediatric patients with use of technology applied to type 1 diabetes

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Background and Aims: The treatment of type 1 diabetes (T1D) requires a great involvement of the patient to achieve optimal blood glucose levels. Technological devices have been developed for individualized treatment, fewer interventions of the patient, and evidence of improved metabolic control.

The aim of the study is to know data on metabolic control in a group of pediatric patients with T1D treated with new technologies, compared to patients treated with multiple daily doses of insulin.

Methods: This is a retrospective observational study of 210 pediatric patients with T1D under follow-up in the Diabetes Unit of University Pediatric Hospital of Badajoz (Spain). Data on metabolic control and glycemic variability were studied in two groups of patients: patients treated with multiple daily doses of insulin with continuous glucose monitoring (DEXCOMG6™) or flash glucose monitoring (FREESTYLE2™), and patients treated with continuous subcutaneous insulin infusion (CSII): MiniMed™640G, MiniMed™670G and MiniMed™780G.

In addition, we value the percentage of patients in each group that achieve the international standards of metabolic control.

Results: A statistically significant reduction in HbA1c was observed, as well as an increase in the time in target range of 70-180 mg/dl, a decrease in the time in hyperglycemia and a decrease in the average blood glucose and CV in the group of patients treated with CSII. No significant increase in time in hypoglycemia was observed.

The results of the study are shown in table 1.

There is a higher percentage of patients in the group treated with CSII compared to the group treated with multiple daily doses of insulin who reach HbA1c target and time in range target (40,7% vs 26,8% and 63,4% vs 21,1% respectively), being evident in the age group between 6 and 12 years.

Conclusions: Treatment with continuous subcutaneous insulin infusion achieve greater benefit on metabolic control in pediatric patients with T1D compared to treatment with multiple daily doses of insulin.

Table 1. Data on glucose control and glycaemic variability in both groups of patients, multiple daily doses of insulin and pump-sensor system (n=210)

	MDDI	CSII	p
HbA1c (%)	7,6	7	<0,001
TIR 70-180 mg/dl (%)	56,4	73,4	<0,001
Time <70 mg/dl (%)	3	2,2	0,117
Time <54 mg/dl (%)	0,6	0,5	0,661
Time >180 mg/dl (%)	26,5	20,7	<0,001
Time >250 mg/dl (%)	15,2	5	<0,001
Mean glucose (mg/dl)	174,5	150,6	<0,001
SD of glucose (mg/dl)	63,8	51,6	<0,001
CV (%)	37,3	33,8	<0,001

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Diabetic Ketoacidosis Resulting From I-port Device Failure In Multiple Cases

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Background: Multiple daily injections of insulin for children and young people with diabetes can be very daunting and, some have a phobia of needles. As a result, for some individuals, the use of an i-port device can be life-changing and help with their diabetes management. The i-port is an injection port that enables diabetes patients to administer their insulin without having to puncture their skin multiple times in a day. In most cases, the i-port can stay in place for up to 3 days, before it needs to be replaced.

We report three type 1 diabetes cases, in which their i-ports failed to deliver insulin and therefore, resulted in all three cases presenting to hospital with DKA (Diabetic Ketoacidosis).

Description: 14-year old girl, who 24 hours prior to her admission, had high blood sugar readings. She and her parents gave insulin correction doses, which did not have an effect on her blood sugar readings.

10-year old girl, whose parents were unable to get her blood glucose and ketone levels in range. It was noted that her i-port cannula was kinked and leaking.

8-year old boy, whose father gave multiple correction doses for high blood sugar readings. However, his blood sugar readings remained high. His father then stopped using the i-port and gave a further dose of insulin subcutaneously. However, by this time he was in DKA.

All three cases presented in DKA due to failure to deliver insulin through their i-port devices. They all required admission to high dependency unit for treatment with intravenous insulin and fluids. All were discharged within 48 hours, with safety netting advice and had one week follow up with the paediatric diabetes nurse, for further education around how to promptly and effectively manage their i-port devices. In addition, they also had follow up in the multidisciplinary paediatric diabetes outpatient clinic.

Discussion: These cases highlight the message that failure of i-port devices can be life-threatening, especially if it is not dealt with promptly. Regular education around the appropriate management and use of i-port devices to patients and their families is paramount.

P2-69

Impact of β-cell function and glucose effectiveness on the development of type 2 diabetes mellitus in obese European children and adolescents

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Objectives: Despite high prevalence rates of childhood obesity, youth-onset T2DM occurs in a comparably lower incidence in Europe than in other world regions. Available data from cohorts of obese children and adolescents living in the US suggest a parallel decline of insulin sensitivity and β-cell function as key factors in the pathophysiology of early-onset T2DM. If these results can be applied to European children and adolescents is currently unknown.

Methods: For this study, 3hr, 8 sample OGTT data of n=13 children and adolescents with T2DM (9 girls, øage 15.2 ±2.8 ys, øBMI z-score 2.85 ±0.67) was analyzed using mathematical modelling of insulin secretion and disposal in combination with a minimal model of glucose to estimate insulin sensitivity SI, β-cell responsiveness Phi, and insulin-independent glucose disposal SG. As control groups, OGTT data from n=39 children and adolescents with normal glucose tolerance (NGT) and n=13 children and adolescents with impaired glucose tolerance (IGT), each matched for age, sex, pubertal stage, and BMI z-score, were analyzed.

Results: Compared to NGT subjects, patients with manifest T2DM were characterized by a globally impaired glucose metabolism with significantly lower insulin sensitivity SI (-71%, $p < 0.001$), decreased β-cell responsiveness Phi (-69.5%, $p<0.001$), and glucose effectiveness SG (-43%, $p<0.001$). IGT was associated with a 58% lower insulin sensitivity, a 39.5% lower β-cell responsiveness, and a 12% lower glucose effectiveness compared to NGT subjects (each $p<0.01$). Furthermore, comparing T2DM patients with their matched IGT peers revealed, that T2DM was associated with a further decline in β-cell responsiveness Phi (-49.7%, $p<0.001$) and glucose effectiveness SG (-35.5%, $p<0.001$), while insulin sensitivity SI was not significantly reduced (0.046 ±0.003 vs. 0.067 ±0.005 dl/kg/h per $mIU_{insulin}$/ml, $p=0.22$).

Conclusions: Obese European children and adolescents affected by youth-onset T2DM are characterized by severe impairment of insulin sensitivity, β-cell responsiveness, and insulin-independent glucose disposal. Comparison to matched controls over the spectrum of glucose tolerance strongly suggests, that significant further worsening of β-cell function and a marked collateral decrease in glucose effectiveness are pivotal pathophysiologic events in the development of youth-onset T2DM.

P2-70

Familial Genetic Syndrome of Severe Insulin Resistance and Hyperandrogenemia in a young girl with Polycystic Ovary Morphology

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Introduction: Signs of hyperandrogenemia are common through adolescent and young females, hirsutism affecting 5% of reproductive -aged women. The most common cause of hyperandrogenemia and insulin resistance (IR) is polycystic ovary syndrome (PCOS) (1). The differential diagnosis includes congenital adrenal hyperplasia (CAH) (2), androgen secreting tumors, but also very rare genetic syndromes of IR.

Case report: A 13 year-old girl presented to our Paediatric Endocrinology Department for severe hirsutism, primary amenorrhea, alopecia and progressive deepening of the voice. Family history revealed that her mother and also her maternal grandmother and great-grandmother had hirsutism and type 2 diabetes mellitus. Physical examination showed a height at presentation of 153,54 cm (-0,72 SD), BMI=17,2 kg/m2(p=23%), B3P5 Tanner stage, androgenic alopecia, clitoromegaly (~ 2,5 cm) and severe hirsutism (preauricular hairiness, upper-lip, white line, chin and on the back). Laboratory exams revealed elevated testosterone level (3x UN), severe hyperinsulinemia (basal insulin > 21uIU/ml, insulin in OGTT> 215uIU/ml), altered glucose tolerance and an elevated 17-OH basal progesterone. Therefore, the Synacthen stimulation test was performed in order to exclude CAH (60 minutes 17-OH progesterone=9,6 ng/ml). The serum concentration of DHEA sulfate, androstenedione and cortisol were within normal limits. Pelvic ultrasound revealed infantile uterus and polycystic ovary morphology. Because the level of testosterone was very high, we decided to perform an abdominal-pelvic MRI that revealed no evidence of ovarian or adrenal masses. Genetic tests identified 46, XX Karyotype and a mutation of P453S (c.1657C>T) CYP21A2. Because of her family history and abnormal levels of basal and stimulated insulin a syndrome of IR was suspected and we decided to continue the genetic evaluation. Treatment with metformin was recommended along with an androgen receptor-blocking agent (spironolactone) to control hirsutism and ensure glycemic homeostasis with a good clinical and biochemical outcome.

Conclusions: Hyperinsulinemia contributes to the marked magnitude of hyperandrogenemia and is a determinant of the severity of hirsutism. There's a group of rare congenital conditions described as inherited severe IR syndromes that can lead to severe hyperandrogenism associated with altered glucose tolerance. Therefore, detailed family history and genetic counselling should be done in such cases.

P2-71

The Effect of Parental Monitoring on Glycemic Control in Adolescents with Type 1 Diabetes

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Introduction and Aim: Adolescence is the period when the management and metabolic control of the disease are the most difficult in type 1 diabetes mellitus, and the adolescent and parents experience the most intense problems. Although there are studies showing that parental support positively affects glycemic control and treatment compliance, studies investigating the effect of parental monitoring on glycemic control are limited. In this study, it was aimed to investigate the effect of parental monitoring on the glycemic control of adolescents with T1DM.

Cases and Methods: Socio-demographic data form (single parent) and Parental Monitoring of Adolescents with Type 1 Diabetes Scale were filled online by the caregivers of children and adolescents aged 12-18 years who were being followed up in the Pediatric Endocrinology outpatient clinic with the diagnosis of Type 1 diabetes mellitus. The relationship between scale scores and metabolic control was evaluated. In addition, the factors affecting parental monitoring were investigated.

Results: 37 patients with a mean age of 15±1.72 (12.25-17.92) were included. The mean age at diagnosis was 9.17±3.63 (1.58-15.58), and the mean duration of diabetes was 5.79±3.85 (0.92-15.25). The mean Hba1c value was 8.30 ±1.98% (6.0-14.0). When the hba1c values of the mothers were compared according to the working status of the mothers, the hba1c of the adolescents whose mothers were working was 9.4%, while the hba1c of the group whose mothers were not working was 7.5%. A positive correlation was found between the parental follow-up score and the hba1c value. As the parental follow-up score increased, the hba1c value also increased. No correlation was found between the follow-up score and chronological age, age at diagnosis, duration of diabetes, education of parents, or income status.

Discussion: Contrary to studies suggesting that parental monitoring increases compliance in adolescents with type 1 diabetes, we found that glycemic control worsened as the parental monitoring score increased. We think that this may be due to several different reasons. First of all, Parents of poorly controlled diabetics may have answered the questionnaire biased with a sense of guilt. On the other hand, parents of adolescents with poor glycemic control need to monitor their children more closely. In addition, although validity and reliability studies have been conducted, adolescents with good diabetes compliance may have received lower follow-up scores, since the current questionnaire questions were aimed at catching poor diabetes follow-up.

P2-72

A rare case of Type 1 Diabetes preceded by Hashimoto thyroiditis and followed by Multiple Sclerosis

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Introduction: Type 1 Diabetes(T1) and autoimmune thyroid disease(AITD) can occur concomitantly. Multiple sclerosis(MS), a chronic condition resulting from dysfunction of the immune system, may co-occur with T1D.

Aim: We present a 17-year-old boy presented with AITD at 10y old and within seven years developed T1D and MS.

Subjects and Methods: The patient presented at the age of 10y old with Hashimoto's thyroiditis.Four years later, while on T4, he was admitted to hospital with diabetic ketoacidosis(DKA), treated according to DKA protocol and then with insulin(MDI) injections to date.Three months later he was readmitted with sudden onset of weakness, hypaesthesia, numbness of upper and lower extremities, blurred vision of 24 hours and tinnitus of 10 days.Normal reflexes, left-sided hypaesthesia, right-sided horizontal nystagmus were noted and treated with steroids. He relapsed three months later with gradual recurrence of MS symptoms-blurred vision of the right eye, hypaesthesia of the left side of the chest. He was treated with steroids and subsequently with interferon beta-1a. He has been well since with occasional short periods of recurrence of weakness. His glycaemic control is good, while on T4 and interferon. He recently had positive antinuclear(ANA) antibodies and is now being investigated for rheumatic disease.His eldest brother also presented with MS symptoms without progressing to overt disease.His mother and maternal grandmother suffer from Hashimoto thyroiditis.

Results: Initial TSH was 8.5(NR 0.3-4.0mU/L), FT4 16.0(NR 10.0-25.0pmol/L), anti-TPO 1262.6(NR 0-100IU/ml), anti-TG 811(NR 0-100U/ml).initial HbA1c was 13.1%(NR 4-6%). IA2 antibodies were 459IU/ml(<30 negative), anti-GAD 88.9u/ml(<10 negative), antiZnT8A 64.8(<15RU/ml negative).HLA haplotype was DRB1*04,*07DQB1*02,*03(HLA-DQ2, DQ8). ANA antibodies are positive (1/160), ACE activity 165.00 (NR 13.3-63.9 U/L). Ultrasound of the thyroid gland showed a heterogeneous, hypoechoic parenchymal echo pattern, decreased echogenicity of the lobes, presence of echogenic septa due to Hashimoto's thyroiditis. Brain MRI findings were in favour of MS demyelinating disease, showing focal areas of high signal in the T2/Flair sequences in the white matter of the right upper ventricle, gliosis elements, smaller foci of high signal in the posterior parietal region on the left and occipital right region and cervical spinal cord.

Conclusions: Concomitant auto-immune disease can complicate diabetes management and has various clinical presentations. The pathomechanism behind the co-occurrence of T1D and MS is unclear; the underlying mechanisms may involve genetic and environmental causes.T1D-MS male patients have a higher rate of thyroid-specific antibodies.Further research is needed.

P2-73

Recurrent glycogenic hepatopathy in an 11-year-old boy with poor glycemic controlled type 1 diabetes mellitus

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Introduction: Glycogenic hepatopathy (GH) is a rare diabetic complication that induces hepatomegaly and elevated transaminases, which can often appear in type 1 diabetes mellitus (T1DM) with poor glycemic control. GH appears when excess glycogen accumulates in the liver through continued hyperglycemia with intensive insulin therapy. We show a pediatric case of recurrent GH due to poor glucose controlled with complicated family environment and mildly intellectual disability.

Case Report: The patient was diagnosed with T1DM due to blood glucose of 516 mg/dL, HbA1c 8.6%, and an anti-insulinoma associated protein-2 antibody 0.9 U/L at six years of age, then intensive insulin therapy was started. Blood glucose was well controlled in the first one year, however, blood glucose was worsened due to complicated family environment. HbA1c worsened from 6.7 to 12.0 % at nine years of age after the end of the honeymoon period. At 10 years of age, AST/ALT deteriorated and elevated to 448/259 U/L in a few months. There were no abnormal coagulation and fibrinolytic system, viral hepatitis, autoimmune hepatitis, or biliary tract diseases. We performed abdominal ultrasonography, CT and MRI, then fatty liver and GH were suspected. Liver biopsy was not performed due to the same treatment approach for fatty liver and GH consulted by hepatologists. AST/ALT improved rapidly with strict glycemic control during hospitalization at 12 days. We recommended continuous subcutaneous insulin infusion (CSII) but declined. He was diagnosed with GH. At 10 years of age, poor glycemic control was observed (HbA1c; 10.1 to 12.4%), and again AST/ALT deteriorated and elevated to 298/146 U/L. GH had repeated and he was re-treated in hospital. The patient and family were persuaded to change the treatment modality from intensive insulin therapy to CSII. Blood glucose was well controlled (HbA1c 8.4%), which was used by CSII, and AST/ALT also improved to 28/22 U/L. HbA1c remained at 8.5-10.0%, and GH recurrence did not occur. WISC-IV was performed at 10 years of age and FIQ was 60 (mildly intellectual disability), which would have made intensive insulin therapy difficult.

Conclusion: There was recurrent GH due to familial environment and mildly intellectual disability, but CSII allowed improved glycemic control.

P2-74

Knowledge and Confidence of Omani Paediatric Residents in Managing Diabetic Ketoacidosis (DKA); A Cross Sectional Survey

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Background: Diabetic ketoacidosis is a common complication of Type 1 diabetes Mellitus (T1DM). Unfortunately, medical errors are not uncommon during management of DKA leading to significant morbidity and mortality. Junior doctors/residents are usually the clinicians who initiate the management of DKA. There are many studies conducted to assess the knowledge of junior doctors, residents, and medical students in management of DKA in many countries including Bahrain, Iraq and Saudi Arabia. To our knowledge this area was not studied among Omani pediatric residents before.

Objectives: The aims are to assess the knowledge and confidence of Omani pediatric residents in management of diabetic ketoacidosis and compare the findings with the results of previous studies from GCC countries to find out if there is a need to intervene in order to boost the knowledge and confidence of our residents.

Methods: a across sectional study include pediatric residents enrolled in Oman medical specialty board, from year one to year four of paediatric residency program in 2021. Data collected by using an online survey.

Results: 69 residents response to the survey (15M:54F), their levels were R1 (34.7%), R2 (24.6%), R3 (13.2%) and R4 (17.4%). Only 7 residents (10%) have not worked in paediatric emergency yet. Initial self-assessment and rating indicated fair level of knowledge among 30.4%, good knowledge in 56.5% and very good among 10.1%. Their responses as tabulated.

	Percentage of correct answers (%)
Detecting symptoms of DKA	94.2
Determining the diagnostic criteria	89.9
Determining the severity of DKA	68
Type and rate of initial IV fluids	87.1
Notifying their seniors immediately	75.4
Avoid giving unnecessary fluid boluses	85.5
Timing to start insulin infusion	88.4
Frequency of checking the glucose level	75.4
Cardiac monitoring and frequency of reviewing it	92.6/95.5
Adding dextrose to IV fluids	84
Awareness of cerebral edema symptoms/signs	84
Dealing with hypoglycemia during DKA management	21.7

88.4% of residents preferred to have more educational sessions about management of paediatric DKA. No significant statistical difference between the answers of different trainees' levels. Their confidence was rated as "very confident" by (4.3%), "confident" (37.7%), "fair" (49.3%) and "no-confidence" by (7.3%). Overall responses were better compared to the previously published studies from Bahrain and Iraq.

Conclusion: There are still some gaps in knowledge to be bridged about management of paediatric DKA. Continuous educational activities are desired. Therefore more sessions about DKA management to be scheduled and perhaps apply simulation training to boost their confidence.

P2-75

Low vitamin D levels are associated with markers of metabolic syndrome in children with newly onset type 1 diabetes mellitus

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Background: Low vitamin D levels are prevalent in pediatric patients with type 1 diabetes mellitus (T1DM) and are associated with increased risk for insulin resistance, type 2 diabetes mellitus and cardiovascular disease. Little is known about associations between vitamin D levels and markers of metabolic syndrome in incident T1DM in children. The aim of our study was to analyze associations between D vitamin levels and metabolic markers in newly onset T1DM pediatric patients.

Methods: Subjects were 34 children with T1DM (57% girls; median age 9.6 +/-3.4 years) who were studied at time of diagnosis. Anthropometrics were assessed and laboratory parameters were measured in fasting blood samples (25-OH vitamin D, triglycerides, LDL- and HDL-cholesterol, glucose, insulin and HbA1c). The relationship between variables was analyzed by Pearson correlation followed by multiple regression analyses.

Results: Lower vitamin D levels were associated in these children with and adverse lipid profile, consisting in higher triglyceride (β= –0.392; p=0.02; adjusted R2=0.126) and lower HDL levels (β=0.437; p=0.01; adjusted R2=0.160), independently of age, sex and BMI. These associations were also relevant for the HDL/triglycerides ratio (β=0.494; p=0.003; adjusted R2 =0.219).

Conclusions: In newly onset pediatric type 1 diabetic patients, lower vitamin D concentrations are independently associated with markers of metabolic syndrome such as serum triglycerides and HDL-cholesterol. Our results indicate that incident T1DM pediatric patients with lower vitamin D concentration may present an increased metabolic risk compared to those with adequate vitamin D levels.

P2-76

Fibroblast growth factor 23 in relation to calcium-phosphate metabolism and cardiovascular risk factors in patients with type 1 diabetes

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Introduction: Cardiovascular disease (CVD) is the major cause of morbidity and mortality in type 1 diabetes (T1D). Recent studies implicated deregulated phosphate homeostasis in the etiology of CVD. The objective of this study is to address the relationship between the phosphate-regulating hormone fibroblast growth factor 23 (FGF23) and cardiovascular risk factors in adults with and without type 1 diabetes (T1D).

Methods: A case-control study was conducted using data from patients with T1D and age- and sex matched controls without T1D from the Lifelines Cohort Study. Baseline demographic and clinical data, along with calcium-phosphate parameters including plasma C-terminal FGF23, were compared between T1D and controls and in subgroups, using the Mann-Whitney test.

Results: We included 302 adults in the T1D group and 302 adults in the control group. Mean age of males was 42yrs, of females 43yrs. Sex (50% female) was identical in both groups. Median HbA1c in the T1D group was 62mmol/l (7.8%).

Median FGF23 in T1D patients was not significantly different from controls. Females with T1D had significantly higher FGF23 than males with T1D (83.3 vs 69.3U/ml, p=0.002), this was not observed in controls (75.6 vs 69.2U/ml, p=0.358).

Serum phosphate, calcium, and alkaline phosphatase levels were higher and PTH levels were lower in T1D patients, compared to controls (all p<0.001), all within normal range. In the T1D group, FGF23 was positively correlated with serum phosphate (p<0.001), alkaline phosphatase (p=0.01) and calcium levels (p=0.001), these correlations were not observed in controls.

In the T1D group the median FGF23 was significantly higher in current smokers (n=65, FGF23 84.9U/mL) than in non-smokers (n=235, FGF23 73.5U/ml, p<0.05). This difference was not present in the control group.

Median FGF23 was not significantly different between subjects with or without hypertension, a decreased estimated glomerular filtration rate (eGFR, CKD-EPI formula) or an elevated urinary albumin/creatinine-ratio in both the T1D and control group. In our population there was no correlation between FGF23 and eGFR, with eGFR being in the normal range for nearly all subjects.

Conclusion: FGF23 in T1D patients was not significantly different from non-diabetes age- and sex matched controls. Serum calcium, phosphate and alkaline phosphatase levels were higher in T1D patients than in controls and were positively correlated to FGF23 in T1D patients. Current smokers with T1D had higher FGF23 levels than non-smokers with T1D. These findings may contribute to the increased risk of cardiovascular diseases in patients with T1D.

P2-77

Rituximab Role in Preservation of Pancreatic Beta Cells in Patients Newly Diagnosed with Type 1 Diabetes Mellitus: A Report of 2 Palestinian Cases

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Type 1 diabetes mellitus (T1DM) is a condition caused by the clonal generation of autoantibodies by B cells. Rituximab, an immunosuppressive agent, has been shown in studies to protect pancreatic function in individuals newly diagnosed with type 1 diabetes mellitus (T1DM). We investigated the effects of rituximab in two individuals with newly diagnosed T1DM. Case 1 was a 10-year-old boy, and Case 2 was a 4-year-old girl, both of whom had T1DM. Insulin secretion capability was still present, as there was a detectable c peptide level in both cases. Rituximab treatment prevented pancreatic cell destruction and preserved some endogenous insulin production. In Case 1, HbA1c levels showed a significant drop on the same drugs and then steadily increased until returning to pre-rituximab levels one year later. In Case 2, however, HbA1c remained below 6.5% for 8 months following therapy and was below 7% after the second Rituximab dose. Both patients were administered a second Rituximab dose one year after the first one. While the second case remained on the same medications for maintenance of HbA1c, the first case was able to be maintained on just long-acting insulin without the need for the short-acting as before. Both patients are under close monitoring for glycemic control, insulin secretion capability, and adverse effects.

P2-78

Complications of COVID-19 on the thyroid gland functioning

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Annotation: Pandemics of coronoviral infection continues affecting the wold community, and with the comprehension of its pathological physiology an interest in endocrine effects of SARS-CoV-2 grows too. It was determined, that the main target organs affected by SARS-CoV-2 were lungs and immune system, while it is still not clear if SARS-CoV-2 has any impact on the thyroid function.

In patients infected with SARS-CoV, coronovirus relevant to SARS-CoV-2, damage of parafollicular and follicular cells in thyroid glands was seen at autopsy.

The Objective: To assess the consequent effect of Covid-19viral infection on thyroid functions prior to operation period.

Materials and Research Methods: While performing retrospective analysis we checked 110 case histories of patients receiving in-patient therapy in Vitamed clinic and Turakulov RSSPMC of Endocrinology from May 2020 to January 2021.We revealed 53 patients who recovered from Covid-19. We checked thyroid hormones (TTH, free T4, total T3), performed ultra sound imaging and histological test of thyroid gland, CBA, and biochemical tests.

Results: Among 53 patients, who recovered from COVID-19, there were 40 (75%) women and 13 (25%) men. The age of the patients varied from 30 to 78 years old (average 52.6 years old). Eleven patients out of 53 complained discomfort at the frontal side of neck, dry skin, feeling of a lump in throat, loss of hair, weakness, and shortbreathing. Ultra sound imaging revealed presence of nodes. Histological tests showed, that 7 patients had thyroid cancer. Ultra sound showed, that six patients out of 11 had TI-RADS 4, four had TI-RADS 3, and one had TI-RADS 5.Histological tests revealed, that six patients out of 11 hadBETHESDA 4, two had BETHESDA 5, and two patients had histologically revealed BETHESDA 2.

Conclusions:

1. According to the results of the performed tests we revealed multinodular goiter after Covid-19 in eleven patients out of 53. That indicates, that Covid-19 affects cells of thyroid gland.
2. Seven patients out of 11 recovered from Covid-19 had thyroid cancer. Ultra sound imaging revealed that, six patients out of 7 had TI-RADS 4, while histological tests revealed BETHESDA4.

P2-79

Association of type 1 diabetes mellitus with autoimmune diseases in children in the Department of Endocrinology-Diabetology and Nutrition at Mohammed VI University Hospital Center Oujda

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Introduction: Type 1 diabetes is frequently accompanied by other autoimmune diseases that can sometimes be integrated into autoimmune polyendocrinopathies.

Through this work, we sought to describe the association of autoimmune diseases with type 1 diabetes in children.

Patients and Methods: This is a retrospective and descriptive study, including 354 type 1 diabetic patients hospitalized in the Department of Endocrinology Diabetology and Nutrition at Mohammed VI University Hospital Center Oujda between 2016 and 2021.All our patients had benefited from a systematic search for autoimmune diseases. The statistical analysis was performed by SPSS version 21 software.

Results and Discussion: The mean age of our patients was 16 ± 1.9 years. Our population was predominantly female with a sex ratio of 0.94. A family history of autoimmune diseases was noted in 6 cases. Anti-IA2 and anti-GAD antibodies were positive in 19% of cases.

Autoimmune diseases were noted in 23 patients, 34.7% of whom were men and 65.8% women. Autoimmune dysthyroidism was the leading cause in 34% of cases. type 1 diabetes mellitus preceded dysthyroidism in 65% of cases. Celiac disease was noted in 30% of cases. Autoimmune polyendocrinopathy was listed in 39.2% of cases and psoriasis in 0.28% of our patients.

Conclusion: The frequency of autoimmune diseases in type 1 diabetics, which can sometimes be part of autoimmune polyendocrinopathy, encourages screening for them when diabetes is discovered. The screening will allow an early management of these disorders and prevent further complications.

P2-80

A MODY2 pedigree with GCK gene mutation and literatures review

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Objective: To report a family with MODY2 associated with GCK gene mutation and improve clinicians' understanding of this gene mutation.

Methods: The clinical manifestations, laboratory examinations and genetic test results of a MODY2 family diagnosed and treated in our hospital were analyzed retrospectively, and the related literatures were reviewed.

Results: The patient is a 6-year-old girl, her family members measured the fasting fingertip blood glucose of the child due to abnormal blood glucose of her sister. Moreover, the postprandial blood glucose fluctuated between 6.2 and 9.2mmol/L. Her HbA1c was 6.2% and fasting venous blood glucose was 8.0 mmol/L. She usually drink more and urinate more, and urinate twice a night, without polyphagia, polydipsia, thirst or weight loss. Her sister was 3 years and 5 months old and had a history of similar abnormal blood glucose. Her mother have a history of gestational diabetes, but poor diet control, whose fasting blood glucose fluctuated between 6 and 8mol/L, and had been given insulin therapy during that time. Now she had oral administration of metformin. The patient's grandmother was diagnosed with type 2 diabetes at the age of 52, with a maximum fasting blood glucose of about 10 mmol/L. On physical examination, she weighed 20 kg, was 116 cm tall, and had a BMI of 14.86 kg/m2, no positive signs. Auxiliary examination: shows that fasting venous blood glucose was 6.1 mmol/L, fasting C-peptide was 174 pmol/L, 2-hour postprandial blood glucose was 8.9 mmol/L, insulin autoantibodies were negative. There was no abnormality in her liver and kidney function, electrolytes, thyroid function and cortisol. The whole exome sequencing presented GCK gene (hg19) chr7:44192993: NM000162.5: c.112114dup: p.Gln38dup (heterozygous mutation), inherited from the mother, the pathogenic grade was unknown mutation. Her sister carried the same gene and the same mutation site.

Conclusion: MODY is a monogenic diabetes characterized by impaired insulin secretion and 14 different genetic variants have been reported. The GCK gene is located on chromosome 7, and heterozygous variants can cause MODY2. MODY 2 is the most common cause of asymptomatic familial hyperglycemia. The insulin secretion function of patients is normal, and the threshold of regulating blood glucose is high. Conventional doses of insulin or oral hypoglycemic drugs can not effectively control patients' blood glucose. Most patients' blood glucose can been controlled through simple diet and exercise, and there are few long-term microvascular or macrovascular complications.

P2-81

Steroid-induced diabetes mellitus in children and adolescents: risk factors, course features, treatment specifics and prognosis on example of 10 patients

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Background: SIDM is not a common complication of high-dose glucocorticoid therapy (HD-GC) in pediatric practice. There are no clear generally accepted approaches to SIDM treatment. In 10 cases, we present the identified patterns of predictors, course, features of the treatment of SIDM in children and adolescents.

Methods: 10 case histories of children with SIDM were analyzed. 4 boys, 6 girls, age 8-17.5 years, median 15 years. Underlying disease: 7 SLE, 1 arthritis with systemic onset, 1 dermatomyositis, 1 cystic fibrosis

Results: Persistent hyperglycemia was detected after 5 days - 1 month from the start of HD-GC (5 dexamethasone 10-16 mg/m2/day, 1 solumedrol 500 mg N5, 4 prednisolone 2 mg/kg/day)

At presentation the average glycemia was 15 mmol/l, massive glucosuria in all patients, the average level of HbA1c was 6.4%, hemophagocytosis in 6 cases (60%), 9 patients had myopathy (steroid-induced) with inability to walk, resistant to treatment nephrotic syndrome in 5 cases, high insulin resistance was in all cases, 8 required of high doses (1.5-2.0 units/kg/day) 2 required of low doses (0.3-0.5 units/kg/day) of insulin, median 1.5 units/kg/day.

The peak of hyperglycemia was after 13.00 in response to maximum steroids administration in the morning (before 10.00)

The criterion for compensation was the absence of massive glucosuria, which was achieved with an average daily glycemia of less than 10 mmol/l.

The classical basal-bolus scheme was used in 2 patients, compensation was not achieved, we observed postprandial hypoglycemia, high hyperglycemia in the evening, increase of the daily insulin doses. All patients received adapted regimen with using long-acting (glargine) and bolus administration of intermediate-acting (actrapid) analogs, the maximum dose of actrapide was admitted in the afternoon.

3 children died (complications of the underlying disease and infections), in 7 children SIDM resolved within 0.5-1.5 months after discontinuation of HD-GC.

In 6 cases there was no recurrence of DM (observation period is more than 1 year), in 1 case IT was completed 3 weeks ago.

Conclusions: SIDM predictors are HD-GC using, particularly dexamethasone, SLE, severe myopathy, and nephrotic syndrome

SIDM is characterized by high specific glycemic profile during the day, requiring modification of the classical basal-bolus regimen, using intermediate-acting analogs improves metabolic control.

HbA1c is an unreliable criterion for compensation in SIDM

SIDM is characterized by a high daily insulin doses, with a high rate of increase and decrease after HD-GC discontinuation.

SIDM is completely resolved.

P2-82

An unusual combination: Wolfram Syndrome Type 1 with type-1-Diabetes mellitus

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Wolfram Syndrome Type 1 also known as DIDMOAD syndrome is an autosomal recessive genetic disorder, characterized by major criteria diabetes mellitus and optic atrophy under the age of 16, as well as minor criteria diabetes insipidous, optic atrophy and diabetes mellitus over the age of 16 years deafness, neurological signs, renal tract structural or function abnormalities, loss of function mutation in WFS1 or CISD2 gene and or family with Wolfram syndrome. Other features could be hypogonadism (by male patients), absence of type 1 diabetes mellitus autoantibodies, bilateral cataract and gastrointestinal disorders.

Today it is established, that the gene WFS1 or Wolframin gene is responsible for Wolfram syndrome Type 1. It codes for the homonym protein Wolframin which is found in endoplasmic reticulum, especially in cells of heart, brain, lungs, inner ear and pancreas. The function of Wolframin is unknown. It is speculated, that Wolframin may help fold protein precursor of insulin and may help maintain the cellular lever of calcium ions. Up today more than 30 WSF1 mutations are identified.

Type of Wolfram Syndrome is caused by mutations in the gene CISD2. CISD2 stands for CDGSH iron sulfur domain 2 a protein found in the outer membrane of mitochondria. It is demonstrated, that it is involved in mammalian live span control.

The prevalence of the disease is between 1-9/ 1 000 000 and the first symptoms manifest in the childhood.

We report on a 17 year old patient, refugee from Syria, who initially presented with Diabetes mellitus Type 1 since the age of 6 years. We then diagnosed deafness and depression. A cranial MRT showed optic nerve atrophy. The discovery of a mutation in WFS1 gene (c.1546_1546delTTC;p.Phe516del) confirmed our diagnosis. Interestingly his 3 older sisters in Jordan hat similar symptoms, as well as renal tract structural anomalies and sensomotoric neuropathy and epilepsy.

This case reminds us, that patients, who present with the combination of diabetes mellitus, deafness and visual impairment are serious candidates for Wolfram Syndrome. Occurrence of type-1-diabetes mellitus in our patient is exceptional. Not all symptoms may manifest during childhood, therefore continuous awareness is mandatory.

P2-83

Arterial Hypertension and Insulin-Dependent Diabetes: Experience Of The Consultation at the Children's Hospital In Rabat

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Hypertension is a frequent chronic pathology in young diabetics. The association of diabetes and hypertension represents a high risk of morbidity and premature cardiovascular mortality. The aim of this study was to evaluate the frequency of hypertension in young diabetics and to assess the associated morbid factors.

Patients and Methods: 357 diabetics aged 3 to 27 years (mean age: 10 years), were followed at the Children's Hospital over a period ranging from 5 to 14 years (mean: 5 years).

High blood pressure is defined as a BP greater than 140 mmHg and a minimum BP greater than 90 mmHg, taken in the supine position and confirmed on a second examination.

Results: Of 357 Children, 25 had hypertension with a maximum BP between 140 and 220 mmHg (mean: 154±14 mmHg) and a minimum BP of 90 to 110 mmHg (mean: 94±4 mmHg).

The hypertensive diabetics were aged between 11 and 22 years (mean age: 16±7 years) at the time of diagnosis with a diabetes duration of 4 to 14 years (mean: 7±3 years).their metabolic control assessed by glycated hemoglobin ranged from 6.4 to 14.3% (mean: 10.4±2.9 %).the mean body weight was 23.15 Kg/m2 (range: 19.91-29.68 Kg/m2). 5/25 hypertensive patients were obese. In 8 hypertensive diabetics, the lipid profile was disturbed. We observed a significant increase in total cholesterol ($p<0.001$), -LDL-cholesterol ($p<0.001$), triglycerides ($p<0.001$) and ApoB ($p<0.01$) compared to the physiological values of the diabetics and to the values of non-hypertensive control subjects of the same age.

Microalbuminuria affects 41/357 subjects and is observed with an increased frequency 68% (17/25) in young hypertensive subjects. The average proteinuria was 2.67 g/l. Subsequently, other complications (nephropathy, retinopathy and neuropathy) exist with a high frequency (48%) in hypertensive diabetics. Converting enzyme inhibitors prescribed in 13/25 diabetic children could prevent the development of degenerative complications by treating hypertension.

Conclusion: This work confirms the relationship between hypertension and diabetic complications and encourages early detection in all young diabetics.

P2-84

Assessment of serum concetrations of decorin, vaspin and kallistatin in children with type 1 diabetes

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The increasing knowledge on the functions of gastric peptides and adipokines in the body allows the assumption of their major role linking the process of food intake, nutritional status, and body growth, largely through the regulation of glucose metabolism and insulin resistance. The aim of the study was the assessment of serum levels of selected gastric peptides and adipocytokines in children with type 1 diabetes, with respect to the disease duration. The study included 88 children aged 1-18 years (M/F- 35/53), diabetic patients of Diabetology Outpatient Clinic and Department of Pediatrics, Endocrinology, Diabetology with Subdivision of Cardiology, Medical University of Bialystok. The group of 43 children with type 1 diabetes (diagnosed by ISPAD criteria) was compared to the control group of 45 healthy children with a negative history of autoimmune diseases, inflammatory diseases and cancer. The diabetic group was divided into 4 subgroups regarding the duration of type 1 diabetes: (I) newly diagnosed patients, after an episode of ketoacidosis (n = 14), (II) patients with type 1 diabetes of duration no longer than 5 years (n = 13), (III) patients with 5 to 10 years of diabetes type 1 (n = 11), (IV) patients with type 1 diabetes of duration longer than 10 years (n= 5). The mean levels of kallistatin, decorin and vaspin in all subgroups were higher than in the control group. The differences between the respective subroups and the control group were statistically significant for decorin and kallistatin ($p<0.0005$), but not for vaspin ($p>0.05$). Moreover, the mean levels of tested peptides were fluctuated during the course of the disease. We observed the highest levels of kallistatin, decorin and vaspin in the subgroup of children with type 1 diabetes of duration not longer than 5 years, which may be of importance in the development of the disease complications.

P2-85

Growth monitoring in children with type 1 diabetes: A single center experience

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Type 1 diabetes mellitus (TIDM) is a very familiar chronic disease among pediatric endocrinologists. It is known that chronic diseases can affect their growth velocity and final height.

The aim of the study is to determine how TIDM affects children's growth velocity during the childhood period.

Material-Method: This cohort study used data from patients with TIDM participating in our clinic for the last 13 years. The patient had other chronic diseases, and missing file records were eliminated. They were divided into three groups, as group 1 was less than 5, group II between 5-10 and group III more than 10 years old. Their length, weight, body mass index (BMI) and standard deviation (SD) beside HbAC1 values were recorded for each year.

Results: Two hundred and fifty patients (53 % girls) at between 1.10 and 17.7 years old were evaluated. Patients in groups I and II showed dramatic decreases according to height and weight SD during the follow-up period. In group I, height lost was almost 1SD. There was also significant weight loss SD in all groups

Table 1. The patients' anthropometric values SD for follow-up period

	Height-SD			Weight-SD			BMI-SD		
Group	I	II	III	I	II	III	I	II	III
at diagnosis	-0.41	0.31	-0.01	-0.07	-0.31	-0.48	0.16	-0.27	-0.57
1th	-0.77	-0.79	-0.11	0.17	-0.43	-0.28	0.99	-0.06	-0.27
2th	-0.62	-0.52	-0.12	0.28	-0.26	-0.30	0.96	-0.11	-0.28
3th	0.15	-0.59	-0.23	0.38	-0.40	-0.33	0.91	-0.16	-0.25
4th	-0.28	-0.72	-0.29	0.26	-0.56	-0.33	0.55	-0.41	-0.18
5th	-0.64	-0.92	-0.25	0.05	-0.79	-0.49	0.54	-0.33	-0.04
6th	-0.77	-0.93	-0.34	-0.15	-0.87	-0.71	0.33	-0.43	-0.03
7th	-0.72	-1.06	-0.53	-0.37	-0.80	-0.80	-0.02	0.35	0.00
8th	-0.89	-1.22		-0.53	-0.65		0.02	-0.01	
9th	-1.29	-1.24		-0.76	-0.74		-0.09	0.00	
10th	-1.47	-0.70		-0.95	-0.81		-0.1	-0.11	
11th	-1.22	-1.25		-0.98	-0.98		-0.24	-0.35	
12th	-1.41	-1.06		-0.93	-0.88		-0.15	-0.55	
13th	-1.36			-0.8			-0.05		

approximately 4 years after diagnosis. In patient group III, BMI-SD showed a sharp increase and then progressively decreased (Table 1). The height and weight gain of patients with poor metabolic control showed more significant changes.

Conclusion: If the diagnosis of TIDM is poorly controlled, it negatively affects the child's growth. In patients diagnosed under 5 years of age, height loss was more pronounced in other age groups. Therefore, it is recommended to be followed more closely, especially in this age group.

P2-86

Type 1 diabetes in children: What are the particularities?

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Introduction: Children's type 1 diabetes is a rare entity, its prevalence is still poorly known, which makes its diagnosis, therapeutic management and prognosis increasingly difficult and uncodified. The purpose of our study is to report the experience of the Endocrinology - Diabetology and Nutrition Department in the management of diabetes in children.

Methods: This is a retrospective, descriptive study including 12 children hospitalized in the Endocrinology-Diabetology and Nutrition Department for the management of diabetes diagnosed before the age of 24 months. All patients underwent a clinical examination and a biological check-up. The statistical analysis was performed with SPSS- Version 21 software.

Results: The average age at admission to the department was 24±9,6 months, and the average age at diagnosis was 12±6 months, with a clear male predominance, (sex ratio M/F: 2,1). Consanguinity was present in only one case (8.3%), diabetes in the family was present in 83.8% of cases. The reasons for hospitalization were various; 8 cases for inaugural diabetes, (66.7%), and 4 cases for unbalanced diabetes (33%). The mode of discovery was ketoacidosis in 66.7% of the cases. 83.3% of cases had cardinal syndrome before diagnosis. The clinical examination found a height and weight delay in 4 cases, and a height advance in 5 cases. The mean HBA1C was 10 ±1.2%. Positive anti-GAD antibodies were found in 50% of cases, and positive anti IA2 antibodies were found in 41.6% of cases. Only 58.3% of cases benefited from the rest of autoimmunity biological analysis, we found anti-TPO antibodies positive in 1 case, and anti-transglutaminase antibodies positive in 2 cases. In terms of therapy, 50% of our patients were under basal bolus insulinotherapy, and 50% on a mixing insulinotherapy, afterwards, one patient benefited from the insulin pump due to low insulin needs and the presence of hypoglycemia, with a switch to a basal bolus schema in 2 patients who were previously on a 2-mix insulinotherapy.

Discussion-Conclusion: Nowadays the incidence of diabetes in children is clearly increasing, it is a diagnostic emergency that requires urgent and specialized management, hence the need for a global awareness of the medical staff on the different ways of discovery.

P2-87

100 years with insulin. Implementation of analogs and technology in our environment

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Almost 100 years ago, a major turning point in the life expectancy of people with diabetes around the world was reached with the discovery of insulin. In 1936, Hagedorn had the ingenious idea of combining insulin with a protein, protamine, and zinc and his NPH was used almost mainly in pediatrics until the end of 2003, when glargine U100 made its appearance.

Objective: To evaluate the clinical experience in the incorporation of different insulin analogues and technology in our current practice

Methods: DM1 patients older than 6 months from the start of follow-up in specialty consultations at our center. Assessment of age, sex, age of debut, HbA1c, type of technology used. Descriptive study IBM SPSS Stastistics 19.0.

Results: 71 children (35♂), mean age 9.8 a [2-17]. HbA1c (DCA): 7.9% [6.1-9.2], debut time 3.9a [0.8-10.1], mean weight -0.32 SDS [-1.2, + 0.8], mean BMI - 0.28 SDS [-1.4, + 0.9]. 84% use MDI, 6 insulin pumps. 98% use some non-capillary glucose monitoring or control system (1 patient refuses), either type continuous monitoring for age <4th or linked to CSII or flash type. Of the 6 pumps, they use lispro (4/6), aspartic (1/6) and another glulisine (1/6) Of the MDIs, as slow analogs NPH 0/65, detemir 12/65 (85% are <6 years), U100 10/65, U300 35/65 liraglutide 8/65. The indication has been for age, comfort, morning / night dissociated doses, variability control and switch due to poor previous basal adjustment. Of the MDIs, such as fast analogues è Actrapid 0/65, lispro 30/65 (1 U200 off labell per dose), aspartic 10/65, ultrafast (15/65) and glulisine 10/65 The indication has been for age, comfort, dose/need for stockings and a pen for this purpose and switch due to poor adjustment of the previous analog. 68/71 patients (100% of> 4th) are on inhaled glucagon. There was no impediment by medical inspection in any prescription except in 1 case (belonging to another health area) with BAQSIMI Previous severe hypoglycemia with previous loss of consciousness in <5% of cases (0.03 patient / year cases). ISCI offered to 70% of families. 80% initial rejection rate by the family or the patient himself.

Conclusion: We assume that this study may have some shortcomings due to the size of the sample, but our study demonstrates the implementation of the most modern analogs in the office, of measurement technology, but the need to advance in the use of insulin pumps.

P2-88

Association of type 1 diabetes mellitus with autoimmune diseases in children in the Department of Endocrinology-Diabetology and Nutrition at Mohammed VI University Hospital Center Oujda

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Introduction: Type 1 diabetes is frequently accompanied by other autoimmune diseases that can sometimes be integrated into autoimmune polyendocrinopathies.

Through this work, we sought to describe the association of autoimmune diseases with type 1 diabetes in children.

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Autoimmune diseases were noted in 23 patients, 34.7% of whom were men and 65.8% women. Autoimmune dysthyroidism was the leading cause in 34% of cases. type 1 diabetes mellitus preceded dysthyroidism in 65% of cases. Celiac disease was noted in 30% of cases. Autoimmune polyendocrinopathy was listed in 39.2% of cases and psoriasis in 0.28% of our patients.

Conclusion: The frequency of autoimmune diseases in type 1 diabetics, which can sometimes be part of autoimmune polyendocrinopathy, encourages screening for them when diabetes is discovered. The screening will allow an early management of these disorders and prevent further complications.

P2-89

Design, certification and evaluation of an Insulin Infusion Therapy Care and Education Program (PAETII) in children/adolescents in a Pediatric Unit

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A structured program of therapeutic education is essential to achieve a good result from the use of technology in the treatment of diabetes.

Objectives: Facilitate knowledge, skills and aptitudes to patients and their families in therapy.

Promote the capacity for self-management and adherence to treatment.

Provide ongoing support to patients.

Improve clinical outcomes, health status and quality of life.

Methodology: In 2019, the multidisciplinary work team made up of pediatricians, endocrinologists and nurses was created. For a year, the PAETII program was developed based on the quality characteristics of the Standard: "Educational program for patients who start therapy with the Subcutaneous Insulin Infusor, ISCI".

The program was planned in 3 parts: structure, educational process and results. Material and human resources were taken into account in the structure: training room, number of sessions and participants per session, schedules and duration, educational techniques and materials, instruments for evaluation, records and number and training of professionals.

In the process, the structured therapeutic education program was developed, which consisted of an initial assessment of the patient and an agreement of objectives with the patient/family, eight training sessions distributed in three modules (previous CSII, CSCI start and CSCI follow-up) and a final stage with three patient control consultations.

For the evaluation of results, 20 quality indicators were defined that will be evaluated annually.

Results: The process map that described how the program worked was defined.

In January 2021, the program was launched and in June, the DNV auditor carried out the first external audit, issuing the Declaration of Conformity.

During the year 2021, nineteen children/adolescents and their families participated in the program in one of the five planned editions.

The results of the annual evaluation are collected in the analysis of indicators, the most significant being: coverage rate 49%, dropout rate 0%, compliance with scheduled visits 97.6%, percentage of patients trained after completing the educational program 100 %, degree of patient satisfaction 9.4.

Conclusions: The annual evaluation of the program has been very good.

Incidents and improvements have been detected that have made it possible to correct some aspects of the program.

Indicators are being worked on to measure health outcomes for children/adolescents.

P2-90

Contribution of 25 Hydroxy Vitamin D to the Risk of Development of Type 1 Diabetes in Children

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Objectives: To study the status of vitamin D (25-hydroxyvitamin D, active form) in diabetic an non-diabetic children in comparison with that of Moroccan children who have immigrated to Italy.

Material and Methods: 25-hydroxyvitamin D levels were measured by chemiluminescence during

the spring-summer season.

Patients and Methods: Our cohort consisted of 25 subjects including 17 (9 Boys/8 Girls) diabetic children and 8 (7Boys/1Girl) non-diabetic children.

The average age of the patients is 8.5±1.3 years (extremes: 5.9-10.5 years). The patients are treated with 2 daily injections of insulin. Their mean HbA1c is 8.1 ± 1% with extremes ranging from 6.2 to 9.6%. The non-diabetic subjects have a mean age of 7.9 ±1.7 years (extremes: 5.9-10 years).

Results: Our diabetic children have a mean serum 25 hydroxyvitamin D level of 21.1 ± 9.8 ng/ml. In non-diabetic children, the mean 25 hydroxyvitamin D level is: 174.5 ng/mL. There was no significant difference between the 2 groups.

In Moroccan children living in Piedmont (Northern Italy), the level of 25 hydroxyvitamin D is 10.1 ng/mL. This level is significantly lower than that found in Moroccan children.

We reported a 25-hydroxyvitamin D level in our diabetic children similar to that obtained in

Italian children (23.3 ng/mL) of the same age.

The results of our study confirm the role of 25-hydroxyvitamin D as an environmental factor in the increased incidence of type 1 diabetes in Moroccan children living in Italy.

Conclusion: Our original study shows that the difference in the incidence of type 1 diabetes is related to the ethnic origin of the groups. Thus, hypovitaminosis D may contribute to the accelerated development of type 1 diabetes in Moroccan immigrant children.

P2-91

Presentation of Newly Diagnosed Type1 Diabetes Mellitus

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Children with early signs and symptoms of Type 1 Diabetes need to be diagnosed promptly, before they become acutely unwell with diabetic ketoacidosis (DKA). Early diagnosis and optimal management of established DKA is key to reducing morbidity and mortality.

To follow the evidence based standards.

To assess whether the newly diagnosed type 1 diabetes were in DKA at presentation or not.

To assess compliance to guidelines on admission.

As per retrospective cohort study, charts of newly diagnosed type 1 diabetes over one year study period reviewed.

Proportion of new on- set type 2 diabetes presentating during this COVID-19 pandemic was higher then previously reported. There was an increase in presentation of severe DKA at diagnosis in children and young people under the age of 16 years old.we were not sure what could account for this rise in proportion.Delayed presentation ranging fear from of contracting COVID to an inability to contact or access a medical provider for timely evaluation. Multicultural nature of our study population could also be a factor.

More public health awareness and diabetes education should be disseminated to healthcare providers on the timeliness of referrals of children with suspected T1D.

Fat, Metabolism and Obesity

P2-92

Different profiles of lipoprotein particles associate various degree of cardiac involvement in adolescents with morbid obesity

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Introduction: Dyslipidemia secondary to obesity is a risk factor related to cardiovascular disease events, however a pathological conventional lipid profile (CLP) is infrequently found in obese children. The objective of our study is to evaluate the advanced lipoprotein profile (ALP) and its relationship with cardiac changes, metabolic syndrome and inflammatory markers in a population of morbidly obese adolescents with normal CLP and without type 2 diabetes mellitus, the most common scenario in obese adolescents.

Methods: Prospective case-control research of 42 morbidly obese adolescents and 25 normal-weight adolescents, whose left ventricle (LV) morphology and function had been assessed. The ALP was obtained by proton nuclear magnetic resonance spectroscopy, and the results were compared according to the degree of cardiac involvement – normal heart, mild LV changes, and severe LV changes (specifically LV remodeling and systolic dysfunction) – and related to inflammation markers (highly-sensitive C-reactive protein and glycoprotein A [GlycA]) and insulin-resistance (homeostatic model assessment for insulin-resistance [HOMA-IR]). A second analysis was performed to compare our

results with the predominant ALP when only body mass index and metabolic syndrome criteria were considered.

Results: The three cardiac involvement groups showed significant differences in HOMA-IR and inflammatory markers (p<0.01). A significant increase was also observed in the ratio LDL-P/HDL-P (40.0 vs 43.9 vs 47.1, p0.01), while when the mild and severe LV changes groups were compared, an elevation in the small LDL-P and decrease in VLDL size were identified. The multivariable model (AUC: 0.91 [95%CI: 0.74-1]) to differentiate normal heart subjects from those with severe cardiac changes included: body mass index, HOMA-IR, blood pressure, GlycA, small VLDL-P, small LDL-P and ratio HDL-TG/HDL-C. In the second analysis, an atherosclerotic ALP was detected in morbidly obese subjects, characterized by a significant increase in large VLDL-P, small LDL-P, ratio LDL-P/HDL-P and ratio HDL-TG/HDL-C. Subjects that meet the criteria for metabolic syndrome presented overall worse ALP and remnant cholesterol values.

Conclusions: The overage of VLDL-P and LDL-P compared to HDL-P and, particularly, the increase in small LDL-P and ratio HDL-TG/HDL-C, appear to be key ALP's parameters involved in LV changes. Morbidly obese adolescents without pathological CLP show an atherosclerotic ALP.

A positive correlation was found between AMH levels and their age (r=0,484, p=0,002), neck (r=0,334, p=0,035), and hip circumferences (r=0,359, p=0,023), body weight (r=0,418, p=0,007), height (r=0,465, p=0,003), and body mass indexes (r=0,329, p=0,038). In addition, a positive correlation was found between serum AMH levels and arm (r=0,677, p=0,015) and waist circumferences (r=0,777, p=0,003), waist-height (r=0,615, p=0,033) and waist-hip ratios (r=0,771, p=0,003, and the weights of prepubertal obese girls (r=0,594, p=0,042).

A positive correlation was found between AMH levels and serum luteinizing hormone (r=0,406, p=0,015), estradiol (r=0,392, p=0,022), and testosterone (r=0,671, p=0,002) levels. In addition, there was a negative correlation (r=-0,628, p=0,038) between serum AMH levels and HbA1c levels in pubertal obese girls.

Conclusions: It was found that the AMH level in obese girls increased moderately in the prepubertal period close to the onset of puberty, slightly decreased when puberty began, and increased significantly in the postmenarche period, similar to healthy girls. In addition, there is a positive correlation between the serum AMH level of obese girls and their age, weight, height, and central obesity.

Key words: AMH, obesity, central obesity, puberty.

P2-93

The Relationship Between Serum AMH Levels and Puberty in Obese Girls

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Objectives: Anti-Müllerian hormone (AMH) is produced by Sertoli cells in the testicles and granulosa cells in the ovaries. Increased abdominal adipose tissue initiates metabolic and endocrine disorders and predisposes to polycystic ovary syndrome. AMH is used as a marker in PCOS. A decrease in AMH levels has been reported in adults with obesity and increased central adiposity.

The purpose of this study was to assess the serum AMH level and related factors in obese girls during their prepubertal, pubertal, and postmenarchal periods.

Materials and Methods: Anthropometric measurements, physical examination characteristics, and laboratory findings of patients diagnosed with obesity between March and April 2021 in the Erciyes University Faculty of Medicine Pediatric Endocrinology Outpatient Clinic and serum AMH levels were evaluated.

Results: Serum AMH levels were studied from a total of 40 obese girls, 12 (30%) prepubertal, 12 (30%) pubertal, and 16 (40%) postmenarcheal. Their ages were 7.7 (±1.7); 10.3 (±2.1), and 5.4 (±1.8) years, respectively. Serum AMH measurements were 2.4 ng/mL (±2.4); 2.1 ng/mL (±1.1); and 4.6 ng/mL (±3.7), respectively. There was no significant difference when compared to normal AMH levels for their age. Serum AMH levels of postmenarche obese girls were significantly different from prepubertal and pubertal obese girls. There was no significant difference between serum AMH levels of prepubertal and pubertal obese girls.

P2-94

Liraglutide associated with a multidisciplinary program for the treatment of adolescents obesity in a low income setting: a real life experience

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Background: The prevalence of childhood obesity is increasing worldwide and Glucagon-like peptide 1 analogs have emerged as a new tool for its management. To date, Liraglutide has been approved for the treatment of obesity in adolescents over 12 years of age by the FDA & EMEA and in Chile (July 2021).

Objectives: evaluate the % decrease in BMI SDS and total body fat percentage in adolescents with obesity who received Liraglutide associated to a multidisciplinary program (nurse, psychologist, dietitian and physical trainer). The secondary objectives were to determine the presence of associated events, assess adherence to treatment and improvement of biochemical alterations.

Methods: Ten obese patients, mean and ranges: 15 years (13.2-17.3), Weight 97.5 Kg (72.9-120.8), BMI (SDS) 3.2 (2.3-3.9) and 38.3 total body fat percentage % (28.6-44.4) were recruited. Prior to treatment 5/10 had hypertriglyceridemia, 6/10 had HDL below normal range, 2/10 had dysglycemia (1 with glucose intolerance and 1 with HbA1c 5.8%) and 6/8 had hepatic steatosis. They started treatment in June 2021 and are ongoing with increasing doses starting at 0.6 mg/d.

Results: Changes in weight, BMI and body fat percentage are shown in table 1. Adverse events, abdominal pain (7/10), headache (7/10), nausea (6/10), abdominal distension (5/10), diarrhoea (3/10), constipation (2/10), dizziness (2/10), fatigue (2/10) and inflammation at the puncture site (1/10) were observed. None presented episodes of hypoglycemia or acute pancreatitis. Two

Table 1.

Baseline Data		Changes	Months of treatment		
Measurement	Mean (range)	Measurement	2	3	6
Weight (Kg)	97.5 (72.9-120.8)	Weight %	3 - 3.1	2.5-7.5	5-14.6
BMI (SDS)	3.2 (2.3-3.9)	BMI (SDS)	0.1-0.2	0.1-0.7	0.2-0.7
Body fat %	38.3 (28.6-44.4)	Body fat %	NA	NA	2.7-8.7

patients had to temporarily suspend the drug due to intercurrent gastrointestinal infections but reassumed without inconvenience. When assessing compliance, one patient discontinued treatment after 2 months due to irregular administration and one after 3 months due to severe mood disorder. Finally, in the group who complete 6 months of treatment, the two patients with dysglycemia showed improvement and of the three patients with dyslipidemia, two decreased triglyceride levels to normal range.

Conclusions: Short term Liraglutide use associated with a multidisciplinary team showed positive results with a decrease in weight, BMI and body fat percentage and a mild improvement in some biochemical alterations. In addition, appears as a safe treatment for obesity in adolescents. The chronic nature of this condition makes us to be cautious of the long-term effectiveness of this drug.

P2-95

Compliance and drop-out in children and adolescents with essential obesity

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Introduction: Pediatric obesity is associated with an increased risk of serious long-term complications. Therapeutic failure is influenced by several factors, such as the high dropout rate. A retrospective study was conducted on a cohort of children and adolescents with essential obesity, in order to evalute (1)the average duration of a correct follow-up and the percentage of weight loss at the end of it, (2)the rate of drop-out, researching related factors.

Materials and Methods: The retrospective, single-center study, involved 489 patients, followed for essential obesity at our Pediatric Endocrinology in the period 2016-2020. The auxological patients' data were collected during the first(V1) and the last visit(V2). Each patient during V1 were subjected to a blood sampling in order to evaluate the metabolic structure (triglycerides, total cholesterol, LDL, HDL, glycemia and insulin). Drop-out was defined as a follow-up of less than 12 months and/or including less than 1 visit every 6 months. To assess the drop-out rate and associated factors, patients were divided into 2 groups: Group A of drop-out (297 patients) and Group B of non-drop-out (192 patients). The difference between the BMI DS at V1 and V2 was considered to evaluate the percentage of weight loss and the associated factors.

Results: The median duration of follow-up was 20.8 ± 23.2 months. In the observed period, drop-out rate was 60.7%. The remaining patients completed follow-up in 12 or 24 months. In group A, the SD BMI and patients with BMI ≥3 SD at V2 were significantly higher than in group B (p=0.002 and p=0.027, respectively). In Group B, the percentage of patients with pathological HOMA-IR was significantly higher than in Group A (51.1% vs 41.3%; p = 0.036), as well as was that of subjects with fasting glucose> 100 mg/dL (16.5% vs 8.9%; p = 0.012). The likelihood of drop-out was positively associated with pubertal stage at V1 (OR 1.39) and negatively with a fasting blood glucose > 100 mg/dl and insulinemia> 15 uI / ml at V1(respectively OR 0.52 and OR 0.64). A negative association was found between weight loss and age > 10 years and a positive association between weight loss and non-pathological HOMA-IR.

Conclusion: The study demonstrated a high drop-out rate during follow-up, mainly among adolescents and patients with no glucometabolic alterations. These patients will need closer monitoring and possible counseling to avoid early abandonment and the development of complications in adulthood.

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SGPT and FT4 correlations among Greek school age children with obesity or severe obesity

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Background/Aims: Pediatric obesity remains an ongoing serious international health concern. Whether liver dysfunction is related to thyroid dysfunction in this population is controversial.

Compare SGPT, TSH, FT4 and insulin resistance indexes between children with obesity or severe obesity.

Methods: 279 children (143 females) with BMI (≥95percentile) (CDC BMI curves) were divided in two groups (Group 1, obese: 95percentile≤BMI<99percentile, Group 2, severe obese: BMI≥99percentile) and analyzed retrospectively. Age, sex, tanner stage, BMI in Kg/m^2 and percentile (%), SGPT (mg/dl), TSH (mIU/ml) and FT4 (ng/dl) levels were recorded. Insulin resistance was defined as HOMA-IR≥ 3 and Matsuda index ≤2.5. Liver dysfunction as SGPT>22mg/dl for females and >26mg/dl for males and thyroid dysfunction as FT4<1ng/dl.

Results: Mean age was 10.5yrs (SD, 2.9), BMI: 30.1Kg/m^2(SD,5.3), BMI percentile: 98.8% (SD,0.8), SGPT: 25.3 (SD, 15.6) mg/dl, TSH: 3.3 (SD:1.5) mIU/ml, FT4: 1.2 (SD: 0.2) ng/dl, HOMA-IR:4 (SD,3.5), Matsuda index:3.2 (SD,2). In the whole population, children with insulin resistance presented more frequently liver dysfunction as opposed to non-insulin resistant (76.6 vs 52.7 and 78.4% vs 58.2%, for Matsuda and HOMA-IR respectively, p<0.001). In addition, those with insulin resistance presented more frequently FT4<1ng/dl than those without (87.5% vs. 41.5%, p<0.001 for Matsuda and 87.5% vs 58.6%, p:0.03 for HOMA-IR index). TSH >5mIU/ml was not appreciated more frequently in the insulin resistant children than the non-resistant ones. Finally, in the entire population there was a significant correlation of TSH and FT4 with BMI z-score (r:0.18, p:0.003 and r:-0.14, p:0.04 respectively), however FT4 but not TSH levels correlated significantly with SGPT levels (r:-0.04, p:0.5 and r:-0.18, p:0.01 respectively).

Conclusions: Children with severe obesity (BMI ≥99%) present similar glycemic profile, liver and thyroid function as compared to children with obesity (95%≤ BMI <99%). In euthyroid obese subjects, FT4 seems more closely related than TSH levels to parameters of cardio- metabolic risk. Thus, levothyroxine substitution treatment could be considered in selected patients.

Table 1. Clinical and laboratory characteristics, Mean (SD)

	Group 1 (n=68)	Group 2 (n=211)	p
Age (yrs)	10.9 (2.1)	10.3 (3.1)	0.1
Sex (males/females)	28/40	108/ 103	0.15
Tanner 1/>2	32/36	121/90	0.14
BMI (Kg/m2)	26.4 (2.6)	31.3 (5.4)	*
BMI (%)	97.6(0.9)	99.2 (0.4)	*
SGPT (mg/dl)	25.4 (22.5)	25.3 (12.8)	0.5
TSH (mIU/ml)	3.0 (1.2)	3.3 (1.6)	0.1
FT4 (ng/dl)	1.2 (0.2)	1.3 (0.2)	0.4
HOMA-IR	3.9 (3)	4.1 (3.6)	0.6
Matsuda	3.1 (1.8)	3.2(2)	0.9

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Linear growth and prevalence of the different components of the metabolic syndrome (MetS) in young obese nondiabetic children (below 5 years) in comparison to older obese children (6-12 years)

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Introduction: In Qatar, the prevalence of metabolic syndrome (MetS) in children and adults is increasing in parallel with the markedly increasing trends in obesity rates. We studied the prevalence of different components of MetS, measure plasma atherogenic indexes (AIP), and linear growth in young obese nondiabetic children (< 5 years) in comparison to older obese children (6-12 years).

Methods: We analyzed the anthropometric and biochemical profile of 135 random sample obese children who attended to the OPD of Hamad Medical Centre (HGH), Doha, Qatar between 1-2018 to 12-2019.

Results: 63.8% of Obese children studied at 5 years were obese at the end of their first year of life. Significant rapid gain in weight and linear growth (catch-up) was observed during the first 6 months of life. Moreover, some metabolic risk factors and high AIP occurred more frequently in older obese children compared to young obese children.

Conclusions: This study documented the early occurrence of different components of the MetS in young obese children and the progressive increase of their prevalence in older prepubertal children. Most obese children who presented at or below 5 years of age had significant obesity and rapid linear growth during the first two years. These findings pointed out the necessity to impose early detection and prevention on a national scale.

Table 1. The proportion of postnatal obesity (BMI-Z > 2) in children who presented with obesity at 5 years of age or below (n= 69)

BMIZ >2	Percent (%)	Mean ± SD
Obese at 5 years	100	4.3 ± 1.5
Obese at 2 years	82.6	5.6 ± 1.6
Obese at 1 year	63.8	2.55 ± 1.3
Obese at 6 months	47.8	1.77 ± 1.2

Table 4. Metabolic risk factors among obese children < 5 years versus those between 6 -12 years

Variables	<5 years	6-12 years	P-value
	%	%	
Number	69	66	
HbA1c > 5.7%	20%	29%	0.51
LDL > 2.7 mmol/L	0 %	8.0%	0.2
HDL < 1.03 mmol/L	20%	20.8%	0.97
TG >1.7 mmol/L	6.7%	8.0%	0.65
Cholesterol > 4.5 mmol/L	10%	20.8%	0.25
ALT > 35 IU/L	10%	25.0%	0.23
Fasting insulin > 15 mU/L	53.3%	72.0%	0.26
IFG > 5.6 mmol/L	23.3%	17.9%	0.29
HOMA IR >2	76.6%	92.7	0.07
HOMA IR > 3.6	55.5%	71.4%	0.17
Hypertension BP >95th centile for age and sex	23.3%	12.5%	0.23
Atherogenic index of plasma (AIP > - 0.23)	55.5%	76.7%	0.06

P2-98

Effects of long-term metreleptin replacement therapy on weight and comorbidities in a patient with bioinactive leptin

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Introduction: Congenital leptin deficiency can be treated with the human leptin analogon metreleptin as first reported in 1999. To date, the long-term effects (> 1 year) of metreleptin treatment on anthropometry and comorbidities have only been described in 8 patients with leptin deficiency. Here, we present the long-term effects of metreleptin substitution on weight and comorbidities in a patient with bioinactive leptin.

Methods: We retrospectively analyzed the effects of seven years of metreleptin treatment on body weight and comorbidities in a female patient with bioinactive leptin caused by biallelic variants in the leptin gene (c.309C>A, p.Asn103Lys).

Results: At initiation of metreleptin therapy, the 9-year old girl had severe obesity (39.3 kg/m^2, BMI SDS 3.5), hyperphagia and several comorbidities such as dyslipidemia, hyperinsulinemia, steatosis hepatis and sleep apnea syndrome. Metreleptin therapy was started with the recommended dose of 0.03 mg/kg lean body weight, was well tolerated, and resulted in controlled eating behaviour and reduced energy intake within few days. BMI decreased by -6.98 kg/m^2 in the first year of treatment, but increased to 37.8 kg/m^2 in the second year and remained constant in the following three years. Periods in which the uncontrolled eating behaviour recurred were not associated with the presence of neutralizing antibodies to metreleptin but with low adherence to daily injections. Increasing metreleptin dose to overcome the recurrence of uncontrolled eating behaviour had little or no effects on weight. Similar BMI reductions as in the first year occurred again in the fifth ($\Delta BMI_{T4\text{-}T5}$: -6.83 kg/m^2) and seventh year of treatment ($\Delta BMI_{T6\text{-}T7}$: -5.48 kg/m^2) and were attributed to periods when the patient changed her lifestyle toward a healthy diet, more physical activity and a strictly structured daily routine, resulting in high treatment compliance. To date, the 16-year old patient is still obese with a BMI of 31.4 kg/m^2 (BMI SDS 2.35), but her eating behaviour is well controlled and her metabolic comorbidities have almost disappeared.

Conclusion: This case report adds new data to the long-term efficacy and safety of metreleptin therapy in patients with leptin deficiency. Metreleptin reduced efficiently hyperphagia, metabolic comorbidities and weight as previously reported in the literature. While periods of low treatment adherence were associated with recurrence of symptoms, high treatment compliance, a healthy diet and sufficient exercise resulted in significant weight loss. Patients should be motivated to follow these treatment advices to maximize the benefits on anthropometry and health of metreleptin therapy.

P2-99

Gender differences in Italian pediatric obese subjects

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Background: Significant aspects of metabolic homeostasis are regulated differently in males and females and sex differences can influence diagnostic approach and therapeutic responses. The underlying mechanisms accounting for gender difference remain to be established and may involve genetic and hormonal factors.

Aim: This study aimed at evaluating gender differences in anthropometric and metabolic parameters in a large cohort of obese children.

Methods and Results: We conducted a retrospective study in 581 children and adolescents referred to our Hospital for obesity (BMI>95°pc). All patients underwent anthropometric, biochemical and hormonal evaluation. All patients underwent OGTT. Subjects were subdivided according to Tanner stage in 269 pre-pubertal (103 F/142 M) and 370 pubertal subjects (204 F/132 M). In pre-pubertal subjects, basal glycaemia was higher in males than females (83.99 ± 7.7 vs 80.94 ± 8.3, p<0.05). Basaline c-peptide (1.54 ± 0.8 vs 1.77 ± 0.8, p<0.05) and insulin at 120' (110.1 ± 115.9 vs 158.3 ± 108.1, p<0.05) resulted higher in females. In pubertal subjects, obese males showed higher BMI SDS (3.08 ± 0.98 vs 2.84 ± 0.98, p<0.05), basal C-peptide levels (3.14 ± 0.17 vs 2.34 ± 0.86, p<0.05), triglycerides levels (105.7 ± 57.3 vs 92.32 ± 47.35, p<0.05), AST (29.7 ± 11.5 vs 25.8 ± 11.7, p<0.001) and ALT levels (28.5 ± 17.9 vs 28.1 ± 8.3, p<0.001). Pubertal males and females showed no differences in prevalence of impaired fasting glycaemia (3% vs 3.9%), impaired glucose tolerance (16.6% vs 16%). Pubertal males had a higher prevalence of abnormal HbA1c than females (7.5% vs 3.9%).

Conclusion: In pubertt, males show a more severe degree of obesity and a worse metabolic profile than females. A role of androgens could be hypothesized. These results suggest that pubertal obese males need a more intensive management to reduce long-term cardiometabolic risk.

P2-100

Comparison between Triglyceride-Glucose Index (TyG) and Atherogenic index of plasma (AIP) in relation to the different components of the metabolic syndrome (MetS) in morbidly obese children

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Background: Metabolic syndrome (MetS) is related to increased cardiovascular complications of obesity. The triglyceride-glucose (TyG) index is frequently used as an indicator of insulin resistance in adults. However, there is scant information on the TyG index in the morbidly obese Pediatric population, nor is its correlation with the components of the metabolic syndrome (MetS).

Methods: We compared the use of TyG versus atherogenic index of plasma (AIP) in relation to different components of MetS in morbidly obese children. The TyG index was calculated as = ln [(triglyceride level, mg/dL) × (glucose level, mg/dL) ÷2] under fasting conditions. Data recorded included: age, gender, weight and height, body mass index (BMI), systolic and diastolic blood pressures. Biochemical data including a lipid profile, glycated hemoglobin (A1C), Oral glucose tolerance (OGTT), fasting insulin, and alanine transferase level (ALT) were recorded and HOMA-IR., AIP, and TyG were calculated for 10 morbidly obese children (11.2 +/- 1.8 yrs.), with BMIZ = 3.54 +/- 0.4.

Results: The different glycemic components, MetS components, TyG and AIP are presented in the table. Half of our patients have high ALT and/or sonographic evidence of NAFLD. Although in adult studies TyG of 8 or more was correlated with NAFLD and insulin resistance, NAFLD occurred in our children with lower TyG values. TyG was correlated significantly with AIP ($r = 0.83$, $P < 0.001$). TyG and AIP were correlated significantly with systolic (SBP) and diastolic BP (DBP), 2h blood glucose after OGTT. While TyG was more correlated to BIMZ and HbA1C, AIP was more significantly correlated with ALT, fasting insulin, and HOMA-IR.

Conclusions: Both the TyG index and AIP were correlated with the MetS components in morbidly obese non-diabetic children. maybe an important prognostic indicator for later cardiovascular adverse events. However, cut levels for TyG may differ in children versus adults.

P2-101

Epicardial fat, interventricular septal and leftventricular posterior wall thicknesses are associated with cardiometabolic risk markers and physical activity in apparently healthy school-age children

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Introduction: Inactivity in children is associated with cardiometabolic risk, while physical activity improves cardiometabolic health. We aimed to determine the association between epicardial fat (Efat), interventricular septal and left ventricular posterior wall thicknesses (IVSthickness and LVPWthickness) with physical activity/inactivity, non-sedentary/sedentary behavior, body composition, and cardio-metabolic parameters in children classified as being: inactive, sedentary physically active (S-PA), and non-sedentary physically active (NS-PA).

Methods: A total of 250 apparently healthy children (111 girls/139 boys; 9.1±1.9 years) were recruited in primary health centers in Girona and classified based on WHO criteria as being: 1) inactive: ≤1hour/day of moderate to vigorous physical activity (MVPA) (N=88); 2) S-PA: >1hour/day of MVPA and screen time ≥2hours/day (N=64); and 3) NS-PA (>1hour/day of MVPA and screen time <2hours/day) (N=86).

BMI, waist circumference (WC), fat mass (FM) and systolic blood pressure (SBP) were assessed. Efat, visceral fat (Vfat), IVSthickness, LVPWthickness and carotid intima media thickness (cIMthickness) were measured by high-resolution ultrasound. Serum lipids, HOMA-IR, C-reactive protein, and high molecular weight (HMW) adiponectin were measured in fasting blood. Children's parents answered the Physical Activity Questionnaire (enKid) to assess physical (in)activity as hours and metabolic equivalents (METs) and sedentary/non-sedentary behavior.

Results: Efat, IVSthickness and LVPWthickness were positively associated with BMI, WC, FM, Vfat, cIMthickness and C-reactive protein, while negatively associated with HDL cholesterol in all groups. In addition, in inactive children, Efat, IVSthickness and LVPWthickness were positively associated with SBP and HOMA-IR, while in NS-PA children they were negatively

Table. Biochemical data for obese children

	SBP	DBP	Fasting glucose	Insulin	HOMA	HbA1c	OGTT	TG	HDL	LDL	AIP	TyG	ALT
Mean	137	78	5.8	38.2	9.8	4.8	7.1	1.22	1.49	2.23	-.08	4.25	23.6
SD	13	8.4	0.36	40.3	10.7	0.41	1	0.35	0.35	0.44	0.23	0.19	11.3

associated with HMW adiponectin and hours/METs of self-organized physical activity behavior (playing alone+playing with others+physical activity).

Interestingly, hours of coach-directed sports activities were negatively associated with Efat in SP-A children, while they were positively associated with IVSthickness and LVPWthickness in NS-PA children. All associations ($p<0.05$ to $p<0.001$) were maintained after multiple regression analyses correcting for age, sex, and BMI.

Conclusions: Higher Efat, IVSDthickness and LVPWthickness are associated with cardiometabolic risk markers in apparently healthy school-age children. Moreover, physical activity may have beneficial effects on cardiometabolic health, but it may fail to induce complete health benefits in inactive and sedentary physically active children. Interestingly, in sedentary physically active children, beneficial effects seem to be induced only by coach-directed sports activities. Finally, higher IVSthickness and LVPWthickness in non-sedentary physically active children could be more related to a physiological adaptation to the training specificity of the particular sport, rather than to a pathological change.

P2-102

Long term effect of metformin therapy in children and young people with obesity - A single center experience

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Introduction: The prevalence of childhood obesity is increasing worldwide, and the management remains a challenge. The mainstay of management is lifestyle modification but if this is not successful, pharmacological agents are considered although the options in children and young people are quite limited. Metformin has been used as an adjunct therapy alongside lifestyle modification in children and young people with obesity. Some studies have shown it to be effective in the short term but evidence regarding long-term benefits is limited.

Aim: The aim of our study was to investigate the effect of long-term metformin use on the body mass index (BMI) in children and young people with obesity.

Method: Retrospective data from a single tertiary children's hospital was collected over 2 years period. Children and adolescents aged 10-18 years with a BMI (SDS) > 2 and on metformin therapy for at least 2 years were identified. Patients with type 2 diabetes mellitus were excluded. All patients had demonstrated insulin resistance prior to commencing metformin therapy. Change in BMI was compared at 6, 12 and 24 months to baseline measurements.

Results: In total, 43 patients were included (27 F: 16 M) with a mean age of 13.44 years (± 3.42). The starting dose of metformin was 500mg daily and it was increased to a maximum dose of 2g daily over the course of 24 months. The mean baseline BMI and BMI SDS were 37.33 (± 8.35) and 3.78 (± 1.05) respectively. The mean BMI (SD) at 6 months was 36.82 (± 8.84), at 12 months was 37.41 (± 8.81) and at 24 months was 37.72 (± 8.03). There was an initial drop in BMI in the first 6 months but subsequently the BMI increased till the end of the 2 years study period. Only 5 out of the 43 patients achieved 5% weight loss at the end of 24 months. The patients who discontinued treatment prior to the two years period (not included in the analysis) did so predominantly due to gastrointestinal side effects.

Conclusion: The results of the study have shown that metformin therapy over two-years was not effective in reducing weight in children and adolescents with obesity. Newer treatment options are needed to manage childhood obesity, along with intense lifestyle intervention, in a multidisciplinary team setting.

P2-103

Reduction of the Nutritional Diagnosis of Eutrophy Among Brazilian Adolescents, Evaluation from 2010 to 2021

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Introduction: Identifying the nutritional diagnosis of adolescents is crucial for developing public health strategies that promote the adequate development of this population.

Objective: To analyze the temporal trends of the BMI of Brazilian adolescents (10 to 19 years old) between 2010 and 2021.

Methods: Descriptive ecological study. Data obtained from e-SUS Primary Care. The prevalence rate of the categories was obtained: severe thinness (ST), thinness (T), eutrophic (E), overweight (OW), obesity (OB), and severe obesity (SOB), and the trend was calculated by segmented linear regression, the variations annual percentages (APCs). In addition, time-series analysis was performed in the Joinpoint Regression Program.

Results: In the analysis of the country as a whole, the BMI showed a decreasing character in the categories "ST" (APC:-2.7; p=0.029) and "E" (APC:-3.8; p=0.008). BP" (APC: 3.0; p<0.031), "OB" (APC: 9;1; p<0.001) and "SOB" (APC: 29.6; p=0.012). The highest annual percentage reduction (APC-) of "E" occurred between 2019 and 2020 (67.78% -> 64.17%). The highest APC+ of "OW", "OB" and "SOB" occurred between 2019 and 2020 ("SB": 18.25% ->19.97%; "OB":7.91% ->10.46%; "SOB":1.8% -> 2.41%). "ST" was stationary in the Northeast and decreasing in the others "T" showed an increasing character in the Northeast, Southeast, and South. In all regions, "E" had a decreasing trend, while we observed an increasing character in the prevalence of "OW", "OB" and "SOB".

Conclusion: The growing trend of the "OW", "OB" and "SOB" categories in the last 12 years evidence exposure to risk factors harmful to the development of this population, such as the intake of hypercaloric foods and a sedentary lifestyle. In addition, the increase in "MA" in some regions highlights the country's socioeconomic inequalities and differences in nutritional profile. The

most considerable reduction in "E" and the most significant increase in "OW" and "OB" in the 2019-2020 period can be attributed to the Covid-19 pandemic's impact on the habits of this population.

P2-104

Leptinemia and cardiometabolic risk factors in genetic obesity syndromic in children: Prader Willi and Bardet Biedl

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Obesity is a state of imbalance between food intake and energy expenditure leading to a positive energy balance. This condition may be due to the existence of a genetic syndrome: the Prader-Willi syndrome (PWS) is the genetic cause the most common obesity and Laurence-Moon Bardet-Biedl syndrome (BBS), autosomal recessive.

Objectives: Our objective is to compare the cardio-metabolic risk factors in children with obesity gene to those of children with simple obesity and those of healthy subjects of similar age and sex.

Materiel and Methods: This is 13 patients with a genetic syndrome (PWS 8 and 5 SBB). They are followed in consultation-Pediatric Endocrinology (HER) over a period of 7 years. Their average age: 8.7 ± 4.1 years, their mean BMI: 31.19 ± 6.24 kg/m2. The subjects with simple obesity (controls) (n = 15) are chosen in a random way same age, same sex and BMI as obese with a genetic syndrome. The controls (n = 14) had a mean age of 8.9 ± 4.6 years. Their average BMI was 17.01 ± 2.13 kg/m2. Serum lipids (TC, HDL-C, TG) and glucose were measured by an enzymatic method. Serum levels of leptin, insulin have been determined by an immunoassay method.

Results: Insulin resistance was assessed by HOMA-IR, FIGR, Fcb and the insulin sensitivity index QUICKI. Patients with a genetic syndrome show a significant elevation of triglycerides, lower HDL-cholesterol and increased plasma leptin. It's increased insulin resistance (HOMA-IR, FIGR, Fcb) and lower insulin sensitivity (QUICKI index). There's an increased rate of leptin, the FIGR and Fcb in obese with a genetic syndrome (PWS and BBS) compared with obese controls.

Conclusion: This work confirms that obesity due to genetic abnormality is associated with disruption of important risk factors cardiovascular.

P2-105

A Comprehensive Multidisciplinary Management Plan Is Effective in Reducing the Prevalence of Overweight and Obesity in Adolescence

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Background: Obesity in adolescence represents a major health problem of our century owing to its epidemic proportions and the associated morbidity and mortality in adult life. In Greece, 41% of adolescents are overweight or obese.

Aim: The aim of our study was to investigate the effectiveness of a comprehensive, multidisciplinary, personalized management plan at reducing the prevalence of overweight and obesity in adolescence.

Methods: Five hundred and forty-four (n=544) adolescents [(mean age ± SD: 12.294 ± 2.102 years), 216 males (39,7%), 328 females (60,3%)] attending our 'Out-patient Clinic for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence' were studied prospectively. Subjects were classified as obese (n=299, 55%), overweight (n=161, 29,6%) or with normal body mass index (BMI) (n=84, 15,4%) according to the International Obesity Task Force cutoff points. All subjects were evaluated by a multidisciplinary team at frequent intervals, received personalized guidance on diet and exercise and were studied prospectively for 1 year. Detailed clinical evaluation and laboratory investigations were performed at the beginning and at the end of the study.

Results: A higher number of girls [114 (34.8%)] were overweight compared with boys ($p < 0.001$). Adolescents with obesity were younger when started to gain weight compared with overweight and normal-BMI subjects ($p = 0.002$). Adolescents with obesity had more frequent episodes of overeating and demonstrated aggressive behavior when food was denied compared with the other two groups. Furthermore, adolescents with obesity had significantly higher systolic (SBP) and diastolic (DBP) blood pressure, waist circumference, hip circumference and waist-to-hip ratio than overweight and normal-BMI subjects on both assessments. In addition, subjects with obesity had significantly higher concentrations of fasting plasma glucose and serum insulin, HbA1C, triglycerides, LDL-cholesterol, uric acid and ApoB, and significantly lower concentrations of HDL-cholesterol, ApoA1 and Vitamin D than their overweight and normal-BMI counterparts. Following 1 year of multidisciplinary management interventions, the prevalence of obesity decreased by 27.1%, the prevalence of overweight and normal BMI increased by 13,4% and 40%, respectively, and all cardiometabolic indices improved significantly in all subjects.

Conclusion: The above findings indicate that a personalized, multidisciplinary intervention program is effective at reducing the prevalence of obesity in adolescence in Greece.

P2-106

Identification of a novel point mutation in APOB gene in a patient with hypobetalipoproteinemia

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Familial hypobetalipoproteinemia (FHBL) is an autosomal codominantly inherited disorder of lipid metabolism characterized by <5th percentile plasma levels of LDL cholesterol or total apolipoprotein B (apoB). LDL cholesterol level is usually between 20-50 mg/dL. FHBL results from mutations in APOB, PCSK9 gene. Patients with homozygous APOB-related familial hypobetalipoproteinemia (APOB-FHBL) may have symptoms of fat malabsorption, steatorrhea, diarrhea, failure to thrive, deficiencies of fat-soluble vitamin, and neurologic dysfunction. They usually have hepatomegaly and hepatic steatosis. These patients may need a low-fat diet and supplementation of fat-soluble vitamins. Patients with heterozygous APOB-FHBL are usually asymptomatic with mild liver dysfunction and hepatic steatosis. They are often diagnosed incidentally due to low cholesterol levels and generally do not require special treatment or restriction of fat intake.

A 14-year-old Korean boy was referred to our clinic due to his low level of low-density lipoprotein (LDL) cholesterol and elevation of aminotransferases. When he presented to our clinic, his height, weight and body mass index were 164 cm (-0.14 standard deviation score [SDS]), 56.9 kg (0.09 SDS), and 21.15 kg/m2 (0.13 SDS), respectively. He complained no specific symptom of hypobetalipoproteinemia, including growth retardation, steatorrhea, and neurologic dysfunction. His laboratory test showed low LDL cholesterol (25.5 mg/dL; reference value, 0-100 mg/dL), low apolipoprotein B (14 mg/dL; reference value, 66-133 mg/dL), and elevated aminotransferases (AST, 41 U/L [reference value, 0~34 U/L]; ALT, 69 U/L [reference value, 10~49 U/L]). Although he was not obese, abdominal computed tomography showed severe fatty liver and hepatosplenomegaly. There was no history of alcohol consumption, systemic infection and exposure to herbal medications or hepatotoxic chemicals, so he was diagnosed with nonalcoholic fatty liver disease. A multigene panel associated with hereditary dyslipidemia was conducted. A heterozygous mutation for p.Lys3846Ter (c.11536A>T) was identified in the APOB gene, which had not been reported in previous studies. That variation was classified as likely pathogenic variant according to ACMG guidelines. The same mutation was not detected in his parents, and his parents showed high or normal LDL cholesterol, and normal apolipoprotein B. Therefore, the patient was diagnosed with de novo heterozygous FHBL. He started oral vitamin E (alpha-tocopherol) 1,000 IU daily because of his low alpha-tocopherol (4.0 mg/L; reference value, 5.5-17.0 mg/dL) and he is being followed up regularly.

P2-107

An obese patient with a pathogenic *PTEN* mutation. A case report

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Introduction: Germline mutations in Phosphatase and tensin homolog (*PTEN*) gene (chromosome 10q23) lead to PTEN Hamartoma Tumor Syndrome (PHTS), which includes Cowden syndrome. *PTEN* encodes a tumor suppressor protein that is a negative regulator of PI3K – Akt signaling pathway, taking part in multiple biological processes, including cellular cycle and regulation of metabolism.

Materials and Methods: We present the case of an 8-year-old female patient followed-up in our Outpatient Obesity Clinic. Clinical examination revealed BMI of 24.8 kg/m^2 (BMI z-score 2.16), macrocephaly, short neck, nasal base subsidence, lip papillomas and lipoma of the right lumbar area. The past medical history suggested fetal macrosomia, lipoma excision at the age of 4 years and multiple oral papillomas. Clinical genetic evaluation suggested the diagnosis of Cowden syndrome. Genetic testing revealed a *de novo* pathogenic missense mutation of *PTEN* [(NM-0013047175): c.1546-2A>G)].

Results: During follow up, thyroid ultrasound showed heterogeneity and two nodules (thyroid function normal, FNA negative for malignancy). Further clinical examination revealed papillomas in the oral cavity and lips and acral keratosis. The BMI initially improved through the implementation of a multidisciplinary personalized lifestyle intervention program, but it gradually increased during puberty (BM: 31.3 kg/m^2; BMI z-score 2.95 at 15$^{8/12}$ years). However, despite increased adiposity, our patient did not develop any signs of insulin resistance [3-hour OGTT: Glucose (mg/dL) 0'-89, 60'-119, 120'-114, 150'-120, 180'-109, Insulin (μIU/mL) 0'-8,93, 60'-20,67, 150'-27,81, 180'-19,95 (HbA1c: 5%, HOMA-IR: 1.96)].

Conclusions: PHTS is a rare syndrome that may present early in life and may be associated with dysmorphic features, thyroid nodules and mucocutaneous lesions and obesity but no signs of insulin resistance despite the marked adiposity. Early diagnosis allows the implementation of a multidisciplinary monitoring to detect and manage tumorigenesis on time, as well as other comorbidities. Further research in Cowden syndrome, as a pathophysiologic model of obesity, and increased insulin sensitivity, can potentially provide a deeper understanding of the underlying mechanisms, and contribute to the development of novel therapeutic targets for type 2 diabetes, based on small molecule PTEN inhibitors with systematic or tissue specific effects, without oncogenic side effects.

P2-108

A Noval De Novo PHIP Variant Contributing to Chung-Jansen Syndrome: A case report and review

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Objectives: ①To present Chung-Jansen Syndrome or CHUJANS by a de novo variant in the pleckstrin homology domain-interacting protein (PHIP) gene and compare the clinical phenotype with previous case reports; ②To provide a novel genetic detection methods with whole-exome sequencing (WES) and whole genome sequencing (WGS) and Sanger sequencing for rare genetic diseases.

Patients and Methods: Following collecting clinical datas of individual and studing systematic reviews, we compare our case with previous reports from variant types and phenotype. In addition to WES to find out the variant site, we add WGS to determine and Sanger sequencing to confirm it.

Results: A 11-year-old male borned with normal vaginal delivery at full term with weighted 3.2kg, measured 50cm, had delayed in motor and language development since childhood like walking alone and calling "father and mother" after 3-year-old. He gained fast weight 4 years old(5kg/kg) which led him to obesity with BMI 29.76kg/m2(>97th percentile). He had poor academic performances and social skills. The examination revealed dysmorphic features like large ears with thick helices and earlobes, full eyebrows,uptured nose, thick nasal alar, slight purple lines in bilateral groins,occult penis. Investigations showed that increased serum AST 69U/L, ALT 118U/L, TG 2.74mmol/L, CHOL 7.46mmol/L, LDL-C 4.91mmol/L, UA 484 μmol/L, decreased serum HDL-C 1.16mmol/L. No abnormalities were found in blood electrolytes, kidney function, thyroid function, cortisol, ACTH, sex hormone and glucose metabolism. Bone age was 11 years and 6 months. Urinary and testicular color doppler ultrasound, heart color doppler ultrasound, the MRI brain and pituitary were normal; Evaluation of intelligence showed intellectual disability; Chromosome karyotype was 46, XY and WES revealed a de novo variant in PHIP Gene in Exon16-19 (NM_017934.6: c.79707131-79713575 del). According to previous reports, there were 35 individuals having unique variants from 37 cases, including missense, nonvariant, frameshift, translocation, splice and multiple gene delete, while two groups of individuals were identified to have similar clinical phenotypes with same variant sites.

Conclusion: The loss-of-function mutation (LOF) in PHIP gene can lead to Chung-Jansen Syndrome, which is a rare chromosomal dominant genetic disorder, characterized by global developmental delay, intellectual disability, obesity, behavioral problems, dysmorphic features. Despite a large fragment deletion as a novel variant, our individual displays similar clinical phenotype comparing with those previously. Therefore, Chung-Jansen Syndrome should be considered with an obese children as well as developmental delay, intellectual disability, behavioral problems, dysmorphic features. Genetic detection methods is beneficial for definitive diagnosis.

P2-109

Updated reference ranges for aminotransferase levels of Korean children and young adolescents based on the risk factors for metabolic syndrome

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We investigated the reference values of liver enzymes based on cardiometabolic risks among children and adolescents using the Korea National Health and Nutrition Examination Survey (KNHANES). A total of 8,091 subjects aged 10-18 years were included data from 2007-2017. Overall, Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and the AST/ALT ratio varied with sex and age. AST levels tended to decrease with age, but ALT levels had a U-shaped curve, which resulted in a gradual increase in the AST/ALT ratio after age 13. The prevalence of MetS was strongly associated with elevated AST or ALT and a decreased AST/ALT ratio. The odds ratios of the development of MetS were elevated in groups with high levels of AST and ALT and a low AST/ALT ratio. Particularly in the combined ALT and AST/ALT analyses, borderline-high levels also showed a high odds ratio of MetS. Liver enzymes were also involved in the increase in the adjusted mean values for each risk factor for MetS. Here, we provided updated reference values for liver enzymes based on the analysis between population-based data and cardiometabolic risk factors; AST, ALT and the AST/ALT ratio might be useful in the early diagnosis and treatment of the MetS.

P2-110

Uric acid as a marker of cardiovascular risk and insulin-resistance in course of pediatric obesity

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Introduction: Many evidences confirmed that hyperuricemia is connected with obesity, insulin resistance, type 2 diabetes and cardiovascular risk, not only among adults. Uric acid (UA) interacts with other factors in the modulation of obesity and its complications, since childhood. The study aims to identify any correlations between AU plasma concentrations and the clinical/laboratory data of a group of obese Italian children living in the province of Salerno, Campania.

Materials and Methods: A retrospective study was conducted on 70 children (30M, 40F, age 5-16 years) with obesity (BMI z-score 2.47 ± 0.28) assessed at the pediatric endocrinology service of the Pediatric Unit - PO di Battipaglia - ASL Salerno from January 2016 to January 2020. All of them practiced: weight, height, BMI z-score, waist circumference (WC), neck circumference (NC) and blood pressure measurement; glucose, insulin (for calculating HOMA index), c-peptide, ALT, AST, gamma GT, total cholesterol, HDL, LDL, triglycerides, ESR, PCR blood dosages. They also

followed the oral glucose tolerance test (OGTT). The correlation coefficient was calculated between UA and clinical/laboratory identified values.

Result: UA significantly increases with weight (r=0.58458 p=0.00001), BMI z-score (r=0.44029 p=0.00247), WC (r=0.54632 p=0.00047), NC (r=0.54286 p=0.00043), gamma GT (r=0.35260 p=0.00296) and gamma GT/HDL ratio (r=0.48958 p=0.00002). An interesting relationship emerged between UA and glucose metabolism. In particular, as UA levels grow, c-peptide (r=0.56330 p=0.00015), insulin (r=0.33270 p=0.00522), HOMA index (r=0,30669 p=0.01097) and HbA1c (r=0.24706 p=0.04724) respectively increase. Finally, a significant negative correlation is noted between UA, FT3 (r=-0.24606 p=0.04005) and Thyroglobulin (r=-0.34416 p=0.02966).

Conclusion: UA can be considered a laboratory marker of pediatric obesity and its hepatomethabolic complications. In particular, the relationship with insulin resistance indicators and glucose metabolism in our obese children is evident. UA action for cardiovascular damage could also be helped by thyroid disfunctions. However, further studies are needed for considering UA as a reliable predictor of the main complications of pediatric obesity.

P2-111

Gamma-glutamyl transferase (GGT) and the GGT / high-density lipoprotein (HDL) ratio: Useful tools for identification of obese children with insulin resistance

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Introduction: The role of gamma-glutamyl transferase (GGT) enzyme as a marker of insulin resistance (IR) in pediatric obesity is well known. Recent evidence, mainly in the adult population, has identified GGT/High-Density Lipoprotein (HDL) ratio as a risk index for hepatic steatosis. The study has the purpose of examining the relationship between GGT, GGT/HDL ratio and the clinical/laboratory data of a group of obese Italian children living in the province of Salerno, Campania.

Materials and Methods: A retrospective study was conducted on 82 children (42M, 40F, age 5-16 years) with obesity (BMI z-score 2.86 ± 0.27) assessed at the pediatric endocrinology service of the Pediatric Unit - PO di Battipaglia - ASL Salerno from January 2016 to January 2020. All of them practiced: weight, height, BMI z-score, waist circumference (WC), neck circumference (NC) and blood pressure measurement; glucose, insulin (for calculating HOMA index), c-peptide, ALT, AST, gammaGT, total cholesterol, HDL, LDL, triglycerides (TG), ESR, PCR blood dosages. They also followed the oral glucose tolerance test (OGTT). The correlation coefficient was calculated between GGT, GGT/HDL ratio and clinical/laboratory identified values.

Result: GGT progressively increases with weight (r=0.33093 p=0.00861), BMI (r=0.48214 p=0.00019), NC (r=0.34778 p=0.02230), WC (r=0.41622 p=0.00401) and also has a significant correlation with insulin function and in particular with c-peptide (r=0.43309 p=0.00188), basal insulin (r=0.46427 p=0.00001), HOMA index (r=0.39320 p=0.00026), insulin levels at 120 minutes during OGTT (r=0.72239 p=0.00106) and TG (r = 0.29235 p = 0.00769). GGT/HDL ratio correlates with an even stronger statistical significance than GGT with TG (r=0.44958 p=0.00003), anthropometric parameters such as weight (r=0.51733 p=0.00003), BMI (r=0.59392 p=0.00000), CC (r=0.51164 p=0.00063), CV (r=0.59944 p=0.00002) and with insulin function indicators such as c-peptide (r=0.59105 p=0.00001), basal insulin (r=0.48467 p=0.00000), HOMA index (r=0.42632 p=0.00009) and insulin levels at 120 minutes during OGTT (r = 0.89387 p = 0.00009). Finally, GGT/HDL ratio decreases with higher Vitamin D levels (r=-0.22923 p=0.04351) and also statistically correlates with TSH levels (r = 0.26460 p = 0.01630).

Conclusion: GGT/HDL ratio shows a significant and stronger statistical association than GGT with anthropometric and laboratory parameters of IR in our obese children population. These data require studies on a larger pediatric population and could be influenced by Vitamin D levels and thyroid disfunction.

P2-112

Prediabetes in obesity adolescents: Frequency, structure, relationship with body mass index

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Background: The increased prevalence of youth obesity has led to raised youth-onset type 2 diabetes mellitus (T2DM), as well as the intermediate condition of prediabetes. Diagnosis of prediabetes can help preventing of the development of T2DM.

Aims: to study the frequency, clinical laboratory diagnostics and relationship of prediabetes with SDS BMI in obese adolescents.

Materials: The study involved 95 adolescents with obesity. Inclusion criteria: SDS BMI≥2.0, Tanner stage ≥II, age <18.0 years, exclusion criteria: diabetes mellitus. The research consisted of the estimate SDS BMI and the measure of HbA1c, insulin, fasting plasma glucose (FPG) and 2-hour plasma glucose (2hPG) during an oral glucose tolerance test (OGTT). Prediabetes in adolescents was diagnosed using American Diabetes Association criteria. Data was analyzed by using SPSS Statistics for Windows, Version 26.0.

Results: Prediabetes was diagnosed in 42.1% (40/95) of cases. One of the three criteria for prediabetes was detected in 85% (34/40), two or more - in 15% (6/40) of cases. In the one-criterion prediabetes group, impaired fasting glycemia (IFG) accounted for 64.7% (22/34), HbA1c≥5.7% - 29.4% (10/34), impaired glucose tolerance (IGT) – 5.9% (2/34) of cases. In the group with two or more criteria, IGT in combination with HbA1c≥5.7% was detected in 50% (3/6) of cases, IGT in combination with IFG - 33.3% (2/6), IFG in combination with HbA1c≥5 .7% - 6.7% (1/6). There was no combination of all three criteria for prediabetes in this sample of patients.

There were statistically significant differences between the indices of groups with prediabetes and normal glucose metabolism: FPG (mean 5.63±0.49; 95% CI: 5.48-5.79 vs 5.03±0.42; 4.92-5.15 mmol/L, p<0.001); 2hPG (mean 7.04±0.93; 95% CI: 6.74-7.34 vs 6.23±0.82; 6.01-6.46 mmol/l, p<0 /001); HbA1c (mean 5.5±0.31; 95% CI: 5.39-5.59% vs 5.2±0.25; 5.15-5.29%, p<0.001).

There were no significant differences in SDS BMI between groups with prediabetes (n=40) and unimpaired carbohydrate metabolism (n=55) (mean SDS BMI 3.1±0.54 vs 3.1±0.54, respectively; p=0.975).

In addition, there were no significant differences in SDS BMI between groups with the one-criterion prediabetes group (n=34) and two or more criteria (n=6) (mean SDS BMI 3.1±0.56 vs 3.3±0.39, respectively; p=0.271).

Conclusions: Prediabetes was detected in almost half of obese adolescents; in most cases it was represented by one criterion and in the order of occurrence in the following sequence: IFG, HbA1c≥5.7%, IGT. No relationship established between the index of SDS BMI and the development of prediabetes.

P2-113

Binge eating disorder in children with different forms of obesity

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Background: Binge-consuming disorder (BE) is mental ilness where people eats large amounts of food over a short period of time with associated negative psychological problems, but wihout the compensatory behaviors. Nowadays this illness is more common in obese children.

Objective: To evaluate the frequency of compulsive overeating in children with obesity.

Methods: We examined 148 children in the University Hospital (Minsk) in 2022. All children were divided into 2 groups: group 1- 84 children (44 boys (B) (BMI 30.38±4.48 kg/m2, 12.34±1.91 years) and 40 girls (G) (BMI 29.35±4.67 kg/m2, 13.68±2.35 years)) with different forms of obesity; group 1 - the control group of 64 children (32 B (BMI 30.38±4.49 kg/m2, 12.34±2.80 years) and 32 G (BMI 28,34±4,68 kg/m2, 13.68±2.37 years). All children participated in the Children's Personality Questionnaire, School Anxiety Scale (SAS), Children Eating Disorder Examination Questionnaire (ChEDE-Q), Birleson Depression Self-Rating Scale for Children (DSRS-C).

Results: The Children's Personality Questionnaire showed that most children have restlessness, insecurity, impulsiveness and tension (p=0.049). School Anxiety Scale showed that all children have hight level of anxiety which may be related to relationships in the family or at school (p=0,002). According to the ChEDE-Q test, 17 children (12 G (BMI 30.1±3.15/m2, 11.87±2.31 years) and 5 B (BMI 30.37±3.87 kg/m2)) could be suspected of Binge eating desease or bulimia. According to the medical history, children do not taste the food, satiety. Based on the DSRS-C 38 children (17 G (BMI 28.34±4.68 kg/m2, 12.35±2.34 years) and 21 B BMI 31.25±3.89 kg/m2, 11.87±2.31 years) could be suspected of mild depression and 9 (5 G BMI 30.89±3.85 kg/m2, 12.95±2.27 years and 4 B BMI 33.25±1.25 kg/m2, 12,11±1.67 years) of moderate-to-severe depression (p=0.047).

Conclusions: We found that obese children more often have eating disorders, compulsive overeating and many children have high anxiety. We discovered 38 children with mild depression and 9 children with moderate depression.

P2-114

Leptin receptor deficiency: A case report

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Background: Leptin receptor deficiency leads to severe early-onset obesity and pituitary dysfunction. Here we present the first case of monogenic obesity due to a novel mutation in *LEPR* gene in Russia.

Case report: 16-year-old female patient was admitted to our hospital with morbid obesity and primary amenorrhea. She was born at term with a birth weight of 3360 g to non-consanguineous parents. She had a mild developmental delay in early childhood. From the first months of life girl had excessive appetite and rapid weight gain: at 3 month she was 7 kg, at 1 year 20 kg, at 9 years 99 kg, at 15 years 161 kg.

At the age of 9 she was first diagnosed as insulin resistant (HOMA-IR 11.8) and hypertensive. The recommendation of dietary and life-style intervention was not helpful and due to overweight, insulin resistance progression type 2 diabetes developed (HbA1c 8.9%). Metformin and hypotensive therapy had been administered. At 16 she was hospitalized in emergency with glycemia of 22 mmol/l, HbA1c was 15.3% so insulin Glargin was added to the therapy.

By physical examination at 16 years: morbid obesity (weight 159kg, SDS IBM 4.75), Tanner stage 2. Investigation indicated dyslipidemia, steatohepatitis, lipomatosis and arterial hypertension. Combination therapy with metformin and insulin improved glycemic control and reduced HbA1c level to 6.5%. LHRH test demonstrated a pre-pubertal response. Other endocrine abnormalities were not found. The presence of severe early-onset obesity with hypogonadotropic hypogonadism and high levels of leptin (157 ng/ml (3.7-11.1) led to the suspicion of leptin receptor deficiency. Genetic testing identified two pathogenic variants in *LEPR* gene: exon4:c.131_132insTGAC:p.Y46X and c.2588_2589delCA:p.H864fsX24 in exon18. Healthy mother was found to be a heterozygous carrier of the c.2588_2589delCA:p.H864fsX24 variant.

Conclusion: Early genetic testing can improve diagnosis of rare monogenic forms of obesity and identify patients whose quality of life can be improved. Targeted therapeutic intervention can protect them from getting obesity complications.

P2-115

Is it Hyponatremia or Pseudohyponatremia? Management of Low Serum Sodium in Patient with Acute Pancreatitis Secondary to Hypertriglyceridemia

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Background: Hyponatremia is an electrolyte disorder, that may lead to severe complications such as rhabdomyolysis, seizures, coma, and death. Clinicians do take hyponatremia seriously. However sometimes clinicians should be careful in interpreting the low laboratory sodium level as it does not necessarily reflect the actual natremic status especially when the patient is euvolemic and having normal serum osmolality, for which pseudohyponatremia should be considered. Pseudohyponatremia therefore is expected in cases of hyperlipidaemia, hyperglycaemia, and hyperproteinaemia.

Case: We are reporting a 4-year-old girl presented with 1-day history of severe, central, non-radiating abdominal pain associated with frequent vomiting, diagnosed with acute pancreatitis secondary to hypertriglyceridemia, found to have low sodium level (120 mmol/L) with normal potassium level of 4.6 mmol/L. Other investigations are tabulated.

The severe hypertriglyceridemia was taken seriously. Conservative management with insulin infusion thought to be superior to plasmapheresis as it is less invasive. Therefore our patient was started on intravenous 10% dextrose mixed with 0.9% sodium chloride solution running at 1.5 times the maintenance fluid rate adjusted for her weight. Insulin infusion was started as 0.1u/Kg/hr, but as her glucose dropped causing mild hypoglycaemia, for which the insulin infusion reduced to 0.05u/kg/hr. No direct treatment intended for the hyponatremia, and it was opted out to treat the hypertriglyceridemia with close monitoring of hyponatremia as pseudohyponatremia was strongly suspected in this case. Within 24 hours of commencing her on insulin infusion, her triglycerides started drifting down leading to massive improvement and subsequently normalization of the sodium level.

Discussion: Normally, most electrolytes including sodium ion are dissociated in the water component of a plasma. When the plasma water volume significantly deviates from 93% due to high concentration of proteins or lipids in plasma, pseudohyponatremia occur.

Improvement in triglycerides level means improvement in lipemic effect on blood, leading to normalisation of the sodium level. Not just that, but we have also observed an improvement of the haemoglobin level. The awareness of this condition saved the patient from receiving unnecessary fluid boluses or hypertonic sodium chloride solution.

Conclusion: Pseudohyponatremia can occur in patients with hypertriglyceridemia. Therefore, lowering the elevated triglycerides results in improvement of sodium levels.

	At presentation	12 hrs later	24 hrs later	36 hrs later	48 hrs later
Amylase (28-100 U/L)	617	417	297		
Lipase (13-60 U/L)	1739		1275		
Triglycerides (0.0-2.3 mmol/L)	80	68	43.9	19	4.7
Sodium	120	130	135		
Haemoglobin g/dL	20	14			

P2-116

Abstract Withdrawn

P2-117

Cardiometabolic risk factor clustering in obese adolescents

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Introduction: The increasing prevalence of obesity has become a major global health issue. Clustering of cardiometabolic risk factors in obese adolescents is associated with reduced life expectancy and impaired quality of life. Due to serious impact of obesity on cardiometabolic health, effective treatment strategies are intensively sought after.

Objectives: The aim of this retrospective cross-sectional study was to examine cardiometabolic risk factor clustering in obese adolescents referred for diagnostic assessment and to evaluate its'

association with the degree of obesity, adipose tissue distribution, and cardiorespiratory fitness (CRF).

Methods: Data from 70 apparently healtyh adolescents with BMI ≥95th percentile for age and sex were retrospecitvely analysed. Their diagnostic work-up included waist circumference measurement, bioelectrical impedance analysis (BIA) for body composition assessment, oral glucose tolerance test (OGTT), fasting lipid profile, serum liver enzyme activity measurement, 24-hour ambulatory blood pressure monitoring, and submaximal treadmill walking test for CRF estimation.

Results: Out of 70 adolescents, 45 (64.3%) were female. All the subjects were pubertal. Their mean age was 14.3±1.8 years (age range 10-17.8), BMI 36.15 ± 4.72 kg/m^2, BMI SDS 2.43 ± 0.35, waist to height ratio 0.66 ± 0.08, and whole-body fat percentage 41.69 ± 7.17%. In the majority (85.7%), cardiometabolic risk factors were detected. The most prevalent cardiometabolic risk factor was dyslipidemia (77.1%), followed by hypertension (27.1%), abnormal liver function tests (21.4%), prediabetes (14.3%) and type 2 diabetes (1.4%). Regarding the frequency of cardiometabolic risk factors, only one was detected in 40%, two in 38.6% and three in 7.1% of obese adolescents. Groups with different number of cardiometabolic risk factors did not differ significantly according to age, sex and puberty stage, but they differed according to BMI (p = 0.038), BMI SDS (p = 0.030), waist to height ratio (p = 0.050) and CRF (p = 0.026). After adjustment for BMI SDS, low CRF remained statistically significant independent predictor of cardiometabolic risk factor clustering (beta coefficient = -0.272, p = 0.036).

Conclusion: A significant proportion of obese adolescents referred for diagnostic assessment already have associated cardiometabolic risk factors. More pronounced obesity, centripetal distribution of adipose tissue and lower CRF were associated with cardiometabolic risk factor clustering. Raising CRF should be an integral part of the therapeutic approach for obese adolescents.

P2-118

Relationship between neck circumference and cardiometabolic risk in children and adolescents with obesity

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Introduction: Pediatric obesity (PO) if not adequately identified and addressed, leads to significant chronic diseases in adulthood. The anthropometric methods for the evaluation of PO have limitations well described in the literature. Neck circumference (NC) is recently proposed as parameter for better identification and evaluation of PO. We verified the relationship between NC, body mass index (BMI), waist circumference (WC) and some laboratory parameters of a chidren and adolescents obese group, with the aim of defining the validity of NC as a clinical marker of PO and its hepato-cardio-metabolic (HCM) complications.

Materials and Methods: A retrospective study was conducted on 48 children (20M, 28F, age 5-16 years) with obesity (BMI z-score 2.86 ± 0.27) assessed at the pediatric endocrinology service of the Pediatric Unit - PO di Battipaglia - ASL Salerno from January 2016 to January 2020. All of them practiced: weight, height, BMI z-score, WC, NC and blood pressure measurement; glucose, insulin (for calculating HOMA index), c-peptide, ALT, AST, gamma GT, uric acid (UA), total cholesterol, HDL, LDL, triglycerides (TG), ESR, PCR blood dosages. They also followed the oral glucose tolerance test (OGTT). The correlation coefficient was calculated between NC and clinical/laboratory values identified.

Results: NC is always higher than the 95th percentile for sex and age (cut off: 30.5 - 46.5 cm) with mean values 35.97 ± 4.2 cm. NC is significantly correlated with weight (r=0.86140 p=0.00000), BMI (r=0.80831 p=0.00000) and CV (r=0.85164 p=0.000005). The correlations between NC and HDL (r=-0.34139 p=0.02692), AST (r=-0.33223 p=0.02951), GGT (r=0.34778 p=0.02230) and UA (r=0.54632 p=0.00047) are also significant. The relationship between NC and the main laboratory indicators of insulin resistance is also significant. In particular, NC correlates with c-peptide (r=0.53912 p=0.01167), insulinemia (r=0.36661 p=0.01694) and HOMA index (r =0.32932 p=0.03551).

Conclusion: Despite the small sample of patients, this study shows that NC could be used as an alternative to BMI and WC to evaluate PO. In particular, it is clear that NC can represent a clinical index of insulin resistance and HCM risk in obese adolescents and children. Therefore, it is advisable to measure NC in all obese children, especially those who show clinical and laboratory signs of hyperinsulinism.

P2-119

Abstract Withdrawn

P2-120

Evaluation of Thyroid Function among children and adolescents with obesity

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Introduction: Obesity is a rapidly growing health problem, with increasing worldwide prevalence. Obesity is accompanied by numerous metabolic and endocrine dysregulation. Thyroid dysfunction is one of the many metabolic aberrations that are associated with obesity. Thyroid dysfunction can be related to obesity, insulin resistance, and dyslipidemia. We aimed to study the

thyroid function in children and adolescents with obesity and the metabolic parameters.

Methods: A total of 60 children with BMI over 95th percentile for their age and sex, were included in the obesity group, and 52 healthy children without obesity (BMI less than 85th percentile) were enrolled in the control group. Thyroid function tests including TSH, T4, and T3 were measured. The levels of insulin, fasting blood sugar (FBS), cholesterol, low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and triglyceride (TG) of the patients were also assessed.

Results: Thyroid function tests were not significantly different between the obesity and the control groups. Additionally, they did not have any significant correlation with the metabolic parameters, neither in the subjects with obesity nor in the control subjects.

Conclusion: Despite the central role of thyroid hormones in the modulation of metabolism, their levels are not influenced by the obesity status

P2-121

Age-related cardiometabolic risk in children and adolescents

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Obesity, the silent pandemic of the 21st century, is being observed at increasingly younger ages. Included in the metabolic syndrome (MetS), it creates a favorable environment for the development of other components, such as impaired glucose tolerance (IGT), insulin resistance (IR), dyslipidemia (DysL) and arterial hypertension (HT). The aim of this study was to asses the influence of birth weight for gestational age (BW-GA) and age on the occurence of MetS and its components. Therefore, a retrospective observational study was conducted over a seven-year period, between January 1, 2015, to December 31, 2021, in the Diabetes and Endocrinology Departments of the „Louis Turcanu" Children's Clinical and Emergency Hospital in Timisoara, Romania. A total of 701 pediatric patients, diagnosed with obesity, included in the study were divided in 2 main study groups: children, < 10 years and adolescents, > 10 years. According to BW-GA, these study groups were each split in three sub-groups: small (SGA), large (LGA), and appropriate (AGA) representing the control group. First of all, it was found that regardless of whether looking at the MetS as a whole, or at its individual components, there is a significant increase in their prevalence among adolescents (see Table 1).

By assesing the influence of BW on the development of MetS components, it was observed that obese SGA adolescents were the most affected in relation to IR, IGT and HT, when compared to controls (IR: 30.2% vs 18.6%; IGT: 22.2% vs 16.6%; HT: 14.3% vs 4.3%). The only discrepancy was noticed in patients with DysL, where obese LGA adolescents were predominant (33.9% and 8.9% respectively). In conclusion, age has an important role in the development of MetS and its components, with adolescents having a significantly higher cardio-metabolic risk. In this age group, BW outside the normal range is an additional risk factor. Among the limitations of this study are the retrospective design that might lead to selection and classification bias and the significantly smaller number of patients in the SGA and LGA groups, compared to AGA controls, that might cause the study's findings to not be representative for the general population.

Table 1. Prevalence of MetS and its components among the studied patients

MetS / Component	Children		Adolescents	
	Number	Percentage	Number	Percentage
IR	50	26.2	141	73.8
IGT	44	27.5	116	72.5
DysL	19	25.2	101	74.8
HT	34	33.3	38	66.7
MetS	2	2.5	78	97.5

P2-122

Pediatric Endocrine evaluation of Marfan syndrome: A case report

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Background: Endocrine disorders associated with tall stature in childhood are frequently evaluated by Pediatric Endocrinologists. The most common non-endocrine genetic cause of tall stature, Marfan syndrome, is a rare autosomal dominant genetic condition of the connective tissue, which presents with specific dysmorphic features, including thin physique, long extremities and normal growth rate. Little is known regarding the association of Marfan syndrome with obesity, insulin resistance and adipose tissue function.

Case Description: We present the case of a 10.38 year old boy with gradual weight gain since the age of 7 years. The past medical history revealed that he had undergone tonsillectomy and adenoidectomy due to episodes of severe sleep apnea. At initial

presentation he was overweight (BMI: 24.3kg/m2, BMI z-score: 1.52), with 36.95 % fat mass and 59.86 % muscle mass in bioelectrical impedance analysis (BIA). His height was above the 97th centile and the respective parental target height, with an increased arm-span (+12.5 cm) and arachnodactyly. He was prepubertal. His bone age was advanced at 14 years. Endocrinologic evaluation revealed normal GH/IGF-I axis (GH suppressed to < 0.05μg/L on OGTT), normal thyroid function and homocysteine concentrations (3.9μmol/L) but elevated fasting insulin (37.73 μUI/mL) concentrations, and insulin resistance on subsequent OGTT (insulin 60'= 263.4μUI/ml). He had a normal karyotype, cardiology examination and MRI scan of the pituitary and adrenal glands. At 10.93 years old he developed idiopathic intracranial hypertension, treated with acetazolamide. Finally, at 11.09 years old, a heterozygous pathogenic variant in the gene of Fibrillin-1 (*FBN1*) (c.7039_7040delAT) and a variant of uncertain significance (VUS) in the Tenascin XB (*TNXB*) gene were detected (c.12350G>A) confirming the genetic diagnosis of Marfan Syndrome (OMIM 154700). At present, he is 15.27 years old, pubertal (testes 10-12ml), with low-normal testosterone concentration (free Testosterone 3.581 ng/dL), and normal AMH and Inhibin B (LH=3.1μU/mL, FSH=4.37mU/mL) concentrations. He remains obese (BMI: 29.7kg/m2; BMI z-score: 2.15; 36.26% fat mass; 60.62% muscle mass) with fatty liver disease and a lipoma of the right thigh. He is on metformin treatment and continues with a life-style intervention program.

Discussion: Marfan syndrome is rare, and has complete penetrance but highly variable expression. Little is known concerning the endocrine follow-up of these patients. The association between Marfan syndrome and insulin resistance is still not clear, however, experimental studies indicate a possible role of *FBN1* mutations in adipose tissue physiology, especially adipogenesis that warrant further study linking *FBN1* with increased adiposity.

P2-123

Diagnosis and management of childhood obesity during COVID-19 pandemic: an audit on clinical practice in a tertiary center

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Background: Childhood obesity represents an important public health problem and its diagnosis and management should be based on current guidelines. Prevalence of childhood obesity in Romania is one of the lowest in Europe but with a positive trend.

Aim: The aim of the current study was to analyze the implementation of the recommendations of the 2017 Endocrine Society Clinical Practice Guideline on Assessment, Treatment and Prevention of Pediatric Obesity in a tertiary Endocrinology center from Targu-Mures, Romania.

Material and Methods: Electronic health records (EHR) of children aged 1-15 years admitted in the Endocrinology Clinic of Targu-Mures, Romania, between 1st of January 2020 and 31st of December 2021 were reviewed. Data was collected on age, gender, body mass index standard deviation score (BMI SDS), overweight or obesity coded as diagnosis, waist measurement availability, assessment of potential comorbidities (blood pressure, blood glucose, total and fractioned (HDL and LDL) cholesterol, triglycerides and liver enzymes) and attending physician.

Results: A total of 691 EHR were reviewed, out of which 31.1% (215) did not contain any information except demographics and 2.9% din not contain the BMI SDS and were therefore excluded. Prevalence of overweight and obesity in the 476 EHR analyzed was 30.4% (145). Obesity was coded in 76.5% of cases (111) with girls more likely to have the diagnosis missed, regardless of age. Comorbidity assessment was complete in 39 records (26.9%) with cholesterol fractions and blood pressure most often missed, especially in younger age groups. Glucose, total cholesterol and liver enzymes were assessed most often (80%). Waist measurement was recorded in 90.3% of cases. Compliance with recommendations was similar between physicians.

Discussion and Conclusions: Compared to data available in the literature, clinical practice in this tertiary center is in compliance with the recommendations of the available guidelines even during the COVID 19 pandemic, but there is still a high percentage of not coded diagnosis and a lack of comorbidity screening, especially blood pressure and cholesterol fractions. The most important issue discovered was the high percentage of missing data in the EHR with the need for future audits in this regard.

P2-124

Abstract Withdrawn

P2-125

Effects of confinement due to COVID-19 in the child population of Álava on vitamin D status, weight and body composition

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The coronavirus disease (COVID-19) pandemic brought with it a state of alarm as of March 14, 2020, which implied a restriction on the mobility of the general population and home confinement. One of the main concerns raised by isolation was the substantial reduction in energy expenditure due to children spending more time sitting or participating in activities that involve very low rates of energy expenditure, such as watching television, managing the different networks social One of the nutrients that could be affected due to these changes in lifestyle is vitamin D

The longitudinal observational study of a single cohort was carried out in boys and girls from Álava aged between 3-16 years,

whose follow-up is carried out in the outpatient clinics of the University Hospital of Álava. For this study, data from a period prior to the lockdown (November 2019-February 2020) was compared with data from the period after the lockdown (May 2020-June 2020).

Once the favorable opinion was obtained and after consulting the database of the Pediatric consultation of the University Hospital of Álava, it was observed that 230 girls and boys met the parameters for inclusion in the study. After eliminating those who did not have a previous or subsequent analysis of vitamin D, the sample size was reduced to 76

Results:

- An increase in size: they are in the growth phase.
- An increase in weight
- An increase in the body mass index: In this case, this index also increased from 19.5to19.9
- A drop in physical activity
- An increase in the number of hours that participants spent on electronic devices.
- An increase in the percentage of girls and boys who help in the kitchen: After confinement, the percentage increased to 70%.
- An increase in the weekly consumption of snacks($p<0.005$).
- There were no changes in the number of daily meals, servings of fruit, vegetables, dairy products, fish, red meat, eggs or sugary drinks- There were no differences in the number of hours the participants slept before and during the lockdown.
- An increase in glucoset ($p<0.005$) although both parameters are within normal values.
- An increase in vitamin D: 22.35 ng/dL on average, which rose to 25.57 ng/dL.This difference is significant ($p<0.005$), although both parameters are within normal levels.This increase may be due to the fact that after confinement the population wanted to go out and took more time in the street.In addition, shops and interior sites were closed.

P2-126

Vitamin D, OPG in Obese Children

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Objective: determination of changes in metabolic status and vitamin D concentrations in obese children.

Methods: We examined 210 children in the University Hospital (Minsk) from 2021 to 2022 yrs. Their anthropometric parameters (height, weight, body mass index (BMI)) were determined. Blood levels of vitamin D, OPG, insulin were determined.

All children were divided into 2 groups: group 1 children with morbid obesity (MO) - 148 patients (88 boys(B)/60 girls(G)) (BMI more than 99th percentile for sex and age) (BMI 33.04±4.67 kg/m2, age 13.17±2.42 years); group 2 - 62 patients (B/G=31/31) with alimentary obesity (AO) (BMI-95-99th percentile for sex and age) (BMI 27.60±2.06 kg/m2, age 13.43±2.27 years). The control group (C) consisted of 60 patients (B/G=30/30) with normal body weight (BMI 19.86±2.24 kg/m2, age 13.32±2.30 years).

Results: In boys and girls with obesity higher concentrations of insulin were detected relative to the control group (AO (G 16.36 (9.90–19.20) μU/ml; B 17.07 (8.40–20.00) μU/ml) and MO (G 21.06 (12.60–24.50) μU/ml; B 20.79 (12.75–25.40) μU/ml); C (G 8.35 (5.90–11.30) μU/ml; B 9.83 (7.90-11.40) μU/ml) (G U_{AO-C}=228.0; $p<0.001$; U_{MO-C}=276.0; $p<0.001$; B U_{AO-C}=493.5; $p<0.001$; U_{MO-C}=641.0; $p<0.001$)).

Insulin resistance index level (HOMA-IR) in patients with AO (G 3.23 (1.97–3.94); B 3.49 (1.75–4.27)) and MO (G 4.14 (2.37–5.32); B 4.31 (2.55–5.46)) was higher than in the control (G 1.60 (0.99–2.18); B 1.89 (1.53–2.30)) (G U_{AO-C}=219.0; $p<0.001$; U_{MO-C}=304.0; $p<0.001$; B U_{AO-C}=1050.5; $p=0.001$; U_{MO-C}=592.5; $p<0.001$).

In patient of the study group a significant decrease in the level of vitamin D in the blood serum was registered in comparison with the control group, regardless of gender (G AO 25.90 (22.53–30.58) vs 39.36 (32.00–45.94) ng/mL, U=67.0, $p<0.0001$, G MO 20.18 (15.22–25.60) vs 39.36 (32.00–45.94) ng/mL, U=36.5, $p=0.001$, BAO 27.57 (24.03–31.78) vs 36.12 (30.77–41.69) ng/mL, U=161.50, p=0, 0001; B MO 23.01 (17.94–28.89) vs 36.12 (30.77–41.69) ng/mL; U=327.0; $p=0.001$).

In boys with obesity higher concentrations of OPG were detected relative to the control group (AO 210.89±20.17 ng/ml vs 189.1±11.21 ng/ml ($p=0.05$), MO 222.22±21.14 ng/ml vs 189.1±10.21 ng/ml ($p=0.03$)).

Conclusion: Changes in metabolic status were registered in obese patients: an increase in insulin, OPG levels and a decrease in vitamin D compared with children with normal body weight.

P2-127

The effects of Long-term (five years) Prednisone Therapy in Frequently Relapsing Nephrotic Syndrome of Childhood: Impact on glycemia and the different components of the metabolic syndrome (MetS)

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Although widely prescribed for their anti-inflammatory and immunosuppressive properties, glucocorticoids have various common metabolic side effects including hypertension, dysglycemia, and diabetes. Proposed risk factors for steroid-induced dysglycemia and metabolic syndrome include cumulative dose, longer duration of steroid course, and high body mass index.

Aim: This study was carried out to investigate the prevalence of different metabolic components and dysglycemia in children with nephrotic syndrome (SSNS) with multiple relapses for 5 years in relation to the cumulative dose of steroids.

Methods: Data of 30 children with childhood Nephrotic Syndrome (NS) was analyzed retrospectively. They received prednisolone treatment according to The International Pediatric

Nephrology Association (IPNA) guidelines for initial treatment and relapse. The cumulative dose of steroids over the period of 5 years was calculated for each child. The growth data were recorded along the treatment period. The different metabolic criteria including impaired fasting glucose (IFG), high LDL and cholesterol, lower HD, and high blood pressure for age and sex were studied over this period.

Results: The mean cumulative prednisone = 100+/- 63 mg /kg/yr given over an average duration of 5 years. Obesity (OB) and overweight (OW) increased from 25% pre-treatment to 59.2% after 5 years of treatment. After 3 and 5 years of treatment IFG was found in 24 and 36 % respectively, high LDL in 89% and 80% respectively, high cholesterol in 85% and 100% respectively. Hypertension (BP > 95th percentile) was detected in 14% and 40% of patients after 3 and 5 years of treatment. The mean serum cholesterol and LDL levels were significantly higher than normal in treated children after 3 and 5 years of treatment.

Conclusion: Long-term prednisone therapy (for 5 years) with a mean cumulative dose of prednisone = 100+/- 63 mg/kg/yr. was associated with increased prevalence of OW and obesity as well as with a higher risk of developing hypertension and dyslipidemia.

Variables	Beginning	3 yr	5 yr	p-value
Number	30	30	30	
IFG (FBG >5.6 mmol/L	15.93%	24.14%	35.71%	0.1
LDL > 2.7 mmol/L	88.89%	88.89%	80.00%	0.35
HDL < 1.03 mmol/L	10.53%	10.00%	0.00%	0.07
TG >1.7 mmol/L	77.27%	33.33%	60.00%	0.23
Cholesterol > 4.5 mmol/L	100.00%	85.71%	100.00%	1
BP >95th centile for age	33%	14.3%	40%	0.9

Fetal, Neonatal Endocrinology and Metabolism

P2-128

Placental Weight and their relation to Infant Birth weight and Gender, Gestational Age, and Maternal Age: (A Population-Based Retrospective Data Analysis (n = 80722)

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Introduction: Many potential factors can affect or be influenced by placental size. These include gestational age, maternal age, race, socioeconomic status, and gender of the baby.

Aim: We investigated the possible association/s between placental weight on the one hand and birth weight, gestational age, maternal age, and gender of the baby in a large cohort of newborns (n = 80722)

Methods: This population-based analysis comprised of a 4-year cohort data (January 2016 to December 2019) for births conducted in all HMC hospitals. These hospitals account for about 90% of all births in the country. The inclusion criterion for this analysis was term singleton live births, 37^{+0} to 42^{+6} weeks gestation (sample size = 80722). Pearson correlation coefficients explored the relationship between placental weight and other variables. The effect point estimates with 95% CI and R2 were obtained.

Results: The placental weight continued to increase through 41 weeks' gestation in all the studied newborns. The mean placental weights were significantly heavier in boys versus girls. Small, appropriate, and large for date infants demonstrated a consistent increase in placental size until 41 weeks of gestation with a mild but significant decrease in the 42nd week.

Placental weight was significantly correlated with birth weight ($r = 0.596$, $p < 0.001$) and gestational age ($r = 0.15$, $p < 0.001$). (Table 2) Placental weight accounted for 43.4% of the explained variability in birth weight. Birth weight was correlated significantly with the gestational age ($r = 0.324$, $p < 0.001$) and decreased significantly after maternal age of 35 years.

Conclusions: Reference standards of our large national cohort were achieved. Newborn infants demonstrated a consistent increase in placental weight until 41 weeks of gestation with a mild but significant decrease in the 42nd week.

Table 1. Placental weight as a function of gestational age (mean +/- SD)

Gestational age (wk)	Mean Pl wt (g)	SD
37.00	629.95	115.51
38.00	648.66	108.61
39.00	661.39	101.22
40.00	677.34	95.14
41.00	687.74	98.08
42.00	672.69	103.56

Table 2. Correlation studies between variables

	Birth wt.	Placenta wt.	Gestation age	Maternal age
Birth wt.	1.000			
Placenta wt.	0.597*	1.00		
Gestation age	0.324*	0.153*	1.00	
Maternal age	0.07	0.04	-0.12	1.00

*P < 0.01

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P2-129

Molecular pathways linking fetal growth restriction to cardiometabolic risk in childhood

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Background: Cardiometabolic (CM) risk is linked to being small for gestational age (SGA, birthweight <-2SDS). Fetal growth restriction (FGR) may not result in SGA. We focused on potential CM risk in children born following pregnancies at higher risk for FGR.

Aims: 1.To identify associations between fetal and childhood weight trajectory quartiles and CM risk markers. 2.To define molecular pathways potentially associated with CM risk.

Methods: We recruited 81 children aged 3-6 years, from term pregnancies at increased risk of FGR. 54% were male and 32% Non-White. Body mass index (BMI) SDS, abdominal circumference (AC), mid-upper arm circumference (MUAC), %fat, systolic blood pressure (SBP) and brachial augmentation index (AI) were recorded. For 31, who provided consent, fasting blood samples were collected for CM markers (insulin & high-density lipoprotein [HDL]), metabolomic and transcriptomic analyses. Standardised weight changes; Δfetalwt ([birthweight minus 23-week estimated fetal weight]/days) and Δchildwt ([weight minus birthweight]/years) were divided into quartiles and comparisons made examining CM differences between Δfetalwt and Δchildwt quartiles. Differentially expressed metabolites (DEMs) and genes (DEGs) were established using MetaboAnalyst and EdgeR. Gene set enrichment analysis (GSEA) identified associated pathways. As an alternative approach, we used k-means clustering to separate participants into groups based solely on their transcriptome, with GSEA on DEGs.

Results: 69% (56/81) had Δfetalwt <0, consistent with FGR, but only 12% (10/81) were SGA. SBP was higher and HDL lower in Δfetalwt Q1 (most negative) versus Q4. SBP, BMI SDS, AC, MUAC, AI and %fat were higher in Δchildwt Q4 (most positive) versus Q1 (all p<0.05). There was a trend towards higher insulin (Q4 mean 29.9pmol/L (SD 13.1) versus Q1 20.5 (10.5), p=0.085). Ornithine was a DEM for both Δfetalwt and Δchildwt. DEGs between Δchildwt quartiles highlighted a pathway including *ANXA3*, encoding annexin A3 which cleaves inositol-1,2-cyclic phosphate, and *ARG1*, encoding arginase which catalyses arginine to ornithine hydrolysis. K-means clustering defined two groups, who had a difference in SBP (median 111mmHg (range 101-134), N=7 versus 102 (89-122), N=24, p=0.009). The most significant DEG was *LATS1,* encoding an enzyme regulating cell proliferation. GSEA identified *GHRL*, encoding a ghrelin and obestatin precursor.

Conclusions: CM markers were related to low Δfetalwt and high Δchildwt, with a less favourable CM profile after pregnancies with suboptimal fetal growth but not necessarily SGA at birth. The arginine-nitric-oxide and phosphatidyl-inositol pathways were associated with adverse growth patterns. Analysis dividing the participants solely on transcriptomics identified a gene related to appetite regulation.

P2-130

Postnatal Growth in Infants of Diabetic Mothers (IDM) (n = 79) Who Were Born at or Near Term and Had Severe Neonatal Hypoglycemia Without Other Comorbidities

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Abnormal postnatal patterns of linear growth and weight gain have been reported in infants born to mothers with gestational diabetes (IDM).

We evaluated the growth pattern from birth to the age of 2 years of 79 IDMs who were born at or near term with significant hypoglycemia.

Anthropometric measures (z scores) from birth, 2,4.6,12,18, and 2 years were measured in 79 IDM who presented with significant neonatal hypoglycemia (plasma value less than 20-25 mg/dL (1.1-1.4 mmol/L)) that required proper therapy (IV glucose bolus followed by IV glucose infusion) for two days or more. Their anthropometric data were compared to standard growth for normal age and sex-matched infants (WHO growth standards)

Results: Their gestational age (GA) at delivery of IDM was 37.28 +/- 2.25 weeks. At birth, they had Wt. z score (WAZ) = -0.8 +/- 1.74, length Z score (LAZ) = -0.6 +/- 1.72 and Wt. for L Z score (WLZ) = -0.96 +/- 1.9. 16/79 had LAZ <-2, 23/79 had WAZ < -2 and 21/79 had WLZ <-2.

After an initial decrease in WAZ for the first two months, they had a progressive gain in WAZ that occurred during the first 12 months (from -0.8 to 0.21). This was followed by a stable WAZ during the second year of age.

After an initial deceleration of LAZ for 2 months, they had a progressive increase in the LSDS for 6 months (from -1 to -0.39) that was followed by stable LSDS (normal growth velocity) for the next 18 months.

By the age of 12 months, 8/79 had LAZ < -2, 3/79 had WAZ <-2 and none had WLZ <-2. 10/79 had WLZ > 2.

By the age of 2 years, 7/79 had LAZ <-2, 2/60 had WAZ <-2, and 1/79 had WLZ <-2. 8/79 had WLZ > 2 (overweight).

Conclusion: IDMs born at or near term with severe hypoglycemia had a special growth pattern during the first two years of life. By the age of 2 years, all growth anomalies disappear with a tendency to overweight.

Table. Postnatal growth of IDM for 2 years (mean values)

Age (mon)	Birth	2	4	6	12	18	24
WAZ	-0.8	-0.96	-0.65	-0.32	0.21	0.18	0.18
WLZ	-0.96	0.05	0.08	0.09	0.53	0.46	0.53
LAZ	-0.6	-1.1	-0.85	-0.53	-0.39	-0.41	-0.4

P2-131

Small for gestational age (SGA) babies identified through in the pilot programme for early detection and follow-up of sga children

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Introduction: Children born small for gestational age (SGA) are extensively studied since the 60s of the last century. Short-term and long term sequels of the condition lead to the concept of necessary follow up throughout childhood and early adulthood. Based on the current knowledge, SGA births are between 5% and 7% of all, with about 10% failing to catch-up up to 2 years of age. The timely capture of such individuals within general practices and even within pediatric practices is still poor. Interventions specially designed to increase awareness among doctors, parents and society, are expected to improve outcomes in such children.

Aim: To assess the first 6 months results of the pilot Programme for early detection and follow-up of SGA children.

Patients and Methods: Being born SGA is generally defined as birth weight and/or length less than the 3rd percentile (-1.88 SD). In 2013 Fenton et al. developed new growth charts combining both pre-term and full term babies born SGA. They suggested that the definition should be updated to babies born less than the 10th percentile (-1.28 SD). In 2021 the pilot Programme for early detection and follow-up of SGA children has been established (www.mgv.growinform.org). A total of 23 neonatology clinics enrolled for participation. There are two coordinators supporting maternities monthly, and 2 education sessions were conducted so far. The study was approved by the University Ethical committee, and written informed consent (IC) was collected from both parents. Participating children will be evaluated at the age of 2 by the geographically nearest pediatric endocrinologist (PE), with 24 participating PE.

Results: For the first six months of the project 275 newborns were identified as SGA, assuming 3.7% SGA births. From those, 139 (50.5%) signed IC. The distribution within the country seemed to be unequal. The only participating University tertiary referrals neonatal clinic registered 6% SGA children. Two big maternities in large cities managed to identify between 8% and 9% SGA births, but only one of them succeeded in acquiring consent from 87.5% of the patients' families. However, most of the neonatal clinics registered only between 1 and 3.4% SGA births. Evaluation of the implementation is currently underway.

Conclusion: The first results of the pilot Programme are failing to support the validity of the chosen approach. Potential pitfalls such as using old SGA definitions, lack of staff and motivation, etc., are currently being evaluated in order to modify the Programme accordingly.

P2-132

Hyperinsulinaemic Hypoglycaemia – are neonates symptomatic during hypoglycaemia?

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Introduction: Over recent years, hyperinsulinaemic hypoglycaemia is being increasingly recognised in at-risk neonates; it is important to recognise and manage this promptly in view of the risk of hypoglycaemic brain injury.

Aims: To recognise signs and symptoms of hypoglycaemia in neonates with hyperinsulinaemic hypoglycaemia.

Methods: Neonates from the neonatal intensive care units at two hospitals (The Royal London Children's Hospital and Tunbridge Wells Hospital) with a diagnosis of hyperinsulinism were retrospectively reviewed over a 3-year period (April 2019 – March 2022) to determine episodes of symptomatic hypoglycaemia. Medical notes were reviewed for signs and symptoms such as lethargy, jitteriness, tachypnoea, tachycardia, change in colour or any abnormal movements at the time of hypoglycaemia. Demographic data including maternal diabetes, birth weight, gestational age, maximum glucose infusion rate (GIR) and outcomes were also collected.

Results: There were 30 neonates in total with a diagnosis of hyperinsulinaemic hypoglycaemia (16 at Tunbridge Wells and 14 at Royal London). Gestation ranged from 28+4 to 41+5 weeks and birthweight was 610-4920g. Of these, 10/30 (33%) were small for gestational age (SGA) with a standard deviation score (SDS) ≤ -2; and 4/33 (13%) were large for gestational age (LGA), SDS ≥2. Four mothers (13%) had either gestational or type 1 diabetes. Out of these, three babies were LGA and all four had asymptomatic hypoglycaemia.

There were 175 episodes of hypoglycaemia recorded in these 30 neonates, with a median of 4.3 episodes per neonate (range 2-14). 8/30 neonates were asymptomatic during every episode of hypoglycaemia. Jitteriness occurred in 9 instances (5%); tachypnoea in 26 (14.9%); hypothermia in 5 (2.9%); tachycardia in 1 (0.6%); lethargy and poor feeding in 2 (1.1%) and possible seizures in 1 (0.6%). In the neonates with tachypnoea, respiratory distress was frequently a confounding factor.

The median maximum glucose infusion rate was 17.1mg/kg/min (range 9.0-26.3mg/kg/min) and 17/30 (57%) of neonates required diazoxide (3-5mg/kg/day).

Discussion: Nearly 50% of these babies were either SGA or LGA and therefore at higher risk of developing hypoglycaemia. 27% had no symptoms during hypoglycaemia and were detected on monitoring for risk factors. However, this is a retrospective study and it is important for staff to document signs/symptoms. More prospective studies are required with prespecified symptoms to chart.

Conclusion: Hypoglycaemia is frequently asymptomatic in neonates with hyperinsulinaemia, making this more challenging to recognise. Neonates at risk of hypoglycaemia should have close monitoring of blood glucose levels to ensure they are managed appropriately.

P2-133

Hypoglycemia as a result of growth hormone deficiency and Glycogen storage disease type 0a in a patient with short stature – case report

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Introduction: Hypoglycemia can be caused by inherited metabolic disorders, but sometimes hypopituitarism causes hypoglycemia separately or in combination with other health problems. It is important to diagnose the medical problem and start the treatment to avoid hypoglycemia complications.

Case Report: 5 years old male patient with recurrent fasting ketotic hypoglycemia, post-prandial hyperglycemia, with short stature, was admitted to Diabetology Department for further investigations. Measurements: Height 102cm, <3pc, HSDS -2,28 SD; body mass 19kg, 75pc, BMI 18,26 kg/m2, 90pc. The patient's bone age was delayed (BA: 3 year and 6 months). Tanner stage 1, testes in scrotum 2ml. OGTT with lactate was performed. Fasting hypoglycemia 42mg%, fasting normal lactate, hyperglycemia 216mg% in the 2nd hour after glucose, and a considerable increase in lactate 8,5 nmol/l were found. HbA1c 4,9%. Cortisol and free thyroxine levels were normal. Total cholesterol, LDL-cholesterol, and triglycerides were elevated. There was no organomegaly. Antibodies for celiac disease and diabetes type 1 were negative. The glucagon test revealed a double increase in glucose levels, GH peak was 6,86 ng/ml. Spontaneous nocturnal GH test was abnormal – GH peak 3,38ng/ml. Clonidine test stimulated GH to 8,73ng/ml. MRI revealed a cavity of the pituitary intermediate layer, not requiring surgery. Genetic test NGS detected pathogenic double heterozygous mutation in the GYS2 gene, which confirms Glycogen storage disease type 0a. The patient was fed 6 times a day, with a low glycemic index, and low-fat meals. Fasting glucose levels in capillary blood after dietary intervention were in the range of 42-70mg%.

Because of somatropin deficiency, the patient started growth hormone therapy. OGTT was performed once more before treatment – fasting glucose was 37mg%, in the 2nd hour 181mg% (glucose intolerance). The rGH treatment was well tolerated all the time, no side effects were reported, fasting glucose levels in capillary blood were 59-80mg%, HbA1c 5,1%; LDL-cholesterol and total cholesterol decreased. After one year of treatment height improved upto 113cm (HSDS -1,73). OGTT did not reveal deteriorated glucose levels -in the 2nd hour glucose level was 173mg%; fasting blood glucose was 58mg% - slightly improved.

Conclusions: Patients with hypoglycemia need to be carefully diagnosed because it could be a complex problem. The right diagnosis may lead to fewer incidents of hypoglycemia and better quality of life. Hepatic glycogen synthase deficiency should be taken into consideration in patients with fasting ketotic hypoglycemia and post-prandial hyperglycemia.

P2-134

Neonatal hypoglycemia in infants of diabetic mothers versus infants of non-diabetic mothers in relation to birth weight

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Timely recognition and treatment of neonatal hypoglycemia are important because of the potential for adverse neurodevelopmental outcomes. One of the major problems in infants born following a pregnancy complicated by diabetes is hypoglycemia. In addition, hypoglycemia occurs in infants of non-diabetic mothers.

We conducted a retrospective cohort study including all infants who had hypoglycemia during the first day of life, between 1-9-2017 and 31-8-2020. We studied the relation between hypoglycemia and birth weight in those born to GDM mothers (IDM) in comparison with those born to non-diabetic mothers (NIDM). Routine screening of neonatal blood glucose levels was performed at 1, 3, 6, 12, and 24 h after birth. Main outcome measures were hypoglycemia as a blood glucose level of <2.6 mmol/L.

Aim: To assess the risk of neonatal hypoglycemia in relation to birth weight in IDM and NIDM infants.

Results: The total number of newborns who had hypoglycemia during the 3 years of study was 2599, 1349 males, and 1250 females. The mean duration of their hospitalization = 8.45 days for all causes. 1673 were IDM, 866 males, 807 females. They were born to mothers with GDM treated either with insulin or without insulin.

In IDM (n = 1673), most of the hypoglycemia (79.4%) was detected in those with a birth weight > 2500 g compared to those with lower birth weight (<2500 g (20.6%). In NIDM neonates (n = 926) hypoglycemia occurred more frequently in infants > 2000 g (90 %) compared to those with birth weight <2000 g.

Conclusion: Increasing birth weight > 2500 g in IDM significantly increases the risk of neonatal hypoglycemia compared to NIDM.

Table. Proportions of hypoglycemia in IDM versus NIDM in relation to birth weight

	IDM		NIDM		Z Score		
	n= 1673	%	n =926	%	p-value	Total	%
<750 g	7	0.42	22	2.37	< .00001	2599	100
<1000 g	15	0.89	40	4.32	< .00001	55	2.1
1000: 1500 g	23	1.37	39	4.2	< .00001	62	2.4
1500: 2000 g	70	4.18	108	11.7	< .00001	178	6.8
2000: 2500 g	228	13.6	332	35.8	< .00001	560	21.5
> 2500 g	1328	79.4	409	44.2	< .00001	1737	66.8

P2-135

Incidence of neonatal hypoglycemia in Qatar: A 3-year study

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Neonatal hypoglycemia is the most common endocrine abnormality in children, which is associated with increased morbidity and mortality. The burden and risk factors of neonatal hypoglycemia in Qatar are suggested to be high because of the high prevalence of gestational diabetes.

Objective: To determine the incidence of neonatal hypoglycemia in Qatar in relation to the etiology (infants of diabetic mothers (IDM) versus infants of nondiabetic mothers (INDM). in Lira District, Northern Uganda.

Methods: We conducted a retrospective cohort study including all newborn infants who had hypoglycemia during the first day of life, between 1-9-2017 and 31-8-2020. We subdivided the etiology of hypoglycemia into two main categories: (infants of diabetic mothers (IDM) versus infants of nondiabetic mothers (INDM). Routine screening of neonatal blood glucose levels was performed at 1, 3, 6, 12, and 24 h after birth. The main outcome measures were hypoglycemia as a blood glucose level of <2.6 mmol/L.

Results: We detected 2599 newborns with hypoglycemia during the first 24h of life. participants of mean age 3.1 days (standard deviation (SD) 2.1) and mean weight of 2.5 +/- 0.8 kg. The 3- years cumulative incidence of Neonatal Hypoglycemia = 10.27 per 1000 newborns. The cumulative incidence for neonatal hypoglycemia in IDM was 6.61/1000 newborns while the cumulative incidence in NIDM was 3.66/1000 newborns.

Discussion: The incidence of transient neonatal hypoglycemia varies between 1–17% of newborns, and in at-risk babies, it may reach up to 50%. The relatively lower incidence of neonatal hypoglycemia in our study can be explained by the effective national program controlling gestational diabetes (GDM) in women despite its high prevalence (20.7% of pregnant women).

Conclusion: The cumulative incidence of neonatal hypoglycemia was 10.3/1000 newborns. Two-thirds of neonatal hypoglycemia occur secondary to gestational diabetes.

Table. Incidence of neonatal hypoglycemia for 3 years

	Number	%	Cumulative Incidence
			per 1000/yr.
IDM	1673	64.4%	6.61
NIDM	926	35.6%	3.66
Total	2599	1.00	10.27

P2-136

Growth patterns in Infants with Significant Neonatal Hypoglycemia during the first two years of age: Comparison of infants of Diabetic Mothers (IDM) versus infants of non-diabetic mothers (INDM)

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We evaluated the anthropometric measures using WHO growth charts (z scores) from birth, 2,4,6,12,18 and 2 years for 79 IDM presented with significant neonatal hypoglycemia in comparison to 51 infants of INDM who had significant hypoglycemia due to transient hyperinsulinemia who required treatment for >2 days.

Result: IDM had WAZ = -0.8 +/- 1.74, L AZ = -0.6 +/- 1.72 and WLZ = -0.96 +/- 1.9. They IDM were heavier and taller than the INDM group WAZ= -2.21 +/- 2.02, and WLZ = -2.47 +/- 2.07 ($p< 0.01$).

In IDM, after an initial decrease in WAZ for the first two months, they had a progressive gain in WAZ occurred during the first 12 months (from -0.96 to 0.21) followed by stable WAZ during the second year of age. INDM had a progressive gain in the WAZ during the first 18 months of life. This was followed by stable wt. Z score. During the first year of life, the WAZ gain was significantly higher in the INDM versus IDM. At 18 months of age, the WAZ did not differ between the two groups.

In IDM, after an initial deceleration of LAZ for 2 months, they had a progressive increase in the LAZ for 6 months (from -1 to -0.5) followed by stable LAZ (normal growth velocity) for the next 18 months. INDM had a progressive gain in the LAZ in the first 12 months (from -2.1 to -0.56) that was followed by stable LAZ. By the age of 12 months, the LAZ did not differ between IDM and INDM.

In Conclusion: Growth pattern differs in the infant of diabetic mothers versus those who were born preterm or near term for non-diabetic mothers. Despite the risk of hypoglycemia in both groups, IDM was born heavier and taller than INDM. IDM remains heavier and taller than INDM for the first 12 months of life. INDM had faster LAZ gain versus IDM during the first year of life.

	birth					6 months			12 months			18 months			2 years		
	GA	WAZ	LAZ	WLZ	WAZ	LAZ	WLZ	WAZ	LAZ	WLZ	WAZ	LAZ	WLZ	WAZ	LAZ	WLZ	WAZ
IDM N=79	Mean	37.28	-0.8*	-0.6*	-0.96*	-0.3*	- 0.5*	0.09	0.21	-0.39	0.53	0.18	-0.41	0.46	0.18	-0.40	0.53
INDM N=51	Mean	36.70	-2.21	-1.90	-2.47	-0.90	-1.13	-0.2	-0.12	-0.49	0.14	0.05	-0.39	0.28	-0.23	-0.46	-0.16
	p-value	0.08	<0.001	0.005	<0.001	0.03	0.05	0.21	0.20	0.93	0.09	0.72	0.54	0.54	0.46	0.75	0.19

P2-137

Relationship between birth body weight<10.th centile (SGA) and insulin-like growth factor binding protein-2 / insulin-like growth factor binding protein-3 ratio in the not-life threatened newborn: Relevance of birth chest circumference / birth body weight ratio

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Birth chest circumference(CC) shows often, like birth gestational age(GA), tight direct relations to birth body weight(BW). However distinct connections of hypoxia/undernutrition with different body structures might be suspected based on brain-, heart- and adrenal-sparing following intrauterine growth restriction and, postnatally, on higher chest size for body mass observed at high altitude. Growth retarded fetuses gestated by hypoxic rats may present increments of blood serum Insulin-like Growth Factor Binding Protein(IB) 2, but not of IB3. Relevance of human newborn(NWB) CC/BW ratio(i.e., CC through BW, CC/BWR) to relationships between BW<=10.th centile for GA(SGA), and IB2/IB3 ratio(IB2/IB3R) was evaluated. NWBs with any among total parenteral nutrition, parenteral nutrition other than dextrose, blood component transfusion, postnatal corticosteroid-, catecholamine- or methylxantine-based treatments, life-threatening disease, diabetes mellitus(DM) or other endocrine diagnosis, malformation, and mother with DM were excluded. 78 included NWBs, all studied before covid-19 pandemic and from conception to study end near sea-level, had complete data for 1) same-day records at one of the first 5 postnatal days(x), 5 days after x(y) and 10 days after x(z) of postnatal age(PNA, unit:day), IB2 and IB3 radioimmunoassay(unit=uM/dl), and for 2) gender(SEX), GA(unit: complete week; extremes=28–42), GA<=36 present(PTB, n=46), CC(25th-75th centiles=27-32cm), BW(25th-75th centiles=1926-2942g), and SGA(n=20)(computations; male SEX(n=43), SGA; condition absent=0, condition present=1). SPSS-27 software was used to generate GA-unrelated CC/BWR standardized residuals(CC/BWRsr)(i.e., Linear regression procedure-Save pushbutton/ Standardized residual checkbox-Continue pushbutton/ regress CC/BWR on only GA). IB2/IB3R(i.e., IB2 through IB3) calculated at x-y-z time-poins, was averaged(i.e., (x+y+z)/3; IB2/IB3RM). IB2/IB3RM normal scores according to Van der Waerden(IB2/IB3RM-NS) were normally distributed. SGA evidenced significantly higher CC/BWR, CC/BWRsr and IB2/IB3RM than non-SGA(Mann-Whitney Test). Spearman rank correlations between the following variable pairs are reported(Rho; significance): GA vs CC/BWR(-.706, p<.0001), GA vs CC/BWRsr (-.024; p=.8315), GA vs IB2/IB3R(-,409; p=.0002), CC/BWRsr vs IB2/IB3R(.346; p=.0019). Partial correlation(pc) coefficient(pcc) of SGA pc with outcome IB2/IB3RM-NS in multiple linear regression(MLR) was significant (t=4.194, p<.0001, pcc=.565) with SEX-GA-SGA-PNAx as predictors, but non-significant with SEX-GA-SGA-CC/BWRsr-PNAx as predictors(MLR R2, .447-.492, always significant). CC/BWRsr could be involved in direct relationships between SGA and IB2/IB3RM-NS after controls including GA in not-life-threatened NWBs.

P2-138

Hypoglycemia in children: Clinical experience of a tertiary care center

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Introduction: Hypoglycemia is a significant cause of morbidity in children, yet is challenging to diagnose and treat due to its heterogeneity.

Aim: To describe the diagnoses and clinical characteristics of children with hypoglycemia referred to a tertiary pediatric center.

Methods: This retrospective study included 155 children (86 males, aged 0-18 years) diagnosed with hypoglycemia in 1992-2018, and followed at a single center. Clinical and laboratory data were reviewed and compared according to etiologic diagnoses and age at referral.

Results: The cohort was divided by clinical diagnosis into six groups: ketotic hypoglycemia (KH) (n=45, 29.0%), congenital

hyperinsulinemic hypoglycemia (CHH) (n=33, 21.2%), transient HH (n=28, 18.7%), metabolic disorder (n=16, 10.3%), systemic disease/syndrome (n=16, 10.3%) and hormone deficiencies (n=10, 6.4%). Two patients diagnosed with insulinoma were not included in the analysis by groups. At diagnosis, 58 (37.4%) were under age 30 days, 23 (14.8%) aged 1-12 months, 59 (38%) aged 1-6 years and 15 (9.7%) aged 6-18 years. The most common diagnoses were: transient HH (48.3%) and CHH (32.7%) in neonates; CHH (34.8%) and KH (17.4%) in infants; KH (62.7%), metabolic disorders (11.8%) and CHH (10.1%) in children aged 1-6 years; and similar frequencies of KH, metabolic disorders and hormone deficiencies and insulinoma in children older than 6 years. The mean age of patients with CHH was younger than of patients with ketotic hypoglycemia. The mean birth weight of patients with CHH was significantly higher than of those with transient HH, and with systemic disease/syndrome. Patients with transient hyperinsulinism were the youngest at diagnosis; and were born earlier and with lower birth weight than children with the other etiologies.

Forty-three patients (27.74%) completed a supervised fasting test as part of the diagnostic evaluation: None was performed during 1992-2000, six were done during 2001- 2010 and 37 during 2011-2018. The test results supported a specific diagnosis in 13 (28.3%) patients. A fasting test was more commonly used in patients with KH (40.0%), metabolic disorders (43.8%) and systemic disease/syndrome (31.2%), than in CHH (15.1%), transient HH (10.7%) and hormone deficiencies (20.0%), $p<0.015$.

Conclusions: Hypoglycemia etiology is heterogeneous and varies among neonates, infants and children. Work-up should be directed for each age group based on clinical, biochemical and imaging findings, combined with next generation sequencing target panels. The benefit of using a fasting test is questionable, and its use should be considered for each patient individually.

P2-139

A stormy neonatal course

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Introduction: Neonatal thyrotoxicosis (NT) is rare but potentially life-threatening condition with high mortality risk due to cardiac failure (12-20%). Affected neonates are born to mothers with underlying thyroid pathology. Estimated prevalence of transplacental transfer of thyroid antibodies occurs 1 in every 70 pregnancies with Graves' disease. Symptoms in the neonate usually manifest by 10 days of life but this can be as late as day 45. We discuss two cases of NT referred to our tertiary-endocrine unit that highlights management challenges in this rare presentation.

Case 1: A preterm female born at 32+5 weeks was admitted to neonatal unit for respiratory distress requiring ventilator support. Mother was previously treated for Graves' disease with radioactive iodine. Antenatal scan reported one episode of foetal tachycardia which was treated with carbimazole. On day two of life, thyroid function showed a T4 52.9 pmol/L, no TSH result. She developed tachycardia (202/min) with acute cardio- respiratory deterioration on day five of life, requiring inotropes, HFOV with nitric oxide. Free T4 >100 pmol/l, T3 >32 pmol/L and TSH <0.01 mU/L. Maternal TRAB antibodies in pregnancy were 187.5 IU/ml. Neonate had thyroid storm and therefore was commenced on combination of carbimazole 0.75 mg/kg/day, Propranolol, potassium iodate and prednisolone 1mg/kg. She responded within 48 hrs. All medications were gradually weaned with steroid titration and stopped at 15 weeks of age. Infant is stable on regular follow up monitoring visits and tests.

Case 2: A three-week-old boy referred for poor feeding and weight-loss. Maternal history revealed T1DM, hypothyroidism and coeliac disease. He had clinical signs of tachycardia HR 160/min and constipation. Investigation showed adj-calcium of 3.9 mmol/L, TSH <0.01pmol/L and T4 35.9 pmol/L. He was treated with hyperhydration and carbimazole of 0.65 mg/kg/day. We observed rapid response within five days of treatment. Carbimazole was stopped on Day 6 but restarted for rebound rise in T4 to 24.4pmol/L. Carbimazole was weaned by 12 weeks of age and patient was safely discharged.

Summary: Although rare, NT poses management challenges as illustrated in our two cases presenting with thyroid storm and hypercalcaemia. Rapid evaluation for associated endocrine dysfunction and initiation of treatment with careful monitoring would prevent adverse outcome. Clinicians should have a high index of suspicion for screening infants born to mothers with underlying thyroid pathology and investigate for associated endocrine conditions that may manifest in the neonatal period.

P2-140

POU1F1 gene mutation as a cause of central hypothyroidism and growth hormone deficiency: A case report

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Background: Thyroid hormones are necessary for normal child development. Hypothyroidism, associated with insufficient amounts of free triiodothyronine and thyroxine, may not only cause poor growth rate, but also results in impaired central nervous system development. In Poland, newborn screening for congenital primary hypothyroidism, the incidence of which is reported to be 1:2500- 1:4000 births, has been performed for many years. Secondary hypothyroidism, caused by abnormal TSH production in the pituitary gland, is much rarer (about 1:16000). POU1F1 gene mutation causes not only TSH deficiency, but also growth hormone and prolactin deficiency.

Case Report: The boy was consulted for the first time by an endocrinologist at the age of 5 months during diagnosis of insufficient growth of body weight and body length. The baby was born from a normal pregnancy, delivered by Caesarean section in 41hbd, in good general condition, weight 3350g, length 54cm. Neonatal period was complicated by increasing jaundice, requiring phototherapy. Because of delayed psychomotor development in the infant, pediatric and neurological diagnostics was performed. Normal TSH levels and very low serum levels of peripheral thyroid hormones were found. During the endocrinological diagnosis, pituitary hypothyroidism was confirmed by the TRH test, pituitary-adrenal axis disorders were excluded. IGF-1 concentration was below normal. Ultrasound examination visualized typical thyroid tissue in an anatomical location. Magnetic resonance imaging visualized a normal small pituitary gland. The cause of central hypothyroidism was determined by genetic testing - PROP1 gene mutation was excluded, POU1F1 mutation was confirmed. The boy is treated with levothyroxine with a good effect. When the patient became euthyroid, he was diagnosed with growth hormone deficiency. Actually during therapy with recombinant growth hormone we observed increasing velocity of growth.

Results: 1/. A normal screening result does not exclude central congenital hypothyroidism. 2/. Whenever hypothyroidism is suspected, serum TSH and fT4 should be measured in the newborn to initiate treatment as soon as possible. 3/. Early diagnosis of hypothyroidism, growth hormone deficiency and appropriate treatment gives a chance for normal development of the child.

P2-141

Relationship between birth body weight<10.th centile (SGA) and insulin-like growth factor-i in the not-life threatened newborn: Relevance of birth chest circumference / birth body weight ratio

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Birth chest circumference(CC) shows often, like birth gestational age(GA), tight direct relations to birth body weight(BW). However distinct connections of hypoxia/undernutrition with different body structures might be suspected based on brain-, heart- and adrenal-sparing following intrauterine growth restriction and, postnatally, on higher chest size for body mass observed at high altitude. Low BW and hypoxia may be associated with circulating Insulin-like Growth Factor-I(IG1) lower levels. Relevance of human newborn(NWB) CC/BW ratio(i.e., CC through BW, CC/BWR) to relationships between BW<=10.th centile for GA(SGA), and blood serum IG1(IG1s) was evaluated. NWBs with any among total parenteral nutrition, parenteral nutrition other than dextrose, blood component transfusion, postnatal corticosteroid-, catecholamine- or methylxantine-based treatments, life-threatening disease, diabetes mellitus(DM) or other endocrine diagnosis, malformation, and mother with DM were excluded. 78 included NWBs, all studied before covid-19 pandemic and from conception to study end near sea-level, had complete data for 1) same-day records at one of the first 5 postnatal days(x), 5 days after x(y) and 10 days after x(z) of postnatal age(PNA, unit:day) and IG1s radioimmunoassay(unit=uM/dl), and for 2) gender (SEX), GA(unit:complete week; extremes=28–42), GA<=36 present(PTB, n=46), CC(25th-75th centiles=27-32cm), BW(25th-75th centiles=1926-2942g), BW standard deviation scores(BW-SDS), and SGA(n=20)(computations; male SEX(n=43), SGA; condition absent=0, condition present=1). SPSS-27 software was used to generate GA-unrelated CC/BWR standardized residuals(CC/BWRsr)(i.e., Linear regression procedure-Save pushbutton/ Standardized residual checkbox-Continue pushbutton/ regress CC/BWR on only GA). IG1s at x-y-z time-points was averaged (i.e., (x+y+z)/3; IG1sM). IG1sM normal score according to Van der Waerden(IG1sM-NS) resulted normally distributed. Mann-Whitney Test: PTB did not differ significantly from non-PTB for CC/BWRsr; SGA showed significantly lower IG1sM than non-SGA. Spearman rank correlations between the following variable pairs are reported(Rho; significance): BW-SDS vs CC/BWR(-.361; p=.0012), BW-SDS vs CC/BWRsr(-.766; p<.0001), CC/BWR vs

IG1sM(-.659, p<.0001), CC/BWRsr vs IG1sM(-.271, p=.0166). Partial correlation(pc) coefficient(pcc) of SGA pc with outcome IG1sM-NS in Multiple linear regression (MLR) was significant(t=-3.349, p<.0013, pcc=-.365) with SEX-GA-SGA-PNAx as predictors, but was non-significant with SEX-GA-SGA-CC/BWRsr-PNAx as predictors (MLR R2, .486-.513, always significant). CC/BWRsr could be involved in inverse relationships between SGA and IG1sM-NS after controls including GA in NWBs free of life-threatenig disease.

P2-142

Case report of an infant with severe symptomatic hypoglycemia and a rare ABCC8 gene mutation inherited from his unaffected father and a focal form of HI

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Introduction: Congenital hyperinsulinism (HI) is the leading cause of persistent hypoglycemia in infants and children. It is a rare glucose metabolism disorder characterized by unregulated secretion of insulin that leads to hyperinsulinemic hypoglycemia (HH). Most cases are caused by mutations in the KATP-channel genes ABCC8 and KCNJ11. KATP-HI can be classified into two distinct histological forms: a diffuse form, in which all of the pancreatic β-cells are affected, and a focal form of localized islet hyperplasia and dysfunction. Differentiating between focal and diffuse HI is of paramount importance as surgical excision of the focal lesion is curative.

Case Report: We present a case report of an infant male, with severe symptomatic hypoglycemia and seizure episode who has a rare ABCC8 gene mutation inherited from his unaffected father and a focal form of HI. These metabolic abnormalities result in a high risk of brain damage and subsequent neurologic sequelae, such as development delays and epilepsy. Infant presented with persistent hypoglycemia shortly after birth. He was admitted to the neonatal intensive care unit where he had repeated episodes of hypoglycemia. Critical specimens confirmed a diagnosis of HI, and treatment was initiated with Diazoxide but without respond to treatment. Then treatment with Octreotid was started and good respond to treatment was observed. Genetic testing revealed a heterozygous paternally inherited ABCC8 missense variant (Chr11:g.17464299). The clinical significance of this variant is currently uncertain. This mutation was inherited from his unaffected father. 18F-DOPA PET-CT scanning was performed and a focal form of HI was diagnosed. PET-CT scan revealed an adenomatous node located in the head of the pancreas. Surgery was performed and a local lesion was removed.

Conclusion: The interest is in the fact that the infant inherited the ABCC8 gene mutation from his unaffected father. The case demonstrates the importance and clinical utility of genetic analyses and PET-CT scanning for informing and guiding treatment and care. Given the presence of a focal lesion this ABCC8 missense variant (Chr11:g.17464299) can be considered as pathogenic. Genetic testing and advanced imaging techniques have allowed for more tailored approaches to treatment, resulting in improved outcomes.

Keywords: ABCC8, Congenital hyperinsulinism, Hypoglycemia, insulin, beta-cell, KATP channel

P2-143

All roads don't lead to rome after all!!

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Hypoglycemia is a frequent and one of the major metabolic emergencies in any age, causing a significant dilemma to reach the correct diagnosis and perform the appropriate management. it Has potentially devastating consequences on brain development and cognitive functions. It Is a heterogeneous disorder with many different possible etiologies, including hyper-insulinism, glycogen storage diseases, fatty acid oxidation defects, hormonal deficiencies (growth hormone deficiency, glucocorticoid deficiency) other inborn error of metabolism, drug poisoning, and others. Congenital hyperinsulinism is the most common cause of hypoglycemic hyperinsulinemia in infants and is due to beta-cell hyperplasia caused by genetic defects. But the genetic testing surprised us by different etiologies and diagnoses.

Methods: we studied 8 cases presented by hypoglycemia; 4 females and 4 males, aging from 20 days to 15 years All were subjected to the following:

- History, full detailed physical examination, Anthropometric measurements: Height standard deviation (SD).
- Liver enzymes (ALT&AST), Liver function tests (albumin and prothrombin time),
- Golden sample of hypoglycemia: serum insulin, serum c-peptide, growth hormone, cortisol, ACTH, ketone bodies in blood,
- ABG and AG
- Chemistry: liver enzyme and electrolytes (sodium, potassium)
- Molecular Genetic Testing by Whole exome sequencing by collecting two millilitres of blood from each subject in a sterile EDTA vacutainer for the genotyping technique

Conclusion: We conclude that hypoglycemia in children is really a difficult challenge to reach the appropriate and accurate diagnosis

GH and IGFs

P2-144

GROWPATI Study: Clinical and genetic characterization of a cohort of patients with short stature due to severe primary IGF1 deficiency

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Background: Severe primary insulin-growth factor-1 (IGF1) deficiency (SPIGF1D) is a rare cause of short stature. Diagnosis is based on low basal IGF1 concentration, short stature, normal or elevated growth hormone concentrations and absence of any secondary causes of growth failure. Thanks to advances in next-generation sequencing (NGS) technologies, genetic etiology of SPIGF1D is expanding.

Objectives:

- Identify the molecular causes of SPIGF1D in a large cohort of patients referred with growth delay
- Describe the growth pattern and pubertal status

Methods: Patients have been recruited during 2004-2009 (Historical Study Cohort, HSC, n=30) and 2016- present (New Study Cohort, NSC, n=25). Genetic analyses used array comparative genomic hybridization, candidate gene approach or NGS gene panel, including genes involved in GH-IGF1 axis. Data were collected concerning growth, puberty, and final height (FH) or near adult-FH, if available.

Results: Fifty-five patients (29 males/26 females) have participated, with mean current age in the HSC and NSC of 20.2 and 11.8 years respectively. Nine patients were lost during follow-up and 2 patients refused genetic tests, leading to 44 patients eligible for genetic analyses. Among 21 patients screened so far, we report a diagnostic rate of 47.6 % with a proven molecular diagnosis in 10/21 patients. The remaining 11 patients have variants of unknown significance or non-pathogenic variants (ACMG criteria), in GH-IGF1 axis genes. Constitutional bone disease has been detected in five patients. Molecular diagnosis concerned hypochondroplasia (n=1), Laron syndrome (n=1), heterozygous GHR mutations (n=2), Noonan syndrome (n=3), Silver-Russell syndrome (n=2), heterozygous ACAN mutation (n=1). At inclusion all patients were prepubertal (T1). Mean (SD) age at last registration of Tanner stage 1 (T1) and first registration of T5 was 12.1 (0.9) and 16.7 (1.1) years, respectively, in boys and 10.3 (1.5) and 14.8 (1.5) years, respectively, in girls. Mean growth puberty spurt for patients who have achieved their puberty with available data (8 males, 6 females) was 24 cm (4.1) in boys and 18.2 cm (5.9) in girls. Among patients with available data in FH, mean adult FH was -2.2 SD (0.5) for 7 boys and -2 SD (0.8) for 6 girls.

Conclusions: Genetic analysis reflects the heterogeneous spectrum of the disease. Detailed clinical and genetic evaluation are necessary to provide a diagnosis in most cases and orient clinical management. Long term follow-up of patients will provide us more insights in the understanding of SPIGF1D.

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P2-145

A user-centred approach to improve digital health solutions in patients requiring growth hormone therapy: Results of a participatory workshop

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Background: Digital health is becoming increasingly important worldwide. However, there is a lack of research on barriers to the implementation of digital health solutions for growth disorders in the Gulf Region. Participatory research can help to understand barriers faced by different stakeholders, design effective solutions and evaluate their implementation, whilst taking cultural aspects into consideration. Involving clinicians in understanding barriers to and opportunities for the implementation of digital health solutions in disorders requiring recombinant human growth hormone (r-hGH) therapy has already been reported.[1]

Aim: Our participatory research aimed to identify factors that could facilitate the use of digital health solutions by healthcare professionals (HCPs) and support the proper implementation of r-hGH therapy by paediatric patients and their families.

Methods: Workshop participants were asked to categorise different features of digital health solutions as either barriers or facilitators of use. Initially, the approach considered the broad population of patients with growth failure and more specific cases were addressed in a second step. In both instances, workshop participants were asked to consider their own patient population and professional experience. Participants were then asked to decide whether they would activate or deactivate different features within a hypothetical app to support r-hGH therapy.

Results: Overall, the workshop participants considered several features to be of high clinical relevance. Material content was seen as an important component that should be accessible at any time through multiple routes. Participants also suggested that calendar scheduling with reminders could help organise visits and improve adherence, including at therapy initiation, by establishing routines after which their frequency could be reduced. It was also suggested that adherence calendars may enhance communication between HCPs and patients, thus enabling dialogue on outcomes. Feedback on growth and motivational elements were also considered to be useful. Participants stated that they would be less likely to activate direct communication with HCPs due to liability issues when utilising the content. Similarly, patient support networks were considered unlikely to be activated unless they could be moderated very carefully.

Conclusion: This project identifies important facilitators and barriers for digital health tools in the context of the cultural and geographical needs within the Gulf region. Considering the identified factors when developing new digital solutions will increase the likelihood of their adoption and, thus, provide an opportunity to further improve the level of care for patients requiring r-hGH therapy.

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P2-146

GH responsiveness and IGF1 P2 promotor methylation

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Background: The methylation of IGF1 promoter P2 was reported to negatively correlate with serum IGF-1 concentration and rhGH treatment response in children with idiopathic short stature. These findings have not yet been confirmed.

Objective: This study aimed to determine IGF1 promoter P2 methylation in short children treated with rhGH and correlate clinical parameters with the methylation status. In addition, long-term stability of methylation during rhGH treatment was studied.

Design: This was a single tertiary center study analyzing clinical GH response and IGF-1 serum concentration changes in patients with GHD (n=40), SGA short stature (n=36), and Turner syndrome (n=16) treated with rhGH. Data were correlated to the methylation of two cytosine residues (-137, +97) of the P2 promoter of IGF1 in blood cells measured by pyrosequencing in 443 patient samples.

Results: Basal and stimulated IGF-1 concentrations, first year increment in height velocity and studentized residuals of a prediction model did not correlate to the methylation of -137 und +97 in IGF1 P2 promoter. The methylation of these two sites was relatively stable during treatment.

Conclusions: This study did not confirm IGF1 P2 promotor being a major epigenetic locus for GH responsiveness in patients treated with a normal dose of rhGH. Additional studies are warranted.

P2-147

Perception of long-acting growth hormone-data from two surveys in Austria

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Background: Due to its short half-life, conventional biosynthetic human growth hormone needs to be given daily which may represent a burden for patients and their families. Novel long-acting growth hormone (GH) formulations are under development and enable reduced injection frequency through once weekly administration. Two surveys were designed to collect first insights and expectations towards new long-acting formulations.

Methods: Between June and October 2021, two surveys were performed among pediatric endocrinologists and parents/caregivers of children receiving daily growth hormone treatment, addressing treatment experiences and attitudes/expectations towards long-acting GH formulations. In total, 20 pediatric endocrinologists and 41 parents/caregivers participated.

Results: Pediatric endocrinologists: Around half (55%) of the endocrinologists expected equivalent efficacy from long-acting GH formulations whereas only 10% expected improved efficacy as compared to daily injections. More than half of the respondents thought that only 70-90% of prescribed doses were actually administered and anticipated improvement of adherence from long-acting formulations (83%). Furthermore, 33% of physicians regarded these new formulations as an advantage for patients with needle phobia and the majority expected significant improvement in the quality of life. Nevertheless, around 50% had concerns regarding pharmacokinetics that might cause unphysiological IGF1 dynamics with implications for safety such as hitherto unknown long-term effects.

Patients/caregivers: Over 40% of patients/caregivers stated that their child was hurt most when excluded from activities because of her/his height although most reported no social or emotional problems. Besides that, a great confidence in growth hormone treatment and very high adherence rates (administration frequency 6.8 days per week) were reported. Overall, most respondents regarded a change in injection frequency from once daily to once weekly very positively, not least due to increase in flexibleness whereas some were concerned quitting the child´s routine with daily injections.

Conclusions: Both surveys showed that most pediatric endocrinologists and patients/caregivers were positive about long-acting GH formulations and expect significant improvement in quality of life. However, there are still some concerns regarding safety and efficacy which need to be evaluated in long-term studies.

P2-148

Height Velocity in Indonesian Children Receiving Growth Hormone Therapy

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Background: Short stature is one of the most common conditions referred to pediatric endocrinology clinics, and treatment with growth hormone (GH) is useful to improve height velocity and adult height, but response may be variable. Growth hormone therapy is indicated in several conditions in pediatric patients, including growth hormone deficiency (GHD) and children born short for gestational age (SGA). We investigated differences in treatment response in Indonesian children with GHD and SGA receiving GH therapy.

Methods: In this study, we report data from the Indonesian cohort of children with GHD and SGA from the Easypod Connect Observational Study (ECOS), which collected data from children using an injection device (easypod™) between 2011-2015. Subjects received GH therapy administered using an electronic injection device.

Results: Nineteen children were included, with an average age of 8.93±2.51 years. The average GH dose was 0.035±0.006 mg/kg body weight/day, with no significant difference in dose between subjects with GHD and SGA. We observed significant increase in height SDS from baseline in the first 6 and 12 months of treatment in patients with GHD. No significant height SDS increase was seen in patients with SGA. Height velocity SDS was highest in the first 6 months of treatment for both conditions. Height velocity SDS at 6 months of treatment was significantly higher in children with GHD compared to SGA (2.38 vs -0.19, p=0.027) and in children with Tanner stage I compared to stage II and III (2.12 vs 0.40 vs -2.13, p=0.014).

Conclusions: In Indonesian children receiving growth hormone therapy, significant changes in height SDS in the first 6 and 12 months are seen in children with GHD. Height velocity is highest in the first 6 months of treatment, in pre-pubertal subjects, and is higher in children with GHD compared to children with SGA.

P2-149

Advancing personalised medicine for growth hormone delivery: mixed-methods participatory study of a next generation, smart auto-injector device

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Background: Treatment of growth hormone deficiency (GHD) requires daily injections over multiple years. Novel technologies facilitate this by automating the injection process – thereby adding comfort and reducing anxiety. An always-connected device, enabled by mobile technologies, also facilitates the collection of injection data such that adherence information is available to healthcare professionals (HCPs) in real-time. In developing new solutions, it is important to account for HCP perspectives.

Aim: To explore the evolution of the next generation easypod® device from the HCP perspective, with a focus on usability, data-enabled insights, and technology acceptance.

Methods: We performed a mixed-methods participatory study to assess the third generation of the easypod® device (easypod® 3) that is currently in development. A participatory workshop was conducted in Zaragoza, Spain. Participants included HCPs experienced in management of growth hormone treatment in paediatric patients. Participants discussed predefined questions and specific case studies as part of group activities. They also completed a 25-item, 5-scale Likert questionnaire to assess the impact the new device can have on usability and acceptability.

Results: Ten HCPs (6 endocrinologists, 2 nurses, and 2 pharmacists) participated in the workshop. Two main themes were identified and further explored during the sessions: user-device interaction and real-time data transmission. Participants considered the touchscreen interface on the easypod® 3 as a substantial improvement. They stated that features such as tactile interaction and automatic data transmission would facilitate training and usability of the device. In turn, this could reduce the time and effort required to train patients and caregivers. Participants agreed that availability of real-time adherence data allows for better treatment monitoring and improved decision-making, as automatic data transmission offers a more reliable and realistic dataset for both adherent and non-adherent patients. However, participants did acknowledge that analysis of such data may increase their workload. All agreed that the new device should be part of a digital health ecosystem that provides complementary functionalities such as data analysis and visualisation. Notifications and reminders with educational and motivational content as part of the digital health solution were seen as additional valuable elements.

Conclusion: This work explored the perceived value seen by HCPs based on their assessment of a next generation auto-injector device for the treatment of GHD. HCPs ranked the new capabilities of the device, including usability and data transmission, as significant improvements. This next generation device will enhance decision making and will allow for more personalised care of paediatric GHD patients.

P2-150

Alterations in stem cell populations during rIgF-1 (Increlex) therapy in patients with SPIGF1D

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Pathway involving insulin-like growth factor 1 (IGF-1) plays significant role in growth and development. Crucial role of IGF-1 was discovered inter alia through studies involving deficient patients with short stature, including SPIGFD individuals. Noteworthy, despite disturbances in proper growth, elevated values for selected stem cell populations were found in IGF-1 deficient patients. Therefore, here we focused on investigating role of these cells - very small embryonic-like (VSEL) and hematopoietic stem cells (HSC), in the pathology. For the first time we performed long-term observation of these populations in response to rhIGF-1 (mecasermin) therapy. Enrolled pediatric subjects with primary IGF-1 deficiency syndrome were monitored for 4-5 years of rhIGF-1 treatment. Selected stem cells were analyzed in peripheral blood flow cytometrically, together with chemoattractant SDF-1 using immunoenzymatic method. Patients data were collected for correlation of experimental results with clinical outcome. IGF-1 deficient patients were found to demonstrate initially higher levels of VSEL and HSC compared to healthy controls, with their gradual decrease in response to therapy. These changes were significantly associated with SDF-1 plasma levels. Correlations of VSEL and HSC were also reported in reference to growth-related parameters, and IGF-1 and IGFBP3 plasma values. Noteworthy, rhIGF-1 was shown to efficiently induce development of SPIGFD patients achieving at least proper rate of growth (compared to healthy group) in 80% of subjects. In conclusion, here we provided novel insight into stem cells participation in IGF-1 deficiency in patients. Thus, we demonstrated basis for future studies in context of stem cells and IGF-1 role in growth disturbances.

P2-151

A novel mutation of LHX3 is associated with combined hypopituitarism and dysmorphic face

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The pituitary gland is a pea-sized organ located at the base of the brain. It synthesizes, and secretes, many hormones that control growth and development, and the functioning of the other endocrine glands. Panhypopituitarism is a condition of inadequate or absent production of all these hormones. LHX3 (LIM Homeobox 3) is a Protein-Coding gene involved in pituitary development. Mutations in this gene may result in a deficiency of multiple pituitary hormones. Here, we present an Iranian female infant with a homozygote mutation in LHX3 gene who was born from distant relative parents. Hypoglycemia and seizure were the first manifestations of the disease in our patient that appeared at the age of two months. At this time, short stature was noticed; both height and weight were below 3rd percentile for age. The patient's clinical history revealed signs of hypopituitarism, so with regard to the probable this diagnosis, more screening was performed. Laboratory tests were sent. The results of complete testing showed deficiency of GH, TSH, ft4, ACTH, and later cortisol hormones. With notice to these finding and associated defects such as short stature, short neck, macroglossia and face hoarseness, Panhypopituitarism was revealed. Therefore, the replacement therapy initiated as soon as possible with Levothyroxine, Hydrocortisone and growth hormone at 2 months old, shortly afterwards blood sugar normalized and she achieved remarkable improvement in height and weight within the first months of hormone replacement therapy

Results: In order to identify the genetic cause of this problem, Whole Exome Sequencing (WES) was performed for this patient. Molecular study revealed a homozygous likely pathogenic variant in exon 5 of the LHX3 gene (c.625C>T; p. Arg209Trp). This mutation leads to complete inactive LHX3 proteins.

Conclusions: panhypopituitarism in infants is rare, but has life-threatening complications if untreated; this report describes the novel LHX3 mutations and highlights the importance of molecular study diagnosis in patients with congenital MPHD for making definite diagnosis and treatment

P2-152

IGF1 as reassessment method of GH deficiency in adulthood

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Background: GH deficiency may not persist into adulthood. Thus, it is recommended to reassess it after reaching adult height. However, according to stimulation tests, they have poor specificity, reproducibility, and poor standardization of hormonal measurement, and they are expensive and involve risks.

Objective and Hypotheses: Establish if IGF1 would be a better reassessing method than stimulation tests in adult GH deficiency.

Method: Retrospective descriptive study for comparison of IGF1 and GH stimulation tests in reassessment of children with isolated GH deficiency into adulthood, in a tertiary hospital in the last 10 years.

Results: We reassessed 61 patients in adult height, previously diagnosed of isolated GH deficiency. Deficit persists according stimulation test in 26/61 (34.66%), and 9/61 (12 %) according to IGF1, with a correlation coefficient of 0.24. Differences between samples with abnormal and normal GH stimulation tests, and patients with abnormal and normal IGF1 in reassessment, are shown in Table 1 (p 0.034).

Conclusion:

In our Study:

- Deficits diagnosed by stimulation tests did not present an abnormal mean of IGF1, while low IGF1 was related to abnormal stimulation test. Therefore, low IGF1 is in favor of GH deficiency.
- Initial size is worse in children with abnormal stimulation test and IGF1 in reassessment, with greater involvement of second one.
- Children with abnormal stimulation test and IGF1, have more delayed puberty and less pubertal gain of height than those with normal reassessment.
- There is greater adult height and total gain of height in patients with abnormal stimulation test and IGF1, with better results in those with abnormal IGF1, so low IGF1 in GH deficiency could be related to a better response to treatment.

P2-153

Avascular necrosis of the hip as a rare complication of growth hormone therapy

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Background: Growth hormone therapy can be indicated for children who are born small for gestation age (SGA) (either birth weight or birth height < -2 SDS) without catch-up growth (height < -2.5 SDS) at age 4 years. Growth hormone therapy is considered a safe treatment.

Case Presentation: A 12-year-old girl was referred to the pediatric endocrinologist for short stature. She was born small for gestational age (birth weight SDS -2.2; height at birth SDS -0.5). Her medical history was uncomplicated. She was treated for migraine with prophylactic propranolol. She exercised regularly. SNP array showed a normal female chromosome pattern. She fulfilled the criteria for growth hormone therapy and started in August 2018. At physical examination in December 2019 showed Tanner M2. GnRH analogue treatment had been proposed but refused by the patient.

Table 1. Results	Patients with abnormal GH in reappraisal (GH<5.6ng/ml) (n=26)	Patients with abnormal IGF1 in reappraisal (IGF1<-2SDS) (n=9)	Patients with normal GH in reappraisal (GH>5, 6ng/ml) (n=35)	Patients with normal IGF1 in reappraisal (IGF1>-2SDS) (n=52)
Age (years)	10.45	10	10.6	10.55
Symptoms	Short Stature	Short Stature	Short stature	Short stature
Initial Height (SDS)	-2.85	-3.17	-2.64	-2.63
Parental Height(SDS)	-1.35	-0.54	-1.49	-1.47
Predictive Height(SDS)	-1.88	-1.73	-1.27	-1.46
Age of puberty girls/boys (years)	12.47/13.14	12.5/13.36	11.54/12.66	11.81/12.64
Puberty Height(SDS)	-1.93	-1.96	-2.15	-2.06
Adult Height (SDS)	-1.52	-1.33	-1.74	-1.62
Pubertal gain of height (cm)	20.15	18.63	22.54	22.96
Total gain (SDS)	1.33	1.84	0.9	1.01
GH (mcg/l) in reappraisal	1.63	3.54	13.91	9.88
IGF1 (SDS) in reappraisal	-1.27	-4.36	0.22	0.34

She had regular checkups (every 3 months), and blood results (thyroid function and IGF1) were within normal ranges.

One and a half years after growth hormone therapy had started, she was referred to a pediatric orthopedic surgeon for hip complaints on the left side. These complaints commenced six weeks before. There was no recent trauma, infection, or fever. Previously prescribed orthotics had no effect on the pain complaints. On physical examination a changed gait pattern was observed. A hip radiograph showed a discrete irregular aspect of the left acetabulum. Additionally, an MRI scan was performed that showed avascular necrosis of the left femoral head with limited cortical depression.

Discussion: Small for gestational age without catch-up growth in the first four years is a common indication for growth hormone therapy. During counseling, patients and parents that fulfill criteria for growth hormone therapy should be informed about advantages and disadvantages. Possible adverse effects are intracranial hypertension and slipped capital femoral epiphysis.

Our patient developed avascular necrosis after 1.5 years of growth hormone therapy. This is a very rare complication, previously described in 7 cases in children with a combination of renal failure and growth hormone therapy.

Conclusion: We present a healthy SGA born girl, with normal renal function, that developed avascular necrosis due to growth hormone therapy. A lesson that can be learned from this case is to consider this rare complication in case of hip pain during growth hormone therapy and early referral to an orthopedic surgeon.

P2-154

Predictive factors of adult height after 2 years of GH replacement therapy in children with growth hormone deficiency (GHD)

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Introduction: Growth Hormone Deficiency (GHD) represents the most common hormone deficiency during childhood accounting for 3% of causes of short stature. Although growth hormone (GH) replacement therapy is available, several studies have shown a different response in terms of height. Therefore, some reports have tried to characterize predictive factors able to define growth gain during treatment.

Objective: Therefore, the purpose of this study was to evaluate the possible predictive factors of change in height SDS in GHD children after at least 2 years of GH therapy.

Results: Data from 77 normal weight children and adolescents with GHD (age: 12.1±2.7 years; Girls/Boys: 24/53) have been included in the study. A complete anthropometric measures (weight, height, BMI, target height, bone age) and biochemical factors (IGF-1, lipid profile, glucose metabolism) at baseline and at follow up were evaluated. A Spearman correlation between height SDS at follow up and the main variables of interest at baseline was performed. A significant difference between baseline and follow up measures was documented for the main anthropometric measures (weight, height, BMI). In addition, a significant increase of IGF-1 values was documented at follow-up. The height SDS at follow up was significantly related with target height, target height-SDS, height, height-SDS, weight, weight SDS; in addition a negatively correlation was documented with GH values obtained during GH stimulation test and IGF-1 values at baseline.

Conclusions: In this study we demonstrated that the main predictive factors of GH therapy are anthropometric measurements and changes in IGF-1 values during treatment. Therefore, both IGF-1 and anthropometric measurements, should be taken into account to provide optimal management of the patient with short stature and to predict therapeutic success.

P2-155

Poor efficacy of growth hormone treatment in a patient with fetal alcohol syndrome

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Fetal alcohol syndrome (FAS) is established based on the presence or absence of characteristic facial features, prenatal/postnatal growth deficiency (height and/or weight < 10th percentile), deficient brain growth, neurobehavioral impairment, and maternal alcohol consumption during pregnancy. There have been no reports of growth hormone (GH) treatment in FAS; therefore, we report a case of GH treatment on FAS for small for gestational (SGA) short stature.

The patient was a girl born at 37 weeks and 5 days of gestation with weight of 2064 g (1.6th percentile), height of 41.5 cm (0.3th percentile), and an Apgar score of 3/4. Distinct facial features, growth deficiency, and mental retardation were observed. The mother was diagnosed as alcohol dependence in psychiatric clinic. She was diagnosed with FAS. Her height was 78 cm (-4.18SD) and weight was 7.305 kg (-3.62SD) at 3 years of age. GH stimulation test was performed for the short stature and GH secretion was normal. GH treatment (0.191 mg/kg/week) was started as an SGA short stature. Weight gain and growth velocity was poor although GH treatment was started. Nutritional assessment was performed in hospital due to concerns about the worsening dietary environment at home. The deterioration of eating habits occurred at home, which was considered as a state of inadequate nutrition. Improvements in eating habits were observed after children were transferred from home to the child's center. IGF-1 generation test was performed to ensure that GH was properly administered to her, then IGF-1 level increased from 59 to 175 ng/mL. It was found that GH was not administered properly at home, then she was started to administer GH daily at the child's center. The dose of GH was increased to 0.43 mg/kg/week, however, the growth velocity remained unchanged, and the height was 98.4 cm (-4.26 SD) at 7 years and 2 months old. In the blood examination, there was a slight increase transaminase and HbA1c.

Postnatal growth failure is affected by both nutrition status and living conditions, but the reasons why growth velocity do not improve in FAS are not well understood. Nutritional status and living conditions were improved, and GH was administered as SGA short stature, but without improvement in growth velocity and short stature.

Conclusion: Growth velocity in the 1st year of GH treated children with GHD in the current study was positively correlated with height SDS at start of treatment and was negatively correlated with chronological age and bone age as was shown in the pubertal group so the early administration of GH therapy lead to pronounced acceleration in linear growth during the first year of treatment.

P2-156

Short Term Effects of Growth Hormone in Children and Adolescents with Growth Hormone Deficiency

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Introduction: Children with Growth Hormone deficiency (GHD) should be treated with r-hGH as early as possible after the diagnosis is made.

The primary objectives of therapy is to normalize growth during childhood and to achieve final height within their genetic potential.

Objectives: To determine impact of GH treatment on short term linear growth in the 1st year of therapy in children with isolated growth hormone deficiency at Maadi Hospital Pediatric Endocrinology clinic to identify the predictors of growth response.

Patients and Methods: This is historical cohort study of 25 short children with GHD.

They were 17 males (68%) and 8 females (32%).

According to Tanner staging, they were classified into 2 groups:

Group 1: 18 pre-pubertal children (72%) and

Group 2: 7 pubertal children (28%).

All children received hGH therapy for a minimum period of 1 year and regularly followed up at 3 months interval.

Inclusion criteria:

A. Proportionate short stature,
B. Age from 2-18 years.
C. Peak stimulated GH less than 10 μg/L by at least one provocative stimulation test (clonidine or insulin),
D. Patients who have already started hGH treatment for at least 6 months before initiation of the study and will complete their treatment in a period not less than 1 year,
E. Height > -2 SDS below the mean height for age and sex.

Exclusion criteria:

A. Chronic illness potentially affecting growth,
B. Genetic syndromes or tumors,
C. Receiving medications affecting growth.

Results: The height velocity in the 1st year of GH treatment ranged from 5.0-9.5 cm with mean ± SD 6.2 ±1.3 cm.

Correlation analysis showed that the change in height SDS in the 1st year had a significant positive correlation with basal height SDS (r= 0.982, p= 0.001) which was evident in both prepubertal and pubertal groups but it was negatively correlated with both chronological age (r= -0.847, p=0.016) and bone age (r=-0.865, p= 0.012) in the pubertal group only.

P2-157

Prevalence of Childhood Short Stature and weight variations Among Primary School Children

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Keywords: short stature, underweight, overweight, obesity.

Introduction: Natural growth is an important indicator of health in childhood. Growth retardation can result from systemic and endocrine diseases or poor diet. Being overweight or obese in childhood increases the risk of morbidity and mortality in adulthood. This study, the first of its kind in Morocco, was conducted to compare the prevalence of growth disorders among children enrolled in public and private schools, in urban and rural areas of the province of Oujda-Angad.

Materials and Methods: A cross-sectional observational study was conducted among primary schools in Oujda-Angad Province, in the eastern region of Morocco, from November 2017 to April 2018, with a stratified random cluster sampling of public, private, urban, and rural primary schools.

Results: A representative sample of 1582 students aged between 5 to 15 years was selected. The study included 779 girls (49.2%) and 803 boys (50.8%), with a mean age of 9.3±1.96 years. The average weight of the students was 29.3±9.6kg, the average height was 133.7±12.16cm and the average body mass index (BMI) was 16.05±3.31kg/m2. Overall, short stature and underweight were significantly more prevalent in public and rural schools, while obesity was more common in urban private schools, which were classified as the schools with the highest socioeconomic status (SES). Female students were more susceptible to becoming overweight and obese, while male students were more likely to be underweight.

Discussion and Conclusion: Our study provides an estimate of the prevalence of overweight, underweight, and stunting in an elementary school population. Our results reflect the need to be vigilant about nutritional status at both the individual and community levels, and the need to implement prevention, diagnosis, and early management strategies before the problem worsens. It is imperative that the school health program periodically monitor the eating habits and physical development of children. Appropriate nutrition advice and exercise counseling should be provided not only to school children, but also to their educators and parents or tutors.

Growth and Syndromes

P2-158

Global recall of a growth hormone jet delivered device: Experiences with children forced to switch from a needle free system to a growth hormone device with needle

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Introduction: Growth hormone (GH) treatment is essential for growth in children with GH deficiency. Also short children born small for gestational age (SGA), and children with syndromes like Turner Syndrome (TS), Noonan Syndrome (NS) and Silver Russel Syndrome (SRS) can benefit from GH treatment. For children with needle anxiety GH delivered by a jet device can be a solution for the daily subcutaneous treatment for many years. In 2021, a global recall of the only GH jet delivered device available was initiated.

Method: After the global recall 95 children from our pediatric endocrine clinic were forced to discontinue GH treatment with the jet delivered device. All parents and children received a video instruction on how to use the new device including written pedagogical instructions. If necessary, parents received telephone guidance afterwards or were invited to the outpatient clinic. Data on age, diagnosis and intervention to switch to a device with needle was collected.

Results: Ninety-five patients between 4 and 18 years of age used a jet delivered GH device. The median (range) age of the patients was 12 (4-18) years. Eighty-six (91%) patients switched to a GH device with needle. In fifty-five (64%) patients, a video instruction at home followed by telephone guidance was sufficient for an uncomplicated switch. An outpatient clinic appointment for pedagogical guidance was needed for 6/18 of the short children born SGA, 6/23 of the girls with TS, 4/38 of the children with GH deficiency, 1 patient with NS, 1 patient with SHOX deficiency and 1 SRS patient. In 12 children (14%) the intervention was unknown. Six children (6.3 %) with a median (range) age of 14 (12-17) years discontinued GH treatment at own initiative and didn't switch to a new device. Another three patients were advised to stop GH treatment because they almost reached adult height (n=2) or because of increased risk developing a malignancy (n=1) (3.2%).

Conclusion: Most patients that used a jet delivered GH device continued GH treatment with a device with needle after the global recall. In the majority of children (64%), a video instruction at home followed by telephone guidance was sufficient for an uncomplicated switch to a device with needle. Twenty-one percent of patients needed pedagogical guidance at the outpatient clinic. The intervention was unknown in 14% of patients. Patient tailored specialized pedagogical guidance needs to be offered to those children with or being at risk to develop needle anxiety.

P2-159

SHOX haploinsufficiency among patients with idiopathic short stature

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Shox gene deficiency which causes short stature is a known indication for treatment with growth hormone. The prevalence of shox deficiency among children with idiopathic short stature has a high variability in different studies and ranges between 1.5-17%. We aimed to determine the incidence of SHOX haploinsufficiency in our region and to assess the genotype-phenotype relation which may help with setting criteria in the decision to which patients should we offer this genetic testing.

Methods: This was a prospective study of patients with idiopathic short stature who had disproportionate stature. In order to find changes in the Shox gene, every blood sample was tested by two **methods:** First, gene sequencing in order to identify point mutations, and thereafter MLPA testing was carried out to diagnose copy number variations.

The second stage of the research examined the clinical characteristics of the patients for the purpose of checking genotype-phenotype correlation.

Results: Shox haploinsufficiency was found in two out of the 24 patients (8 adults, 16 children) after testing by the MLPA method. Gene sequencing was found intact among all those tested. The prevalence of Shox gene haploinsufficiency was 8.3%.

In comparing the phenotypical characteristics between the patients with Shox haploinsufficiency as opposed to patients who were not found to have this gene deficiency the average height SDS is -2.6 according to age and sex in both groups (P=0.939).

Shox patients were found to have a statistically significant higher sitting height to standing height ratio (P=0.017). Likewise, upper to lower segment ratio was significantly higher among Shox patients (P=0.017).

These parameters express the unique characteristics of Shox haploinsufficiency short stature which presents with mesomelic short stature.

Nevertheless, we did not find a significant difference in the arm span to height ratio between the two groups. (P=0.19)

Conclusions: There is great importance in diagnosing shox gene deficiency as a cause for short stature. As was demonstrated in this study the prevalence of shox haploinsufficiency is not insignicant and further research, with wider scope is needed. Using special criteria based on the mesomelic short stature characteristics can pinpoint the suspected patients who need genetic evaluation

for shox deficiency and further genetic counselling. Examining family history where only some members suffer from short stature can strongly suggest the presence of monogenic hereditary disorder.

The research emphasizes the importance of using the MLPA method in order to assess the presence of shox gene deficiency.

P2-160

Evaluation of the first year of growth hormone treatment in Prader-Willi Syndrome Patients followed at an Expert Center of Rare Endocrine Diseases

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Introduction: Prader-Willi syndrome (PWS) is a rare imprinting disorder with evidence of increasing incidence. Treatment with recombinant human growth hormone (rhGH) has been shown to improve growth, body composition and final height. It is officially approved by the US Food and Drug Administration since 2000, but still not official indication in many countries.

Aim: The aim of the current study is to assess the results of the rhGH treatment at the end of the first year in PWS patients followed at an Expert center for rare endocrine diseases, participating in the European Reference Network for Rare Endocrine Diseases (Endo-ERN).

Patients and Methods: The study is a retrospective evaluation of regularly followed PWS patients at the Center since 2011 after the start of the official reimbursement in the country. All study participants were treated with rhGH for at least one year. A total of 18 patients with genetically confirmed PWS (11 DEL, 2 UPD, 5 with positive methylation test) participated in the study. The dosing was assessed every 3 - 6 months by attained auxological parameters (weight, height and BMI according to cdc growth reference, BMI after 2 years of age), IGF-1 levels and other safety parameters according to the Recommendations for the Diagnosis and Management of PWS patients (Goldstone, 2008) and the relevant requirements of the National health insurance fund.

Results: The age at diagnosis was from 0.08 to 14 years. The girls' mean age was 8.0±3.1 years, significantly higher than boys' (1.9±3.7 years, p=0.05). The mean age at rhGH start was 5.15±4.96 years (0.33-14.66), at a mean dose of 0.025±0.006 mg/kg/d (0.010-0.035).The latter did not change by the end of the 1st year (0.025±0.005 mg/kg/d, 0.017-0.032). The 1st treatment year height gain was 10.01±4.84 cm (2.5-19), more in boys than in girls (p=0.047). SDSIGF-1 before and after one year of treatment increased significantly (-1.62±0.7 vs. 0.72±1.54, p=0.001). SDSBMI decreased significantly during the 1st year of treatment with 0.39±0.51 (from 2.5±1.1 to 2.1±0.94, p=0.005). No adverse events were reported.

Conclusion: The early diagnosis and respectively, earlier start of treatment with rhGH in PWS patients increases initial height gain and provides faster decrease in BMI, especially in boys in our study group. Faster introduction of reimbursed PWS treatment with growth hormone worldwide is warranted as well as improvement of care at expert university affiliated establishments.

P2-161

Noonan syndrome-like disorder with loose anagen hair (NSLH1): watch out for the red hair

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Introduction: Noonan syndrome-like disorder with loose anagen hair (NSLH1), also known as Mazzanti syndrome (OMIM#607721) is a RASopathy due to missense mutation (c.4A>G, p.Ser2Gly) in SHOCK2 gene. The NSHL1 is characterized by Noonan syndrome-like facial dysmorphisms, easily pluckable, slow growing, sparse and thin hair, growth retardation, variable neurocognitive impairment and cardiac anomalies.

Aim: To present an additional new phenotypic variation associated with the c.4A>C change in NSHL1.

Material and Methods: A 2 $^{3/12}$ years old Greek girl was diagnosed with NSHL1. She presented failure to thrive since 34th day of life and referred to the Pediatric Endocrinology Unit at the age of 9 months. She was born at 38+2 days weeks, small for gestational age in weight and length, with no episodes of hypoglycemia. Fetal ultrasound at 12th week of gestation revealed increased cervical transparency. Chorionic villi sample analysis revealed a normal karyotype (46, XX).

The patient was diagnosed with atrial septal defect (ASD) and pulmonary valve stenosis at the age of 5 months and was under investigation for gastro-oesophageal reflux.

Results: At presentation her weight and height were 5,550 gr (<3rd centile) and 63,5 cm (<3rd centile), respectively. Head circumference was 44,5 cm,50th centile, despite the evident prominent fronthead. Clinical examination revealed low set ears, flat nasal bridge, epicanthal folds, long philtrum, bell-shaped thorax, remarkably red, sparse, thin, easy pluckable hairs. Neurological evaluation revealed mild hypotonia and congenital torticollis, while developmental milestones have been achieved within the normal range. Due to the audible systolic murmur and the history of ASD, a new ultrasound of the heart confirmed the wide ASD accompanied by dilatation of both right atrium and ventricle. Coeliac disease and metabolic disorders were excluded. The ophthalmological and audiometric evaluation were within normal. The diagnosis of growth hormone deficiency was established. Hypothalamic-pituitary MRI imaging revealed normal findings. Next Generation Sequencing analysis was performed, which allowed the heterozygous dominant missense change (c.4A>C, p. Ser2Gly) to be identified in SHOC2.

Conclusion: NSLH1 is characterized by distinctive features resembling Noonan syndrome. The most prevalent feature is the

easily pluckable, thin, sparse and slow growing hair. In this case the patient presents most characteristics of the typical NSLH1 phenotype, with the addition of the oddly red hair. This trait is present in contrast with the 'silver-blonde hair', described in the initial presentation of the disorder by Mazzanti. It is crucial to provide evidence for phenotypic variations in increased clinical suspicion.

P2-162

Long term effect of growth hormone treatment in a patient with growth hormone deficiency and mitochondrial disease due to TMEM70 gene mutation

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Context: Mitochondrial encefalo-cardio-myopathy due to TMEM70 mutation is a very rare disease with frequent neonatal onset accompanied by laptic acidosis, hyperammonemia and 3-methylglutaconic aciduria.

Case Presentation: Patient DT presented at 7.5 years due to short stature (height -3.11 SDS, MPH -1.09 SDS; weight -4.41 SDS), in the context of a complex syndromic picture characterized by intrauterine growth retardation, oligohydramnios, prenatal onset microcephaly; dysmorphism (carinated chest, irregular palmar folds, long poorly designed filter, thin vermilion, wide nostrils, thick and arched eyebrows, operated umbilical hernia, camptodactyly, congenital clubfoot), neurologic and neuromuscular involvement (mild mental retardation with mixed specific learning disorder-mixed type; chronic peripheral sensory neuropathy, with myoclonia, mild hypotonus and ligamentous laxity, vermian hypoplasia Dandy Walker like), cardiac involvement (repaired interatrial septal defect, aortic arch dilation, interventricular septum thickening, Wolff-Parkinson-White syndrome), audiological involvement (mean bilateral hearing impairment for acute frequencies). At the age of 14, DT was hospitalized for metabolic coma during a viral gastroenteritis with finding of metabolic acidosis, hyperlactacidemia, hyperammonemia with subsequent diagnosis of a mitochondrial disease (homozygous pathogenetic variant in the TMEM70 gene associated with type 2 ATP synthase deficiency inherited in an autosomal recessive manner) for which he started integration with iron, thiamine, carnitine, riboflavin. Since the age of 8, DT started growth hormone (GH) treatment due to a partial growth hormone deficiency (peak-stimulated GH: 9.76 ug/l and 4.65 ug/l, n.v. >10 ug/l, IGF1: 54 ng/ml, n.v. 64-345 ng/ml); MRI showed a normal hypothalamic-pituitary region. The remaining pituitary tropins were always normal; puberty was regular in its onset and course. GH therapy was well tolerated and effective. At the last visit (16 years), height was 163 cm (-1.46 SDS), weight 44.3 kg (-2.49 SDS), Tanner stage P4G4, testicular volume 15 ml.

Discussion: Endocrine dysfunction is often observed in genetic mitochondrial diseases, including growth hormone insufficiency. According to the literature, faltering growth is present in 94% of surviving children with TMEM70 deficiency and short stature in 89%, while hypospadia and/or cryptorchidism are present in 50% of males. To the best of our knowledge, growth hormone deficiency and good response to GH treatment in these patients have not been reported so far.

P2-163

Beckwith-Wiedemann Syndrome: Two Familial Cases with CDKN1C gene variants

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Introducción: Beckwith-Wiedemann syndrome (BWS) is a congenital disorder that includes features such as overgrowth, macroglossia, abdominal wall defects, neonatal hyperinsulinism, lateralized overgrowth and predisposition to embryonal tumors during infancy. BWS may be clinically diagnosed by a scoring system and genetic diagnosis is mainly focused to imprinting disorders on the 11p15.5 region. The presence of pathogenic inactivating variants on the maternal CDKN1C gene, although rare in sporadic cases, explains up to 50% of familial cases of BWS.

Objective: We describe two familial BWS cases and their genetic study.

Case 1: 8 year old boy, born preterm with macrosomia, macroglossia, nevus simplex, cryptorchidism and typical ear creases. BWS scoring=7.5 and negative screening for embryonal tumors. His mother was unaffected and two half-sisters had a clinical diagnosis of BWS, one with macrosomia, macroglossia, omphalocele at birth, and neuroblastoma at 3 months of life, the other with macrosomia and neonatal hypoglycemia.

Case 2: 18 month-old boy, born preterm with macroglossia, ear creases and aortic coarctation. BWS scoring=5. Macroglossia and omphalocele at birth was confirmed in the mother and five maternal family members.

Methods: Genomic DNA was isolated from peripheral blood and CDKN1C gene was studied by PCR amplification and Sanger sequencing variants were classified according to ACMG guidelines.

Results:

- Case 1: We found an already reported heterozygous pathogenic nonsense variant in exon1, NM_000076.2:c.388G>T, NP_000067.1:p.(Glu130Ter). The same loss of function variant was present in his unaffected mother (carrier), and his 2 half-sisters with BWS.

- Case 2: Sanger sequencing revealed a novel heterozygous variant in exon 2, NM_000076.2:949T>C, NP_000067.1:p.(Ter317Argext*49). The same variant was found in his affected mother. According to ACMG classification criteria this is considered a variant of unknown significance (VUS). Segregation study in other affected and unaffected family members (in process) may add information for further classification of the variant as likely pathogenic.

Conclusion: Presumptive diagnosis of familial BWS orientated the molecular study strategy. Genetic confirmation allowed a supported genetic counseling including 50% recurrence risk in each pregnancy for both, BWS and unaffected, female variant carriers. Also, knowing the molecular mechanism underlying BWS allows individualized surveillance protocols.

P2-164

Growth of extremely low birth weight infants (ELBW) at a tertiary hospital: catch-up growth continues during the 3rd year of life

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Introduction: An extremely low birth weight (ELBW) infant is defined as one with a birth weight of less than 1000 g. This study evaluated the postnatal growth of infants born with ELBW for 3 years.

Method: Anthropometric measures (z scores) from birth, 2,4.6,12,18,24, and 36 months were measured in 87 randomly selected infants who were born with a birth weight below 1 kg (between 9-2016 and 9-2018). Their anthropometric data were compared to standard growth for normal age and sex using WHO growth standards without correction for gestational age. All preterm babies received preterm formula for an average of 4-6 months.

Results: Their gestational age (GA) at delivery ranged between 23 and 27.5 weeks. They had weight z score (mean +/- SE) (WAZ) = -7.7 +/-0.14, length Z score (LAZ) = -8.8 +/-0.25 and weight for length Z score (WLZ) =-5.6 +/-0.39 and head circumference z score (HCZ) = -8.8 +/-0.3.

ELBW infants had a progressive gain in WAZ for the first 24 months (from -7.7 to -0.52). The catch-up in WAZ stopped during the third year of life. They had a progressive increase in LAZ for 3 years (from -8.8 to -0.34). The catch-up in LAZ continued considerably during the third year of life. Their WLZ increased significantly during the first year (from -5.6 to -0.1) with maximum gain during the first 6 months of life. This can be explained by a faster gain in weight compared to the gain in length during this period. They had a mild decrease in WLZ during the next two years. This is due to a relatively faster gain in LAZ compared to WAZ.

Conclusion: ELBW who were fed preterm formula for 4-6 months had a significant fast postnatal growth pattern with normalization of their LAZ, WAZ, and WLZ during the first 12-18 months of life. Catch-up in LAZ continues during the third year of life.

P2-165

Postnatal growth in Preterm infants as a function of their weight for gestational age (GA) (WAZ) at birth: Comparison between those who were born underweight (WAZ <-2) compared to those with normal weight (WAZ > -2)

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Introduction: Small size at birth is only a proxy for the pathological process of intrauterine growth restriction.

Aim: To study the effect of different birth weights on postnatal growth.

Method: We studied the linear growth of 59 infants who were born preterm (GA = 33.5 +/- 2.2 weeks) with birth weight >1.5 < 2.5 kg) for two years. They were classified at birth into two groups (group 1 with WAZ <-2) (underweight) and (group 2 with WAZ > -2).

Results: Preterm infants with birth WAZ <-2 increased their WAZ at 6 months and 12 months from -2.8 to -1.5 and -1.1 respectively. After an initial decrease in LAZ during the first 6 months of life from -1.5 to -1.7 they had LAZ catch up at the next 18 months (from -1.5 to -0.2). Their WLZ increased markedly from -5 at birth to -0.6, - 0.84, and -0.47 at 6, 12, and 24 months respectively.

Table 1. Postnatal growth data for infants born with ELBW (for 3 years)

		0.00	2 mon	4 mon	6 mon	12 mon	18 mon	24 mon	36 mon
WAZ	mean	-7.72	-7.69	-4.98	-3.20	-1.41	-0.75	-0.52	-0.59
	SE	0.14	0.19	0.19	0.17	0.14	0.13	0.14	0.15
LAZ	Mean	-8.78	-8.34	-5.93	-4.46	-2.34	-1.37	-1.07	-0.34
	SE	0.25	0.20	0.28	0.23	0.17	0.15	0.14	0.15
WLZ	Mean	-5.60	-3.21	-1.00	-0.02	-0.19	-0.10	-0.42	-1.10
	SE	0.39	0.39	0.21	0.17	0.17	0.13	0.15	0.21

		Birth				6 months		
		Gest age	WTSD	LSD	WT/L	WTSD	LSD	WT/L
WTSD <-2	Mean	36*	(-2.83) *	(-1.48) *	-4.95	-1.49	-1.71	-0.56
N= 09	SD	2.50	0.38	0.51	2.61	0.91	1.08	1.63
WTSD >-2	Mean	33.14	-0.48	-0.04	-3.96	-1.35	-1.68	-0.42
N= 47	SD	1.68	0.96	1.26	1.14	1.28	1.17	1.41
	p-value	0.0079	<0.000001	<0.000001	0.323	0.703	0.949	0.846

12 months			18 months			24 months		
WTSD	LSD	WT/L	WTSD	LSD	WT/L	WTSD	LSD	WT/L
-1.07	-0.84	-0.84	-0.95	-0.75	-1.20	-0.70	-0.16	-0.47
1.09	1.11	1.33	1.19	34.29	1.45	1.41	1.25	1.01
-0.48	-1.09	-0.12	-0.28	-0.91	0.25	-0.37	-0.51	-0.10
1.37	1.35	1.19	1.34	1.33	1.15	1.32	1.73	1.41
0.177	0.585	0.264	0.152	0.77	0.084	0.522	0.569	0.507

Preterm infants with birth WAZ > -2 had decreased WAZ during the first 6 months from -0.48 to -1.35. This was followed by a gradual increase of WAZ at 12, 18, and 24 months (-0.48, -0.28, and -0.1 respectively. Their LAZ decreased significantly during the first 6 months (from 0 to -1.7). During the next 18 months, LAZ increased to -1.1, -0.9, and -0.5 at 12, 18, and 24 months. WLZ increased from -4 at birth to -0.5, -0.12, and 0.25 at 6, 12, and 18 months respectively.

Despite the significantly decreased LAZ and WLZ scores in the group with WAZ < -2 at birth, at two years none of the growth parameters (WAZ, LAZ, and WLZ) differ significantly between the two groups.

P2-166

Postnatal growth in Preterm infants as a function of their head size (head circumference Z score (HCZ) at birth: Comparison between those who were with a large head (HCZ <-2) to those with normal Head size for gestational age (HCZ > -2)

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Suboptimal head growth in utero and in early neonatal life may affect linear growth and weight gain during infancy.

We studied linear growth and weight gain of 56 preterms (GA = 33.5 +/- 2.2 weeks) with birth weight >1.5 < 2.5 kg) for two years. They were classified at birth into two groups (group 1 with HCZ <-1) (relatively small head for GA) (35 +/- 2 weeks) and group 2 with HCZ > -1 (GA = 33 +/- 1.7 weeks)

		Birth				6 months		
		Gest age	WTSD	LSD	WLZ	WTSD	LSD	WLZ
HCSD <-1	Mean	34.77*	-2.16*	-1.54*	-4.76	-1.82	-2.04	-0.72
N= 14	SD	1.70	0.81	0.62	2.12	1.06	1.45	1.53
HCSD >-1	Mean	32.89	-0.42	-3.53	-3.90	-1.23	-1.57	-0.34
N= 42	SD	1.72	1.05	1.28	1.14	1.25	1.05	1.40
	p-value	<0.01	<0.000001	<0.000001	0.183	0.0961	0.138	0.485

12 months			18 months			24 months		
WTSD	LSD	WLZ	WTSD	LSD	WLZ	WTSD	LSD	WLZ
-1.4*	-1.06	-1.1*	-1.36*	-1.30	-0.99*	-1.1 *	-0.99*	-0.50
1.02	1.67	1.08	1.02	1.34	1.22	1.07	1	1.27
-0.29	-1.04	0.11	-0.06	-0.75	0.40	-0.19	-0.25	0.00
1.32	1.17	1.12	1.28	1.31	1.10	1.33	1.1	1.38
0.0024	0.971	0.004	0.000614	0.15	0.0059	0.0146	0.02	0.327

Results: Preterm infants with birth HCZ <-1 increased their HCZ from -1.95 at birth to -1.5, -1.1, and -1.1 at 6, 12, 18, and 24 months. Their WAZ at 6 months, 12 months, and 24 months from -2.16 to -1.8, -1.4, and -1.1 respectively. They had a maximum catch-up in LAZ during the second 6 months of the first year. After an initial decrease in LAZ during the first 6 months of life from -1.5 to -1.7 they had a normal gain in length.

Preterm infants with birth HCZ > -1 had a significant catch-up in WAZ at the end of the first year, WAZ was stable (normal weight gain) during the second year. LAZ increased progressively from -3.5 at birth to -1.6, -1.04, -0.75 and -0.25 at 6,12.18, and 24 months respectively.

Conclusion: At birth, preterm infants with smaller HCZ were significantly shorter and lighter compared to those with bigger HCZ. At the end of the first and second years of life, the group with larger HCZ at birth was still significantly taller and heavier compared to the group with smaller HCZ at birth.

P2-167

Short stature and mild developmental delay in a child with partial duplication of DIAPH2 gene: good response to recombinant Growth Hormone therapy: A Case Report

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Introduction: The DIAPH2 gene (Diaphanous homolog 2 Drosophila) is a Protein Coding gene found on the long arm of the X chromosome and is a member of the FH1/FH2 protein family. Members of this family affect cytokinesis and other actin-mediated morphogenetic processes required in early gonadal development.

Case Description: An eight-year-old girl was referred with a chief complaint of short stature. She is a product of normal vaginal delivery term with a birth weight of 2.2 kg. Her slow growth was noted at the age of 5 years. She had delayed speech development and mild intellectual disability. Measurements showed microcephaly (HCSDS= -3.5), short stature (HtSDS -3.5), and underweight (WtSDS = -2.5). Mid parental height SDS was 0.5. She had down slanting eyes, a round face, full cheeks, a short neck, and a shield chest. She was prepubertal.

Investigation showed normal hemogram, liver and renal function tests, and thyroid function. Bone age corresponded to her age. Her IGF-1SDS = -1.3 and peak GH level after clonidine stimulation was 15 ng/mL.

US Pelvis showed: Uterus is 10.2 x 5.4 mm. Right ovary measures 3.6.cc (3.3 x 1.9 x 1.0 cm) with multiple follicles seen and the left ovary measured 1 cc (1.7 x 1.6 x 0.6 cm).

Microarray analysis revealed a gain of ~422-kb of the long arm of chromosome X within cytogenetic band Xq21. The copy number change results in partial duplication of the DIAPH2 gene.

She was started on rhGH therapy, (Somatropin 0.05mg/kg/d) and oral nutritional supplements. Eighteen-month follow-up showed a good response to GH therapy. She gained 1.7 SD in HtSDS and 1 SD in WtSDS. (Table)

Child growth parameters responded to GH therapy as following

	At presentation	6 months follow up	18 months follow up
HtSDS	-3.5	-3.16	-1.8
Ht. Velocity	5cm / year	4 cm / 6 months	10 cm / year
WtSDS	-2.5	-2.2	-1.8
WGD	1.8 g/d	9g/d	7g/d
BMISDS	0	-0.4	-0.8
IGF-1SDS	-1.3	---	0
Bone age SDS	0	---	0

Discussion: Literature reported few cases with GH deficiency (GHD) associated with Xq duplication, but all were associated with hypothyroidism or empty sella. Our patient had dysmorphic features, microcephaly, congenital heart disease, and normal GH secretion. Her HtSDS increased by 1.7 SD after starting rhGH therapy.

Conclusion: Female patients with duplication in Xq had growth retardation, after checking the GH-IGF1 axis, a trial of rhGH therapy is warranted.

P2-168

Two siblings whose differential diagnosis with rickets; Schmid Metaphyseal Chondrodysplasia

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Entry: Rickets is a generalized metabolic bone disease manifested by the abnormal increase in osteoid tissue, defective mineralization and deformation of the epiphyseal plate, which occurs as a result of vitamin D and mineral deficiency before epiphysial fusion occurs in adolescence. Although rickets is mostly seen due to vitamin D deficiency, it can rarely be seen in vitamin D metabolism disorders and diseases that cause phosphorus loss.

Clinical findings such as late closure of fontanel, delayed teething, hypotonia, rachitic rosary, harrison groove, delay in walking, gait disturbance and O/X leg deformity (genu varum/valgum) suggest rickets. Irregularity in the long bone epiphyses, bowl formation, decrease in bone density and greenstick fractures can be seen on radiography. Some systemic diseases causing bone involvement and skeletal dysplasia can be confused with rickets. Incorrect treatment can cause complications.

Material and Methods: We described the striking features of two sibling cases who were considered to be differentially diagnosed with rickets with their presentation and radiological findings.

Cases: Two siblings, 3 and 1.5 years old whose parents were not consanguineous, presented with delay in walking, crooked gait, O-bain deformity, bone pain and short stature. Similarly, the father had short stature, genu varum, and bone pain, primarily X

or autosomal dominant inherited hypophosphotemic rickets was considered. Ca, P, Alp, PTH and vitamin D levels were evaluated and found within normal limits. In the bone survey radiographs of both brothers, there were coxa vara, femoral bowing and increased lumbar lordosis findings in addition to the appearance compatible with rickets in the long bone metaphyses. They were followed up for short stature and bone dysmorphism until the age of 12.5 and 10.5, respectively. Growth hormone treatment was not initiated because both cases had sufficient response to growth hormone stimulation tests. In genetic evaluation, a known heterozygous pathogenic variant was detected in the COL10A1 gene, consistent with Schmid Metaphyseal Chondrodysplasia, an autosomal dominant inherited chondrodysplasia.

Conclusion: After the vitamin D prophylaxis program started in May 2005 in Turkey, the frequency of nutritional rickets decreased. For this reason, raising awareness about rare forms of rickets and hereditary bone diseases facilitates early and accurate diagnosis of patients. Therefore, the diagnosis of rickets should not only be made based on physical examination and radiological findings, but should be evaluated together with serum calcium, phosphorus and vitamin D levels.

Keywords: Short stature, rickets, vitamin D deficiency, Schmid metaphyseal chondrodysplasia, O-Bain.

P2-169

Response to treatment with recombinant growth hormone in children and adolescents with short stature associated with noonan syndrome

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Introduction: Noonan Syndrome (NS) is a genetic disorder caused by mutations in the RAS/MAPK pathway. The clinical phenotype is variable; however, short stature is present in more than 80% of cases. Several clinical trials have been conducted over the last decades using recombinant growth hormone (rhGH) in NS to treat short stature demonstrating efficacy and safety which lead to the European Medicines Agency (EMA) approval in 2020.

Objective: Describe the efficacy and safety of rhGH treatment for short stature associated with NS in real life.

Subjects and Methods: Longitudinal study of subjects with clinical and genetic diagnoses of NS, with associated short stature (<-2.5 SD) who completed the first year of rhGH therapy. Data were collected during the clinical visits including clinical characteristics, genetic and laboratory study, anthropometric measurements, bone age, and rhGH dose.

Results: A total of 9 subjects were included; 5♂ / 4♀; 77,7% presented the genetic mutation in PTPN11; 7 of them had congenital heart disease, with pulmonary stenosis being the most common. The clinical characteristics of the subjects at the beginning of the treatment are described in Table 1.

The rhGH dose administered was 0,038 ± 0,002 mg/Kg/day (range 0,035 to 0,040 mg/kg/day).

After 12 months with rhGH there is a significant increase in height – SD from -2,96 ± 0,54 at baseline to -2,45 ± 0,53 at 12 months (p <0,0001). Growth velocity (GV) also increases from 4,8 ± 0,9 cm/year at baseline to 7,3 ± 1,8 cm/year at 12 months (p = 0,002), as well as GV – SD from -0,51 ± 1,40 to 2,45 ± 2,21 (p = 0,003). IG-1 - SD levels increased from -1,4 ± 1,24 at baseline to 0,21 ± 1,14 at 12 months. None of the IGF-1 values rose above +2 SD. No side effects were reported during the first year of rhGH treatment.

Conclusions: First year treatment with rhGH in NS with short stature improves height and GV. However, clinical follow-up of a greater number of cases until reaching adult height is necessary to determine the benefit of such treatment.

Table 1. Clinical characteristics of the subjects at the start of rhGH treatment

	Mean	SD
Age (years)	9,8	2,8
Weight (kg)	24,2	8,08
Weight -SD	-1,63	0,38
Height (cm)	121,7	15,01
Height-SD	-2,96	0,54
BMI (kg/m2)	15,89	1,97
BMI-SD	-0,77	0,49
GV (cm/year)	4,8	0,9
GV -DE	-0,51	1,4
Bone age (years)	7,7	1,4
IGF-1 (ng/ml)	105	38,3
IGF-1 –SD	-1,4	1,24

P2-170

A rare case of a child with Type 1 diabetes who was subsequently diagnosed with both growth hormone deficiency and Turner Syndrome

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Background: The association between Turner syndrome and Type1/ Type 2 diabetes is well known. Growth hormone is also utilized in Turner syndrome to improve height outcomes, but association of Turner patients with growth hormone deficiency is rare. To my knowledge, there are no cases of concurring Turner syndrome, Type 1 diabetes, and growth hormone deficiency.

Objectives: To describe a rare case where a child diagnosed with Type 1 diabetes was found to have both Turner syndrome and growth hormone deficiency.

Methods: A 5-year-old Caucasian female presented in diabetic ketoacidosis with diagnosis of new onset Type 1 diabetes. A1C was 10.1% and Insulin Ab positive.

Patient was noticed to be very small for height. After initial diagnosis and improvement of hyperglycemia, her weight returned to baseline at 17% and BMI of 80.68%, but she remained petite with height plotting at 1.11% for age. Mid-parental target height was 66.9 inches (80%). Growth velocity was slow at 3.84 cm/year.

Initial labs evaluating short stature showed low normal IGF-1 of 40 ng/mL (36-214 ng/mL) and normal IGF-BP3 of 2457 ug/L

(1854-5242 ug/L). Bone age was 3 years 10 months at chronological age 5 years 8 months. Growth hormone stimulation testing with arginine and clonidine demonstrated peak growth hormone level of 7.6 ng/mL. MRI of the brain showed mildly diminished pituitary gland size.

Karyotype was performed and patient diagnosed with 45, X/47, XXX mosaicism. She did not have overt dysmorphic features aside from slightly low set, posteriorly rotated ears and ptosis of the upper eyelids.

Growth hormone was initiated with good response, height increased from 0.25% to 5.15%.

Results: This is a case report of a rare incidence in which a child diagnosed with Type 1 diabetes was found to have both growth hormone deficiency with small pituitary gland and mosaic Turner syndrome.

Conclusion: Girls with Turner syndrome have an increased risk of developing diabetes, most commonly Type 2 diabetes due to insulin resistance. There is also an increased risk of autoimmune disorders, most commonly celiac and thyroid disease but includes Type 1 diabetes. Turner syndrome is associated with use of growth hormone, rarely has a diagnosis of growth hormone deficiency been made. This case provides an example that evaluation for growth hormone deficiency may be important in girls with Turner syndrome in addition to providing evidence for the potential autoimmune role in some cases of growth hormone deficiency.

P2-171

Case report of a child with cerebellar-facial-dental syndrome and multiple coexisting genetic, endocrine and neurological diagnoses

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Cerebellar-facial-dental syndrome is a rare autosomal recessive disorder due to biallelic variants in the BRF1 gene. It is characterised by cerebellar hypoplasia, intellectual disability, dysmorphic facial features and short stature. There have been only 12 patients described in the literature to date.

We report a case of a 9-year-old non-consanguineous Caucasian boy with cerebellar-facial-dental syndrome and multiple coexisting diagnoses, including Klinefelter syndrome (XXY karyotype), confirmed growth hormone deficiency, alpha-1-antitrypsin deficiency (SZ phenotype) and focal epilepsy. He is pre-pubertal, with otherwise stable pituitary function and normal pituitary on MRI.

Both the patient and his brother have cerebellar-facial-dental syndrome with biallelic variants c.413T>C l.Leu138Pro (maternally inherited) and c.422G>A p.Arg141His (paternally inherited) in the BRF1 gene. The patient's brother shares several features of the syndrome, but does not have the coexisting diagnoses of Klinefelter syndrome, growth hormone deficiency and alpha-1-antitrypsin deficiency.

We confirm features of cerebellar-facial-dental syndrome previously described in the literature, including cerebellar hypoplasia, microcephaly, short stature, scoliosis, dysmorphic facial features, learning difficulties and sensorineural hearing loss.

This combination of diagnoses has not been described previously and illustrates the role of genetics, imaging and a multidisciplinary approach in diagnosing and managing children with complex clinical features.

P2-172

Practicability and user friendliness of height measurement by proof of concept APP using Augmented Reality, in 22 healthy children

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Background: Child growth is a dynamic process and influenced by various environmental factors. When measured at short intervals, growth of healthy children shows certain characteristic patterns, which have rarely been studied, but are of great importance for clinical purposes. The study was approved by the Ethical Committee of the University of Potsdam.

Aim: To see whether measurements of height using photographic display (Iphones XR, manufactured by Apple) and visual analysis by Augmented Reality (AR, Quantum Interface) are practicable and user friendly.

Methods: Recruitment of families started within the personnel from University of Potsdam and then extended to befriended and close living families. The recruitment was done via email, the study started with a visit at the family home for the set-up of the measurement site, a conventional height measurement of the children and an initial training of the measurement process. Follow-up appointments were made at four, eight and twelve weeks to check the height of the children via conventional method and potentially correct the measurement process. The same person was responsible for the families from the beginning of the recruitment process until the end of the measurement period. Eight weeks after starting the recruitment, 13 out of 14 contacted families signed up for a study-period of twelve weeks, with altogether healthy 22 children aged 3 to 13 years. The height of the children was measured at daily intervals over a period of three months at their family homes.

Results: The parents recorded 1704 height measurements and meticulously documented practicability and problems when using the devices, at almost daily intervals for 3 months. 231 measurements were missing mainly due to one family that temporarily lost the iPhone during house moving, and a few holidays, mainly during Christmas time. This success was achieved by maintaining a high motivation within the families, created through a constant contact person, who was permanently available, open communication, personal training and contact during the appointments at the family homes.

Conclusion: AR can be used for height measurements at home. Measuring height by photographic display is interesting for children and parents. The very successful recruitment of children with a positive response rate of 13 out of 14 families with altogether 22 healthy children highlights the convenience and user friendliness of AR height measurements and suggests that AR is a promising tool for longitudinal growth studies.

P2-173

Case report of Leprechaunism syndrome in an Algerian child

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Introduction: Leprechaunism syndrome is a very rare genetic autosomal recessive disorder (prevalence 1 in a million births), and is caused by mutations in the insulin receptor gene.

Case Presentation: We report the case of a 5-month-old Algerian female, born to consanguineous parents. Birth was via caesarean section at 37 weeks gestation due to severe intrauterine growth restriction: birth weight 1800 g (< - 3.66SD), head circumference 32 cm (< - 2.6SD), length 42 cm (< - 5.37 SD). Apgar scores were 9/10 and 10/10.

The child was admitted to our department at the age of 4 months in a critical condition, presenting with tachycardia, high fever (39.7°C), cholestatic jaundice, and distended abdomen.

Clinical examination showed a septic child with emaciation, weight: 2200 kg (-7.7), length: 45 cm (-7.6 lipoatrophy, clitoromegaly, skin abnormalities, abdominal distension, hypertrichosis, and dysmorphic features including craniofacial abnormality with elfin facies and large, low-set ears. Neurological examination was normal. Laboratory results revealed hyperinsulinism, 560.4 pmol/L (14 – 140), fasting hypoglycaemia (24 mg/dL) and postprandial hyperglycaemia (170 mg/dL), hypocholesterolemia (50 mg/dL), hypotriglyceridemia (36 mg/dL), cholestatic jaundice (direct bilirubin: 4.6 mg/dL; indirect bilirubin: 6.5 mg/dL), C-Peptide: 947 pmol/L (reference range 95.4 - 455.8). C-reactive protein level: 65 mg/L

Based on the typical dysmorphic characteristics and laboratory findings especially the exaggerated hyperinsulinemia, a clinical diagnosis of Donohue syndrome (Leprechaunism) was made. This was confirmed by DNA analysis which showed a homozygous deletion in 19 p13.2 encompassing exon 2 of the insulin receptor gene (INSR). Immediate antibiotic treatment was administered and growth hormone therapy was started because of poor weight gain in the dose of 0.35 mg/k/dy. However, three days later, the patient's condition deteriorated dramatically with bradycardia, leading to cardiac arrest and death from apparent septicaemia (blood cultures positive on anaerobic culture).

Discussion: In this case we report Leprechaunism syndrome in an infant featuring typical phenotypic abnormalities, metabolic symptoms, severe pre- and postnatal growth retardation and multiple endocrine dysfunctions with insulin resistance.

The typical phenotypic features and the metabolic syndrome in Leprechaunism disease might be explained by the reduction of sex hormone-binding globulin provoked by insulin action via the type 1 insulin-like growth factor (1 IGF) receptor, which has functional and structural similarities with the insulin receptor

Conclusion: This very rare genetic disease is challenging to treat clinically. Its prevalence in Arab countries is accounted for by the high incidence of consanguineous marriage.

P2-174

Lysine urinary protein intolerance with lupus kidney, lupus brain and extremely short stature: A case report and literatures review

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Objective: To report the clinical and gene mutation characteristics of a patient with lysine urinary protein intolerance (LPI) characterized by lupus nephritis, lupus encephalitis and extreme short stature, so as to improve understanding of the clinical characteristics of LPI caused by SLC7A7 gene mutation.

Methods: The clinical manifestation, laboratory examination and gene test results of a child with LPI diagnosed and treated in our hospital were analyzed retrospectively, and the relevant literature was reviewed.

Results: A 7-year-old boy with growth retardation, rash, systemic edema and mental abnormalities came to our hospital. He had anorexia of high protein food since childhood, and had growth and mental retardation since 3 year-old. At the age of 6, he was diagnosed as nephrotic syndrome due to multiple rashes, proteinuria, edema of eyelids and limbs. After administration of prednisone, the rash and edema subsided. However, mental symptoms such as indifference, delirium and gibberish began to appear. On physical examination, he weighed 13.7 kg (- 3.3 SD) and 99.8 cm tall (- 5.4 SD). He appeared with round face, slightly wide eye distance, dark skin all over the body, and obvious pigmentation at the extremities and joints. Laboratory examination showed that Hb 104g/L, anti SSA antibody (+), anti nuclear antibody (+), complement C3 and C4 decreased. Blood LDH and blood ammonia increased, serum alanine, citrulline and glutamine increased, uracil, urinary whey acid and urinary 4-hydroxyphenyllactic acid increased. But the child had multiple system involvement and extremely short stature that could not be explained by SLE, Whole exon sequencing showed that it was a double heterozygous mutation of SLC7A7 gene (c.551A>C and c.719C>T). The mutation came from his mother and father respectively, and was diagnosed as LPI complicated with SLE.

Conclusion: The clinical manifestations of LPI are not characteristic. Lupus nephritis and lupus encephalitis are very rare. When there is protein intolerance, growth retardation and multiple system damage, we should be alert to the possibility of LPI. Blood and urine amino acid analysis, blood ammonia and renal tubular function can help the diagnosis. SLC7A7 gene sequencing is the basis for the diagnosis.

P2-175

Central Hypothyroidism as a manifestation of X linked *IGSF1* Deficiency Syndrome: A case report

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Introduction: The *IGSF1* gene deficiency syndrome (IDS) is an X-linked disorder involving hormonal disfunctions. We report a case of Central Hypothyroidism (CH) due to a Xq26.1q26.2 microdeletion including the *IGSF1* gene.

Case: this boy was referred to our clinic for thyroid dysfunction. He was born at term by caesarean section due to maternal uterine myoma. Pregnancy was normal, parents were non consanguineous. Birth weight was 3412 gr (0.3 SDS), length was 51 cm (0.63 SDS) head circumference was 36 cm (1.42 SDS). Maternal family history was significant for intellectual disability, mother had hypoprolactinaemia and was unable to brestfeed. Due to speech disorder and stereotypies, neuropsychiatric evaluations were performed and autism was diagnosed. Electroencephalogram, brain MRI and metabolic investigations were normal. Ophthalmological evaluation showed possible astigmatism. Mild hearing loss was also found. Genetic investigations included *FMR1* molecular analysis (negative) and CGH-array, that showed a q26.1q26.2 microdeletion inherited from the mother, including the *IGSF1* gene. At the first evaluation at the age of 3 years and 6 months height was 111.7 cm (2.86 SDS), within the family range, weight was 24.4 kg (3.57 SDS), head circumference was 54.5 cm (3.39 SDS). Testicular volume was 3 ml. Phenotype was normal, bone age was 6 months delayed according to Greulich & Pyle atlas. Blood exams showed low levels of FT4 associated with normal TSH according to laboratory reference ranges. TRH test was performed revealing normal values of TSH after stimulation and low FT4. Blood levels of other hormones were normal and thyroid ultrasound showed a normal thyroid gland. As low FT4 was persistent with increasingly lower FT3 levels in addition, Levothyroxine was started (25 mcg/die) and progressively increased according with blood FT4 values and auxological parameters. TSH levels gradually decreased during months becoming not measurable (< 0,01 microU/ml) at the age of 5 years and 8 months. Growth rate persisted normal. Relative macroorchidism was present, hormonal assessment was prepubertal.

Discussion: The most frequent endocrine condition associated with IDS is CH, that presented gradually in our patient. IDS may also involve delayed testosterone rise in puberty, macroorchidism in adult age, variable prolactin deficiency, occasional partial GH deficiency and overweight habitus. Levothyroxine replacement therapy is required as well as biochemical and auxological follow-up, to identify potential onset of hormonal defects and promptly start treatment. Due to X-linked inheritance, genetic evaluation of family members should be considered.

P2-176

A case of 1q21 recurrent microdeletion syndrome with growth hormone deficiency, facial dysmorphism, and microcephaly

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1q21.1 recurrent microdeletion syndrome is a rare chromosomal disorder caused by a genetic abnormality of non-allelic homologous recombination in the sequence of flanking a copy number variation event during meiosis. The characteristic features of 1q21 microdeletion syndrome are dysmorphic facial appearances with microcephaly, and mild to moderate developmental delay of speech and motor, eye abnormality, short stature, skeletal malformation, and psychiatric and behavioral disorders. Only a few people have autism spectrum disorder or brain malformation. In this report, there is a 9-year-old female from non-consanguineous parents who came to the clinic because of short stature with breast budding. Complete growth hormone deficiency with elevated basal and stimulated LH was revealed by growth hormone and gonadotropin releasing hormone stimulation test. The girl also presented microcephaly with a dysmorphic facial appearance including frontal bossing, prominent nasal bridged with a bulbous tip, full cheek, and short neck. Short stature with brachydactyly of 4-5th metacarpal hypoplasia and lumbar scoliosis was found by skeletal X-ray analysis. She had behavior problems derived by mood disorder and slightly low intelligence (Full scale intelligence quotation 80, Korean Wechsler Intelligence Scale of Children-IV). The brain abnormality was not found by brain magnetic resonance imaging. Based on these characteristics, microarray-based comparative genomic hybridization was conducted and revealed microdeletion at chromosome 1q21.1 and 1q21.1q21.2. Furthermore, chromosomal microarray analysis of both parents revealed that her mother has the same chromosomal defects on 1q21.1, even though she did not show characteristic phenotypic features except short stature. 1q21.1 recurrent microdeletion syndrome should be suspected in patients with developmental delay, mild to moderate intellectual disability, mild dysmorphic facial appearances and microcephaly. Since these genetic diseases have variable phenotypic expressivity, this case can help clinician to know how they assess a patient with mild dysmorphic facial features and intellectual disability at the scene of clinic and to apply appropriate diagnostic tools for genetic confirmation

P2-177

Effects of Somatropin treatment in different groups of patients with indication for replacement therapy: isolated growth hormone deficiency, small for gestational age, Turner syndrome and Prader-Willi syndrome

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Introduction: Somatropin has been the standard treatment for Growth hormone deficiency (GHD) since 1985. Nowadays, has been approved for the treatment of other diseases, as: Small for gestational age (SGA), Turner syndrome (TS) and Prader-Willi syndrome (PWS).

Aims: Assess the efficacy of somatropin in children followed in a tertiary Hospital, at 12 and 24 months of treatment, and to compare the results based on the patient's disease.

Methods: Fifty patients, who met the rigorous inclusion criteria and did not present any exclusion criteria, were divided in 4 groups based on their disease: isolated GHD (iGHD), SGA, TS and PWS. They were analysed in a retrospective, observational, descriptive and analytical study. Auxological and analytical parameters were collected at baseline, 12 months and 24 months of treatment. Descriptive and comparative statistics were performed.

Results: At baseline, the SGA group had the lowest height, weight and BMI SDS, and the iGHD group, the lowest corrected height, bone age and IGF-1 SDS. Only BMI SDS had a significantly difference in variation between groups, with a variation of -0.28±0.15 SDS (p=0.037) in the TS group, after 12 months. From baseline, iGHD and SGA groups improved significantly in weight, height, corrected height, bone age and IGF-1 SDS, either at 12 or 24 months. TS group improved significantly, from baseline, in height and corrected height SDS, at 12 and 24 months, and in IGF-1 and BMI SDS at 12 months. PWS group improvements didn't reach significancy. There were not reported any major adverse effects during treatment.

Conclusions: The findings of this work allow us to conclude that somatropin is an effective and safe treatment, and can significantly increase height in iGHD, SGA and TS patients in the short term. However, despite having positive results for PWS patients, they failed to reach significance.

P2-178

A Rare Cause of Proteinuria Presenting with Short Stature, Cataract, and Dysmorphic Findings: Lowe Syndrome with A Novel de Novo Mutation in the OCRL1 Gene

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Oculocerebrorenal syndrome of Lowe (OCRL) is an X-linked and multisystem disorder with clinical symptoms of congenital cataracts, severe mental retardation, hypotonia, areflexia, and incomplete Fanconi syndrome of the proximal renal tubules. We report a 15-year-old short stature male with a severe form of OCRL syndrome, diagnosed based on bilateral congenital cataract, proteinuria, tubulopathy, and dysmorphic findings. The physical examination revealed a height of 152 cm (-2.77 SD), a head circumference of 54 cm (-1.89 SD), and a weight of 45.2 kg (-2.11 SD). Additionally, he had dysmorphic findings, including bitemporal narrowing, deep-set eyes, microphthalmia, lens opacity in the left eye, prominent eyelashes, full lips, long philtrum, dysplastic ears, joint hypermobility, and hypoplasia in the nails. The neurological examination revealed stereotypic hand movements. In previous tests, it was observed that there was positive intermittent proteinuria in urine. The sequence analysis of OCRL1 revealed a novel and de novo hemizygous c.1432_1437delAAGTAT (p.Lys478_Tyr479del) nucleotide deletion in the patient, but not in his mother. Our aim is to draw attention to the rare cause of short stature presenting with proteinuria, and cataract, also emphasizes the importance of being careful when evaluating the laboratory.

P2-179

The syndrome behind the short stature! The difficult approach in Turner Syndrome with Y-chromosome sequences present

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Introduction: Short stature is a term applied to a child whose height is 2 standard deviations (SD) or more below the mean for children of that sex and chronologic age (and ideally of the same racial-ethnic group).

Case Report: We present a case of a girl aged 12 years, with normal perinatal and neonatal periods, GA=40 weeks, BW=2700 g, BL=49 cm, no medical history, no family history. The clinical exam revealed normal weight (BMI=18.4 kg/m2 P54) and short stature (-3.66 DS, H=125.5 cm), absence of breast development, pubarche, or adrenarche (Tanner stage B1P1), and shield chest, webbed neck, hand lymphedema. Based on the clinical exam we went further with the investigation for the diagnosis of short stature and its cause.

Laboratory and Intervention: The common laboratory features were within normal limits. The hypothalamic-pituitary-gonadal axis revealed hypogonadotropic hypogonadism (low value of Estradiol with very high values of gonadotropins). Values of Growth hormone and IGF1 (Somatomedin C) were normal, same as thyroid function, the autoimmune disease screening was negative.

The chromosomal analysis identified the presence of two abnormal cell lines (chromosomal mosaic) - mos 45, X [40] / 46, X, + mar [3] For the exact description of the marker chromosome, it is recommended to complete the investigations with Fluorescence in situ hybridization. Thereby the presence of the Y chromosome and the SRY region is confirmed

Imaging investigations: Pelvic ultrasound identified a small, tubular shape uterus, no visible endometrium, and ovaries; Pelvic and abdominal MRI: identified a small uterus 18/7 mm and absence of ovaries; horseshoe kidneys The next step was to repeat the MRI with higher Tesla in the attempt to detect gonads finding a hypoplasic uterus, possible hypoplasic left ovary possible testicular mass anterior of the right kidney. Hand X-Ray revealed a 2-year delay in bone age.

Discussion: Particularity of our case were the delayed bone age (difference of 2 years), high values of gonadotropic hormones with inhibited estradiol, and the result of pelvis ultrasound with a small size of the uterus and the absence of the ovaries. These features led us to explore a molecular karyotype and thus the positive diagnosis of Turner syndrome with Y chromosome mosaicism. Due to the presence of the Y chromosome, affected patients should still undergo prophylactic removal of the gonads (oophorectomy or salpingo-oophorectomy), even if they appear to be streak gonads. Therefore, hormonal treatment can be initiated only after the removal of the gonads/streak gonads.

P2-180

Beckwith-Wiedemann Syndrome: Three case reports

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Beckwith-Wiedemann Syndrome (BWS) is an overgrowth disorder, occurring in 1/13,700 births. BWS is usually sporadic, but 15% of cases are familial. Variable phenotype may include overgrowth, macroglossia, abdominal wall defects, neonatal hypoglycemia, lateralized overgrowth and predisposition to embryonal tumors. We describe three male cases of BWS followed at our clinic.

Case 1: Born of a gestation complicated by gestational diabetes. Delivery at 36 weeks by cesarean section with birth weight of 4600g (Z-score 4,12). The neonatal period was uneventful. At five years old, he had learning disability and a language disorder and on physical exam macroglossia and dysmorphic facial features were noticed. Genetic testing confirmed BWS. He was lost to follow-up and reevaluated at 17 years-old. Abdominal ultrasounds and cardiac evaluation were normal. He is currently 18 years-old, and his height is 196 cm (Z-score 2,97).

Case 2: Born at 27 weeks by spontaneous vaginal delivery, with birth weight of 1350 grams (Z-score 2,20), APGAR score 8-5-5, requiring neonatal resuscitation. There were no records of hypoglycemia events. Physical examination revealed macroglossia, umbilical hernia, abdominal and occipital hemangiomas and facial nevus flammeus. Abdominal ultrasound showed hepatic hemangiomas. Genetic testing confirmed BWS. At the 9 months, he developed non-autoimmune primary hypothyroidism and started levothyroxine replacement. Later on, development delay and learning disability were noticed. Abdominal ultrasound and α-fetoprotein (AFP) screening were normal. He is currently six years-old and measures 116,5 cm (Z-score 2,00).

Case 3: Born at term after an uneventful pregnancy, with birth weight 3090 grams (Z-score 0,32). He presented seizures in the first hours of life. Laboratory workup revealed polycythemia and severe hypoglycemia (<20mg/dL). Relevant findings on physical examination included dysmorphic facial features, macroglossia, aplasia cutis and hypospadias. Genetic testing confirmed BWS. Neurodevelopment assessment revealed development delay. Scheduled screening evaluations have been normal so far. He is currently seven years-old and his height is 133,4cm (Z-score 2,00).

Conclusion: BWS remains a diagnostic challenge and the existence of milder forms of the disease probably underestimates its incidence. Infants with BWS are at increased risk for mortality, due to complications of prematurity, macroglossia, hypoglycemia, tumors, and, rarely, cardiomyopathy. These cases presented with macroglossia, one with hypoglycemia and two with prematurity but none developed tumors. The increased risk for neoplasia occurs in the first eight years of life. Prognosis is generally favorable after early childhood. Embryonal tumors' screening should be stratified according to genotype and multidisciplinary approach should be performed.

P2-181

IHH gene variant causing short stature and minor skeletal disorders

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Introduction: Short stature is a frequent reason for consultation in the paediatric age group. After appropriate clinical, radiological and laboratory evaluation, up to 60-80% of children are classified as idiopathic short stature (ISS) because no underlying cause can be found. Nowadays, the spreading of molecular is

revealing that many of the patients initially classified as TBI, have variants in genes involved in the growth plate development.

IHH gene is involved in endochondral ossification of the growth plate by promoting proliferation and differentiation of the chondrocyte. Variants in this gene have been identified as a cause of short stature and minor skeletal disorders. Homozygous variants result in skeletal dysplasia known as Acrocapitofemoral Dysplasia causing extreme disproportionate short stature and cone-shaped epiphyses while heterozygous variants cause A1 Brachydactyly, characterized by short stature and shortening of the middle phalanges.

We present the case of a patient with a deletion in the IHH gene classified as likely pathogenic variant and previously only described in a single patient in the literature.

Clinical Report: A 12-year-old girl followed in our Paediatric Endocrinology clinic since she was 11, due to decreased growth velocity. Her anthropometry at birth was normal and the remaining personal history had no relevant findings. She had a family history of short stature especially at the maternal branch, and the mother has a heigh at -2.75 SDS. The patient's height was at p4 at examination with adequate arm-span and sitting height/standing height ratio. She had short fingers and bilateral preauricular appendices

Peripheral blood karyotype and the first level survey for growth study found no alterations. Given the familial short stature and brachydactyly history, it was decided to perform a skeletal dysplasia panel. This panel detected a heterozygous variant in the IHH gene (c.568_570del) classified as likely pathogenic variant and previously described in another patient, which would explain our patient's phenotype.

Conclusion: The study of a patient with short stature or decreased height velocity deserves a careful physical examination for minor skeletal alterations. When these are present, and especially with a positive family history, molecular genetic testing is an unvaluable tool.

P2-182

Persistent leukocytosis in a Noonan syndrome-neurofibromatosis type 1 patient treated with recombinant human growth hormone

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Introduction: Noonan syndrome-Neurofibromatosis type 1 (NSNF) is a genetic disorder characterized with clinical features of both Noonan syndrome (NS) and neurofibromatosis type 1 (NF1). Recombinant human growth hormone (rhGH) has been widely used in NS patients as well as in some patients with NF1 but there are only a few published cases of rhGH treated NSNF patients. We report a patient with NSNF with short stature who started rhGH treatment with subsequent persistent leukocytosis.

Case Report: A 4-year old girl presented for the first time with short stature. She was previously diagnosed with NSNF based on her typical NS phenotype (relative macrocephaly, low set ears, low posterior hairline, hypertelorism, short neck, broad chest with widely spaced nipples and lower pectus excavatum) and a proven mutation in the NF1 gene inherited from her mother (Exon 29: c.3884C>T heterozygous (p.Thr1295lle). At presentation to us her height was 93.2 cm (-1.97 SDS) and her weight was 13.8 kg (-1.24 SDS). Bone age (BA) was delayed by 1.6 years (-2.99 SDS, evaluated by the Greulich&Pyle reference, BoneXpert) and IGF-1 was 62 ng/ml (-0.93 SDS). During her evaluation, the blood tests showed leukocytosis with no signs of infection. Blood smear was microscopically evaluated by pediatric hematologists. No abnormalities were found and rhGH treatment was considered safe to initiate. After beginning of the treatment she had multiple outpatient blood tests performed with persistent leukocytosis, some of them during mild upper respiratory tract infections with the characteristics of viral ones, with the highest value being 27.62x109/l. A new blood smear was performed at clinical visit and again no abnormalities were found. Continuation of rhGH treatment was considered safe. Due to the high malignant risk in part of the RASopathy patients and the proliferative effect of rhGH a genetic evaluation for Noonan syndrome and a virtual consultation at the Clinical Patient Management System (CPMS) is underway.

Conclusions: The current case report describes an NSNF patient with short stature who is treated with rhGH. Multiple blood tests showed leukocytosis without signs of infection. Patients with RASopathies are known to have increased risk for malignancy. Due to the well known proliferative activity of rhGH, the safety of rhGH treatment in this patient is carefully monitored.

P2-183

First Korean case of a novel ZC4H2 mutation in Wieacker-Wolff syndrome with recurrent hypoglycemia

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Wieacker-Wolff syndrome, first described in 1985, is a rare congenital syndrome caused by ZC4H2 mutation reported in 9 family and 6 sporadic cases to date. It is an X-linked recessive disorder characterized by congenital joint contractures, mental retardation, progressive neurologic muscular atrophy, scoliosis, and hypoglycemia. A nine-year-old boy with brain atrophy, mental retardation, scoliosis, developmental dysplasia of the hip, convulsions, and exotropia presented to our institution with recurrent hypoglycemia since infancy. A physical examination showed facial dysmorphism and no hepatomegaly. Hyperinsulinism, growth hormone deficiency, cortisol deficiency, and fatty acid oxidation defects were ruled out based on the results of the appropriate tests. In the "critical sample," his hypoglycemia was consistent with ketotic hypoglycemia. Whole exome sequencing and Sanger sequencing revealed a hemizygous mutation on ZC4H2 in the patient and his mother, who has mild mental retardation and exotropia, but not in his father and brother. Here, we report the first Korean case of a boy with multiple anomalies and recurrent hypoglycemia with a novel ZC4H2 mutation.

P2-184

Clinical characteristics and genetic analysis of BLM gene mutation with Bloom syndrome without facial erythema changes

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Objective: To retrospectively analyze the clinical data, laboratory examination, gene test results, diagnosis and treatment of a case of small gestational age, short stature and microcephaly in the department of Endocrinology, Genetics and Metabolism of Jiangxi Children's Hospital.

Methods: The detailed clinical symptoms and family history of the children and their families were evaluated. 2ml peripheral blood of the children and their parents were collected for whole exon sequencing, which was verified by Sanger method.

Results: The proband was male, 1 year old and 2 months old, younger than gestational age, short stature (<-2SD), microcephaly (<-2SD), the facial skin was normal, a 5cm*5cm scar was visible on the chest (three-wave burn), and there was no family history of genetic disease or tumor.BLM gene c.772_773delCT (from mother), c. 1289_1290insAT (from father and grandfather) and c.1296_1297insCCATAGGGCCT (from father and grandfather) heterozygous frame-shift mutations, all of which were rated as pathogenic changes by ACMG guidelines.

Conclusion: The main manifestations of Bloom syndrome in childhood are small for gestational age, microcephaly and short body, without typical facial erythema changes. It is necessary to conduct genetic testing as soon as possible to identify the cause and provide reliable genetic evidence for family reproduction.

Keywords: Bloom syndrome; BLM gene mutation; Small for gestational age; Microcephaly

P2-185

Coexistence of (likely) pathogenic variants in two genes, *EZH2* and *PTEN*, contribute to overgrowth and developmental delay phenotype in a female patient

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Introduction: Overgrowth syndromes comprise an heterogeneous group of rare disorders characterized by generalized or segmental excessive growth commonly associated with additional features, such as developmental delay, visceromegaly and macrocephaly. They may present with inherent health concerns and, in some instances, an increased risk of tumor development requiring prompt diagnosis and appropriate referral.

Objective: to describe a female patient with an overgrowth syndrome and developmental delay with variants in *EZH2* and *PTEN* genes. Variants were classified according to ACMG guidelines and ClinGen PTEN Expert Panel Specifications.

Case: a 7-month-old female patient was referred due to overgrowth and developmental delay. She was born from non-consanguineous parents at 37 weeks of gestational age, birth weight: 3575 gr (+1.85 SD), length: 48 cm (+0.74 SD) and head circumference (HC): 33 cm (+0.34 SD). Target Height was normal (+ 0.34 SD). At first visit, height was 72.5 cm (+2.44 SD), weight: 10.4 Kg (+3.3 SD) and HC: 48.2 cm (+3.9 SD). Physical examination showed macrocephaly, hypertelorism, hypermetropia, depressed nasal bridge, long philtrum, microretrognathia, low set ears, hoarse voice, broad thumbs, developmental delay and hypotonia. Bone age was advanced in 1.5 years. Clinical exome sequencing (TSO-Illumina) revealed a likely pathogenic heterozygous variant in ***EZH2*** gene: NM_004456.4:c.475G>A, p.(Gly159Arg), described in Weaver syndrome, and a pathogenic heterozygous variant in ***PTEN*** gene: NM_000314.4:c.388C>T, p.(Arg130Ter), described in PTEN hamartoma tumor syndrome (PHTS). Segregation analysis suggests that both variants have arisen *de novo* in this patient. Last visit at 5.3 years height was 119 cm (+1.7 SD), weight: 24 Kg (+1.4 SD) and HC: 56.3 cm (+3.9 SD). Two previously undetected lipomas (clavicular area and leg), clinical findings suggestive of PHTS, were found on physical examination.

Conclusion: The coexistence of pathogenic variants in two genes, *EZH2* and *PTEN*, contribute to overgrowth and developmental delay phenotype in this girl, associating both, Weaver syndrome and PHTS. Surveillance program for early tumor detection is warranted because of the risk of early, bilateral and/or multifocal neoplasia associated to pathogenic *PTEN* variants.

P2-186

Effect of growth hormone therapy on height in children: Idiopathic gh deficient, family short stature, small for gestational age

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Objective: To investigate response to growth hormone (GH) treatment for idiopathic GH deficient (GHD) and family short stature (FSS) and Small for Gestational Age (SGA) patients or Combined group.

Design: GHD, FSS, SGA and Combined group patients who were currently receiving GH and had completed treatment with treatment duration of more than 6 months (from 8/2019 to 5/2021) at International Vinmec Central Park hospital. Measurements Growth hormone dose, change in height and growth velocity (GV) were recorded and compared. The effect of incremental dosing was assessed.

Result: A total of 31 pediatric patients with growth hormone deficiency (GHD) and 5 children with a combination of growth hormone deficiency and family short stature (GHD-FSS), and 2 children with a combination of growth hormone deficiency and small for gestational age (GHD–SGA), who received rhGH (recombinant human growth hormone) treatment were enrolled. There were no children with simple idiopathic short stature (FSS) or small for gestational age (SGA).

At the beginning of treatment, chronological age, bone age, height, and BMI were statistically signifcant between the tree groups. rhGH dosage in GHD (0,042 ± 0,004 mg/kg/day) was signifcantly higher compared with GHD-FSS (0,038 ± 0,003 mg/kg/day) and GHD-SGA (0,03 ± 0,003 mg/kg/day). Height before and after GH hormone replacement therapy in 3 groups were: GHD group (before: 131 ± 15,4 cm, after: 138,5 ± 13,8) with the average duration of treatment in this group is 9,6 ± 6,2 months, GHD-FSS group (Before: 123,1 ± 16,7 cm, after: 130,8 ± 18,2 cm) with mean duration of treatment is 10 ± 3,5 months, GHD-SGA group (before: 116,5 ± 16,3 cm, after: 125 ± 16,3 cm) the average duration of treatment in this group is 12 ± 7,1 month) Height velocity after rhGH therapy was higher in the GHD group (0,91 ± 0,75 cm/month) compared with the GHD-FSS group (0,76 ± 0,86 cm/month) and GHD group (0,69 ± 0,65 cm/ month).

Conclusions: rhGH increases the height growth in children with idiopathic GH deficient (GHD), combination of growth hormone deficiency and family short stature (GHD-FSS), combination of growth hormone deficiency and small for gestational age GHD-SGA. height velocity after rhGH therapy was higher in the GHD compared with the GHD - FSS and GHD-SGA.

P2-187

Combination Down / Klinefelter syndrome – A Clinical Case

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Introduction: The combination Down/Klinefelter syndrome was first described in 1959 by Ford. Its frequency is 0.4-0.9 / 10,000 newborn boys.

Case Presentation: A boy aged 5 y 4 m, born from a 2nd high-risk pregnancy (mother aged 44 with 1st pregnancy resulting in spontaneous abortion at 12 gestational weeks and with twice-established anemic syndrome) with (+) biochemical screening for Down syndrome. Birth was given via planned cesarean section at 38 gestational weeks, with birthweight 3000 g, body length 50 cm and head circumference 34 cm. APGAR on the 1st minute was 8, increasing to 9 on the 5th minute. In the early neonatal period, the child was raised on a thermal bed, additionally plasma transfusion treatment, phototherapy, intravenous infusions, and antibiotic therapy were applied. Stigmas for Down syndrome have been identified at birth. From the karyotype: two chromosomal pathologies - 48, XXY, + 21. Cytogenetic analysis was carried out with preparations, made from peripheral lymphocyte cultures and was performed by GTG-banding. The final analysis was conducted based on the International Cytogenetic Nomenclature.

The following were diagnosed by observation: primary hypothyroidism from 1 y 6 m, epilepsy between 6 m -4 y, severely impaired dental health. Due to muscular hypotension and retardation in psychomotor development the patient is directed to a consultation and rehabilitation center from 10 m. a., specializing in early diagnosis, rehabilitation, and prevention of child abandonment in an institution.

The growth of the child coincides with that of the general population SDS +0.09. Yearly checks were performed in the following areas: full blood profile, blood glucose levels, ophthalmology, cardiology, celiac disease, deafness status, genetic counselling. Good adaptation in a mass kindergarten from 4 years of age, where he worked additionally with a speech therapist and a resource teacher. He continues to use social services. Psychological examination at 4 y 2 m observes: progress in patient's independence and fine motor skills, the appearance of anxiety attacks, moderate mental retardation, more apparent in the social and emotional areas, alongside expressive speech.

Conclusions: Periodic consultation with a team of geneticists as to facilitate the personalized clinical treatment is advisable. Early and accurate diagnosis, the cross-specialist communication, trust both between teams and family are fundamental principles for achieving personalized care and social independence to the maximum extent possible for the patient.

P2-188

Kearns-Sayre syndrome – a rare cause of growth hormone deficiency

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Background: Kearns – Sayre syndrome (KSS) is a rare mitochondropathy. Among chronic progressive external opthalmoplegia, pigmentary retinal degeneration and ataxia that are present in most patients before age of 20 years, a significant proportion of patients also have various endocrine deficiencies.

Case Report: We report on a previously healthy boy who presented at the age of 8 years to the endocrine clinic due to short stature (height 116 cm; -2.15 SD, weight 18 kg; -2.2 SD). At the time of presentation he had mild unilateral ptosis, and was a bit clumsy while the rest of his clinical status was unremarkable. Growth hormone (GH) stimulation tests were performed confirming growth hormone deficiency. Before GH treatment introduction brain MRI was performed showing hyperintensities in globus pallidum, thalamus, mesencephalon, pons and cerebellum. Due to brain MRI results additional workup was done revealing pigmented retinitis, external ophtalmoplegia, high levels of lactate and protein in cerebrospinal fluid. Diagnosis of KSS was established and afterward molecularly confirmed in urine sample (large 7.6 kb deletion described in 65% mtDNA). Due to ambiguous literature evidence

on GH treatment efficacy in KSS patients as well as potential neurological side effects, parents initially decided not to initiate GH treatment.

Over the next two years, neurological symptoms including ophtalmoplegia and ataxia gradually worsened, the boys' growth velocity decreased significantly and finally, GH treatment was introduced which had a positive effect on growth and no side effects.

Conclusion: KSS is a rare and slow-progressing condition. Despite the fact that the first symptoms appear at a young age, they are usually extremely faint at first, and the diagnosis is made much later. Heart block, the most serious complication of KSS can cause death in some patients even before they are diagnosed. Short stature and GH deficiency can be a part of KSS and are usually evident before the onset of visible neurological symptoms. Early diagnosis is crucial to introduce endocrine treatment, routinely screen for comorbidities that are part of KSS, prevent complications and sudden death, and subsequently improve quality of life.

P2-189

Does she need growth hormone treatment?

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Growth retardation in children with type 1 diabetes (T1D) is mostly associated with longterm poor metabolic control or combination with other autoimmune diseases. Although rare it could be due to growth hormone deficiency.

We present eleven-year-old girl, diagnosed with T1D at age of 2y6mo., on multiple daily injections (MDI) with analogues. She is raised in poor social conditions – low parental education and income, rare follow-up due to difficult access to healthcare provider. Growth retardation was established at the age of 5y6mo. On this point she had a poor long-term metabolic control (HbA1C 13,22%) with unstable blood glucose levels. First insulin doses were adjusted, thyroid function was assessed and tissue transglutaminase antibodies (anti-tTG) were measured. She was negative for coeliac disease, but Hashimoto disease was diagnosed on re-evaluation at age of 7y (TSH 230 uIU/mL; fT4 4,0 pg/mL, TPO 4000 IU/L). Although thyroid hormone replacement treatment was started, short stature remained.

On last evaluation auxology showed height 120,8 cm (<3P, -3,42 SDS), weight (<3P, -2,24 SDS), significant retarded bone age (equal to 9y). Physiological puberty was started – telarche 2nd st; pubarche 1-2nd st. She was retested for coeliac disease – negative anti-tTG Ab. Poor adherence to L-Thyroxin treatment (TSH 100 uIU/ml; fT4 12,19 pg/ml) and very low IGF-1: 77,8 ng/ml (136-315) were found. Imaging of head for anatomical abnormalities is negative.

But does she need growth hormone treatment? Growth failure in T1D is often multifactorial. Among other factors affecting growth in children with T1D, downregulation of insulin like growth factor-1 (IGF-1) and insulin like growth factor binding protein-3 (IGFBP-3) with growth hormone resistance or even growth hormone deficiency could be considered. Afterwards growth hormone stimulation tests are appropriate only after better insulin treatment adherence and euthyroid state are achieved.

P2-190

Results of treatment with recombinant human growth hormone (rhGH) in patients with Turner syndrome. Albanian experience

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Introduction: Turner syndrome (TS), sometimes referred as congenital ovarian dysgenesis syndrome, is a genetic disorder that results when one of the X chromosomes (sex chromosomes) is missing (monosomic) or partially absent (mosaicism). It can cause a variety of medical and developmental problems, including short height. It is one of the most common syndromes that is included in the list of diseases treated with rhGH during the last 22 years in Albania. This study is the first attempt to evaluate the effect of this treatment on the near-final height of Albanian patients with TS.

Aim: To evaluate the growth indicators on patients with TS, before treatment (on time of starting treatment) and after rhGH treatment. We also are interested to compare the difference between the group with monosomy and mosaicism forheight improvement as a point of view.

Patients and Methods: In this study we have assessed the frequency of karyotypes of patients with TS from January 2000 to December 2021. We evaluated growth indicators at the time of initiation of rhGH therapy, as well as growth indicators at the end of treatment for patients who completed treatment with rhGH. Growth indicator data were elaborated by Anthro-plus software and statistical processing was done by SPSS.

Results: During the period mention above, 57 patients with TS have been diagnosed. 27(47.37%) of them resulted to have monosomy (45, X0) and 30(52.63%) mosaicisms. The age of rhGH's onset was 11.87±3.32 years. 41(72%) of all patients completed rhGH treatment reaching near-final height, 12/57(21%) are still under treatment with rhGH and only 4 out of 57(7%) have stopped the treatment for unknown reasons. The height (expressed in HAZ=Height for Age Z-score) of patients who completed treatment up to their near-final height have changed from -3.64±0.99 z-score at the beginning of treatment, to -2.79±0.84 z-score at the end of treatment, during 3.41±2.04 years of treatment. Among the 2 subgroups, the largest improvement in terms of HAZ, was made by the subgroup with mosaicism compared to that with monosomy (means difference: 0.61 z-score, two-sided p-value=0,019).

Conclusions: This study support the claim that the use of rhGH in patients with TS shows that is effective in improving the final height. The most noticeable improvement was in the mosaicism's subgroup.

Keywords: Turner syndrome, recombinant human growth hormone therapy, HAZ (Height for Age Z-score), near-final height.

P2-191

A case report of gonadal Y-chromosome mosaicism 45, X Turner syndrome complicated by HCG-secreting gonadoblastoma

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Objective: We report a case of a 5y3m patient who complained of breast development with "45, X Turner syndrome (TS) and HCG-secreting gonadoblastoma (Gb)" with Y chromosome mosaicism. Aim to understand the diagnosis of TS and improve the diagnosis and treatment of HCG-secreting tumors.

Methods: The data of clinical diagnosis and treatment of this patient were summarized, and the literatures were reviewed.

Results: The 3y2m patient was diagnosed with "pulmonary venous malformation + atrial septal defect" when she attended a local hospital due to breast development for 2 months. She underwent cardiac surgery. Her breast development was progressive, with accelerated growth and marked progression in bone age. At the age of 3y7m, the local whole-exome sequencing results were suspected to be 45, X karyotype, which was confirmed by the latter two hospitals. At the age of 4y6m, serum β-HCG was found to be elevated (24.94mIU/mL), and the lesion was unknown. Physical examination: slightly wide eye distance, high palatal arch, mild cubitus valgus. The height was 113.7cm (+0.1SD), the muscles were strong. Tanner stages: B4, PH3, female vulva and the clitoris was hypertrophic. Blood test: FSH 0.12 IU/L, LH 0.02 IU/L, E2 28 pg/ml, T 1.96 ng/ml, β-HCG 32.33 mIU/mL, AFP 0.94 μg/L. Bone age was 10.5 years. Blood SRY gene (PCR) (-), FISH (CEPY/CEPX probe) found only one X centromere. Thoracic and abdominal CT, head and pelvic MRI were normal. Laparoscopic gonad exploration (tumor appearance on the left, cord on the right), bilateral gonadal venous blood collection (β-HCG, E2 and T higher than left > right > peripheral venous blood), gonadal resection (bilateral gonads blastoma), bilateral gonadal SRY gene was positive. After surgery, E2, T, β-HCG decreased to normal. The patient received chemotherapy. After 9 months of follow-up, her growth slowed down, breasts became softer and smaller, clitoris was reduced and pubic hair was reduced. The level of E2, T, β-HCG were normal.

Conclusion: The risk of Gb in TS containing Y component is high. Gb with breast development as the main clinical manifestation is rare, Gb secreting HCG is even rarer. Therefore, TS with atypical clinical manifestations should pay attention to mosaicism. For TS with virilizing characteristics, the presence or absence of Y chromosome (component) should be identified, including tissue mosaicism. This case is the fifth report of Gb secreting HCG in the world. Precocious puberty regardless of gender, the testing of HCG, AFP are required.

P2-192

Acromelic dysplasia: A case report

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Acromelic dysplasia is a rare inherited bone dysplasia with 2 subtypes acromicric and gelophysic dysplasia. The prevalence is estimated <1/1 000 000, This condition is inherited either in an autosomal dominant pattern due to FBN1 mutations or in an autosomal recessive pattern due to ADAMTSL2 mutations characterised by growth drawfism, disproportionate short hands and feet, mild facial abnormalities, and characteristic x ray bones abnormalities.

The condition appered to be sporadic but in our case report we describe a familial abnormalities.

This is a 14-year-old patient from unrelated parents; reffered for growth retardation he had a history of placement of trans tympanic ventilation tubes at 12years of age, with no hearing improvement complicated by vocal cords paralysis, during intubation with implementation of a tracheotomy cannula.

Our patient and his mother have the same clinical abnormalities: short stature with pseudomuscular appearance, short extremities, thick skin, facial abnormalities with a round face and jovial air, a short nose with anteverted nares, a wide nasal ridge, a long and flattened philtrum, a thin upper lip and narrow palpebral fissures.

Typical radiological signs are: short metacarpals, thick proximal phalanges, cone epiphyses, long tubular bones shortened and stocky, small femoral head, hip dysplasia, vertebral abnormalities as moderate platyspondyly.

A genetic study is requested to confirm the genetic mutation.

Conclusion: The suspicion of an acromelic dysplasia should lead to the referral of the patient to the endocrinologist pediatrician in order to confirm the diagnosis and put in place appropriate management and monitoring measures to prevent respiratory and cardiac complications.

P2-193

Spontaneous final adult height in patients with idiopathic short stature

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Background: Idiopathic short status (ISS) is defined as a height more than two standard deviations (SD) below the mean for age and sex and population group without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities. Children with ISS have normal birth weight and GH secretion.

Aims: Aim of the study was to analyze the final adult height in a group of patients with idiopathic short stature.

Methods and Patients: Inclusion criteria were:

- height below 3 pc,
- growth hormone secretion above 10 ng/ml in at least one of the two performed stimulation tests - after clonidine, glucagon, insulin, arginine or after the sleeping
- absence of chronic diseases that could be the cause of short stature, such as: celiac disease, inflammatory bowel diseases, cystic fibrosis, chronic renal diseases, decompensated hypothyroidism, asthma, hematooncological diseases, heart defects, autoimmune diseases of musculoskeletal system and exclusion of chronic glucocorticosteroids therapy
- Turner syndrome excluded and lack of signs suggesting other chromosomal abnormalities.

We evaluated the auxological data of 10 patients among 22 patients with ISS (8 girls and 2 boys) who completed the process of growth. Final adult height (FAH) was established when growth velocity was below 1 cm/year. X-rays of nondominant hand and wrist were evaluated using the Greulich and Pyle atlas. Predicted adult height (PAH) was estimated based on Bayley-Pinneau method.

Results: Mean FAH in the study group was 150,2 cm and mean final adult height SD score (FAH SDS) was -3,03. Target height SD score (TH SDS) in boys subgroup was 0,5 SDS and 0,7 SDS, in girls subgroup was from -2,0 SDS to 1,6 SDS, mean TH SDS in girls subgroup was -1,24 SD, none achieved target height. Corrected final height SD score (corr FAH SDS) was -2,15. Mean difference between FAH and TH (Δ FH - TH) was 12,4 cm, in girls subgroup was 10,4 cm, and in boys subgroup was 20,5 cm. Statistical analysis revealed positive correlation between FAH and TH (r=0,933, p<0,001) and between FAH SDS and TH SDS (r=0,901, p<0,001). Statistical analysis revealed positive correlation between FAH and PAH based on prepubertal bone age (r=0,945, p<0,001). Statistical analysis revealed also positive correlation between FAH SDS and height SD score (height SDS) at the age of 4 and 6 years.

Conclusions: Predicted adult height based on prepubertal bone age and height SDS at the age 4 years and 6 years can be helpful in estimating the final adult height.

P2-194

Growth hormone deficiency and SHOX variants present in 2 siblings short for the family target

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P1 was referred with short stature aged 2.4 yrs (HtSDS -2.1). Mother's height 165cm (+0.5 SD), father's 185cm (+1.55 SD). Growth hormone (GH) deficiency was diagnosed following two GH stimulation tests (peak GH 6.8 ng/ml at 3.2 yrs, 5.17 ng/ml at 3.7 yrs) IGF1 4.6 nmol/L (1.7-27.6) at 2.5 yrs. Pituitary MRI was normal. GH treatment was started at 5 years at HtSD –2.2. Once P1 demonstrated catchup growth (up one centile in 7 months), P1's older sister P2 was referred for investigation of short stature (HtSDS –1.5). She was not dysmorphic but her mother noted antenatal scans had short foetal femur lengths on the 5th centile. Birth weight was on the 10th centile at 2.65kg at 38 weeks gestation. Short stature was present from age 3 with height tracking along the 2nd centile. Her GH was 7.17 ng/ml at time 0 on a growth hormone stimulation test, IGF1 25.9 nmol/L (3.1 - 51.9). This was performed during the COVID pandemic and could not be repeated. It was felt that GH deficiency was unlikely so a skeletal survey was requested. This showed mild Madelung deformity and short 4th/5th metacarpals. Subsequent SHOX analysis revealed that she was heterozygous for 2 SHOX dosage abnormalities in cis. The first was a deletion located between 133 kb and 163 kb downstream of the SHOX gene. The second was a duplication that included the final exons of the SHOX gene (exons4-6a). Family testing revealed the same SHOX variants in P1's father, who was the smallest in class in early childhood and had grown late into adulthood, reaching a tall final height at aged 21. Mother and P1 did not have these SHOX variants. P1 has demonstrated excellent catch-up growth on GH treatment, HtSDS +0.4. IGF1 36.5 nmol/L (2.7-45.5) at 7.3 years. P2 has been on GH treatment for over a year, latest HtSDS - 1.

Conclusion: Both siblings were short for the family target. Following a diagnosis of GH deficiency in one sibling, the investigative pathway for the other was assumed. Routine karyotype was performed after GH stimulation test with SHOX analysis requested after the skeletal survey report. The siblings' father has the same SHOX variants as P2 and is tall. Biological effects of SHOX deletion appears to be variable in this family and is present in P2 radiologically. The duplication is of uncertain significance.

P2-195

Syndromic Disorders with Short Stature

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Keywords: short stature, Noonan syndrome, Prader-Willi syndrome, Silver-Russell syndrome, genetic syndromes

Introduction: Short stature is one of the major components of dysmorphic syndromes. Growth failure may be due to a wide variety of mechanisms, either related to the growth hormone (GH)/insulin-like growth factor axis or to underlying unknown pathologies.

At present, GH therapy is used in most syndromic disorders, although long-term studies evaluating this treatment are insufficient and some controversies exist with regard to GH dose, optimal age to begin therapy and adverse effects.

Objective: To study etiological, genetic and diagnosis aspects of children with dysmorphic short stature.

Methods: Retrospective study including 60 children and adolescents with syndromic disorders with short stature admitted in the Department of Endocrinology diabetology and nutrition. The related anthropometrics and laboratory examinations were assessed in all participants.

Results and Discussion: We report 60 children and adolescents with short stature aged 14 ± 3.3 years, including 34 boys and

26 girls, were analysed in this study. The mean weight standard deviation score (SDS) and height SDS were -2.67±1.28 and -4,06±1.51 respectively. The majority of the children (56,9%) were prepubescent. The mean difference in bone age from chronological age was 25 months ±9. A propranolol-glucagon test was evaluated in 48,3% of patients.

The causes of syndromic short stature in our study are represented mostly by: malformation of the pituitary gland in 26,7% and Turner syndrome in 11,7%, followed by MOC (8,3%), prader wili syndrome (6,7%), Noonan's syndrome in 3,3%, 3M syndrome in 8,3%, waardenburg syndrome in 3,3%, russell-silver syndrome in 3,4%, DMC in 3,3%., and lastly 3A syndrom in 1,7%, Meier-Gorlin syndrome in 1,7%, as well as Eliis van Creveld syndrome. The genetic evaluation is still ongoing in 19,9% of the cases.

Conclusions: Genetic disorders are among major causes of short stature in children. Genetic testing is mandatory, in dysmorphic short stature. Patients should be referred to tertiary care centers for an individualized management.

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A retrospective analysis of short stature patients in the pediatric department of CHU Mustapha Pacha, Algeria between 2014 and 2022

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Introduction: Growth retardation is a frequent reason for consultation in pediatrics. The interrogation, the reconstruction of the evolution curve of the height and the weight, the clinical and paraclinical examination make it possible to orient the diagnosis.

The etiologies are multiple, but most often the growth retardation is isolated, it is then said to be constitutional.

Patients and Methods: This is a prospective descriptive study on the records of 384 patients followed in the pediatric department of the CHU Mustapha Algiers.

The aim of the study is to analyze the different etiological diagnoses and the therapeutic possibilities.

Results: The average age of our patients was 6,5 years, 174 patients (45%) are female and 210 (55%) are male, the sex/ratio is 1.2.

The paraclinical explorations made it possible to confirm the etiological diagnosis in 157 (41%) patients: 55 cases of GH deficiency, 40 cases of Small for Gestational Age (SGA), 08 cases of hypothyroidism, 20 cases of bone causes (MOC), 15 cases of celiac disease, 05 cases of Prader Willis syndrome (genetic study), 14 cases of Turner syndrome.

No etiology was found in 177 (46 %) patients, and 50 patients (13%) lost sight of.

Conclusion: Monitoring height and weight growth is an essential step and must be part of the systematic follow-up of any child.

The measurements must therefore be reported on the reference curves, on the health record and/or the child's medical file. This is the condition that allows a practitioner to detect growth abnormalities without delay and to detect certain serious illnesses early.

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Characterization of a patient with "rasopathies" type of noonan syndrome due to mutation of PTPN11 in a pediatric endocrine consultation

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Introduction: Noonan syndrome (NS) is an autosomal dominant disorder that involving multiple organ systems, with an incidence of 1:1,000 to 1:2,500. The clinical features as short stature, dysmorphic facial features, congenital heart defects most commonly pulmonary valve stenosis, typical chest, cryptorchidism.

The PTPN11 gene is located on the long arm of chromosome 12q24.1 and encodes for the non-receptor protein tyrosine phosphatase SHP-2 (SHP2), generating a gain of its function. Mutations in the PTPN11 gene are present in up to 50% of NS cases, followed by mutations in SOS1 and RAF1, KRAS, BRAF.

NS and other clinically overlapping conditions such as NS with multiple lentigines (formerly called LEOPARD syndrome), cardiofaciocutaneous syndrome, or Costello syndrome, are caused by mutations in genes encoding proteins of the RAS-MAPKinases pathway. Because of this shared mechanism, these conditions have been collectively termed «RASopathies».

Objective: To characterize the patients with "RASopathies" Type Noonan Syndrome with PTPN11 mutation of the pediatric endocrinology consultation during the years 2016-2021

Results: We describe 4 patients with mutation in the PTPN11 gene: 3 men, 1 woman, with averages of: 37.6 weeks of gestational age, 2.7 kg of weight and 47.6 cm of height at birth. 100% had: palpebral ptosis, winged neck, pectum carinatum and short stature, 75% heart disease type subaortic stenosis and ventricular septal defect, and 33% hearing loss and alteration of genitalia.

The mutations found in the PTPN 11 gene, all heterozygous were: in the males heterozygous and sporadic: Exon 7 c.836 A>G. pTYR:279cys, and c.417G>C (p.Glu139Asp) and p.Asn 308 Ser, c.923A>G, the female with mutation of c.417G>C (p.Glu139Asp) whose mother has SN.

Analysis: Although the diagnosis is clinical, this mutation according to the literature is found in 50% of patients, found in almost 60% of familial cases and in almost 40% they are sporadic. We found the mutation the PTPN11 gene in all our patients with NS, and 75% sporadic and 25% familiar. There is a phenotype-genotype correlation and they should be monitored for predisposition to malignancy

Conclusion: It is essential that physicians involved in the care of these patients are familiarised with their manifestations and clinical follow–up, especially due to predisposition to malignancy.

P2-198

Efficacity of Growth Hormone Treatment in Children with Intrauterine Growth Restriction IUGR

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WHO defines children born with intrauterine growth restriction (IUGR) as those with a birth weight below the 10th percentile of recommended birth weight by sex for gestational age. When gestational age is not available, a birth weight < 2500 g should be considered. The adult height in IUGR children treated with GH depends mainly on the duration of treatment and the age of initiation. Early diagnosis and early management before puberty are therefore imperative.

Aims: To study the auxological and diagnostic parameters of children with IUGR and to assess the response to treatment with growth hormone.

Materials and Methods: This is a descriptive retrospective study over a period of 6 years (2014-2020) within the endocrinology consultation of the Pierre and Marie Curie Center (CPMC) in Algiers.It concerned the pediatric population entrusted to the center for short stature.

The inclusion criterion is: a birth weight and/or height < −2 SD) and/or a birth weight < 2500 g

The following data was collected: Events during pregnancy or childbirth as well as term and syndromic signs and skeletal abnormalities were sought. Child's age, height, weight, mother's and father's height, pubertal stage, GH treatment data and adverse events.

Results: The total number of children IUGR evaluated is 50 children, (25 girls and 25 boys), i.e. a sex ratio of 1. The average age of the consultation was 6.92 +3.15 years. A single syndromic case of Pierre Robbin syndrome has been documented. The average birth weight was 2.37kg + 0.55 and the average birth height was 44.59cm + 3.39.

Of the 50 children, 45 benefit from treatment with rGH. The average age of these treated children was 8.21 years + 3.28. They presented an average delay of (-1.8DS) compared to the parental target size. Height gain in the first year of GH treatment averaged 7.64cm + 2.19

Treatment monitoring did not reveal any adverse effects leading to treatment adjustment or discontinuation.

Conclusion: Despite efforts to promote early referral of IUGR children over the past decade in most countries, a varying percentage of these children present late. Treating early has been recommended since the 90s, effective advice, but which comes up against the persistence of rather late consultations. It seems desirable to us that as many children born as possible IUGR be referred to a specialist consultation at the ages of 2 to 4 years.

P2-199

Challenges of late diagnosis of turner's syndrome: A case report of 18 women

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Introduction: Patients with Turner syndrome (TS) diagnosed beyond the age of 12 years present a real challenge for therapeutic management. Indeed, compromises must be made between the progressive induction of puberty and an efficient treatment with growth hormone to have the best possible results.

Patients and Methods: Our study concerns 18 cases of patients followed for ST in endocrinology consultation (CHU Constantine-Algeria).

Results: The reason for consultation was stunting in 12 cases, severe in 10 patients, and primary amenorrhea in 3 cases. Dysmorphic syndrome was found only in 3 patients.

The mean age at diagnosis was 15 years and the mean bone age was 11 years. The karyotype identified a monosomy in 55% of cases and mosaics in the rest.

Osteoporosis was found in 10 cases and growth hormone deficiency was associated with ST in 04 cases.

Progressive estrogen therapy was concomitant with recombinant GH treatment in 14 patients (77%). The mean statural gain was 06 cm.

Conclusion: The late presentation of ST, with its bone consequences in particular, has become an increasing concern requiring simultaneous and multidisciplinary management. However, early diagnosis will allow better social integration, growth hormone may help to achieve a near-normal adult height and concomitant estrogen therapy will be beneficial for bone integrity and good sexual function.

P2-200

Growth of children with cow milk allergy on the elimination diet

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Background: Compared to children without the disease, children with food allergy are stunted, which is positively correlated with the amount of food eliminated and the duration of the diet.

Objective: To compare the effect of an elimination diet on growth between children with cow milk allergy and those who are healthy as control subjects.

Subjects and Methods This study was carried out on forty children with cow milk allergy attending and nutrition clinic in Alexandria University Children's Hospitals and compared to forty apparently healthy children of matched age and sex as a control group. Anthropometric measurements; including weight, height, BMI, head circumference were measured.

Results: the weight Z score, height Z score and body mass index Z score were significantly lower in children with cow milk allergy compared to control.

Conclusion: A careful follow-up of patients with cow milk allergy should include the monitoring of growth during long-term elimination diets.

P2-201

Association between Turner Syndrom and GH deficiency: 04 case

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Introduction: Turner Syndrom (TS) is one of the most common chromosomic abnormalities. It associates almost constantly an ovarian dysgenesis and a growth delay (GD). The GD is often secondary to a peripheral resistance to the growth hormone (GH).

The GH deficiency (GHD) is a rare cause of growth delay, the association between these two condition is even rarer.

Patients and Methods: We describe here the cases of 4 patients, seen in our consultation for growth delay and delayed puberty. The mean age was 13 years, the mean height was 124 cm (- 6 SD in 1 patient, -3SD in 2 patients and -2SD in 3 patients). The mean bone age: 9 years. The dysmorphic syndrom was present in 3 patients.

Biological assessment: Low IGF1 in the 4 patients, positive anti TPO antibodies without thyroïd dysfunction in 1 case. All the other investigation were normal.

The Avlocardyl-Glucagon and insulinic hypoglycemia tests, showed an isolated GHD in the 4 patients. (GH peak < 7ng/ml)

Pituitary MRI: Pituitaty hypoplasia in 2 patients.

GH treatment was conducted in the 4 patients, although a poor response was noted. (The mean height gain 04cm). The caryotype was done one year after the treatment initiation: 3 cases monosomy, and one case mosaïc.

Conclusion: Turner Syndrom must be evoked in every girl wih growth delay. In our series GHD was searched before the establishement of the TS diagnosis, due to the caryotype unavailability.

Multisystem Endocrine Disorders

P2-202

AgRP neurons mediate sex differences in response to the activity-based anorexia model

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Anorexia nervosa (AN) is a multifaceted and debilitating illness characterized by self-induced starvation, persistent anxiety about weight gain, preoccupation with body image, and maladaptive food choices. It is characterized by the disruption in homeostatic energy balance mechanisms and the persistence of homeostatic hunger is overridden by dysfunctional self-regulatory and reward pathways that drive food aversion and severely restrict food intake. Epidemiological studies have consistently shown that (AN) has a higher incidence among females than males.

Starvation is associated with elevated activity of hypothalamic neurons that produce AgRP, which cells are crucial for feeding and controlling compulsive exercise and survival in the activity-based anorexia model (ABA).

Here, we interrogated whether these hypothalamic neurons mediate sex differences during the ABA paradigm. Using a combined pharmacologic and genetic approach, we found that when AgRP neurons are ablated, male mice exhibited higher food intake, lower body weight loss, and decreased physical activity during the food intake and the post-prandial period compared to age-matched female mice.

Our results suggest that when AgRP neurons are ablated, male mice are less prone to develop AN and shed new light on sex differences in fundamental homeostatic neural circuits.

P2-203

A Case of SHOX Deletion Due to Isodicentric Y Chromosome Anomaly with Multiple Endocrine Disorders

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Introduction: Isodicentric-Ychromosome;has phenotypic findings such as gonadal dysgenesis, short stature, Turner syndrome in girls, infertility in boys, and insufficient virilization. Here,a case with growth retardation, short statureand infertility

findings, and isodicentric-Ychromosomal anomaly(in addition to tuberosclerosis) who underwent endocrine follow-up due to obesity will be presented.

Case: The patient, who was admitted with obesity at the age of 8, was born 3000g at term, was operated at the age of 2 for coarctation of the aorta, at the age of 7 years for adenoid hypertrophy and strabismus, and at the age of 6 he wasdiagnosed with tuberosclerosis-(Heterozygous mutation in theTSC2 gene)-due to recurrent seizures. He is receiving multiple antiepileptic therapy. There is mild mental retardation. There is a third degree consanguinity between the parents. His height127cm(25-50p), weight 43kg(>97p), no acanthosis and striae. In his laboratory examination; liver-kidney functions, fasting-lipid profile, glucose metabolism were normal. Low free-T4(0.75ng/dl), normal TSH(3.6μIU/mL) value was found, anterior pituitary hormones were found to be normal, LT4 treatment was started.In imaging examinations; mild-hepatosteatosis, horseshoe kidney, increased convexity in favor of puberty in the upper part of the pituitary gland, multiple localized cortical tubercles were detected. While he was 10.5 years-old, bone age was 11.5years, height134cm (1SDS), body weight 44 kg (1.2 SDS), testicular volumes 6/6 ml, and the growth rate was 4cm/year. Peak growth hormone response to growth hormone stimulation tests was found to be sufficient. IGF1 value was between mean/+1SDS.He was 14.5 years-old, bone age was 16.5 years, height was 149.9 cm(-2.15 SDS), body weight was 68.05kg(0.69 SDS), testicular volume was 12/15 ml, growth rate was 1.6cm/year.Final height was150.9cm(-4SDS). It was observed that testicular volumes didnot increase. FSH:26.26mIU/mL, LH:8.54mIU/mL, TotalTestosterone: 233.25ng/dL, AMH:7.6ng/ml(normal), inhibinB:9pg/ml(low). Karyotype:45, x, inv(9)(p12q13)[4]/46, xy, inv(9)(p12q13), idic(y)(p11.3) was found to be compatible with isodicentric-Y chromosome. In microarray analysis,1.6 millionbase deletion in Yp11.32 region and 26 million base duplication were detected in the Yp11.31q11.23 region. Inaddition, three PAR2 regions[pseudoautosomal region at theends of Yq(PAR2)] were detected, one of which is on the longarm of the X chromosome. There is SHOX gene in theYp11.32 region, which is a deletion, and it explains the short-stature. Bone densitometry was found to be osteopenic.

Conclusion: In cases with isodicentric-Ychromosome, hypogonadism/azoospermia, Noonan/Turner phenotype occur. The follow-up of our case is important in terms of predictingthat patients with this chromosomal anomaly may developshort stature and infertility in the follow-up.

P2-204

Early detection of gastrointestinal polyps and neoplasia following radiation for childhood-onset cancer

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Exposure to abdominal radiation for childhood cancer has been associated with an increased risk of gastrointestinal polyps and neoplasia. These patients have a similar risk of developing colorectal cancer (CRC) as those with two or more first-degree relatives with CRC. There has been an inconsistency in clinical practice guidelines, partly due to limited evidence that treatment-associated colorectal cancer has a preceding screen-detectable phase. The previous recommendation from the Children's Oncology Group (COG) for starting screening was from age 35, but guidelines have been revised to recommend 3-yearly stool test and 5-yearly colonoscopy from age 30 (or 5 years after radiation, whichever occurs last).

We describe a case series from one centre of 12 survivors of childhood cancer with gastrointestinal polyps detected on gastroscopy/colonoscopy, with a median age of 26 years (range 20-41 years). Most of these had preneoplastic lesions (tubular adenomata). The median age of radiation exposure was 6 years of age, and the time to development of polyps was a median of 26 years. In all these reported cases, their radiation was not direct abdominal radiation for abdominal/pelvic malignancies, but rather craniospinal radiation or total body irradiation prior to bone marrow transplant. Three of these individuals were found to have colorectal malignancy (ages 20, 28 and 36), one of whom died from metastatic bowel cancer. One was confirmed to have Turcot syndrome, a rare association between primary brain tumours and colorectal cancer to be considered in all cases with medulloblastoma.

A small number of multicentre case series (and one prospective study) are reported in the literature to date, emphasizing the significance of this number from one centre. Teepen et al (2018) described 17 childhood cancer survivors with colorectal adenomas before the age 30, in addition to Au et al (2018) reporting 12 individuals under the age of 35. It is imperative to increase awareness about bowel cancer risk post radiation and to include screening as a regular part of late effects care. Even with the revised guidelines, most of our described cases would be detected late, hence screening recommendations need to be adhered to, regarding commencing surveillance from 5 years post radiation, to avoid missing the under 30 year age group.

P2-205

A novel mutation of *AIRE* gene in a patient with Autoimmune Polyglandular Syndrome type I (APS1), a case report

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Introduction: Autoimmune Polyglandular Syndrome Type I (APS1) is a rare condition caused by mutations in the *AIRE* gene (autoimmune regulator). The diagnosis is challenging and delayed due to its non-specific clinical manifestations such as candidiasis, hypoparathyroidism and hypoadrenalism. More than a hundred mutations of this gene have been described and hereby we present a girl who was found to have a novel mutation of *AIRE* gene with pathologic significance.

Case Presentation: A 5-year-old girl who had a history of consanguinity but no family history of diseases, presented to the emergency room with a tonic-clonic seizure. She was admitted the hospital where she was found to have an electrolytic imbalance. At this moment it was also noted that since she was 2 years old, she had several consults due to mucocutaneous candidiasis that didn't improve with antifungal treatment, as well as frequent diarrhea episodes and dental problems.

She was found to have a total calcium of 6.9 mg/dl (normal range: 8.8-10.8 mg/dl) and an ionic calcium of 3 mg/dl (normal range: 4.6-5.08 mg/dl). Her phosphorus was elevated at 11.4 mg/dl (normal range: 3.2- 5.8 mg/dl) and her PTH was extremely low at < 1.20 pg/ml (normal range: 1-13 pg/ml). Given the presence of chronic mucocutaneous candidiasis (CMC) and hypoparathyroidism, an extensive endocrine workup was performed. It revealed no other autoimmune endocrine diseases, but the presence of anti-insulin, anti-thyroglobulin and anti-microsomal antibodies was confirmed. Candida infection was confirmed by culture.

A genetic testing of *AIRE* gene was required. A Next Generation Sequencing analysis was performed by using Clinical Exome Solution v2 and Sophia DDM™ Platform (Sophia Genetics SA, Saint Sulpice, Switzerland) in a Miseq NGS device (Illumina Inc, San Diego, CA, USA). A gross homozygous deletion of the genomic region encompassing exons 1-3 of the AIRE gene, which includes the initiator codon, was detected. This alteration abrogates the first 463 nucleotides of *AIRE* gene coding sequence, resulting in the loss of a CARD domain, a HSR domain and NLS domain which is expecting to result in an altered or absent protein product. It was defined as pathogenic variant based on PVS1, PM2 and PP4 ACMG criteria.

Conclusions: In our patient two out of three diagnostic criteria (CMC and hypoparathyroidism) and other classic symptoms of APS1 were present, revealing a novel pathogenic variant in the *AIRE* gene.

P2-206

Rare association of hyperinsulinemic hypoglycemia in a pediatric patient with oculofaciocardiodental syndrome and mother with neuroendocrine pancreatic tumor

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Background: Hyperinsulinemic hypoglycemia is a heterogeneous condition characterized by inappropriate insulin secretion in the presence of low blood glucose levels. It can have various causes, including genetic, metabolic, syndromic, autoimmune, insulinoma, non-insulinoma pancreatogenous hypoglycemia or non-islet cell tumor hypoglycemia. On the other hand, oculofaciocardiodental syndrome is a rare X-linked dominant condition characterized by multiple congenital abnormalities, such as congenital cataracts, multiple minor facial dysmorphic features, congenital heart defects, and dental anomalies. To our knowledge, there is one single case of hyperinsulinemic hypoglycemia due to pancreatic microadenomatosis associated with oculofaciocardiodental syndrome described until present.

Case Presentation: We want to report the case of a 17 years old female adolescent, who presented in our service for recurrent hypoglycemic episodes. She was diagnosed at the age of 10 with hyperinsulinemic hypoglycemia, having no visible pancreatic lesion on abdominal ultrasound and CT. At time, she was successfully treated with diazoxide for two years. She is also known with cryptogenic epilepsy, cerebral arachnoid cyst and congenital cataract, and her mother had a history of pancreatic neuroendocrine tumor. At physical examination, she associated nystagmus, dental anomalies and congenital camptodactyly. Laboratory tests in our clinic showed glucose level of 24 mg/dL with inappropriate detectable insulin (6,05 uUI/mL) and C-peptide (0,502 ng/mL). Abdominal gadolinium MRI scan showed no pancreatic lesion. The familial history and clinical presentation raised the suspicion for a genetic syndrome, including MEN 1. Genetic evaluation and whole genomic sequencing emphasized a likely pathogenic mutation in BCOR gene, confirming the diagnosis of oculofaciocardiodental syndrome, but with no characteristic mutation for MEN 1 syndrome. Localizing the secretory lesion requires further investigation. Consequently, endoscopic ultrasound and EUS-guided fine needle aspiration are to be performed, and in the case of negative results, exploratory laparotomy and intraoperative ultrasonography of the pancreas will be envisioned. Other investigations, such as intra-arterial calcium stimulation or 68Ga-DOTATATE PET/CT have a high sensitivity for pancreatic mass detection, but are unavailable for now due to resource limitations.

Conclusion: This case poses multiple challenges for diagnosis and treatment. First, it is the insulin hypersecretion, most probably of pancreatic origin, with negative conventional anatomical imaging (US, CT, MRI), which requires multiple investigations for diagnosis. Second, it is the high clinical suspicion for MEN 1

syndrome, with no genetic mutation confirmation. Third, it is this rare oculofaciocardiodental syndrome, which, up to now, has been associated with hyperinsulinemic hypoglycemia in one single reported case.

P2-207

Bisphenol A (BPA): A hidden enemy

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Introduction: Endocrino disruptors (EDs) are substances that interfere with hormonal function. The long list of EDs includes multiple natural compounds and numerous synthetic chemicals such as bisphenol A (BPA). BPA is present in plastics used in common products (packaging, bottles, toys, digital media, etc). Several studies have shown its ability to alter the regulation of developmentally relevant genes, inhibit the synthesis of sex hormones and induce the proliferation of cancer cells in sex organs. In addition, the environmental exposure is associated with reproductive and behavioral abnormalities.

Objectives: To determine the urinary concentration of BPA (UBPA) in children between 5 and 12 years with variants of puberty (PP) or gynecomastia. To assess a possible association between the presence of elevated UBPA levels and the clinic studied.

Material and Methods: We randomly studied 35 children who consulted for PP variants and/or gynecomastia in a Pediatric Endocrinology Section (03/2020-06/2021). UBPA was determined in the first morning urine using the solid-phase extraction as a method of sample preparation, gas chromatography to separate compounds, and mass spectrometry for the UBPA detection and quantification. Hormonal studies and tumour markers were also carried out. Personal and family history and clinical manifestations were collected. The hospital ethics committee approved this study and participants and their legal representatives signed informed consent.

Results: 31 UBPA determinations of the 35 initially recruited patients (19 girls and 12 boys) were validated: 6 children with gynecomastia and 25 cases with PP variants [pubarche (12), thelarche (8), early puberty (2), adrenarche (1), menarche (1) and true PP (1)]. Only one child with gynecomastia reported regular use of a possible hormone disruptor (tea tree). Hormonal results were normal in all cases except in a 7-year-old girl with true PP. In two cases (6.5%) the levels of UBPA were elevated (gynecomastia and early puberty in a girl). No relationship was found between the UBPA levels and diagnosis or hormonal variables. No association was found between UBPA levels and home area or personal background.

Comments: The small sample size does not allow us to establish associations between UBPA and variants of PP and/or gynecomastia, but the extrapolation of 6.5% of children exposed to the general population may be significant. The high presence of EDs in our environment requires large and well-designed studies to assess its exposure and consequences in the pediatric age group.

P2-208

Precocious puberty before and after the COVID-19 pandemic

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Introduction: A novel coronavirus defined as coronavirus disease 2019 (COVID-19) was first detected in China at the end of 2019 and spread rapidly all over the world. As the covid 19 pandemic has led to changes in life all over the world, the prognosis of diseases have also been affected. This study presents how early puberty has been affected during the pandemic period.

Method: A total of 210 subjects; 113 individuals (94 girls; 3 boys) after the covid19 (2020-2021) and 97 individuals (104 girls; 9 boys) before covid19 (2018-2019) evaluated with suspicion of precocious puberty at the Pediatric Endocrinology department of Erciyes university. Age, sex, the time of pubertal signs, initial admission findings, exposure to endocrine disruptors, bone age, anthropometric measurements and tanner stages at the first examination, MRI results, peak FSH, peak LH and basal E2 levels, the time between bone age and chronological age, uterine long axis and ovarian measurements were collected from clinical records.

Results: Before covid19, the median age of 97 patients was 7,58 (3.6- 9.8) years while after covid19, the median age of 113 patients was 8,04 (5,1-10,6) years. The increase was observed in patients with precocious puberty during covid19 period. The mean of bone ages before covid19 were 8.5 years (+1.81) while after covid19 was 9.4 years (+1.51). The time between bone age and chronological age; pre-pandemic mean was 1.1 (+1.14); post-pandemic was 1.4 (+1.24). The body mass index (BMI) SD value was:0.81 (+1.1) at the first admission before the pandemic, it was 1.14 (+1.08) after the pandemic. Before and after the pandemic statistically bone ages ($p<0.01$), BMI (p:0.032) SD value, patient ages ($p<0.01$), FSH peaks (p:0.034) were evaluated and the results were significant. Girls presented with precocious puberty more frequently in both periods before and after the pandemic. The most common complaint was thelarche in both periods. Endocrine disruptor exposure was found to be increased in the post-pandemic group and it was statistically significant.

Conclusion: The Covid 19 epidemic was effective in precocious puberty cases as well as in many diseases. During this period, a significant increase was observed in endocrine disrupting exposure and the increase in bone age and BMI SD value of the patients were notable.

P2-209

Fahr's syndrome in children: About 2 cases

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Keywords: Basal ganglia calcifications, hypoparathyroidism, farh's disease

Introduction: Fahr syndrome is a rare anatomical-clinical entity, defined radiologically by the presence of bilateral, symmetrical, non-arteriosclerotic triatopallidodentate calcifications. Its diagnosis is radiological, and must be distinguished from Fahr's disease, which corresponds to the presence of calcifications without abnormalities of phosphocalcic metabolism. We report two pediatric cases of Fahr syndrome.

Observations:

1st Case: A 12-year-old female patient, was admitted in the emergency room for tetanic seizures, whose biological assessment revealed a severe hypocalcemia. The ECG was normal. The diagnosis of primary hypoparathyroidism was confirmed in the patient. The brain computed tomography (CT) revealed bilateral and symmetrical calcifications of the pallidum of the lenticular nuclei and the dentate nuclei, suggesting Fahr's syndrome. A clinical and biological improvement was noted after initiation of the substitutive treatment.

2nd Case: A 16-year-old female patient, consulted for generalized tonic-clonic seizures associated with cognitive impairment since the age of 14 years. A cerebral CT scan revealed bilateral and symmetrical calcifications of the lenticular and dentate nuclei, raising the suspicion of Fahr syndrome. Phosphocalcic assessment showed hypocalcemia secondary to primary hypoparathyroidism. The ECG showed a prolongation of the QT space. A clinical and biological improvement was observed after initiation of the substitutive treatment.

Discussion and Conclusion: Fahr's syndrome is a rare entity contrasting severe and varied symptoms with a simple and effective treatment. Our observations underline the importance of investigating phosphocalcic metabolism and searching for cerebral calcifications in patients with neuropsychiatric disorders in order to adopt the appropriate therapeutic approach.

P2-210

Glucose dysregulation and Diabetes mellitus in ROHHAD syndrome - possibly centrally driven?

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Background: Rapid-onset obesity with hypothalamic dysregulation, hypoventilation and autonomic dysregulation (ROHHAD) is a rare syndrome with a high risk of morbidity and mortality. Blood glucose dysregulation is not widely recognised as a feature of ROHHAD and the mechanism is not well understood. We describe glucose dysregulation in two children with ROHHAD syndrome.

Case 1: The patient presented at 6 years with rapid weight gain (BMI-SDS +2.45). She had hyperprolactinaemia, central diabetes insipidus (DI), growth hormone deficiency (GHD) and central hypothyroidism. MRI pituitary was normal. At 14 years she developed central hypoventilation requiring nocturnal BiPAP.

Aged 14 years she developed glucose dysregulation with intermittent hypergylcaemia, HbA1C of 59mmol/mol (NR<48mmol/mol) but a normal oral glucose tolerance test (OGTT). A year later, her HbA1c had risen to 64mmol/mol and she had raised blood sugar level (BSL) on OGTT (2 hours BSL 22.5mmol/L; NR <11.1). She was diagnosed with diabetes and commenced metformin (1g twice daily) and insulin (0.5units/kg/day). Auto-antibodies were negative.

BSLs rapidly normalised and insulin was discontinued after one week. Metformin was continued and liraglutide (0.6mg/day for 2 weeks, then 1.2mg/day) was commenced for weight management. Within two months her HbA1c normalised (39mmol/mol). Continuous glucose monitoring sensor (CGMS) showed daily hypoglycaemic episodes with approximately 30% of time <3.9mmol/L. Therefore, liraglutide was discontinued and the hypoglycaemia resolved. BMI-SDS is now +2.72. She continues metformin with normal HbA1c (41mmol/mol), average BSL 7.2mmol/L and 92% time in range.

Case 2: The patient presented in cardio-respiratory arrest aged 4 years following a 6-month period of rapid weight gain (BMI-SDS +3.1). She had central hypoventilation requiring nocturnal BiPAP, central DI, hyperprolactinaemia and GHD. MRI pituitary was normal.

Aged 5 years, despite a significant improvement in her BMI-SDS (to +1.35) she had persistent high random BSLs (12-16mmol/L) on multiple occasions. Her OGTT (2 hours BSL 12.2mmol/L) was suggestive of diabetes, but with a normal HbA1c (33mmol/mol) and no symptoms of diabetes. Auto-antibodies were negative. BSLs subsequently normalised and therefore treatment was not commenced.

Conclusions: The mechanism of glucose dysregulation and diabetes in these patients is unclear, possibly related to the hypothalamic or autonomic dysfunction characteristic of ROHHAD. CGMS may be useful in ROHHAD to evaluate glucose dysregulation. Hypoglycaemia is not a well described side-effect of liraglutide, however, in the context of ROHHAD, this could be centrally mediated or due to an exaggerated incretin response. Further exploration is required in this area to understand the underlying, potentially novel, mechanism.

P2-211

McCune Albright Syndrome in children- Case series from a Tertiary Care Centre- Sri Lanka

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McCune Albright syndrome (MAS) is rare with a prevalence of 1 in 100,000 to 1 in 1,000,000, characterized by the triad of monostotic/polyostotic fibrous dysplasia (FD), café au lait skin pigmentation, and hyperfunctioning endocrinopathies caused by somatic activating mutations of the GNAS1 gene encoding the α subunit of guanine nucleotide-binding protein.

Here we are reporting three cases of MAS who are actively being followed up in a leading Children's Hospital in Sri Lanka.

Patient 1: 3 year old boy presented with bilateral frontal prominence, multiple café au lait spots, large hands and feet with height >97th centile, right leg deformity and pubertal genitalia. Investigations revealed increased testosterone with undetectable gonadotrophins, increased Prolactin and growth hormone. He had hypophosphatemic rickets and features of fibrous dysplasia in the skull. He was started on spironolactone, cabergoline, Phosphate buffer, 1 alpha calcidol with regular intravenous bisphosphonate. He continued to have high IGF-1 and GH level needing long acting octreotide at 11 years. He's now 17 years and 2 months and his serum cortisol and thyroid function remained normal throughout with no effect on hearing and vision.

Patient 2: 3 year old boy presented with right leg deformity and fracture of the right humerus. He had multiple café-au-lait spots with frontal prominence and prepuberal genitalia. He had fibrous dysplasia in the right femur and humerus with a fracture in the latter requiring intravenous bisphosphonate and vitamin D supplements. At 5 years, he was found to have gonadotrophin independent precocious puberty (GIPP) with bone age of 10-11 years requiring Letrazole and Spironolactone. Later he developed hypophosphatemic rickets, high Prolactin needing phosphate buffer with 1 alpha calcidol and Cabergoline. Other endocrinopathies are absent at 8 years and 10 months.

Patient 3: 2 year old girl presented with a history of low impact R/femur fracture, multiple café-au-lait spots and thyrotoxicosis and commenced on regular intravenous Bisphosphonate, antithyroid drugs and beta blockers. She is on phosphate buffer and 1 alpha calcidol for hypophosphataemic rickets. She underwent thyroidectomy at 4 years due to uncontrolled thyrotoxicosis and she's currently on Thyroxine replacement. At 2years and 9 months, she developed vaginal bleeding, diagnosis of GIPP was made and started on oral Letrazole. Other endocrine functions are normal at 5 years.

MAS has various different presentations therefore it's important to follow them up regularly and actively look for developing endocrinopathies.

P2-212

Endocrinological Evaluation in a Case with WAGR Syndrome

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Introduction: WAGR syndrome was first described in 1964 by Miller et al. And is characterized by Wilms tumor, aniridia, genitourinary anomalies, and developmental delay. Endocrine/metabolic problems (obesity, dyslipidemia, hypertension, short stature), especially obesity, are seen in more than 70% of cases with WAGR syndrome. Here, we aimed to present a case with WAGR syndrome for endocrine evaluation.

Case: A 12-year-old 9-month-old male patient with an operated Wilm tumor followed in the oncology department was consulted our clinic in terms of endocrine complications of cancer treatment. It was learned that he was born on term, with 2850 gr. At the age of two, he underwent left nephrectomy due to Wilms tumor and received chemotherapy. Orchiectomy was performed at the age of four because of unilateral atrophic testis due to undescended testis (pathology: immature testis tissue). He was followed up in the ophthalmology department due to aniridia. There was no consanguinity between the parents. On physical examination, height: 144.4 cm (-1.66 sds), weight: 38.5 kg (-1.17 sds), body mass index: 18.5 kg / m2 (-0.43 sds), blood pressure arterial :130/80 mmHg, left testis 15 ml and other system examinations were normal. In laboratory examination; complete blood count-biochemistry-thyroid function tests were normal, FSH:13.62 mIU/ml, LH:7.78 mIU/ml, total testosterone:344.73 ng/dl, AMH: 4.02 ng/ml. In scrotal USG, left testis was 26x12x12 mm, parenchyma echo was normal and millimetric microlithiasis was detected. His chromosomal microarray analysis revealed that a 7-mb deletion in the 11p14.1p12 region. When hypertension was detected at the age of 15, amlodipine treatment and also methylphenidate treatment were started for attention deficit/hyperactivity disorder. He is 18 years old and short for age and overweight now. His follow-up continues as multidisciplinary.

Result: Ambigus genitalia, undescended testis, hypospadias, polycystic ovary syndrome, streak ovary, obesity, short stature, metabolic syndrome, hyperlipidemia and rarely diabetes and adrenal insufficiency can be seen in cases with WAGR syndrome. We thought that multidisciplinary follow-up of patients with WAGR syndrome and endocrine evaluations from the first diagnosis are important.

P2-213

Clinical and endocrine characteristics of Algerian children with McCune-Albright Syndrome

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Introduction: McCune-Albright Syndrome (OMIM #174800) is a mosaic disorder, characterized by "café-au-lait" spots, fibrous dysplasia, and autonomous hyper function of one or more endocrine organs, within the peripheral precocious puberty remains the most common manifestation.

This disease is caused by GNAS gene activating mutations.

Objective: To describe clinical and endocrine characteristics in ten patients with McCune-Albright Syndrome (MAS).

Population and Methods: Retrospective clinical study of patients with MAS followed up at the Department of pediatric endocrinology of Algiers Hospital (CHU DEBAGHINE LAMINE), between 2009 and 2021.

The diagnosis is based on the presence of at least two symptoms.

Results: Nine females and one male are described in this study; their age at onset of first signs was early (3, 27 ±1, 13) whereas their age at presentation was (5, 17 ±2,16years).

All patients had café-au-lait skin spots.

Seven girls developed peripheral precocious puberty (PP) among them five presented ovarian cysts however there was one female patient with precocious puberty associated to pituitary microadenoma.

One female patient, MAS was associated with Turner Syndrome.

On the other hand, the male patient had developed unilateral machroorchidism.

Bone age was advanced in all patients.

Fibrous dysplasia was detected in four patients.

Cushing's syndrome occurred early in one female patient.

Discussion: McCune Albright Syndrome is characterized by a broad clinical spectrum.

This study described multiple clinical and endocrine manifestations, in 10 Algerian patients with MAS.

Peripheral PP helped to make an early diagnosis of MAS in most female patients, while the male patient presented unilateral machroorchidism.

Conclusion: Systemic approach is mandatory, in the diagnosis and management of MAS, to allow an early intervention, and thereby improving outcome in patients with the MAS.

Pituitary, Neuroendocrinology and Puberty

P2-214

Central precocious puberty - an unusual paraneoplastic manifestation of a nephroblastoma?

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Introduction: Nephroblastoma or Wilms tumor is the most common pediatric abdominal malignancy. Typically, it is found in children younger than 5 years old, girls being more likely to have Wilms tumor than boys. The etiology of the disease is genetic, due to alteration in the development of the genitourinary tract.[1] Treatment is represented by surgery (unilateral nephrectomy), chemo- and radio-therapy. Paraneoplastic endocrine disorders may occur, but there are few data about the association of central precocious puberty (CPP) and nephroblastoma [2].

Case Report: We report a case of a 7-year-old Caucasian girl with a history of nephroblastoma that was admitted in our pediatric endocrinology department for the evaluation of premature thelarche. She was diagnosed at the age of 3 with stage 3 Wilms tumor, underwent surgery, followed by systemic chemotherapy (vincristine/dactinomycin and doxorubicin) and local radiotherapy (total dose 10.8 Gy). The family history was positive for pulmonary and gastrointestinal cancers. At the admission in our clinic the patient was pubertal (B3 Tanner stage), she had advanced bone age (+1 SD) with prepubertal LH and E2 serum levels (LH=0.67 UI/L, estradiol=29.5 pg/ml). We identified an accelerated linear growth (height velocity 19 cm in 13 months), with a height at presentation of 133.4 cm (+1.96 SD, +0.89 SD for bone age). A gonadotropin-releasing hormone analog (GnRHa) stimulation test was performed and it showed a pubertal response (LH=16.3 UI/L, estradiol=377 pg/ml). Lab tests revealed a mildly raised IGF-1 (376.1 ng/ml, normal values: 24-293), with normal thyroid function test and human chorionic gonadotropin (hCG) serum levels. Pelvic ultrasonography showed a pyriform shaped uterus with visible endometrium and the ovaries presented 7, respectively 10 follicles. Thoracic CT scan identified a 2 mm pulmonary nodule, unmodified from the previous imaging. Treatment with GnRHa 3.75 mg, 1 subcutaneous administration at 26 days was recommended along with magnetic resonance imaging of the suprasellar region and oncologic reevaluation.

Conclusion: Central precocious puberty is an unusual paraneoplastic manifestation of a nephroblastoma secondary to its specific treatment or the disease itself. We strongly recommend

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multidisciplinary medical teams (oncologist, endocrinologist, radiologist, surgeon) in the management of children with cancers.

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P2-215

Congenital Hypopituitarism and Diabetes Insipidus with Normal Radiological Pituitary Gland and a Mutation in IRF2BPL

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Background: Congenital hypopituitarism (CH) is a group of disorders characterized by deficiencies in one or more hypophyseal hormones and a marked variability in genotype-phenotype correlations. Central diabetes insipidus (DI) is caused by a decreased release of ADH and results in a variable degree of polyuria. Their association is normally found in congenital cerebral midline abnormalities, such as septo-optic dysplasia.

Objective: Reporting a patient with CH and neurogenic DI and normal pituitary gland and midline brain structures in magnetic resonance imaging (MRI) without mutations in previously reported pathogenic variants known to cause hypothalamo-pituitary disease.

Method: Patient's DNA was analysed with comparative genomic hybridization (CGH) array and exome sequencing.

Case Report: A two-day-old term male neonate (ovodonation pregnancy) was admitted after seizures and a cardiopulmonary arrest in the context of hypoglycaemia. Laboratory results (4 days after birth, glucose 24 mg/dl): cortisol 0.5 µg/dl, ACTH 11 ρg/ml, TSH 3.17 µg/dl, FT4 0.99 ng/dl and GH 7.2 ng/ml. In day 11 after birth polyuria (7.8 ml/kg/h) was detected (serum osmolality 312 mOsm, urine osmolality 84 mOsm/kg), with good response to subcutaneous desmopressin. Other laboratory findings (17 days of age): LH 6.25 µU/ml, FSH 1.25 µU/ml, testosterone 0.41 ng/ml, IGF-1 34 ng/ml (45-93) and IGFBP3 1.4 µg/ml (1.2-1.8). MRI showed subcortical and subependymal heterotopia, without any alterations of the hypophysis or other midline structures. Oral hydrocortisone and levothyroxine were started. During the clinical follow-up, a switch to oral desmopressin was made with poor clinical results, so subcutaneous administration is still ongoing.

Results: We identified a heterozygous frameshift insertion mutation (loss of function) in *IRF2BPL* c.320_321insGC; p.(GIn108Hisfs*45). Mutations in this gene have been reported to cause neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures (OMIM#618088) and also changes in female pubertal-timing.

Discussion/Conclusion: this patient presents with CH and DI without neuroimaging alterations in the typical structures when both conditions coexist. Furthermore, genetic analysis does not show mutations already linked to CH. Although the mutation found affects Wnt signaling pathway (mutations in this pathway have been described to produce CH), functional studies are required to determine its pathogenicity in CH. With the widespread use of next generation sequencing, more mutations in non-previously described genes associated with CH will appear and this will lead to achieve a better understanding of this complex group of disorders.

P2-216

β-hcg secreting intracranial germinoma in a girl with isosexual precocious puberty: A case report and review of literature

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Objective: To analyze the clinical characteristics and treatment of non-germinomatous germ cell tumor (NGGCT) in one girl with the initial onset of homosexual peripheral precocious puberty (PPP) and central diabetes insipidus (CDI) and eventually progressed into central precocious puberty (CPP).

Methods: The clinical data of a girl who was diagnosed as NGGCT with the onset of PPP and CDI and eventually progressed into CPP was analyzed. Related literature up to November 2021 was searched with the terms of "(precocious puberty OR PP) AND (non-germinomatous germ cell tumor OR NGGCT)"in Wanfang, CNKI and PubMed database in Chinese and English. The characteristics of the disease were summarized.

Results: A 6 years and 9 months old girl with complaining of polyuria, polydipsia and breast development was admitted to the First Affiliated Hospital of Sun Yat-sen University Pediatric Department in June 2020. Upon admission, the initial serum showed low luteinizing hormone (LH), low Follicle-stimulating hormone (FSH) and high estradiol (E2). β-human chorionic gonadotropin (β-HCG) level was extremely high in both serum and cerebrospinal fluid (CSF). Pelvic ultrasound showed enlarged uterus and premature follicle. The baseline cerebral MR Perfusion showed occupation of suprasellar and pineal gland. The girl was diagnosed as the β-HCG secreting NGGCT. After the chemotherapy treatment course, her breast return to Tanner I, the follow-up cerebral MR Perfusion showed the occupation had almost disappeared and the β-HCG level of CSF and serum had descended to normal. After 7 months of the cessation of chemotherapy, breast development showed again and finally diagnosed as CPP after GnRHa stimulation test and treated with GnRHa.

Conclusion: We reported a girl of β-HCG secreting NGGCT with onset of precocious puberty which was very rare. For those PP girls especially in the young age, β-HCG should also be screened to rule out NGGCT. Meanwhile, for the NGGCT patients, routine follow-up of clinical manifestation, hormones, hypophysis MR, β-HCG level in serum and CSF are necessary.

P2-217

A rare case of Cystic fibrosis and Pallister-Hall syndrome combination in a 3-year-old boy

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Introduction: Pallister-Hall syndrome (PHS) is a rare disease with autosomal dominant pattern of inheritance caused by CHD7 gene mutation and characterized by epiglottis malformation, polydactyly or oligodactyly, hypothalamic hamartoma and visceral abnormalities. Central precocious puberty is the most common endocrine abnormality detected in PHS. Regardless isolated growth hormone deficiency, pan hypopituitarism and genitourinary malformation are reported in PHS it is still not clear if they are secondary due to hamartoma or represent independent manifestations of hypothalamic-pituitary dysfunction.

Case Report: patient S. was admitted to the Pediatric department of «Endocrinology Research Center» at the age of 3 with complains to precocious puberty and increased height velocity. Anamnesis revealed that from the day one after birth, the boy suffered from respiratory insufficiency. The malformation of the larynx and the right side of the bronchial tree was diagnosed, which required tracheostomy followed by several stages of reconstruction of the epiglottis and larynx. Also, hypoplasia of the right kidney, hypoplasia of the gallbladder, oligodactyly of both hands and syndactyly of 1 and 2 fingers of the feet were revealed.

Due to intestinal obstruction in neonatal period cystic fibrosis was suspected. The diagnosis was confirmed by positive results of neonatal screening and genetic test (two heterozygous pathogenic variants in CFTR gene (NM 000492.4)).

By physical examination: increased height velocity (height SDS: +2, 47), Tanner genital stage 3 (testicular volume 15 ml), advanced bone age (8,5 years by TW-20). GhRH stimulation test showed pubertal LH peak (25 u/L). MRI revealed a hypothalamic hamartoma.

Given the presence of malformations of larynx and kidneys in combination with oligodactyly and hamartoma, which are not typical for cystic fibrosis, full exome sequencing was conducted. Heterozygous variant c.3454G>T: p.E1152X in GLI3 gene was detected.

Conclusion: the primary criterias for diagnosing PHS are hypothalamic hamartoma, oligodactyly or polydactyly and epiglottis malformation. Imperforate anus, renal malformations, congenital heart disease, growth hormone deficiency or hypopituitarism and genital hypoplasia are also common. Due to the autosomal-dominant type of inheritance, presence of pathogenic variant in GLI3 in combination with one of the diagnostic criteria is sufficient to confirm the PHS. It helps to diagnose patients with partial forms (sub-PHS) of disorder.

P2-218

Evaluation of The Effects of Carob *(Ceratonia Siliqua* L.*)* Fruits on the Puberty of Rats

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Introduction: *Ceratonia siliqua* L. (CS) is from the legumes (Fabaceae) family, and different forms such as carob extract and flour are preferred by parents because it is a natural sweetener and a source of vegetable carbohydrates. CS is rich in polyphenols and flavonoids. When we questioned histories of the cases of early puberty and puberty variants who applied to our clinic, we noticed long-term and regular use in some cases. We planned to experimentally determine the effects of CS use on puberty.

Methods: CS fruits were collected from Mersin-Turkey province in 2021. CS extract was given to rats in a 0.5% carboxymethylcellulose (CMC) solution. Forty-eight Wistar albino rats on a postnatal day 21, were assigned into 2 groups as female(n=24) and male(n=24). Groups were divided into four groups as Control group(CG)-Group1(GP1)-Group2(GP2) and Group3(GP3). CMC (0.5 %) to the CG 150 mg/kg/day to the GP1, 300 mg/kg/day to the GP2, 600 mg/kg/day to the GP3, CS extract was given by oral gavage. The treatments were performed once daily until first sign of puberty. Serum FSH-LH-Estradiol-Testosterone-Leptin and Glutathioneperoxidase (GPx) were studied with rat kits by ELISA method. Testis and ovary tissue were examined histologically.

Results: The median time of preputial separation in male rats were 38th-31st-31st-31st days, CG-G1-G2-G3 sequentially. The day of beginning of puberty was earlier in G1-G2-G3 to CG.($p=0.04$)

The median time of the vaginal opening day in female rats were 39th-31st-34th-31st days in the CG-G1-G2-G3, respectively. ($p> 0.05$)

FSH-LH-Testosterone(male)-Estradiol(female)-Leptin levels of groups are similar ($p>0.05$). GPx levels were higher in the groups given C. Siliqua extract compared to the control group both male($p=0.001$) and female group($p=0.008$).

Testicular and ovarian tissues were concordant with the pubertal period in all groups. As the dose of CS increased; it induced spermatogenesis and spermiogenesis, caused abnormal changes such as ondulation in the basement membrane, capillary dilatation, and increased congestion in male.

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Edema and congestion in the medulla gradually increased with increased dosage and the separation of granulosa cell connections was detected in G2-G3 in female.

Conclusion: We demonstrated that CS caused early puberty and increased spermiogenesis and folliculogenesis. We discovered that antioxidant mechanisms might affect this, but it may cause tissue damage at high doses. Foods consumed due to organic nutrition can become endocrine disruptors when the amount and duration of use increase.

P2-219

Central diabetes insipidus in children – analysis of the different clinical picture

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Background: Central diabetes insipidus (CDI) is a rare disorder in the pediatric population. CDI may be the first symptom of a brain tumor, metastatic lesions, or granulomas. The close follow-up of patients with CDI may early detect pathologic processes, especially intracranial tumors.

Methods: We present four pediatric patients diagnosed with CDI of different etiology.

Results: Patient 1: A 5-year-old girl with 10 months history of polydipsia and polyuria was diagnosed with CDI. At the time of diagnosis, moderately increased β-hCG, thickened pituitary stalk (PS), and heterogeneous signal in the anterior lobe in MRI was observed. After 1 month, multihormonal pituitary insufficiency (PI) developed, and GCT of a suprasellar region secreting β-HCG was diagnosed. Four years after completing oncologic therapy, the girl is disease-free, but panhypopituitarism is still present.

Patient 2: A 13.5-year-old girl with a history of polydipsia and polyuria from early childhood. The multihormonal PI, including CDI, was diagnosed. Based on the patient's overall clinical picture (PI, features of optic nerves hypoplasia, and midline brain malformations like septum pellucidum deviation and thinning of the corpus callosum), septo-optic dysplasia diagnosis was brought up.

Patient 3: A 3 years-old girl with chronic otitis media history, polydipsia, and polyuria. MRI of the pituitary gland and a clinical picture correlated with CDI diagnosis. A few months later, the patient was admitted to diagnose a right parotid gland region lesion. Further diagnostics revealed Langerhans cell histiocytosis.

Patient 4: A 10 years-old boy with a history of polydipsia and polyuria for 3 months. Due to laboratory tests and MRI, CDI was diagnosed. Coexisting GH deficiency was present, although his height was normal. At the age of 11.25 years, the control MRI showed thickening of the PS. After the next 6 months, a pathological change in PS and the anterior lobe was described. Laboratory tests revealed hyperprolactinemia and hypothyroidism. Although β-hCG and AFP in multiple laboratory tests were normal, GCT was suspected.

Conclusions: CDI was the first manifestation of a tumor or granulomas in all presented patients with acquired pathology. Lack of posterior pituitary bright spot was present in all cases and is an inherent part of CDI diagnosis. The coexistence of other pituitary hormones deficiencies suggests a more complicated diagnostically problem. Because in the last case, from the CDI diagnosis to the occurrence of pathological change in PS, 1.5 years have passed, this highlights the need for a high clinical suspicion in patients with CDI.

P2-220

Pituitary macroadenomas in childhood and adolescence. Clinical analysis of 7 cases

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Introduction: Pituitary adenomas (PPAs) are uncommon in childhood and adolescence, accounting for 2-6% of all intracranial neoplasms. Most data are based on case reports and only a few series have been reported. Delayed puberty, short stature, galactorrhea and weight gain are common features at presentation in pediatric patients. Functional tumors constitute a vast majority (90%) of PPAs including corticotropinomas in the first decade followed by relative upsurge of prolactinomas and somatropinomas in the second.

Patients and Methods: A retrospective review of clinical features, hormonal status, pituitary imaging, management and outcome of 7 pediatric patients with pituitary macroadenomas are reported. We include PPAs in patients under 18 years at diagnosis with diameters larger than 10mm by magnetic resonance (MRI).

Results: Six patients were males (85%), age at diagnosis ranged from 8 to 15 (median 14+/-2.8DS). Symptoms that primarily led to medical attention were short stature (case 1,2), acromegaly (case 4,5), secondary amenorrhea (case 2), headache (case 6) and polydipsia/polyuria (case 7). At diagnosis three patients (case 1,3,7) presented signs and/or symptoms of endocrine dysfunction: delayed or arrested puberty (case 1,2,7) with galactorrhea (case 1) and short stature in two (case 1,3). Visual field was reduced in three cases (42%). Suprasellar extension was present in 3 subjects, in particular patient 5 had a giant adenoma. Adenomas were clinically functioning in 6 patients (85%). Cases 1-3 had prolactin levels elevated and were classified as prolactinomas. Cases 4-5 had elevated IGF-1 levels and were classified as somatropinomas. Case 6 had no elevated hormones and no deficiency, classified as non-functioning and case 7 had hormone deficiency with FSH elevated. Prolactinomas responded to treatment with cabergoline, case 4

required transphenoidal surgery and cases 5-7 surgery and radiotherapy. All patients undergoing radiotherapy have secondary panhypopituitarism. In relation to the genetic studies, two patients present a pathogenic mutation of the AIP gene, one of the MEN1, two are pending results and in two it has not been carried out.

Conclusions: Pediatric pituitary macroadenomas are a distinct entity, majority in males, with a predominance of functional tumors leading to detrimental effects on growth and puberty besides neuro-ophthalmological manifestations. It is important to perform genetic studies in patients with macroadenomas appearing under the age of 30 years as genetic and syndromic associations are more frequently seen. Once the genetic alteration has been identified, a better follow-up and treatment can be done together with a family study.

P2-221

Clinical and laboratory assessment of children with central precocious puberty during and after stoppage of treatment with gonadotropin-releasing hormone agonist

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Central precocious puberty (CPP) caused by early maturation of the hypothalamic–pituitary–gonadal axis, resulting in early appearance of secondary sexual characteristics That affects children's normal life and their adulthood's final height. GnRH agonist therapy inhibits stimulating effects of endogenous GnRH by desensitizing hypophyseal gonadotropic cells and thus acceleration in bone maturation and early puberty is suppressed.

So the aim of this longitudinal observational study is to assess the clinical, laboratory and radiological follow up of cases with CPP under treatment of GnRH agonist or after completion of treatment.

Methods: The study was conducted on (40) children (9 males, 31 females) diagnosed as CPP under or completed treatment of GnRH analogue by 3.75 mg monthly injection. All patients were assessed clinically by anthropometric measurements, predicted adult height PAH, Tanner stage of puberty at onset of treatment and after one year follow up. Laboratory (FSH, LH, 17 β-estradiol or testosterone according to sex) and radiological (MRI pituitary with contrast, pelvic US, bone age) were assessed

Results: the higher percentage (~78%) was for females with age of pubertal onset for both sexes (0.5-9 years) which was closely equal to age of onset of treatment, with duration of treatment (1.25-8 years). After one year of treatment, the percentage of females with breast (B) B2 decreased from 25.8% to 22.6%. Cases without menstruation increased from 71% to 100%. Pubic (P) hair P1 increased from 32.5% to 77.4% and P4 decreased from 17.5% to 3.2%. The percentage of male children with P3 decreased from 55.6% to 11.1% while there was no change in penile length or testicular volume. There was statistically significant increase in weight SDS, PAH, BMI, BMI SDS. While Ht SDS was significant decrease in females while there was no significant difference in males. There was statistically significant stoppage of accelerated bone age during follow up after treatment. There was statistically significant decrease of median FSH, LH, testosterone and 17β-Estradiol levels from baseline, 6 months and 12 months of treatment among studied groups. Abnormal MRI findings are detected among 47.5% of the cases at baseline that decreased to 27.5% after 12 months of treatment. There was statistically significant decrease in uterine length, uterine/cervical ratio. Also there was decrease of ovarian enlargement, ovarian follicles & cysts.

Conclusion: cases with CPP under treatment of GnRH agonist showed effective regression of pubertal changes which assessed clinical, laboratory and radiological.

P2-222

A rare case of Langerhans cell histiocytosis of the central nervous system in a child

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Case Presentation: We report the case of Imad, a 2-year- old Algerian boy referred with a 2-month history of polyuria and polydipsia. Diabetes insipidus was diagnosed by confirming hypernatremia with hyperosmolar serum and inappropriately dilute urine.

His polyuria and polydipsia improved dramatically using the oral vasopressin analog.

The child had no clinical signs of underlying disease, serum tumor markers were not detected and a skeletal survey suggested no evidence of bone lesions.

Magnetic resonance imaging revealed the absence of the posterior pituitary bright spot in T1, consistent with the diagnosis of central DI.

A diagnosis of idiopathic central diabetes insipidus was made, and this was well-controlled on oral Desmopressin 120 μg daily

The patient was then lost to follow-up until he presented to the neurosurgical department aged 4 years with vomiting, headaches, and blurred vision. CT Scan at admission demonstrated obstructive hydrocephalus and cerebral edema. He underwent an emergency ventriculostomy drain but at this time no diagnosis of the underlying cause was made. He was then admitted to our department aged 6 years suffering from ataxia, dysarthria, and dysmetria.

On examination, the patient was short: height 104 cm (< - 2.4 SD), with slowing of height velocity during the previous year, and decrease in weight from 27 kg to 20 kg during in the past 6 months. The boy showed abnormal behavior, ataxia, and dysarthria

Anterior pituitary function tests showed complete GH deficiency (<0.1 ng/dl) with no other defect and normal repeat tumor markers

MRI demonstrated several large brain lesions and infiltrative changes in the cerebellum. The differential diagnosis included intracranial infection and Acute disseminated encephalomyelitis (ADAM). Biopsy was not performed.

Given the clinical history of DI, the neurological picture, compatible imaging findings, and the absence of other systemic signs, the diagnosis of a neurodegenerative form of Langerhans Cell Histiocytosis (LCH) was made. Blood CD1a analysis was negative.

The patient received systemic treatment with 12 cycles of intravenous immunoglobulin to prevent disease progression together with GH replacement therapy. Unfortunately, the evolution has not been satisfactory, and his neurological status continues to deteriorate.

Conclusion: We present a case of neurodegenerative LCH which highlights the complex and evolving nature of this rare condition. DI may be the presenting feature of LCH diagnosis and often precedes the eventual diagnosis by several years. Our case illustrates the need for long-term follow-up in children with cranial DI.

P2-223

Double Pituitary gland-pulse syndrome ((DPG)-plus syndrome) and idiopathic infantile hypercalcemia: a combination of rare disorders- Case report and review of literature

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(DPG)-plus syndrome is a rare craniofacial anomaly. It usually occurs in combination with other craniofacial defects. The etiology of this condition remains unknown. Survivors to late childhood have either preserved pituitary function or central precious puberty. Idiopathic infantile hypercalcemia (IHH) is another rare condition that predominantly affects infants. The co-occurrence of (DPG)-plus syndrome and IIH has not been reported previously.

We will also present a case report of pediatric patient with double pituitary gland-plus syndrome who was also found to have Idiopathic infantile hypercalcemia.

We will also present a summary of 37 reported cases of DPG in children, and 7 summary of 7reported cases in adults. The summary tables include their age of detection of DPG, the pattern of pituitary hormone deficiency, the radiological finding of pituitary and associated brain abnormalities and summary of other associated endocrine disorders including precious puberty.

Case Description: We report for the first time in medical literature, a case of a 2 years 4 months old female with (DPG)-plus syndrome and (IIH). (DPG)-plus syndrome was diagnosed in early neonatal period; she has preserved pituitary function up to the time of writing this report. Regarding IIH, she was kept on low Ca diet until the age of 2 years when hypercalcemia resolved spontaneously.

Conclusion: (DPG)-plus syndrome is a recently described entity in medical literature (1) (2). Both (DPG)-plus syndrome and IHH are rare conditions. The potential cause of the coexistence of these conditions in our patient is not fully understood. IHH can cause hypercalciuria and nephrocalcinosis if it remains unrecognized and untreated. We suggest that infants with DPG-plus syndrome should be routinely screened for IHH.

Apart from pubertal disturbances, other abnormalities involving the hypothalamic-pituitary axis have not been previously described in pediatric individuals with double pituitary gland (DPG), including those with (DPG)-plus syndrome who survives to late childhood.

P2-224

Case report of familial X-linked hypopituitarism, without confirmed genetic mutation

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Introduction: Hypopituitarism is the partial or complete insufficiency of a single or multiple pituitary hormones. The clinical manifestation of hypopituitarism varies depending on the number and severity of hormone deficiencies. Familial cases are rare, compared to the sporadic ones. Its estimated incidence is between 1:4000-1:10000 live births.

Case Report: We report the clinical case of familial hypopituitarism in a family where are six children-three male and three female. All three males have Hypopituitarism, and all three females are healthy. The onset of clinical signs of hypopituitarism in all three males started in an early age. The manifestation of Hypopituitarism initiated with Diabetes Insipidus. Afterwards the elder and the middle males were diagnosed with Secondary hypothyroidism, Secondary Adrenal insufficiency, then Growth hormone deficiency at the age of 4-5. The youngest has only Diabetes Insipidus. It's noteworthy that in all 3 boys MRI showed Hypoplasia of adenohypophysis, agenesis and posterior dislocation of the neurohypophysis. According to the performed studies of genetic examination data none of the studied mutations connected to hypopituitarism such as PROP1, SOX3, POU1F1, HESX1, IGSF1, LHX3, LHX4, PAX6, ARNT2, GH1, GHRH, GHRHR, GHSR, GLI2, SHH have not been found. Patients are receiving hormone replacement therapy (elder male-Hydrocortisone, Desmopressin, Levothyroxine, Testosterone, GH, middle male-Hydrocortisone during stress, infectious diseases, Desmopressin, Levothyroxine, Testosterone, GH, youngest male-Desmopressin). Since the maternal uncle, who refused to be examined, is short in height, infertile and the females are healthy, the growth proceeds normally, the elder ones menstruate, therefore it can be assumed this familial case is X-linked. As it was mentioned above, all three males have different levels of expressed clinical hypopituitarism, mostly expressed in elder male. Its noteworthy to know that the elder male's biological father differs from the other ones. Therefore it is required to perform a genetic examination of Y-chromosome.

Conclusion: The studies have shown that in the majority of cases of familial hypopituitarism mutation is not identified. The males are required to perform further examinations to identify the genetic cause. We assume in the case of X-linked hypopituitarism the clinical manifestation may be possibly to some extent depend on Y-chromosome. The detection of a genetic mutation will help preventing 3 healthy female mutation carriers from passing the mutation to the next generation.

P2-225

Clinical Characters and Prognosis of a Case with Bifocal Germ Cell Tumors in Children

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Background: In children and adolescents suffered form primary intracranial germ cell tumors, bifocal GCTs are rare and were reported a bad prognosis. In this study, we report a case and summarize the clinical characteristics and prognosis.

Methods: A boy suffered form bifocal GCTs (Basal ganglia and pineal region) was diagnosed in our hospital and accepted chemo therapy+radiotherapy, and was followed up.

Results: 1. A 8 year and 2 month old boy came to our hospital because of enlargement of the penis for 5 months with pubic hair-growth. Facial acne, beard, depening of the voice, gynecomastia and enlarged penis(9cm*3cm) were found. Bilaterallytesticular volume :8mL. Tanner stage of pubic hair: stage 3. No headache, nausea or vomiting, and no abnormal signs ofnervous system.

2. Laboratory data: Basal FSH and LH levels decreased, with the elevated serum testosterone levels: 9.35ng/ml. And the gonadotrophin-releasing hormone agonist (GnRHa) stimulation test showed GnRH independent precocious puberty. Serum β-human chorionic gonadotropin(β-hCG) increased (22.3mIU/ml), along with elevated cerebrospinal fluid (CSF) β-hCG (21.31mIU/ml), but both serum and CSFlevels of the AFP were normal. MRI scans revealed bifocal germ cell tumors located in the pineal gland and basal ganglia. No other extracranial metastases were found. When compared to other primary solitary intracranial GCTs cases (published before by our team), no differences of the serum and CSF β-hCG levels, serum testosterone levels and clinical manifestations were found.

3. The boy accepted regular chemotherapy and radiotherapy. After one course of chemotherapy, the serum levels of β-hCG, as well as the CSF β-hCG levels decreased significantly. Serum testosterone levels returned normal.

Conclusion: Peripheral precorcious puberty is usually the first or one of the typical symptoms in boys with hCG-secreting GCTs. There are no differences in clinical manifestations between solitary and bifocal primary intracranial tumors. Patients with basal ganglia lesions do not necessarily have neurological symptoms. The combination of the detection serum hCG and CSF hCG levels may be significant for early diagnosis, the determination of the tumor locations.

P2-226

Polyuria-polydipsia- first sign of a rare hematological disease

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Introduction: Central diabetes insipidus (CDI) is a rare disorder in children. The etiology of CDI in childhood is heterogeneous: tumors or surgery in the hypothalamic-pituitary region, head trauma, vascular and inflammatory diseases. Neuroimaging plays an important role in the differential diagnosis of CDI in children and adolescents. The MRI may detect brain malformations, but also is the gold standard when evaluating the sellar-suprasellar region in CDI.

Case Presentation: We report a 12-year old girl who presented in Endocrinology Department for progressive weight gain in the last years and oligomenorrhea. On endocrine examination she had obesity, goiter and poliuro-polidipsic syndrome (ingestion of 10 liters liquids /24h and diuresis of 10 liters/24h). The laboratory assessment revealed low urine gravity (1004 g/24h, normal range 1005-1030 g/24h), autoimmune thyroiditis and normal function of the anterior pituitary. The water deprivation-vasopressin test confirmed CDI. The diagnosis was further supported by serum copeptin measurement (<1.2 pmol/l, reference range 1.5-15.3) and desmopressin treatment was initiated. Imaging examination showed a pituitary microadenoma (3/3.5/3 mm) and thickening of the pituitary stalk (3.4/3.8 mm). Thus, infiltrative diseases were considered in the differential diagnosis. Bone X-ray showed multiple lytic bone lesions in the left femoral bone and skull. Langerhans cell histiocytosis (LCH) was confirmed by pathology of the biopsy specimen from the skull lesion. Systemic therapy containing steroids and vinblastine induced remission.

After 6 months, she was reevaluated in our Pediatric Endocrinology Department. Hormonal measurements showed secondary adrenal insufficiency (8 am serum cortisol<1 mcg/d, ACTH 1.65 pg/ml; normal range 4.2-22 mcg/dl, 7.2-63.3 pg/ml), side-effect of the systemic glucocorticoids she had received for LCH. At this time, pituitary MRI identified a regression of the pituitary stalk thickening (2.2/2.6 mm), but an increase in the size of the pituitary microadenoma (6/5/4.5 mm). Nevertheless, diabetes insipidus persisted with normal secretion of the anterior pituitary hormones.

Conclusion: Isolated CDI can be the first manifestation of LCH. LCH is a rare disease in children, with variable clinical spectrum including localized and disseminated forms mostly occurring in children. Pituitary insufficiency may occur in the context

of the disease or secondary to systemic treatment. The most common type of hormone deficiency in children with LCH is growth hormone (GH) deficiency, followed by ACTH deficiency. For this reason an adequate follow-up to monitor for disease progression, relapse, and sequelae is recommended.

Keywords: Langerhans cell histiocytosis, children, diabetes insipidus.

P2-227

Growth Hormone Deficiency in a Boy with Duplication 5Q35.2q35.3

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Introduction: The genomic disorders caused by rearrangements in region 5q35, including the *NSD1* (nuclear receptor SET domain containing protein-1) gene have various phenotypes depending on presence of deletions, duplications or inversions. Patients carrying microduplication have microcephaly, short stature, and mild to moderate intellectual delay or learning disability.

Patients and Methods: A six-year-old boy was born small for gestational age (SGA) with birth weight (BW) (-1.1 SDS) and birth length (BL) (-2.83 SDS), in the 31st gestational week (GW). He had microcephaly (- 3.4 SDS), short palpebral fissures, strabismus, myopia, a long nose with long nasal tip and a thin upper lip. He had speech, motor, and intellectual delay with learning disabilities. His younger brother (4.5-year-old) was also born preterm in 32nd GW with normal birth parameters. His development was normal. Both boys had short stature (-3.5 SDS) and (-3.0 SDS). Clinical examination, imaging studies, hormonal and molecular analyses were performed.

Results: The older brother had hypothyroidism (TSH=11.9 uIU/ml and T4=1.13 ng/ml) with Hashimoto thyroiditis (anti TPO antibodies >1000 IU/ml). After few weeks of levothyroxine replacement therapy, he became euthyroid. His IGF1 and IGFBP3 values and growth hormone (GH) concentrations in 2 stimulated tests were within reference range. The performed electroencephalogram (EEG) and brain MRI were uneventful. The younger boy had normal thyroid hormone concentrations, while his IGF1 (48.1 ng/ml) and IGF BP3 (2.01 μg/ml) serum concentrations were low, as well as two tests of pituitary reserve (peak 4.05 ng/ml). MRI of hypophysis was uneventful. The multiplex ligation probe amplification analysis detected duplication in 5q35.2q35.3 region containing the *NSD1* gene, with minimal length of two Mb in both brothers, inherited from their mother. The growth hormone treatment started and increased significantly the growth velocity.

Conclusions: Herein we present a boy with a rare genetic disease associated with growth hormone deficiency. His brother with the same genetic variant has hypothyroidism and Hashimoto thyroiditis. Molecular analysis confirmed maternal origin of duplication in the critical region containing the *NSD1* gene.

Keywords: microduplication, hypothyroidism, Hashimoto thyroiditis, growth hormone deficiency.

P2-228

Infection with SARS-CoV-2 may alter the half-life of desmopressin (DDAVP) in children with central diabetes insipidus

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Background: Central diabetes insipidus (CDI) is characterised by a central deficiency of arginine vasopressin (AVP) with polyuria and polydipsia. The etiology is heterogeneous. The treatment of choice is the oral or nasal application of DDAVP (synthetic analogue of AVP). CDI in the context of coronavirus disease 2019 (COVID19) has been reported in an individual case.

Case Report: We present a 9-year old male with CDI of uncertain etiology. The reason for presentation was polydipsia (5 liters/day) and polyuria/ nocturia. MRI showed a nodular thickening of the pituitary stalk and lack of T1w hyperintensity of the neurohypophysis. As expected, the level of CT-proAVP (copeptin) in serum was very low (< 2.7 pmol/litre) despite increased osmolality in serum of 306 mosm/kg. Sodium in serum was high with a maximum of 151 mmol/l. Laboratory analysis showed no involvement of other pituitary axis. Therapy was initiated with DDAVP at 1.2 μg in the morning and 0.6 μg in the evening (nasally). Treatment showed normalisation of polyuria, polydipsia, serum sodium levels and drinking quantity (2 liters/ day). The most recent dose was 6 μg in the morning and 1.8 μg in the evening. One year later the patient complained of sore throat. The pain was gone the following morning. A PCR test was positive for SARS-CoV-2. Surprisingly, with the onset of the sore throat, the half-life of the usual dosage of DDAVP therapy was significantly prolonged. Thus, the boy received the usual 1.8 μg of desmopressin in the evening (day of onset of symptoms). The effect lasted for 17 hours. Thus, the duration of action was prolonged by approximately 6 hours. The morning dose was skipped. The evening dose of 1.8 μg was then administered again at 1 p.m. at noon. This lasted for 18 hours. Thus, the duration of action was prolonged again by approximately 5 hours. After three days, the regular dosage and timing could be reintroduced. Furthermore, there was no adjustment of the dosage and no change of the manufacturer, pharmacy, application or storage of the preparation in the temporal context.

Conclusion: In the context of a clinically mild infection with SARS-CoV-2, the half-life of DDAVP was significantly prolonged with the onset of clinical symptoms. Our case report is of clinical relevance, as even mild COVID19 may lead to a change in DDAVP pharmacokinetics. This knowledge may reduce the risk of dilutional hyponatremia.

P2-229

12 years follow-up of GH/PRL secreting pituitary macroadenoma in a child with McCune Albright syndrome

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Background: McCune-Albright Syndrome (MAS) includes fibrous dysplasia (FD), cafe-au-lait spots and gonadotropin-independent precocious puberty (PP). Adenohypophyseal hyperfunction syndromes is uncommon but may be potentially severe complication.

Objective: To report a girl who has been confirmed McCune-Albright syndrome and has been found pituitary adenoma during follow-up.

Methods: A girl with typical type of MAS had gradually progressive manifestations due to GH/PRL secreting pituitary macroadenoma during follow-up. The clinical characteristics and managements were reviewed.

Results: The first visiting age was 4.5 years of age, with a 3 years history of recurrent breast development and virginal bleeding. She was diagnosed tipical type of McCune-Albright syndrome according to fibrous dysplasia (FD), cafe-au-lait spots and gonadotropin-independent precocious puberty accompany with recurrent ovarian cyst. At the age of first visiting, serum PRL has been found increased but no lactation, and GH as well as IGF-1 were within normal range. Letrozole was prescribed and followed by remission of the vaginal bleeding and breast development. However, she presented progressive facial and extremities asymmetric, and lactation at the age of 14 years. She also had bone fracture for twice. Her height was 173.2cm, Body weight 61 kg. Fasting GH level 14.77ug/L, but Serum IGF-1:621ng/ml(566.9±168.9ng/ml). GH can not be suppressed by oral glucose test. No visual impairment. Thyroid function and adrenal function were normal. Macro-adenoma was confirmed by MRI scan. She accepted Bromocriptine combined with Octreotide therapy, but the PRL and GH levels remained elevated, and thus the transsphenoidal pituitary tumor resection was performed. Histological result showed that the adenoma was pituitary mammosomatotroph tumor. However, the adinoma can just be partial removed because of difficulties of the operation, due to the FD in sphenoid bone. GH levels remained abnormal after operation and octreotide therapy still needed.

Conclusion: GH/PRL secreting pituitary macroadenoma can be found in children with MAS, and can lead to severe complications. The history of the pituitary adenomas may be long and the initial manifestations may be occult. Thus long term follow up is recommended. In children with MAS and functional adenomas, Bromocriptine and Octreotide may be effective, but in some cases, other therapy including transsphenoidal pituitary tumor resection may be needed.

P2-230

Pituitary stalk interruption syndrome presenting with catch up of growth

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Introduction: Pituitary stalk interruption syndrome is a rare congenital abnormality of the pituitary that is responsible for anterior pituitary deficiency. It is characterized by a classic triad of interrupted pituitary stalk, absent or ectopic posterior pituitary, and anterior pituitary hypoplasia or aplasia. Clinical presentation varies according to age. Early diagnosis and treatment of this rare disease can prevent permanent short statue of the patient. We report the first case of pituitary stalk interruption syndrome with unusual growth.

Case Presentation: A 14 months old young boy presented with with micropenis and cryptorchidic testis: his height was 76 cm -1DS and weight 10 kg. Father's height 175cm and mother's height 164 cm. His lab investigations showed that his thyroid stimulating hormone (TSH) was 3.46uIU/mL (0.25 to 4),his free thyroid hormone level FT4 was 9.24 pg/dL (7 to 18), and his baseline cortisol was 645 nmol/L (123to 626), his insulin like growth factor IGF-1 was 13.01ng/mL (50 to 143), his testosterone level was 0.16 nmol/L, his follicle stimulating hormone FSH was 0.84uIU/mL (0.0 to 10.0), and his leutinizing hormone LH was 0.42uIU/mL (1.2 to 7.8). After HCG test the right testis descends in the scrotum and after 01 year of fellow the left testis was in scrotum. With this presentation pituitary magnetic resonance imaging was performed The results consists in pituitary stalk interruption syndrome. After one year of follow-up a stagnation of growth was observe the height was – 3 DS compared to parental target height, growth hormone therapy was initiated at the age of 24 months.

After 05 years of follow with GH therapy the height of the 7 years boy was +2 DS compared to parental target height. The IGF1 135 ng/ml (49-283), the bone age was 6 years. We stopped GH therapy and a second pituitary MRI was performed with the same results PSIS. After 1 year without GH treatment, the height was still at + 2 SD and the IGF 1 was 62.80 ng/ml (52-297). An insulin test is performed results is in progress.

Conclusions: Despite the fact that this is a rare disorder, we describe an exceptional presentation of congenital PSIS with catch up of growth in young boy who presented with short stature at diagnosis and was found to have pituitary stalk interruption syndrome.

P2-231

Epidemiological characteristics, treatment and its outcomes in children presenting with Craniopharyngioma at a tertiary care center

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Introduction: Craniopharyngiomas are benign midline intracranial tumors commonly seen in pediatric population. They constitute approximately 10% of primary brain tumors in children which can cause considerable morbidity and mortality due to local aggressiveness of tumor itself or its treatment effecting hypothalamo-pituitary axis, visual defects, and effects of raised intracranial pressure The aim of this study is to report the characteristics of epidemiological features of pediatric patients with craniopharyngioma from our part of the world, treatment modality used in managing and to highlight the outcomes.

Keywords: Craniopharyngioma, hypothyroidism, Diabetes insipidus, transcranial, trans sphenoidal

Methodology: A Retrospective review of the records of children aged 1-18 years diagnosed with craniopharyngioma presenting between 2010 to 2020 was done

Results: Out of total 44 files reviewed, 52% were male and 48% were female, the mean age of presentation was 11.2 years, the most common presenting features were headache, visual defects and vomiting (80%,75%,50%). In 38 children (86%) tumor was removed through transcranial approach, while in 6 (14%) transsphenoidal technique was used. In 11 (25%) omaya reservoir was placed for interferon therapy out of which 5 patients underwent for debulking surgery due to disease progression. Overall 12(27%) patients were retreated for relapse. Only two patient received radiotherapy. There was a high incidence of postoperative thyrotrophin deficiency 38(86%), diabetes insipidus 36(81%) followed by adrenocorticotropin deficiency, growth hormone, and gonadotrophin deficiency 68%,45%,45% respectively. Majority of patients developed post-operative panhypopituitarism.

Conclusion: We found that the incidence of craniopharyngioma is more common in adolescent age group with male predominance. Transcranial approach is the modality of choice for majority of surgeons. The most frequent endocrine complication observed in our was hypothyroidism followed by diabetes insipidus.

P2-232

Clinical and para clinical features, effect of triptoreline 11.25 mg every 3 months in patients with central precocious puberty after 6 months of treatment

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Background: Precocious puberty is defined by the development of secondary sexual characteristics before the age of 8 in girls and before the age of 9 in boys. if not diagnosed and treated at an early stage, precocious puberty can compromise final adult height and trigger psychological disturbances. Gonadotropin- releasing hormone analogs (GnRHa) contributes to achievement of target final height by reducing the acceleration of bone maturation.

Objectives: To analyze clinical and para clinical features in patients with precocious puberty, effect of triptoreline in improvement of secondary sexual characteristics and predicted adult height (PAH) after 6 months of treatment.

Subjects and Method: Case-series study included 49 patients with precocious puberty at Vinmec Central Park International Hospital from June 2019 to March 2020.

Results: After 6 months of treatment, secondary sexual characteristics reduced or ceased, acceleration of bone age decreased, sexual hormonal levels fell below puberty range. In addition, PAH improve significantly in female group with initiation of treatment before the age of 8.

Conclusions: Triptoreline decreases secondary sexual characteristics such as menarche, breast development, pubic hair, body odor and reduces the concentration of hormons (FSH, LH, Estradiol, Testosterone). In addition, Triptoreline increased PAH resulting in improving final adult height.

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Central precocious puberty in a girl with vasculitis-related moyamoya syndrome

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Object: To raise the awareness of clinical manifestations about vasculitis-related moyamoya syndrome by summarizing the clinical characteristics of a girl with central precocious puberty, vasculitis-related moyamoya syndrome and reviewing the literature.

Method: We carried on the review analysis to the patient with central precocious puberty, vasculitis-related moyamoya syndrome and reviewed the literature.

Result: The bilateral breast development was the primary symptom in this patient at the age of 1 year and 6 months, and she was diagnosed as central precocious puberty. At the age of 3 years and 1-month, pituitary MRI, MRA, MRS, DWI and SWI were performed in our hospital to diagnose "vasculitis associated moyamoya syndrome"; Due to the poor control of bone age under the treatment of GnRHa, 17 OHP was found to be high, and the NCCAH was considered by adrenocorticotropic hormone provocation test.

Conclusion: We reported a rare case of CPP with V-MMS for the first time in China. It is suggested that V-MMS can coexist with CPP and may be the etiology of the latter.

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Management of precocious puberty in girls with McCune–Albright syndrome

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McCune-Albright syndrome is a rare, sporadic disorder defined by the triad of café-au-lait spots, fibrous bone dysplasia, and endocrinopathy. The diagnosis is often made on bone or endocrine involvement, but must be suspected on the particular morphology of café-au-lait spots. We report a case of McCune-Albright syndrome diagnosed on these cutaneous signs and precocious puberty.

This is a 4.5-year-old girl referred by a gynecologist for a pediatric endocrinology opinion. The patient had consulted for abdominal pain with an ultrasound image of a right latero-uterine cyst measuring 48/50mm in diameter, for which the patient was scheduled for surgical removal. On clinical examination, his weight was 22 kg, height 105 cm (-0.2 SD). she had two giant café-au-lait spots on her face and back associated with a picture of precocious puberty with M3 P1 A1, abundant leucorrhea and marked estrogenization of the external genitalia, suggesting McCune Albright syndrome, age bone was at 7 years and a half, the examination of the skeleton objectified a slight fibrous dysplasia, the LH / RH test was negative, the estradiol very high and FSH, LH collapsed. The thyroid ultrasound found 3 small nodules of subcentimeter size, with a thyroid assessment and normal renal function. The patient was placed on peripheral anti-estrogen Letrozole at 2.5 mg/day continuously, the response was spectacular after 4 months with a reduction in the volume of the cyst to 22/20 mm, and an almost total disappearance of the latter. At 6 months of treatment, on the other hand, the number of thyroid nodules increased from 5 to 3 months to 8 to 6 months of treatment, the thyroid balance remained normal.

McCune-Albright is a rare cause of peripheral puberty, easy to diagnose due to the association of the triad of precocious puberty, bone fibrous dysplasia and café au lait spot, the treatment is generally disappointing, unlike our patient who presented an excellent response but the stature prognosis is always at stake and does not constitute an indication for treatment with growth hormone.

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Precocious puberty revealing a McCune Albright syndrome: About a case

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Introduction: McCune Albright syndrome (MAS) is classically defined by the clinical triad: fibrous dysplasia of bone, café-au-lait skin pigmentation and endocrinopathies: The most frequent is precocious puberty. Linked to a somatic mutation of the α subunit of the Gs protein, this syndrome leads to a constitutive activation of adenylate cyclase, to the excessive production of AMPc

Case Presentation: Here we report a case of a 3-year-old girl, consulting for vaginal bleeding since the age of 03 months with breast budding at 18 months. On physical examination the patient weighed 18.2 kg (+3.05 SD) for a height of 108 cm (+4.24 SD), abnormal genital bleeding with Tanner stage III for breast development, Tanner stage I for pubic hair, and also for axillary hair, her external genitalia and clitoris were not appropriate for her age. There was café-au-lait skin pigmentation with irregular contours on the left leg and the external genitalia. The examination did not find any signs of hyperandrogenism, nor any deformities or bone pain. Hormonal analysis revealed an increased serum estradiol (E2) levels 275.9 pmol/L (< 70) and normally low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels as a prepubertal girl. FSH: 0.10 ui/l (4) LH: 0.10 ui/l (1.4). Pelvic ultrasound showed a 39 mm right ovarian cyst with a prepubescent uterus. At that time, her bone age was 10 years old.

- Brain magnetic resonance imaging thickening of the entire frontal and occipital cranial vault as well as the sphenoidal body and the clivus and the parasellar Evoking lesions of fibrous dysplasia + thickening of the roof of the cavum

Treatment with anti-aromatase at a dose of 2.5 mg/day allowing the disappearance of metrorrhagia, improvement of hyperestrogenia with good hepatic tolerance with a follow-up of 04 years.

Conclusion: The diagnosis of MAS is not always straightforward, particularly in the absence of the classic triad. We should think about it especially before any precocious puberty in order to start an effective therapy allowing a good clinical improvement.

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Challenges in the era of COVID-19: Starting from the clinical examination

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Introduction: Physical examination remains the cornerstone of medical practice. However, its importance has been underestimated during COVID-19 pandemic because of concerns related to

exposure risk and use of personal protective equipment. Solitary median maxillary central incisor (SMMCI) may be an isolated clinical trait or associated with other anomalies and endocrine pathologies including hypopituitarism, hypothyroidism, isolated growth hormone (GH) deficiency, precocious or delayed puberty, short stature without GH abnormalities.

Aim: The aim of this case presentation is to underline the significance of clinical examination, as in SMMCI, an important clinical finding that may lead to an early diagnosis of hidden endocrine abnormalities.

Material and Method: A $7^{8/12}$-year-old girl was hospitalised because of an episode of acute headache with walking instability. Her past medical history was uneventful except for premature adrenarche since the age of $5^{6/12}$ years. A paediatric endocrinologist had estimated her 2 years before, at the onset of the COVID-19 pandemic and ordered hormone assays and a Synachten test. Because of her past medical history and the positive family history for type 2 diabetes, she underwent a detailed hormone laboratory evaluation including oral glucose tolerance test (OGTT) and LHRH test. Furthermore, because of the borderline response in 17-hydroxyprogesterone following ACTH stimulation, CYP21A2 gene analysis was performed.

Results: Her clinical examination revealed excessive body mass index (18.9 kg/m^2, 90th percentile) and B I and PH II-III Tanner stage with axillary hair and odor. OGTT revealed insulin resistance (HOMA-IR 3.38). Based on the increased LH response in GnRH test (LH at 30 min 3.8 IU/L) in association to the increased ovarian volume (3.25 and 5.3 ml with 6 and 9 follicles respectively), she was diagnosed with central precocious puberty (CPP). At the time of final clinical and laboratory overview by the Chief of the Unit, the girl was asked to put off her mask, unraveling a SMMCI, a finding not having been identified and correctly evaluated until then. Consequently, a pituitary gland magnetic resonance imaging (MRI) was mandatory, revealing ectopic posterior pituitary at the pituitary stalk with hypoplasia of anterior pituitary, possibly implicated in the CPP aetiology. The patient was prescribed triptorelin and is on regular endocrine follow-up.

Conclusion: SMMCI, so easily diagnosed, may be the cardinal clinical feature guiding further physical, endocrine laboratory and imaging investigation and leading to early diagnosis of endocrine pathology. Clinical examination remains the key of paediatric endocrine evaluation, overcoming any potential risk in the era of COVID-19.

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Gigantism and Central Precocious Puberty in Egyptian Female Pediatric Patient due to benign Pituitary gland Hyperplasia

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Pituitary hyperplasia (PH) is absolute increase in the number of one or more adenohypophyseal cell subtypes, manifesting radiologically as pituitary enlargement beyond what is considered normal. Diagnosis of PH remains predominantly clinical, hormonal, and radiological. Case presentation: we present a clinical course, diagnosis, and management of a case of pituitary gland hyperplasia in 10 years old Egyptian girl, one of twins who sought medical advice when the mother noticed rapid progressive increase in body weight, advancement of height and pubertal advancement compared to her twin sister. Upon examination: her height was on +1.21 SDS, weight on +2.93 SDS, BMI was on +3.29 SDS. She had Tanner 3 breast, Tanner 2 pubic hair, no axillary hair, no menarche. She had enlargement of her extremities (Hands and Feet), enlarged tongue affecting articulation. Bone age was 2 years advanced. Laboratory investigation revealed non- suppressible growth hormone level by performing growth hormone suppression test. High level of IGF-1. GNRH stimulation test revealed LH levels that coincides with central precocious puberty. Dynamic MRI with contrast of pituitary gland revealed bulky pituitary gland with no sizable focal lesion. Diagnosis of pituitary gland hyperplasia manifesting with growth hormone excess (Gigantism) and central precocious puberty was made based upon clinical and laboratory criteria. Growth hormone antagonist (Octreotide) and Gonadotropin releasing hormone analogue (GNRH) were initiated to slow down growth, pubertal progression and advancement respectively. Growth hormone level and IGF-1 returned back to normal levels 3 months after initiation of therapy. Conclusion: PH should be managed by experienced multidisciplinary team. Surgery should be avoided in PH as it rarely progresses. Close follow up is recommended for early detection of any pituitary microadenoma that may develop.

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Rare causes of hypopituitarism in children

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Background: Septo-optic dysplasia (SOD) is characterized by two or more features of the triad: optic nerve (ON) hypoplasia, middle brain defects and pituitaty deficiencies. Pituitary Stalk Interruption Syndrome (PSIS) presents as a lack of a visible pituitary stalk and/ or no eutopic posterior lobe hypersignal in the shallow sella turcica. Both conditions usually result in hypopituitarism. The diagnosis is based on clinical signs and MRI findings; only small number of patients have molecular diagnosis. We describe a patient with SOD and PSIS symptoms' co-existence.

Presentation: The girl was born at term from non-consanguineous parents. Prolonged neonatal jaundice; congenital nistagmus were seen. Neonatal brain US described the ON hypoplasia and septum pellucidum cyst. The early history was remarkable for hypoglycemia, febrile seazures with anticonvulsants taking. The patient was followed by ophthalmologist, neurologist. Her first visit to paediatric endocrinologist was at the age of 6 5/12 for weight excess, tall stature, the history of hypoglycemia. Her height and weight were more +3SDS. An elevated TSH, low FT4; cortisol and ACTH in low reference were detected. The hypopituitarism was suspected; the family was called urgently for treatment. However, the patient escaped from the follow-up and arrived to our Center after 4 years. At the age 10 5/12 she was tall, obese,

taking 37,5 mcg of L-T4 (previous dose of 50 mcg was reduced due to low TSH; from mother's note, the child became more active after that). The girl assisted specialized school for children with eyes disabilities. The lab demonstrated low cortisol and ACTH; with hydrocortisone prescription and L-T4 dose adjustment. Pituitary MRI found small anterior pituitary, thin pituitary stalk, the absence of septum pellucidum, ON and chiasma hypoplasia; the hyperintensive focus in the third ventricle which may present an ectopic posterior pituitary. After she reached 10y., her GV decreased, low IGF-1 level was found. She entered spontaneous puberty but sex steroid replacement was needed after age of 15. At 15 6/12 due to excessive weight gain, muscle weakness GH in metabolic dose was given with patient improvement. Currently she is under HRT in transition to adult endocrinologist in our Center; no adrenal crises known.

Conclusion: Our case demonstrated late diagnosis of hypopituitarism in a child with simultaneous features of SOD and PSIS. Making diagnosis early in life should be a great challenge as patients with hypopituitarism require life-long follow-up due to evolution of pituitary deficiencies and risk of endocrine emergencies.

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Interest of LHRH test in the exploration of precocious puberty

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Introduction: We refer to precocious puberty when signs of puberty appear early: before the age of 8 in females and before the age of 9.5 in males. The objective of our study is to evaluate the interest of the LHRH test in the exploration of early puberty.

Materials and Methods: A retrospective descriptive study including 19 cases who presented with signs of precocious puberty. A clinical and hormonal evaluation was performed in all cases. The statistical analysis was performed by the software SPSS version 21.

Results: This study included 19 children; 17 girls and 2 boys, sex ratio M/F :0.11. The average age of the first consultation was 5 years and 8 months (1-9 years). The reasons for consultation were appearance of pilosity in 21.1% of cases, mammary development in 47.4%, appearance of pilosity associated to mammary development in 21.1% and occurrence of menarche in 10.5%. The LHRH test was performed in all patients. The results revealed a central origin in 31.6% of the patients with a peak LH between 12 and 71 IU/L and a FSH/LH ratio between 1.23 and 3.77. In 31.6% of patients, the diagnosis of peripheral precocious puberty was retained, the peak LH after LHRH test was between 0.25 and 4.2 IU/L with a FSH/LH ratio between 0.12 and 1.27 and a median peak FSH level at 5.8±3.7 IU/l. A dissociated precocious puberty was found in 36.8% of the girls with a mean age of 4 years (1-7 years), the LHRH test showed a peak of LH between 0.08 and 7.5 IU/L with a FSH/LH ratio at 0.23 on average and a median peak FSH level at 20.6±9.4IU/l.

Discussion and Conclusion: Precocious puberty can be the manifestation of a significant pathological illness, either central or peripheral. Premature thelarche can be regarded as variant of regular puberty in girls, which is why LHRH testing is used to distinguish between a true precocious puberty and its variants.

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Report of a case of central precocious puberty in girls associated with pilocytic astrocytoma

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Central precocious puberty is more common in girls than boys and over 90% of girls central precocious puberty is idiopathic

Pathological causes of central precocious puberty in very young girls include tumors, hydrocephalus, CNS infections, or post-traumatic events

Astrocytoma is one of the very rare causes.

Pilocytic astrocytomas are usually benign and may be diagnosed before the onset of precocious puberty due to neurological symptoms or be diagnosed for the first time in children presenting for pubertal symptoms.

We report a case of a 7-year-old girl admitted to the hospital with breast enlargement (Tanner B3-4), with vaginal discharge

Five years ago, the patient had weakness in the left side of the body with brain MRI showing a large tumor in the pituitary fossa and right hemisphere.

The medical team concluded that she had a juvenile pilocytic astrocytoma (JPA) tumor based on biopsy collected from the surgery.

Following the surgery, the medical team continued to have MRI scans in the following 3 months and decided that she had to go through a chemotherapy (carboplastine & vincristine) for another 1 year due to the fact that the tumor exhibited pattern to grow back

After the baby was treated for astrocytoma, she was quite stable and recovered well, & then she showed symptoms of precocious puberty.

The cause-and-effect relationship between this tumor and her precocious puberty not much has been described in the literature.

Current endocrine tests are qualified to diagnose central precocious puberty with LH: 4.63mUI/ml, FSH: 5.59mUI/ml, Estradiol: 48.8pg/ml, bone age is 9 years old.

The patient was treated with triptorelin 11.25 mg every 3 months.

After 12 months of treatment, clinical and laboratory signs of precocious puberty were completely suppressed.

Clinical presentation of stable neurologic deficit with left hemiparesis.

To our knowledge, this is the first description in Vietnam of a case of central precocious puberty in a juvenile pilocytic astrocytoma that was previously treated with combined partial resection and chemotherapy.

Among them, pilocytic astrocytoma is one of the very rare causes with a good prognosis.

Timely detection and treatment can help prevent symptoms of precocious puberty.

In this case, we found that the combination of partial tumor resection with chemotherapy has a relatively good prognosis, especially according to the literature most of these tumors are benign.

Treatment of precocious puberty in this child with triptoreline was effective and did not increase the size of the tumor or other neurological symptoms.

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Primary polydipsia in a male adolescent

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Introduction: Primary polydipsia is rare during adolescence and is known to be associated with psychiatric disorders or psychological stress. Differential diagnosis includes endocrine, neurologic, renal, and iatrogenic causes.

Case Report: A 14-year-old male presented with polydipsia and polyuria that persisted for 6 years. His fluid intake was about 9 liters a day and he woke up for voiding once or two times every night. He had no fever, headache, abdominal pain, weight loss, vomiting, or any other neurological deficit. His past medical history was unremarkable. Also, there was no family history related to endocrine, renal, or psychiatric diseases. His physical and intellectual development was normal. On physical examination, his height was -0.47 standard deviation score (SDS), weight -0.73 SDS, and body mass index -0.72 SDS. Neurologic examination revealed no abnormality. Laboratory data showed normal concentrations of serum sodium, potassium, creatinine, and glucose. Serum and urine osmolality was 281 and 91 mOsm/kg, respectively. Hormonal studies revealed normal thyroid-stimulating hormone, thyroxine, cortisol, and adrenocorticotropic hormone. A 12-hour water deprivation test showed an increase in urine osmolality up to 778 mOsm/kg, with no changes in serum sodium, osmolality, and antidiuretic hormone. He was diagnosed with primary polydipsia and recommended to restrict fluid intake. His polydipsia and polyuria disappeared completely within 2 weeks after fluid restriction.

Conclusion: This case report suggests that primary polydipsia might be observed in adolescents without psychological risk factors. Sufficient awareness of clinical features and biochemical characteristics including a water deprivation test is important to identify this disorder.

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McCune-Albright Syndrome: knowing how to think about it

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Introduction: McCune-Albright syndrome (MAS) is characterized by fibrous dysplasia (FD), cafe-au-lait skin spots and precocious puberty (PP). SAM is a rare disease and its prevalence is estimated between 1/100,000 and 1/1,000,000. Somatic activating mutations of the GNAS gene located on chromosome 20q13 encoding the α subunit of the regulatory protein Gsα are responsible for the entity.

Case Report: This is a patient referred by her attending physician at the age of 6 years and 5 months for treatment of precocious puberty. She is 1m22 tall and weighs 23 kg. The patient has already presented a pubertal episode at 5 years of life, characterized by pink leucorrhoea. She then presented an S2 status breast augmentation. Developed and pigmented lips, and type P2 pubic hair. The biology shows an E2 increased to 75 pg/ml with the indosable gonadotropins. Pelvic ultrasound shows a stimulated uterus with polycystic ovaries. She also has a unique, irregular patch of café-au-lait skin on her right flank. Bone age is overmature 1 year. The thyroid balance is normal as well as the androgens. treatment with an aromatase inhibitor was initiated.

Discussion: Diagnosis is usually clinical. Evaluation of patients with MAS should be guided by knowledge of all possible impairments and appropriate investigations. Genetic testing is possible, but not routinely available.

Conclusion: MAS is a rare disease. Genetic counseling should be offered although SAM is not hereditary. Malignant transformation of DF lesions is rare and probably occurs in less than 1% of cases.

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Delayed puberty by anomalies hypo-gonadotropic hypogonadism, hyper-gonadotropic hypogonadism and puberty induction

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Introduction: Delayed puberty is defined as the absence of the development of sexual characteristics beyond the age of 14 for boys and 13 for girls.

To better understand this pathology, we conducted a retrospective study over a period of 7 years; between 2013 and 2020, involving 11 patients with a delayed puberty, followed by a pediatric endocrinology consultation at the children's hospital Ibn Sina in Rabat.

Patients: Our patients are divided into 18.2% of girls and 81.8% of boys with a sex ratio of 4.5 (Boys/Girls). The average age for recognizing a delayed puberty is 14 years for girls and 15 years for boys. Statural delay is found in 72.7% of patients with a delayed puberty. The latter is severe in 18.1% of the cases (-4DS). Complementary examinations carried out for our patients led to the following diagnoses:

Simple pubertal delay in 3 patients; 3 patients have hypergonadotropic hypogonadism;

5 patients présentent un hypogonadisme hypo-gonadotrope. 5 patients were treated with sexual androgens and 3 of them showed a marked improvement in puberty.

Conclusion: Delayed puberty is a multi-factorial process whose diagnosis is based, firstly on the clinic but also on the realization of the hormonal assessment, the bone age, as well as other biological and radiological examinations. Moreover, the pubertal induction by sexual androgens is the cornerstone of the treatment of delayed puberty.

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Congenital Hypopituitarism: a pathology not to be ignored

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Introduction: Pituitary deficiency, or hypopituitarism, is defined by insufficient synthesis of one or more anterior pituitary hormones (growth hormone, TSH, ACTH, LHFSH, prolactin) associated or not with diabetes insipidus (ADH deficiency). In children it is more frequently congenital, due to abnormal pituitary development; it is then a rare disease with an estimated prevalence of between 1/16.000 and 1/150.000.

Case Report: A 2-month-old female infant, the first full-term born of a consanguineous couple. The diagnosis is revealed by the presence since the neonatal period: of hypotonia, prolonged jaundice as well as recurrent hypoglycaemia suggestive of a hypotalamo pituitary deficit. Hormonal exploration revealed combined pituitary damage: adrenal insufficiency, central hypothyroidism with GH deficiency. RMI showed hypoplasia of the anterior pituitary. the malformative assessment returned to normal.

Discussion: Our patient presented a severe anterior pituitary deficit explaining the clinical picture. the diagnosis of congenital hypopituitarism is important from birth to avoid hypoglycaemia and adrenal insufficiency and their cerebral and vital risks. the prognosis is good if diagnosed and treated early.

Conclusion: Congenital hypopituitarism is a rare disease. responsible for an isolated or combined deficit. MRI is currently the most efficient means for diagnosis and a prognostic approach. Treatment is based on hormone replacement therapy. Between 80 and 90% of congenital hypopituitarism cases remain unresolved in terms of molecular genetics.

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To give or not to give GnRH agonists in central precocious puberty due to pituitary microadenoma?

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Background: Functioning gonadotroph adenomas (FGAs) are very rare gonadotropin-secreting pituitary adenomas. Clinically, FGAs present only with mass effects. Nevertheless, central precocious puberty (CPP) has also been reported. Published data have demonstrated controversial opinions on the use of GnRH agonists in these patients, considering the risk of increase in tumor size and stimulating gonadotropin secretion.

We herein report 3 cases diagnosed with CPP due to pituitary microadenoma in Alexandria University Children's Hospital, and their course whether treated or not with GnRH agonists.

Case 1: A 4.6-year-old girl presented with precocious puberty; which started with breast enlargement at age 2 years, followed by cyclic vaginal bleeding for 4 months. Her height was 111.6cm (+3SD), with bone age 11 years. She had breast Tanner III, no pubic or axillary hair, and a left preauricular skin tag. Ultrasound pelvis revealed a right ovarian cyst. Basal LH was pubertal, and serum estradiol level was elevated. MRI brain showed an enlarged pituitary gland, with a small pituitary microadenoma. She started GnRH agonist therapy. At age 5.7 years, her height is 116cm (+0.4SD), Tanner staging didn't progress, and her MRI showed a stationary course.

Case 2: A 7.8-year-old girl presented with breast enlargement Tanner III, and pubic hair Tanner II. Her height was 135cm (+1.5SD), and her bone age was 8.5 years. Basal LH was prepubertal, so GnRH stimulation test was done showing pubertal response. Her brain imaging showed a pituitary microadenoma. Her ovaries and adrenals were normal by ultrasonography. After agreement with the parents, the decision was not to treat her. After 1 year, her growth velocity normalized, pubertal development didn't progress, and the size of microadenoma remains the same.

Case 3: A 10-year-old boy presented with rapidly increasing height and pubic hair noticed since age 8 years. His height was +3.1SD, and he had advanced bone age (13 years). His physical examination revealed pubertal testicles, penile length 13cm, and pubic hair Tanner IV. Basal LH and serum testosterone were significantly elevated. MRI brain showed a tiny pituitary microadenoma. He received GnRH agonists for 2 months, then he developed diplopia with right severe and left mild visual field defects, so he is planned for surgery.

Conclusions: Despite the scarcity of reported cases, FGAs can present with CPP. In these patients, the risk of using GnRH agonists needs to be kept in mind and further research is required to decide how to manage them.

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Short Stature as the Presenting feature of a case of Pediatric Isolated Hypothalamic-Pituitary Axis- Langerhans Cell Histiocytosis

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Langerhans cell histiocytosis (LCH) is a rare disorder of unknown etiology affecting the mononuclear phagocyte system. It is characterized by clonal uncontrolled proliferation and accumulation of immature dendritic cells in different organs. Affected cells express CD1-alpha and/or CD207 (Langerin) on immunohistochemistry. Although bone is the most commonly affected organ (80%), all other organs can be affected either alone or in combination.LCH is classified into Single system (SS) or Multisystem (MS). MS-LCH carries a worse prognosis and is classified into "with risk organ as liver, spleen or bone marrow" or "without risk organ". Classically, Hypothalamic pituitary axis (HPA) affection is commonly associated with multisystem severe disease leading to Central Diabetes Insipidus and less commonly Anterior pituitary deficiencies. In this case we present a case of Isolated HPA-LCH that presented primarily with short stature.

An 11.5 year old male presented with proportionate short stature and no dysmorphic craniofacial features. We found central hypothyroidism and severe Growth hormone deficiency by two different provocation tests (peak 0.8 and 0.9). Water deprivation test revealed central diabetes insipidus. ACTH and cortisol at 8 am and 8 pm were found normal.

MRI sella tursica with contrast revealed: absent posterior pituitary gland bright spot and diffuse thickening of the pituitary stalk with intense post contrast homogenous enhancement. The radiological findings pointed us to the diagnosis of pituitary LCH. Differential Diagnosis included germinoma or primary lymphoma. Whole body scan using TC-99 showed no bone involvement. Although biopsy was not feasible, the patient follow up in the oncology department excluded the possibility of a neoplasm. Genetic testing for LCH was not possible owing to the high cost and unavailability. MRI sella was repeated after 1.5 years, showing a stationary course of the same lesions and confirming the diagnosis LCH.

We started treatment with Minirin and thyroid hormone after the initial investigations. Growth Hormone was added after 2 years of follow up. 18 months later, we observed recognizable increase in growth velocity and no deleterious effects on LCH disease activity.

Conclusion: Although rare, isolated HPA-LCH can present primarily with short stature as part of panhypopituitarism. Therefore, any case of GH deficiency should be thoroughly investigated for an underlying cause.

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„In her bigger sister's footsteps". A case of precoccious puberty in 2 caucasian sisters

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We present the cases of a 3 yo girl diagnosed with precoccious puberty, with a personal history of premature telarchy, genital hair development and vaginal blood discharge at 1yo 2mo, currently in treatment with GnRH agonist, and the case of her younger sister, aged 1 yo, who also presented with premature telarchy. They have 2 older siblings, both of them are clinically healthy boys. Their mother and paternal aunt had normal pubertal development. No other history from females of paternal side is known.

In physical examination at the initial presentation, the older sister, aged 2yo 6mo, had 20 kg, 110cm, situated on the 65th percentile of BMI, bilateral flat feet, genu varum, multiple pigmentary nevi, Tanner stage B4P3. According to Romanian growth charts, height SD score was +4.9 SD and -1.9 SD adjusted for bone age (nondominant hand wrist X-ray showed 6yo 6mo aspect). Paraclinic examination showed basal LH=9.30mUI/mL, Estradiol=38.68pg/mL with normal levels of Testosterone, 17OH-progesterone, DHEA-S, Androstendione, Prolactin. McCune-Albright syndrome was suspected because of the association between leg abnormalities and precoccious puberty. Because the genetic mutation causing this syndrome produces stimulation of endocrine glands, the patient was screened for other endocrinopathies. Hormonal samples and tests showed that thyroid function, adrenal glands and somatotrophic axis were normal. Pelvic US showed enlarged uterus of 3.7/1.7 cm, presence of endometrial layer, follicular aspect of the ovaries. Hypothalamic-hypophyseal MRI excluded a tumor, and GnRH agonist treatment was initiated. The patient is currently responding properly.

The younger sibling, aged 1yo 2mo at the first evaluation, had breast development at the age of 1 yo. At physical examination patient had 83 cm, which corresponds to +2.03 SD, and -3.15 SD adjusted for bone age of 3 yo, 10,8 kg, 87th percentile of BMI, Tanner stage B3P1. Hormonal samples showed basal LH=0.13UI/L, FSH=5.09UI/l, Estradiol<5pg/ml, with normal 17OH-progesterone, DHEA-S, Androstendione, Prolactin, IGF1, thyroid and adrenal function. The pelvic US showed an uterus of 2,28/1,3 cm, left ovary of 1,39/0,87 cm. No therapeutical approach was initiated for this patient yet.

Further investigations will follow, as the family is schedueled for genetic counselling because the main suspicion of etiology in this cases is a genetic disorder.

There are multiple causes of precoccious puberty, either central, or peripheral, idiopathic or organic, but the particularity of this two cases is the similar pattern of manifestations in both sisters manifested at a very young age, with unaffected mother.

P2-248

McCune-Albright Syndrome: knowing how to think about it

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Introduction: McCune-Albright syndrome (MAS) is characterized by fibrous dysplasia (FD), cafe-au-lait skin spots and precocious puberty (PP). SAM is a rare disease and its prevalence is estimated between 1/100,000 and 1/1,000,000. Somatic activating mutations of the GNAS gene located on chromosome 20q13 encoding the α subunit of the regulatory protein Gsα are responsible for the entity.

Case Report: This is a patient referred by her attending physician at the age of 6 years and 5 months for treatment of precocious puberty. She is 1m22 tall and weighs 23 kg. The patient has already presented a pubertal episode at 5 years of life, characterized by pink leucorrhoea. She then presented an S2 status breast augmentation. Developed and pigmented lips, and type P2 pubic hair. The biology shows an E2 increased to 75 pg/ml with the indosable gonadotropins. Pelvic ultrasound shows a stimulated uterus with polycystic ovaries. She also has a unique, irregular patch of café-au-lait skin on her right flank. Bone age is overmature 1 year. The thyroid balance is normal as well as the androgens. treatment with an aromatase inhibitor was initiated.

Discussion: Diagnosis is usually clinical. Evaluation of patients with MAS should be guided by knowledge of all possible impairments and appropriate investigations. Genetic testing is possible, but not routinely available.

Conclusion: MAS is a rare disease. Genetic counseling should be offered although SAM is not hereditary. Malignant transformation of DF lesions is rare and probably occurs in less than 1% of cases.

Sex Differentiation, Gonads and Gynaecology, and Sex Endocrinology

P2-249

5 Alpha Reductase Deficiency as the Etiology of Primary Amenorrhea in a Girl with Thalassemia Major

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Introduction: Beta thalassemia major (βTM) is an autosomal recessive anemia characterized by a defect in the production of the β-globin chain of hemoglobin. There may be endocrine problems secondary to hemochromatosis in the clinical follow-up of the patients. Here, a case who was followed up with the diagnosis of βTM, consulted for primary amenorrhea and diagnosed with 5-alpha reductase deficiency (5ARD) is presented and clinical follow-up experiences are shared.

Case: A 15-year-old refugee girl born from consanguineous marriage was consulted from the hematology department because of primary amenorrhea. In her history, it was learned that she was diagnosed with βTM at the age of five months, received erythrocyte transfusion every three weeks, used deferiprone, had a splenectomy at the age of six, and was not followed up regularly. The patient who migrated to our country with her family was followed up in the hematology clinic. A 21-year-old older sister also had primary amenorrhea and gender preference was male. She had two siblings with a diagnosis of βTM. The patient's weight was: 42.4kg (-2.23 SDS), height: 143.4cm [-3.1SDS), BMI: 20.62kg/m2 (-0.15SDS)]. She had typical thalassemic facial appearance, 2/6 systolic murmur, female external genitalia, bilateral breast stage I, pubic hair stage I, a long 1.5 cm diameter mass in the bilateral inguinal region. Inguinal masses were interpreted as testis by ultrasound. Genetic analysis revealed IVS-I-110 (G>A) heterozygous mutation in the Beta thalassemia gene. Laboratory examination results were consistent with hypogonadotropic hypogonadism and primary hypothyroidism, LT4 treatment was started. Peak LH response was 6.54 mIU/mL in the LHRH stimulation test, and the anterior pituitary gland was 4 mm in the pituitary MRI. Karyotype analysis was 46,XY. in the hCG stimulation test (1500 IU/day, 3 days); basal and stimulated total testosterone levels were 46.45 and 118.95 ng/dL, respectively. The testosterone/Dihydrotestosterone ratio was found as 65. Genetic analysis revealed NM_000348,3c.269A>C(p.His90Pro) homozygous variant in SRD5A2 gene. She adopted the male gender as her sexual identity. The patient's family did not approve of this sexual identity preference. In the follow-up, insulin dependent diabetes developed and insulin therapy was started.

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Conclusion: The endocrine problems associated with hemochromatosis are expected in βTM. Here, the 5ARD' diagnosis process in a βTM case with primary amenorrhea is presented. In this case, both genetic conditions are together, and sexual preference and the problems of being a refugee provide important experiences.

P2-250

Clinical case: Diagnostic / therapeutic procedure of a 46,XY complete gonadal dysgenesis

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The proband is a Caucasian girl with primary amenorrhea and no breast development at the age of 16 11/12 yrs. Unrelated parents; an older brother in good health and a twin brother (GA 31 days; BW 1450g) with reported agenesis of the corpus callosum and socio-emotional behavioral problems. The mother (menarche 14 yrs. and bicornuate uterus) presented four early spontaneous abortions and one stillborn fetus (46, XX) in the 6th month of pregnancy; remaining negative family history. The patient (BW 859g) presented with typical female external genitalia (EGS = 2), scarce pubic and axillary hair, and absence of telarche. After endocrinological and genetic counseling, in the suspicion of DSD, the determination of the karyotype (2017) was normal 46, XY with positive FISH SRY. Pelvic ultrasound and subsequent magnetic resonance imaging (MRI) of the pelvis showed a hypoplastic uterus (STAP 40x13x8 mm) and no identifiable gonadal tissue. Laboratory evaluation revealed elevated gonadotropins, with undetectable gonadal sex steroids and AMH consistent with gonadal insufficiency. Therefore, the clinical-instrumental and laboratory data were compatible with a complete gonadal dysgenesis.

In 2018 the following were negative: molecular analysis of the *NR5A1* (*SF1*) and *SRY* genes, and MLPA of the *NROB1 (DAX1), WNT4, SOX9, NR5A1, SRY* genes. The CGH array has identified two microduplications with no clear pathological significance transmitted by the mother. Finally (04/2020), the analysis of an NGS panel with 33 DSD causative genes showed the presence in heterozygosity of the variant c.556A> G, (p.Arg186Gly) in *MAP3K1*, not described in the literature and classified as "probably pathogenetic".

With the consent of the patient, a feminizing hormone replacement therapy was started (07/2019) at moderately progressive doses of only natural estrogens in patch (18 months) and then sequential estrogen-progestogens (03/2021); the first cycle occurred 23 days after the therapeutic change. Laparoscopy performed on 03/2022 showed a normal-sized uterus and gonadal strips (streaks) that were removed for cancer prophylaxis. This report adds a new pathogenetic alteration in the *MAP3K1* gene, and highlights the clinical importance of considering defects in *MAP3K1* in the differential diagnosis for complete or partial gonadal dysgenesis.

P2-251

Clinical and ultrasound diagnosis of a complicated giant ovarian teratoma

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Introduction: A 12-year-old girl has been accepted in our emergency room for persistent abdominal pain associated with nausea, dysuria and difficulty walking. Abdominal pain is localized on the left side and is acute, stabbing, intermittent and non radiating. The menstrual cycle is normal, both in duration and intensity. Family history does not reveal a significant background. The girl is apyretic with normal vital parameters. The abdomen appears expanded and prominent. Giordano's maneuver is positive, more to the left. On palpation, a hard mass of increased consistency is appreciated, not painful to palpation and expanded from the pelvis to the epigastrium.

Materials and Methods: Emergency laboratory tests are performed including tumor markers and pregnancy tests. An abdominal ultrasound is done for immediate evaluation of the suspected abdominal mass.

Results: The emergency blood tests (blood count, inflammatory indices, clinical biochemistry and coagulation function) are negative as well as the pregnancy test and tumor markers. Ultrasound shows the presence in the median area up to the left quadrants of a voluminous formation of 17 centimeters at least, extending from the epigastrium to the pelvis, with corpuscular fluid content, internal mobile septa and evidence of iso/hypoechoic solid components, partly fluctuating, lobulated and irregular, containing in turn some inscribed calcific cores. This formation compresses and moves down the bladder and uterus making it impossible to evaluate the adnexa. On the other hand, a bilateral calico-pyelo-ureterectasia is visible with an antero-posterior diameter of the right and left renal pelvis of 19 and 15 millimeters, respectively. After pediatric surgical consultation, teratoma excision is performed through laparotomy with Pfannenstiel incision. The histopathological picture describes immature and mature structures such as squamous, respiratory, bone, cartilage, bone marrow, lymph nodes, smooth muscle, nervous, fatty, glandular, lymphoid and gastric tissue.

Conclusion: The pathological picture confirms the diagnosis of mixed cystic ovarian teratoma. The postoperative course has no complications. The ultrasound follow-up shows the progressive

resolution of the calico-pyelo-ureterectasia. Teratomas are embryonic neoplasms consisting of tissues of 2 or 3 germ layers (ectoderm, endoderm and mesoderm). Ovarian teratomas are the most common germline cancers, the most common of which in children is the mature cystic type (or dermoid cyst). In the presence of an ovarian mass, there are no specific symptoms or a characteristic physical examination for which diagnosis may be delayed. Ultrasound imaging is essential because if it occurs early it can avoid complications such as ureterohydronephrosis.

P2-252

Premature ovarian failure in two female patients with 47, XXX karyotype

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Introduction: Premature ovarian failure (POF) is defined as a heterogeneous disease leading to amenorrhea and ovarian failure before the age of 40 years. It is found in 1-3% of women of reproductive age, with some negative consequences such as cardiovascular disease, osteoporosis and sexual dysfunction. Triple X syndrome is characterized by POF with primary or secondary amenorrhea, tall stature, large feet. Girls with triple X syndrome show accelerated growth until puberty, occasionally delayed speech development, and low self-esteem. They often need of psychological, behavioural and educational support.

Case Presentation: We present two patients with triple X syndrome. Patient 1 was a girl at age of 16.7 years with secondary amenorrhea three years after menarche. On initial examination her Tanner stage was B4P5A4. The girl had tall stature (90p), rougher facial features, and no speech problems, communication or learning difficulties. The hormonal profile showed hypergonadotropic hypogonadism and undetectable level of AMH. The karyotype was revealed as 47, XXX. The pelvic ultrasound and MRI confirmed normal uterus without atretic follicles in ovaries. To reduce the risk of osteoporosis and cardiovascular disease, the girl was started on gestagen/ethinylestradiol replacement therapy. Psychological support was provided. She was referred to a reproductive health center for oocyte cryopreservation. Patient 2 is a 17 years old girl with tall stature, scoliosis, mild mitral insufficiency, and normal menstrual cycle 4 years after menarche. She also had normal neurological and psychological development. The hormonal profile showed normal levels of gonadotropins and estradiol, but low level of AMH, indicating diminished ovarian reserve. Pelvic ultrasound was normal. Oocyte criopreservation was recommended.

Conclusion: The presented patients show the need for comprehensive approach in girls with tall stature with or without secondary amenorrhea. Cytogenetic analysis should be considered even in the absence of hypergonadotropic hypogonadism and secondary amenorrhea. As shown, patients with Triple X syndrome may have diminished ovarian reserve even without the presence of menstrual irregularities. Early diagnosis, evaluation of ovarian function and the currently available new reproductive technologies are an opportunity to preserve their fertility and quality of life.

Keywords: premature ovarian failure, triple X syndrome, amenorrhea

P2-253

Clinical characteristic and testicular function in children with 46 XY disorder of sex development in a developing country

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Disorders of sex development (DSD) comprise a heterogeneous group of conditions involving interference with normal sex differentiation and hormonal production in the embryo resulting in relatively rare conditions having diverse pathophysiology. The aim of the current work is to study the clinical characteristics and testicular function of patients with 46 XY DSD. A cross-sectional study was done included children with initial presentation of atypical genitalia and satisfied the criteria of DSD classification. Hormonal assays for luteinizing hormone, follicle-stimulating hormone, testosterone, dihydrotestosterone, androstenedione, AMH & Inhibin B and human chorionic gonadotropin (hCG) stimulation were done. A total of 33 patients were included with a mean age of 1.89 ± 2.44 years. Ambiguous genitalia were the commonest presentation (82%). Majority of patients (75.8 %) were reared as males. There were significant positive correlations between basal inhibin B, AMH, FSH and testosterone response after hCG stimulation test ($p < 0.029$, <0.001 and <0.004). Similarly, there was a significant positive correlation between basal AMH and inhibin B ($p < 0.025$). Five alpha reductase enzyme type 2 deficiency was the most common diagnosis (45.5% of cases). We concluded to elucidating the exact cause of 46 XY DSD is often cumbersome and challenging in a resource constrained developing countries. Despite the clear genital ambiguity, most of our patients were reared as males. Basal AMH or inhibin B is highly predictive of the presence and function of testes although that cannot obviate the need for hCG test in the work-up.

P2-254

Intracranial beta human chorionic gonadotropin (β-hCG)-secreting germ cell tumor in a girl with central precocious puberty

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Background: Precocious puberty is common in boys occasionally in girls with beta human chorionic gonadotropin (β-hCG)-secreting intracranial tumors, and is reported to be peripheral precocious puberty exclusively.

Object: To described a girl with intracranial β-hCG-secreting germ cell tumor (GCT) who presented with central precocious puberty (CPP).

Method: We described the clinical data of the 8 years and 9months girl with intracranial GCT and reviewed the relative literatures.

Result: The girl was admitted to our hospital because of breast development for 1.5 years without experience of menarche, and was diagnosed with CPP concurrently with elevated serum β-hCG levels (56.45-20.7 mIU/mL) for 7 months at local hospital. On admission, physical examination revealed precocious puberty (breast B3, axillary hair A2, pubic hair PH1), without neurological findings. Serum and cerebrospinal fluid (CSF) β-hCG was 40.03 and 103.22 mIU/mL, respectively. A magnetic resonance imaging scan of the head with enhancement revealed a 7*2mm lesion at the lenticular nucleus in the right basal ganglia considered to be the GCT focus, and an 11*8mm pineal cyst. Intracranial non-germinomatous germ cell tumor was diagnosed, and combination chemotherapy was initiated with GnRHa therapy for CPP. The girl was transferred to another brain hospital due to the stable response of chemotherapy, and the pathology of pineal lesion was 'central neurocytoma'.

Conclusion: This is the first female case of intracranial β-hCG-secreting germ cell tumor concomitant with CPP. In this case, CPP seems unlikely to attribute to the elevated β-hCG secreted by the tumor. CNS lesion due to the tumor in the right lenticular nucleus and the pineal lesion may contribute to CPP. Detection of serum HCG (AFP) is indispensable for the diagnosis of precocious puberty, regardless of boys or girls. Cranial MRI/CT is also necessary in girls with CPP even older than 6 years of age under certain circumstances.

P2-255

Expression of adam and adamts proteases following currative gnrha treatment for cryptorchidism

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Aim of the Study: ADAM/ADAMTS family members encode extracellular, multidomain proteolytic enzymes. Mutant Adamts16 mice display cryptorchidism and sterility. We hypothesize that gonadotropin-regulated ADAM/ADAMTS genes are involved in testicular development during mini-puberty. Patients and

Methods: Testicular biopsies for histological and RNA-Sequencing analysis from bilateral cryptorchid boys were analyzed. RNA samples were processed using a standard RiboMinus Gold/TrueSeq (Illumina) RNA protocol. Absence of spermatogonia was used to identify high infertility risk patients (HIR) who were randomized for treatment either with surgery in combination with GnRHa or surgery only. Four biopsies before (testis 1) and four after six months of GnRHa treatment (testis 2), were compared to three samples before (testis 1) and three samples after six months of surgery only.(testis 2)

Main Results: Surgery alone did not affect ADAM/ADAMTS expression. Expressions of Leydig cell specific ADAM23 as well as ADAMTS20 was decreased in HIR in comparison to LIR patients. (Table 1) Importantly, ADAMTS20 expression increases after GnRHa treatment. (Table 1) Furthermore, testis specific ADAM 29,30 and ADAMTS,16,18 genes showed identical expression level between HIR and LIR but were up-regulated by the GnRHa treatment. (Table 1) These genes are implicated in extracellular matrix remodeling and organogenesis.

Conclusions: We show for the first time that testes from cryptorchid boys with abortive mini-puberty display decreased expression of ADAMTS20 and that expression is upregulated by GnRHa. This indicates a novel role for ADAMTS20 in the development of Ad spermatogonia and the establishment of fertility. Taken together, these results disclose involvement of ADAM23,29,30 and ADAMTS16,18,20 in a reproductive ADAM system that functions in fertility.

Table 1. ADAM/ADAMTS-gene expression in LIR and HIR boys with cryptorchidism, before and after GnRHa treatment; FDR; false discovery rate, RPKM; median expression values expressed in reads per kilobase per million

Gene	HIR/LIR (RPKM)	log2FC / FDR	-/+ GnRHa treatment (RPKM)	log2FC / FDR
ADAM23	1.64/3.23	-1.0/0.0008	1.8/3.1	n.s.
ADAM29	0.16/0.11	n.s.	0.02/1.1	2.45/2.8E-05
ADAM30	0.14/0.10	n.s.	0.06/0.8	2.25/0.0002
ADAMS16	0.36/0.48	n.s.	0.41/1.13	0.73/0.033
ADAMTS18	015/0.35	n.s.	0.24/0.70	1.18/0.006
ADAMTS20	0.30/0.85	-1.67/0.0008	0.36/1.52	1.06/0.001

P2-256

Case report: Roumanian baby with cytochrome P450 oxidoreductase deficiency

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Background: POR deficiency is a rare form of congenital adrenal hyperplasia, transmitted in an autosomal recessive trait, that is characterized by ambiguous genitalia, impaired steroidogenesis and skeletal malformations similar to those of Antley-Bixler syndrome. It is caused by mutations in the P450 oxidoreductase gene (POR), an electron donor for all microsomal P450 enzymes including the three steroidogenic enzymes P450c 17 (17 alfa-hidroxylase /17,20 lyase), P 450c21 (21-hydroxylase) and P450 aro (aromatase). To date, more than 140 PORD cases have been reported worldwive.

Case Presentation: We report the case of a Roumanian baby that was reffered to our pediatric endocrinology department soon after birth (day 6) for the investigation of ambiguous genitalia. She was diagnosed in utero with skeletal abnormalities and the genetic tests excluded osteogenesis imperfecta. The antenatal caryotype was 46,XX. She was the first child of a healthy unrelated couple delivered by cesarean at 39 week. It is noteworthy that the mother, developed a deepening of her voice during pregnancy. The clinical examination revealed facial dysmorphism: large domed forehead, flat nose and midface hypoplasia, hypertelorism, dysplastic ears, stenotic external auditory canals, short and deep philtrum, lips bifidas, limited movement of the elbows and metacarpophalangeal joints, arachnodactyly, thenar and hipothenar muscle atrophy, bowing of lower extremities with limited movement. External genitalia were severy virilized (Prader stage 5) with a phallus like structure of 2.0 cm long and complete labial fusion, the meatus opened at the tip of the phallus-like structure. Serum steroid profiles indicated elevated androgen precursors (17-OH-pregnenolone and 17-OH-progesterone) with normal adrenal androgens (dehydroepiandrosterone sulfate and androstendione), high baseline adrenocorticotrophic hormone (ACTH) with normal serum cortisol, low estradiol. Adrenal insufficiency was detected by corticotropin stimulation test. Wholebody X-Ray showed bilateral femoral deformations (bent femur) and radiohumeral synostosis. Abdominal ultrasound was normal. The diagnosis of PORD was suspected on clinical background (Antley-Bixler phenotype, ambigous genitalia) together with the hormonal profile and the patient was referred to the clinical genetician for genetic confirmation. The patient started replacement therapy with hydrocortisone 7 mg/m2.

Conclusions: PORD is a very rare disease that needs to be suspected in patients with disorder of sexual development especially when combined with skeletal deformities. It is possible that PORD remains undiagnosed in some patients. Molecular analysis of the POR gene is crucial for making correct diagnosis. With careful airway management, many children with ABS survive and the prognosis may be reasonably good

P2-257

A novel discovered role for CFTR in azoospermia and wolffian duct maldevelopment caused by cryptorchidism

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Aim of the Study: Cryptorchidism occurs more frequently in CF-children, and malformed epididymis was found more in cryptorchid boys with abrogated mini-puberty. Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) is transporter protein that acts as a chloride channel. Specifically, CFTR is associated with spermatogenesis and fertility.

Patients and Methods: Testicular biopsies for histological and RNA analysis from bilateral cryptorchid boys were analyzed. RiboMinus Gold/TrueSeq (Illumina) RNA protocol was utilized. No Ad spermatogonia identified high infertility risk patients who were randomized for treatment either with surgery and GnRHa or surgery only.

Main Results: In cryptorchid boys, hypogonadotropic hypogonadism induces the reactivation of transposons and suboptimal expression of ASZ1, PIWIL genes and CFTR. (Table 1) Curative GnRHa treatment stimulates expression of CFTR and PIWIL3 genes which are important for the development of Ad spermatogonia and subsequent fertility. (Table 2) Furthermore, GnRHa stimulates the expression of androgen sensitive epidydimal genes: CRISP1, WFDC8, SPINK13, PAX2. The high incidence of abnormal epididymis in HIR patients may stem from a combination of hypogonadotropic hypogonadism and insufficient CFTR activity.

Conclusions: Novel observation is that in cryptorchid boys CFTR is controlled by LH and testosterone influencing activities of genes that are important for fertility and the differentiation of the Wolffian duct.

Table 1.

Gene	HIR/LIR (RPKM)	log2FC / FDR	-/+ GnRHa treatment (RPKM)	log2FC / FDR
FOXA1	0.11/0.47	-1.59/0.006	0.19/0.71	1.15/0.03
ASZ1	0.75/309	-2.32/0.001	n.s.	n.s.
COX20	13.5/13.6	n.s.	13.6/12.04	-0.67/0.005
HSP90AA1	71.2/102.3	-0.53/0.01	75.6/78.1	-0.65/0.01
HENMT1	7.52/20.11	-1.34/0.0001	9.69/10.5	-0.7/0.004
FKBP6	0.47/2.16	-2.34/0.0001	0.68/1.42	n.s.
PIWIL1	0.39/2.21	-2.97/0.0001	n.s.	n.s.
PIWIL2	3.22/16.66	-1.75/0.0008	n.s.	n.s.
PIWIL3	0.22/0.41	-1.0/0.015	0.17/0.95	1.52/0.002
PIWIL4	1.72/7.32	-2.09/0.0001	n.s.	n.s.
PNLDC1	0.52/3.05	-2.41/0.0006	n.s.	n.s.

Table 2.

Gene	HIR/LIR (RPKM)	log2FC / FDR	-/+ GnRHa treatment (RPKM)	log2FC / FDR	Affymetrix probeset identifier (highest variance probe set per gene)	Descended / undescended (HIR+LIR, median log2 signal)	log2FC / FDR
CFTR	0.24/0.79	-1.50/0.001	0.29/1.54	+1.35/0.002	205043_at	3.39/3.50	n.s.
SLC9A3R1	0.69/2.07	-1.43/5.77E-05	n.s.	n.s.			
SLC9A2	n.s	n.s.	0.13/1.00	+2.18/1.69E-05			
SLC9A4	n.s	n.s.	0.13/0.42	+2.12/0.0001			
SLC9A9-AS1	n.s	n.s.	0.32/2.39	+2.77/0.001			

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Comparative characterization of hypogonadotropic hypogonadism and constitutional delayed puberty in girls

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Objective of the Research: to compare clinical laboratory and genitometric parameters in girls with hypogonadotropic hypogonadism (HH) and constitutional delayed puberty (CDP).

Materials and Methods: 23 female patients with delayed puberty are included in the study.

Inclusion Criteria: absence of secondary sexual characteristics at age ≥13 years or absence of menarche at age ≥15 years or absence of menarche for 3 years or more from the onset of estrogen-dependent signs of puberty.

Noninclusion Criteria: age ≥18 years, abnormal external genitalia, hypergonadotropic hypogonadism.

All patients were evaluated the stage of puberty according to the Tanner scale, anthropometric parameters, bone age according to the Greulich-Pyle method, genitometric parameters, LH (1.9-14.2 mIU/mL), FSH (2.5-11.2 mIU/mL), E2 (30-393 pmol/L), inhibin B (20-177 pg/mL), AMH (<8.9 ng/mL), prolactin (70-600 mIU/L), testosterone (0.29-1.67nmol/L), insulin-like growth factor (IGF-1; 188.4-509.9 ng/mL) in serum, GnRH analogue test results (triptorelin 0.1 mg).

Results: All patients were divided into 2 groups: girls with HH (group I) and girls with CPD (group II). HH was detected in 39.2% (9/23) of the girls. CDP was detected in 60.8% (14/23): 28.5% (4/14) of girls had no secondary sexual characteristics in their decree periods, and 71.5% (10/14) had primary amenorrhea.

The reasons for treatment did not differ between the two groups: secondary sex characteristics were absent in 66.6% (6/9) of group I patients and 28.6% (4/14, p=0.102) of group II patients. Girls in both groups had similar height, body mass index, and bone age.

According to the hormonal examination, girls with HH had significantly lower serum levels of E2, inhibin B, prolactin, and basal levels of gonadotropic hormones. The groups did not differ in serum AMH levels. According to GnRH analogue test results, the maximum LH level after 1 hour was significantly more frequent in group I, after 4 hours with equal frequency in both groups, after 24 hours - significantly more frequent in group II. Girls with HH had significantly lower uterus volume, ovaries volume, and linear M-Echo size.

Conclusions: HH in girls is characterized by low serum levels of gonadotropic hormones, estradiol, inhibin B, IGF-1, and prolactin, a less pronounced LH and FSH response to stimulation with GnRH analogue, smaller uterus volume, ovaries volume, linear M-echo size, and delayed bone maturation compared with constitutional delayed puberty. No patient with CDP had a stimulated LH level less than 3.39 mIU/mL on the GnRH analogue test.

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A case of 46, XX female with short stature, primary ovarian insufficiency and kidney dystopia due to two novel mutations in MCM8 gene

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Primary ovarian insufficiency (POI) affects about 1% of females under 40 and represents a major cause of female infertility. Approximately one third of POI are of genetic in origin, including FMR1 premutation, Turner syndrome and approximately 60 other genes, involved in development, hormonal signaling, cell division and survival, immunity, and metabolism. MCM8 is a recently

discovered gene that plays an important role in homologous recombination and DNA repair and only up to ten mutations have been described in the medical literature so far. Identification of causes of POI is very important for early determination of reproductive prognosis and though for improving reproductive outcomes.

We describe a 13-year-old girl, from non-consanguineous family, 1st non-remarkable pregnancy and delivery, born term, 2900 gr and 49 cm. Her linear growth delay was noticed from 8 years and by 11 years it was -2SDs. Body proportions US/LS 0.99. Mild cubitus valgus, hypermobile joints, mild shortening of the 4th metacarpals, hypertrychosis with normal shaped chest and neck were seen phenotypically, intelligence age-appropriate. Bone age was delayed with 3 years. Ultrasound examination revealed rotation of the right kidney and dystopic left kidney, but kidney function remains normal on annual control. Pelvis MRI showed agenesis of ovaries and small hypoechogenic uterus. Thyroid status, serological markers of celiac disease, IGF-1, IGFBP-3 were normal, FSH as well LH were markedly elevated, AMH were extremely low. Cytogenetic analysis confirmed 46,XX karyotype. Whole exome sequencing (WES) was performed, which revealed two novel heterozygous variants in MCM8 gene: c.278_271del, p.(Ile93Argfs*22) and c.703T>C, p.(Cys235Arg). Currently the patient is on transdermal estrogen treatment for 6 months. Her bone age is still delayed with two years, and height velocity remains in prepubertal range, but breast development started and the size of the uterus increased and became more structured.

The presented case is noteworthy in several ways. Firstly, it highlights the importance and diagnostic utility of WES in the context of unexplained POI. Secondly, we describe two novel mutations in MCM8 gene, broadening the mutation spectrum of the MCM8-related disorder. Finally, presented case broadens the phenotypic spectrum of this rare disease prompting clinicians to suspect genetic etiology of POI in the context of short stature and kidney malformations.

P2-260

Analysis of the spectrum of disorders of sex development in Diabetes, Endocrine and Metabolism Pediatric Unit, Cairo University, Egypt

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Background: The incidence of Disorders of sex development (DSD) in Egypt was reported to be 1 in 3,000 live births. Late diagnosis, severe salt wasting with high morbidity and mortality, and inappropriate sex -assignment are challenging problems that constitute medical and social emergencies. Serum Anti Mullerian Hormone (AMH) and Inhibin B levels are possible tools for assessment of Sertoli cell function that can help early diagnosis of patients with suspected 46 XY DSD.

Objectives: To describe the different spectrum of clinical, laboratory and radiological findings in Egyptian infants and children with DSD following in Endocrine Unit, Cairo University and to assess value of AMH and Inhibin B in early diagnosis of 46 XY DSD

Methods: Retrospective analysis of the medical records of established DSD cases in addition to prospective analysis of data of newly diagnosed patients were performed and followed up for 2 years.

Results: A total of 451 cases of DSD were classified according to the DSD classification (proposed by the international consensus conference on intersex). 46 XY DSD constituted 74.5% (n=336), 46 XX DSD 21.7% (n=98), while sex chromosome DSD constituted 2.7% (n=12). In patients with 46 XY DSD, the most common cause was partial androgen insensitivity/5 alfa reductase deficiency (45.2% n=204), while in 46XX DSD cases, congenital adrenal hyperplasia (24.2 %) constituted the commonest diagnosis with predominance to the salt losing 21 hydroxylase deficiency CAH (82.6%). Patients had various presentations: atypical genitalia was the most frequent complaint (76.7% n=346), other presentations included delayed puberty and salt losing manifestations. There was positive correlation between AMH level and the post hCG stimulation DHT and testosterone levels ($p < 0.001$, $r = 0.4$). Moreover, there was positive correlation between levels of AMH and Inhibin B in patients with 46 XY DSD ($p = 0.03$ and $r = 0.3$).

Conclusion: DSD is not uncommon in the Egyptian community. It requires early detection, appropriate investigations, and prompt treatment to avoid serious medical, psychological, and social sequelae. Inhibin B and AMH levels add valuable tools to the differential diagnosis of DSD, with low levels in global testicular disorders and normal or elevated levels in disorders of androgen biosynthesis or action.

Keywords: Disorders Of Sex Development, Atypical Genitalia, Congenital Adrenal Hyperplasia, Androgen Insensitivity Syndrome, Karyotype, Anti-Mullerian Hormone, Inhibin B

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VSD genetic diagnosis exploiting single-cell expression data and deep learning

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The majority of patients with Variations of Sex Development (VSD) lack a genetic diagnosis. Patients that are born with atypical chromosomal, gonadal, or phenotypical sex, present a wide spectrum of phenotypes that are often associated with ambiguous genitalia, infertility as well as increased susceptibility to testicular or ovarian cancer. Many different genetic causes of VSD have been reported [2], but for more than 50% [3] of all VSD patients, the molecular cause of their condition remains unknown, further complicating clinical management. The low rate of diagnosis is explained by the still incomplete knowledge of the molecular mechanisms of gonad morphogenesis and sex development. Recently, next-generation sequencing (NGS) enhanced clinical diagnosis but the value of NGS relies on the ability to analyze the gigantic amount of data in a reasonable and time-efficient manner. After the exclusion of known VSD causes and standard variant filtering methods, about 1000 variants per patient remain for further analysis.

To accelerate and specify variant interpretation, we combine RNA single-cell sequencing (scRNA-seq) data of the developing

human gonads [4] with known gene interaction networks (STRING) and deep learning methods to develop an encoding scheme for gene expression data. We use a convolutional neural network (CNN) structure to develop our model. To this end, we transformed single-cell 1D expression data into a gene interaction co-expression image-like 2D object [5]. With this data, we trained our deep learning structure to learn the gene expression network landscape of the developing gonads. Next, the model was retrained with the same data structure but specific for VSD. To evaluate the performance of the VSD trained model, we used 3-fold cross-validation and measured the overall area under the precision-recall curve. After training, we validated the accuracy of the prediction of known VSD genes which reached 85%. Applying our trained model to the remaining variants in VSD patients we were able to rank them from predicted to be "highly" to "less likely" VSD-related candidates. By selecting the top 10 genes from this ranked list, we were able to identify several genes that are tightly involved in sex development disorders and potentially new VSD candidate genes. This translational approach advances our knowledge of human sex development and potentially improves the diagnosis and management of its variations.

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Analyze of clinical, biological and therapeutic aspects of 46 XY DSD

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Background: Clinical spectrum of 46 XY DSD is characterized by a greatest diversity. Atypical sex development can occur through different steps of testicular differentiation. Etiologies of 46 XY DSD are termed gonadal dysgenesis, hormonal dysfunction and action. Its global incidence is unknown but the most common presentation, hypospadias, is understood to occur in 1 in 125 male births, and complete androgen insensitivity has an incidence of 1:20,000 people.

Aim: The aim of this study is to determine clinical, biological and outcome of infant, children and adolescents attended to the endocrine unit of the central hospital of army for management of 46 XY DSD.

Method: All the patients attended to our unit from 2009-2022 for management of 46 XY DSD benefited clinical exam and classified according to the external masculinization score (EMS). Karyotype, AMH and androgens were analyzed in all the patients. HCG test was done in children and adolescents. Ultrasound and genitography evaluate internal genital tract. Genetic analyze was done only in two patients.

Results: 30 patients were attended to our unit, mean initial age was 60,66 ± 110 months, sex assignation was male in 76,7% of patients. Familial history of DSD was found in 25% of the studied cases. 17,8% of the studied patients born SGA and one mother took progesterone medication during pregnancy. Consanguinity was found in 35,7 % of the studied cases. Mean EMS score was 6,81 ± 2,70. It was highest in patients with PAI than the others etiologies ($p<0,01$). Etiologies of 46 XY DSD in our study termed PAI in 46,7%, gonadal dysgenesis in 13,3 %, PMDS in 13,3%, 5α R deficiency in 10%, vanishing testis in 6,7%, TAI in 3,3%, 17β OH ase deficiency in 3,3% and Leydig cells agenesis in 3,3%. Genetic evaluation found WT1 mutation in one GD and AMH mutation c.368-371del,Arg123Profs*15. One patient was reassigned as male at the age of 11 months and 68% of the patients benefited a surgical refection of their genital organs at mean age of 56,4 ± 57,5 months. Androgens were prescribed in 32% of male assigned patients.

Conclusion: This study reveals a delayed diagnosis, a significant rate of consanguinity and family history of DSD. PAI is the most common diagnosis. We note a low rate of reassignment. Masculinization surgery was necessary in the majority of patients.

P2-263

Complete androgen insensitivity syndrome: A case report

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Background: Loss-of-function mutations of the androgen receptor (AR) gene result in androgen insensitivity syndrome (AIS) in 46,XY individuals, causing a disorder of sex development. AIS has a clinical continuum according to the resistance severity, being classified into three main categories: complete (CAIS), partial (PAIS), and mild (MAIS).

The authors present a female phenotype patient with CAIS.

Case Report: An otherwise healthy 16-year-old girl was sent to a paediatric clinic for primary amenorrhea investigation. She had thelarche and pubarche at 10 and 12 years old, respectively, and a normal pubertal growth spurt. Her family history was unremarkable. Examination showed a female phenotype with breast Tanner stage IV, and thin and scarce pubic and axillary hair. There were no abdominal palpable masses, and the remaining observation was otherwise normal. Laboratory testing revealed LH 32,6 mUI/mL, FSH 9,5 mUI/mL, oestradiol 53 pg/mL, and total testosterone 0.13 ng/mL. Abdominal ultrasound showed no uterus or ovaries. Pelvic magnetic resonance imaging confirmed the uterus and ovaries' absence, unveiling a short and blind-ending vagina, as well as images consistent with testes adjacent to the inguinal canals' inner rings. As the whole constellation was suggestive of CAIS, she was then referred to our hospital center, where a paediatric multidisciplinary approach has taken place: endocrinology, surgery, genetics, and psychology. Genetic exams revealed a karyotype 46,XY, and a hemizygous likely pathogenic allelic variant in the AR gene (c.2086G>A).

Gonadectomy was performed and histologic evaluation presented features of undescended testes, such as hyperplasia of

Leydig cells and no spermatogenesis. There were no findings of malignancy. Hormone therapy with oestrogen was then started and gradually increased according to serial blood testing.

Discussion: In individuals with CAIS, there is no therapy able to prevent or reverse the effects that occur during embryogenesis. For this reason, management is focused on gonadectomy, hormone replacement, and psychological support for the patients and their families. Since these individuals have a normal growth spurt and feminize at the time of expected puberty, gonadectomy should be performed after sexual maturation is complete, given the risk of malignancy. After surgery, hormone replacement is ought to be started. These patients should be followed in a center with expertise, enabling a multidisciplinary approach, and always providing counseling, not only at diagnosis but also as required along the way.

P2-264

StAR gene mutation: Description of puberty development and genital life from 6 patients 46,XX with classic Congenital Lipoid Adrenal Hyperplasia

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Introduction: Congenital Lipoid Adrenal Hyperplasia (CLAH) is a severe deficiency of adrenal and gonadal steroidogenesis, caused by mutations in the StAR gene and the accumulation of cholesterol in the outer mitochondrial membrane due to steroidogenic acute regulatory protein (StAR) deficiency. Affected patients present peripheral adrenal insufficiency with early onset, and variable phenotypes at the age of puberty.

Objective of our Study: To describe in 46,XX girls and women, the clinical and biological development of puberty, the occurrence of ovarian cysts, the fertility, as well as the mutations found and the circumstances of diagnosis of this pathology, in order to suggest hypotheses on the physiopathology and to propose an adapted management to each problems encountered.

Material and Methods: This observational, retrospective, national and multicenter study described the clinical, biological and imaging data of 46, XX patients aged at least 10 years old and presenting a classic form of CLAH.

Cases Synthesis: Six patients 46,XX from 10 years and 8 months old to 41 years old, have been described. Three patients had spontaneous puberty, including one with spontaneous menarche. One patient had hormonal pubertal induction, the last two patients had not started puberty at 11 years and 10 years and 8 months. Five patients presented recurrent ovarian cysts, including two before puberty.

One patient, who had a pubertal induction, had three children by In Vitro Fertilization. The six patients had different mutations in the StAR gene

Conclusion: StAR gene mutations in 46 XX patients are responsible for heterogeneous clinical presentations. This pathology must be diagnosed early, and patients should benefit from clinical, biological and ultrasound peri-pubertal monitoring. Hormone replacement therapy aimed at inducing or supporting puberty, regulating cycles and preventing ovarian cysts could be assessed on a case-by-case basis. Furthermore, fertility preservation could be offered to patients.

Keywords: steroidogenesis, StAR gene, lipoïd congenital adrenal hyperplasia, adrenal failure, puberty, ovarian cyst, fertility, medical assistance for the procreation,

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Gynecomastia and short height;45,X[2]/46,X, +mar[28] karyotype

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Introduction: Physiological pubertal gynecomastia is common in adolescents aged 13-14 years. Most physiological pubertal gynecomastia regresses spontaneously within 1-2 years. In studies: If it lasts more than 2 years, if prepubertal has started, endocrine evaluation is recommended. Sex differentiation disorders or genital abnormalities such as increased aromatase activity, adrenal/testicular neoplasia, partial androgen insensitivity syndrome and Klinefelter syndrome,46,XX,testicular(SRY+) related hypogonadism should be investigated in these cases.

Case: The patient who was admitted with hair growth in the genital area at the age of 8 years and 6 months; height:128.2 cm (25-50 p;-0,24 sds), %Ideal Weight: 111, Physical Examination; Testicular volume: 2 ml/2 ml, Pubic Hair: Stage2, Axillary

Hair:none. Lab; Thyroid Function Tests: normal, T.testosterone: 0.14ng/dL, DHEAS: 70µg/dL, 11DOC: 2.7ng/dL, 17OHP: 0.98ng/dL. In the 12 years and 11 months control of the patient, who developed obesity in the follow-up and regressed in the height percentile; height: 146.2 cm (3-10p; -1.46 sds), %Ideal Weight:138, Physical Examination; Testicular volume: 2 ml/2 ml, Pubic Hair: E4, and bilateral gynecomastia (breast right Stage 2, left Stage 2) was detected. AFP: <1.7ng/mL, E2 <11.8 ng/dL, beta hcg<2, prolactin:21.9ng/mL,FSH:1.26IU/L,LH:0.36IU/L,t.testosterone:17.11 ng/dL, DHEAS: 135 µg/dL, 11DOC: 0.58ng/dL, 17OHP: 0.69 ng/dL, breast USG: left 38x15 mm right 15x4 mm fibroglandular tissue was detected. Chromosome analysis was sent because the patient had prepubertal gynecomastia.

Chromosome Analysis: 45,X[2]/46,X, +mar[28].

FISH: nucish (DXZ1 x 1,Yp11.31 x 0, DYZ1 x 0)[5/ 50] /(DXZ1 x 1, Yp11.31 x 1, DYZ1 x 0)[45/ 50] Comment: 50 interphases nucleus was analyzed, a signal of each DXZ1 and SRY region was detected in 45 cells, but no signal could be obtained with the probe attached to the Yq11,31 region. A single signal of the DXZ1 region was observed in 5 cells.

Conclusion: Cases of 46,X,+mar karyotype, non-mosaic karyotypes in males with testicles without normal structural Y chromosome have been rarely reported. A marker chromosome is a structurally abnormal chromosome with no identifiable parts by conventional cytogenetic chromosome analysis. In the literature, similarly short stature and obesity have been observed in cases with 46,X,mar karyotype; pubertal gynecomastia was reported in one case.

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From urine progenitor cells to induced pluripotent stem cells

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Human sex development relies on differentiation of the gonads, in which Sertoli and granulosa cells play a key role for men and women respectively. Many variations of sex development (VSD) are due to alteration of these two cell types. The study of the mechanisms underlying these conditions is crucial for optimal clinical management of VSDs, as for more than 50% [1] of all VSD patients, the molecular cause of their condition remains unknown. The collection of primary cells is invasive and cumbersome for the patients and their in vitro culture extremely difficult due to short lifespan and the loss of the unique characteristics. Additionally, the available cell models do not reproduce the patient-specific mechanisms of the disease. An attractive alternative are patients-derived cells which would allow a "personalized" clarification of the pathophysiology of disease. Eventually, the analysis of several patients would identify common pathways and shed more light on the origin of these disorders. Human induced-pluripotent stem cells (iPSCs) are developing as exciting cell sources for applications in regenerative medicine and drug discovery, primarily based on their extensive similarities to their human embryonic stem cell counterparts and shared properties of self-renewal and multilineage differentiation capabilities. iPSCs can be derived from somatic cells like fibroblasts, peripheral blood mononuclear cells (PBMCs) or urinary progenitors cells (UPCs) via ectopic expression of transcription factors SOX2, OCT4, KLF4, NANOG, C-MYC and LIN28 [2]. UPCs are a powerful source with great potential for reprogramming into iPSCs, as the collection is simple, inexpensive, and non-invasive. In addition, UPCs have properties such as clonogenicity, expansion and self-renewal capacity [3, 4].

In this study the focus lies on the generation and characterization of the UPCs and iPSCs, as it is crucial to know the sources before differentiating into Sertoli or granulosa cells. The reprograming from UPCs to iPSCs was performed with either nucleofection or magnetofection, two viral vector-free methods. The characterization was done qualitative with antibody staining and quantitative with qPCR. For the analysis the following markers were chosen: CD73, CD44, CD146, OCT4, NANOG, SSEA-1, SOX2, and TRA 1-81.

UPCs expressed CD44, CD73, CD146 and stem cell markers such as OCT4 and NANOG, but not SOX2 and TRA-1-81. The iPSCs expressed all stem cell markers examined here.

UPCs-derived iPSCs may become an alternative source for generating human cell models ideally directly from the patients and could be of great importance for basic research in sex development and reproductive medicine.

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Gonadal Dusfunction in Polytransfused Beta-Thalassemia Patients

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Introduction: B-thalassemia is a chronic hereditary hemolytic anemia characterized by a defect of synthesis of beta-globin chains, particularly common in the Mediterranean region, southern Asia, and the Middle East. Chelation therapy significantly prolonged the life expectancy of patients. This has led to an increase in the prevalence of endocrine complications, linked to iron overload.

Gonadal Dusfunction is a frequent complication in polytransfused beta-thalassemia patients. The key factor involved is iron overload, which causes oxidative damage to the hypothalamic-pituitary-gonadal axis.

Objectives: Describe the frequency of Gonadal Dusfunction in patients with polytransfused β-thalassemia.

Study the relationship between Gonadal Dusfunction and serum ferritin level, mean transfusion volume (VTM), duration of transfusion treatment, splenectomy, and compliance with chelation therapy.

Method: This is a descriptive, analytical and monocentric cross-sectional study which was carried out in the CHU Mustapha pediatric department and which concerned 32 patients of pubescent age (20 girls and 12 boys), followed regularly for several years for the most of them, and treated by a transfusion regimen (more than 10 transfusions) combined with chelation therapy.

All patients were assessed by history taking, somatic examination, and pubertal developmental stage assessment followed by

follicle-stimulating hormone (FSH) and luteinizing hormone (LH) assay, testosterone for boys and estradiol for girls, as well as a GnRH test, bone age, and pelvic ultrasound in girls.

Results: Hypogonadism affected 23 (72%) patients, with 15 (65.2%) girls and 8 (34.8%) boys. Among the 15 girls with hypogonadism, delayed puberty affected 13 (62%) patients, three (13%) patients presented with primary amenorrhea, 4 (17.4%) developed secondary amenorrhea and 2 (8.7%) %) patients had menstrual irregularity. The 8 boys with hypogonadism showed delayed puberty.

There is no significant correlation between hypogonadism and serum ferritin level in our study.

Conclusion: Hypogonadotrophic hypogonadism is common in young adults with thalassemia and contributes to low fertility in this population. Early detection of pituitary iron overload is important because severe hypogonadism is not fully reversible by iron chelation.

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Case Report: Clinical and genetic features of 46, XY DSD caused by a mutation in DHX37 gene

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The DHX37 gene has been identified to cause 46, XY disorders of sex development (DSD), yet there are no reports in China. Here, we report a Chinese pediatric case of 46, XY DSD identified by Whole-exome sequencing which carried a heterozygous missense mutation c.2020 C > T (p.R674 W) in DHX37 gene (NM _ 032656) inherited from the mother. Gonadal pathology showed that the left gonad was structured with a vas deferens and epididymal duct, and the right gonad had vas deferens, epididymal duct, and fallopian tube structures. This is the first case of 46, XY DSD caused by DHX37 gene mutation in China, which will give new insights for the diagnosis and treatment of pediatric disease and reliable genetic evidence for family reproduction.

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A Case of Under virilized Male with 18q Partial Monosomy and 10p Duplication

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Objective: Monosomy 18q and 10p duplications rare chromosomal disorders that are caused by deletion of a part of the long arm (q) of chromosome 18 and duplication of genetic material on the short arm (p) of chromosome 10 respectively. In both disorders the phenotype is highly variable and; includes short stature, developmental delay, hypotonia, and facial dysmorphic features. Also, genital abnormalities could occur in both disorders. Genital abnormalities (cryptorchidism, micropenis, rarely hypospadias in boys; hypoplastic labia in girls) have been reported in 25-63% of individuals with monosomy 18q syndrome, and in nearly 50% of cases with 10p duplication. In most cases, there is more one segmental imbalances that accompanies each other due to inherited segregation of unbalanced translocations. Here, we present an undervirilized male case with 18q monosomy and 10p duplication.

Case: A five-month-old male patient was referred for hypospadias. He was born at 36 weeks of gestation with a birth weight of 2630 gr after an uneventful pregnancy to parents who were nonconsanguineous. He was followed in the neonatal intensive care unit due to suspicion of congenital adrenal hyperplasia and during follow-up, no hypoglycemia or electrolyte disorder was detected. He presented with a weight of 6.5 kg (-1.2SDS), a height of 63 cm (-1.24 SDS) and a head circumference of 39 cm (-3.02 SDS). There was an umbilical reductable hernia. The gonads (1/1 ml) were palpable in the labioscrotal folds the phallus was 2.5 cm in length and the cavernous tissue was thin. The urogenital sinus had one opening into the perineum. Gonadotropins and androgens that measured during the minipuberty (1 month old), ruled out the diagnosis of androgen synthesis defects and hypogonadism (FSH 3.7 mIU/Mll, LH 14.88 mIU/Ml, total testosterone 262 ng/dl, 1.4-Delta androstenedione 1.94 nmol/L). Due to microcephaly, VEP was performed and bilaterally prolonged p100 latency was detected; BAEP and cranial MRI was unremarkable. Chromosome analysis revealed 18q monosomy and 10p duplication (46,XY, der(18) t(18;10)(q21;p11.2)). In the segregation analysis, the father's chromosome analysis was 46,XY,t(10;18)(p11.2;q21) and he was a translocation carrier.

Conclusion: Chromosomal anomalies should be kept in mind in patients with multisystemic findings in addition to genital anomalies. This case has a very rare association of 18q partial monosomy and 10p duplication and is one of the segmental anomalies that can be diagnosed by chromosome analysis.

Keywords: micropenis, hypospadias, microcephaly, translocation, anosomy, monosomy

P2-270

What lessons from past history of patients with CAH in a Sub Saharan country?

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Introduction: Congenital adrenal hyperplasia is the most common cause of primary adrenal insufficiency. It is a rare monogenic recessive disorder. In African setting in absence of neonatal screening, the diagnosis is still late, based on a clinical approach. During this clinical enquiry, information form past history or pedigree of the patient are of a huge importance and may revealed surprises

Patients and Methods: In this observational study, past history and pedigree of 41 patients from two endocrinopeadiatric centers in Cameroon, were studied. The diagnosis of CAH was retained based on a high 17 hydroxyprogesterone level in addition to clinical and morphological findings.

Results: A contributive past history was found in 14 families (35%). In 12 (30%) families, we found 18 reported deaths of infant less than 12 months. In this 12 families, half of the patients followed had 21 hydroxylase deficiency and had 11 hydroxylase deficiency. Unsurprisingly, we suspected adrenal insufficiency in these patients at verbal autopsy even in families with a patient with 11 hydroxylase deficiency. Other non DSD malformations or genetic disorders with apparently no link with CAH was reported in 3 families. The father of a patient reported to have hypospadias.

Conclusion: Each diagnosis of CAH made in our context is visible part of an iceberg. Behind a diagnosis of CAH made in our setting, is a long course of care, a dramatic past history. Neonatal screening should thus be considered as an emergency.

P2-271

Wide phenotypical spectrum with the same karyotype: Mixed gonadal dysgenesis

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Context: The 45,X/46,XY mosaicism poses a great clinical challenge influencing gonadal development, histology, hormonal balance, and growth. Patients present a wide spectrum of phenotypes with varying degrees of genital ambiguity from Turner Syndrome to male. Here, we present five children with 45,X/46,XY mosaicism presenting with different clinical phenotypes.

Case Descriptions:

Case 1: An 11 years-old girl was presented with short stature and typical female genitalia. Initial clinical diagnosis was Turner Syndrome with short stature, high gonadotropin concentrations and small uterus, undetectable ovaries on pelvic ultrasonography. After karyotype analysis, gonadectomy was performed and the histological examination revealed bilateral streak gonads.

Case 2: A 2 days-old neonate was presented with asymmetric genital appearance. In physical examination, the left gonad was in the scrotum and the right gonad was unpalpable. The karyotype confirmed 45,X/46,XY mosaicism. The right streak gonad, right side of the uterus and tuba were present, in the laparoscopy. Histological examination revealed testis in the left gonad. The patient was raised as a male and was followed at 3-6 months` intervals for malignancy risk. Growth hormone treatment was started at the age of seven, when the growth rate decreased.

Case 3: A 14 years-old boy was presented with short stature. His height was 146 cm (-2.8 SDS), target height was 178.5 cm (0.37 SDS). At the presentation, testes were 15/8 cc, palpable in the scrotum, penile size was 5x1 cm and there was no hypospadias. After karyotype confirmed 45,X/46,XY mosaicism, testicular biopsy was planned but the parents refused.

Case 4: A 18 months-old girl was presented with isolated clitoromegaly. Uterus and ovaries were visualized on pelvic ultrasonography. After karyotype confirmed 45,X/46,XY mosaicism, laparoscopic gonadectomy was performed. Histological examination revealed an ovotesticular gonadal phenotype: ovarian stroma in the left gonad and testis in the right gonad. Growth hormone treatment was started at the age of three, when the growth rate decreased.

Case 5: A 15 years-old boy was presented with gender dysphoria. He had typical male genitalia and normal hormonal tests. There were no erection and ejaculation problems. The karyotype confirmed 45,X/46,XY mosaicism, the patient refused testicular biopsy.

Conclusion: 45,X/46,XY mosaicism is associated with variable clinical phenotypes irrespective of degree of mosaicism in blood. Short stature is an important problem in all phenotypes for which GH therapy is indicated. In cases without band/dysgenetic gonads in laparoscopy, the decision for prophylactic gonadectomy should be considered according to the histopathological assessment.

P2-272

A rare HSD17B3 gene variant presenting virilization at puberty: Management and treatment in adolescent age

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Introduction: pathogenetic mutations in the HSD17B3, located on chromosome 9q22, lead to 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3) isoenzyme deficiency, etiopathogenetic for a disorder of sex development (DSD) with 46 XY karyotype and female phenotype at birth. 17β-HSD3 isoenzyme, expressed at testicular tissue, catalyzes the synthesis of testosterone from Δ4-androstenedione, allowing the correct development of male external genitalia during the fetal life; its deficiency results in the development of female external genitalia while maintaining male internal organs. Often at birth this condition is not diagnosed, seeking medical treatment during adolescence for primary amenorrhea and virilization.

Case Report: A 13-year-old adolescent with Morris Syndrome diagnosed at birth, comes to our observation for virilization during puberty. At birth the patient presented female genitalia with a 46 XY karyotype at amniocentesis results. A diagnosis of Complete Insensitivity to Androgens (CAIS) has been performed and she was raised as a female. The parents didn't search for a specialist care until puberty when the patient began to show virilization.

Genetic investigations for CAIS, in particular the NGS panel associated with DSD, did not detect variants of pathological significance. Hormonal investigations showed low testosterone/androstenedione ratio (T/A ratio) 0,4 (normal range > 0,8). The HSD17B3 gene analysis revealed the presence in heterozygosis of two variants: c.221A>C, p.Asn74Thr in exon 3, absent in the international database, and c.227+4A>T in intron 3, classified as pathological. Parent's HSD17B3 gene analysis showed c.221A>C, p.Asn74Thr in mother's line and c.227+4A>T in father's line.

The patient was treated with GnRH-agonist to interrupt pubertal development and to reduce male virilization. She promptly has started psychological support that confirmed her female identity.

She is followed by a multidisciplinary group to establish the correct surgical treatment.

Conclusions: 17β-HSD3 deficiency should always be taken into account in patients with DSD and 46XY karyotype, further genetical investigation at birth or at puberty in late diagnosis are mandatory for a correct management.

Still an open question is the timing of the choice of gender identity and the consequent surgical intervention in adolescent age, at the moment not described.

P2-273

Isodicentric Y Chromosomes in Patients with Disorders of Sex Development

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Introduction: Isodicentric Y chromosome[idic(Y)] is one of the most common structural abnormalities of the Y chromosome and has been observed in patients with disorders of sexual development. Most idic(Y) chromosomes are found in mosaic form with a 45, X cell line.

Methods: The aim of this study was to investigate the genotype and phenotype variability of patients with idic(Y). The clinical data from five patients was extracted from medical records in a tertiary care centre after consent was obtained.

Results: Isodicentric Y chromosomes were found in all five patients. Four out of the five isodicentric Y chromosomes had a breakpoint in Yq11.2. *i),ii)* Two cases presented at birth with hypospadias, phallus, bifid scrotum and unilateral cryptorchidism. No Mullerian structures were noted on imaging and both children were raised as male. Proportion of 45 X cell line was 30% in one and 73% in the other. *iii)* A 4 month old baby presented with perineal hypospadias, 2.7cm phallus, bifid scrotum and bilateral cryptorchidism. Uterine like structure was noted on imaging. Child was raised as male. Proportion of 45 X cell line was 30%. *iv)* A 2.5 years old child presented at birth with hypospadias, 2.1cm phallus, bifid scrotum and bilateral cryptorchidism. Pelvic ultrasound revealed an uterine-like structure. Child underwent laparoscopic examination whereby left orchidopexy was done and right gonad was removed. Pathology showed no ovarian stroma and was consisted with immature testicular tissue. Proportion of X cell line was 37% and the child was raised as a boy. *v)* A15 year old raised as female presented with delayed puberty and virilization (cliteromegaly, deepening of voice). Uterine like structure was noted on imaging however no gonads were identified. Proportion of 45X cell line was 36%.

Conclusion: There is a wide range of somatic, genital, and gonadal phenotypic manifestations among patients with an isodicentric Y. This phenotypic variability could be attributed to various factors such as the proportion of the 45,X cell line and on the various locations of the breakpoints. However it is likely that there may be other factors which may influence this. The incorporation of cytogenetic and molecular techniques would offer a more comprehensive understanding of this structural chromosomal abnormality. This would aid counselling in terms of gender assignment and fertility.

P2-274

Congenital hypogonadotropic hypogonadism caused by a novel mutation of GnRHR gene: A case report

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Hypogonadotropic hypogonadism is characterized by low levels of gonadotropins and delayed or absent sexual development. Most of the patients reach the diagnosis in late adolescence or in adulthood. A timely, appropriate diagnosis implicates a better clinical outcome and treatment timing.

We describe the clinical case of a 15-year-old girl with primary amenorrhea. Stature and weight were in accordance with mid parental height; Tanner stage: PH2 B1. FSH, LH, oestradiol showed prebubertal levels; IGF-1, TSH, fT4, prolactin, ACTH, cortisol were in the normal range. Organic diseases (Crohn disease, Celiac disease, etc) were excluded. Pelvic ultrasound showed ovaries and uterine prepubertal morphology and diameters. Encephalic, hypothalamic and hypophyseal MRI was normal.

NGS analysis for the study of genes associated with hypogonadism, showed that our patient had two heterozygous GnRHR mutations: c.159T>G (p.Asn53Lys) in exon 1, Chr4 and c.317A>G (p.Gln106Arg) in exon 1, Chr4. These mutations were studied by Sanger sequencing in the parents, confirming that they were inherited from the father (c.317A>G (p.Gln106Arg) in exon 1, Chr4) and the mother (c.159T>G (p.Asn53Lys) in exon 1) and were in trans, confirming their pathogenetic role in the clinical phenotype. The variant c.317A>G (p.Gln106Arg) is a rare mutation associated with hypogonadotropic hypogonadism; the variant c.159T>G (p.Asn53Lys) is a new mutation defined as VUS.

According to the diagnosis, timely estrogenic treatment, with a slow dosage increase and a a further association with progesterone, can be given for the patients to induce puberty with beneficial effects for metabolic, bone, sexual and psychological health.

NGS is a valid support to the genetic study of patients with hypogonadism, contributing to recognize also rare genetic mutations and to support the clinician in the management of rare diseases.

Reference

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P2-275

A female with 46,XX gonadal dysgenesis presenting with hypergonadotropic hypogonadism and normal height

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Introduction: Genes on the X chromosome (BMP15, FMR1) and autosomal chromosomes (FOXL2, RSPO1, WNT4) are known to influence ovarian development. 46,XX gonadal dysgenesis is a rare disease caused by chromosomal abnormalities, genetic mutations, and postnatal ovarian damage, leading to premature ovarian failure.

Case Report: A 16-year-old female presented with primary amenorrhea and poor breast development. She was born at 40 weeks of gestation with a birth weight of 3.79 kg. She had no personal or family medical history. Her physical and intellectual development were normal. On physical examination, her height was 0.29 standard deviation score (SDS), weight 1.73 SDS, and body mass index 2.10 SDS. She revealed no feature of Turner syndrome or dysmorphism. On pubertal assessment, her breasts were Tanner stage 1 and her pubic hair was Tanner stage 3. Bone age measured 13 years. Hormonal studies revealed: serum follicle-stimulating hormone 104.9 IU/L, luteinizing hormone 26.4 IU/L, estradiol <4.0 pg/mL. Serum β-human chorionic gonadotropin, prolactin, testosterone, and thyroid hormones were within normal limits. Chromosome analysis revealed a 46,XX karyotype. A pelvic ultrasonography showed a streak uterus (fundus 21 mm, cervix 5 mm), with the absence of bilateral ovaries. Multidisciplinary management including hormonal replacement is necessary. Additionally, advanced diagnostic approaches using array-comparative genomic hybridization and next generation sequencing are prerequisites for genetic counseling.

Conclusion: Further research on the genetic and non-genetic pathogenesis of 46,XX gonadal dysgenesis can contribute to better strategies for diagnosing and treating this rare disease.

P2-276

The challenge of gender identity due to 5α-reductase deficiency- A case report

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The 5α-reductase deficiency type 2 is a rare autosomal recessive 46, XY disorder of sexual development (DSD), presenting with a wide clinical spectrum ranging from a male phenotype with

hypospadias to a female phenotype with wolffian structures. Here we report about the clinical, hormonal and molecular characterization of two siblings with a mutation in the SRD5A2 gene, as well as the challenge of gender identity and the importance of psychosocial care.

The older sibling (pat.1) presented at the age of 1 year with labia synechia and mild clitoris enlargement. The younger sibling presented postnatal with gonads inguinal. The basal levels for gonadotropins and sex hormones were appropriate for age. A stimulation of the gonads by human chorionic gonadotropin showed a rise in plasma testosterone (pat.1: 0.06 µg/l to 5.89 µg/l), corresponding to a normal Leydig-cell function, and a slight increase in DHT, resulting in a high testosterone/DHT ration (pat.1: T/DHT-ratio 29.5). Karyotyping of DNAs extracted from peripheral blood lymphocytes showed 46,XY. A homozygous mutation in exon 1 of SRD5A2 (c.176C>G) was detected in both individuals. The nonconsanguine parents were heterozygous genetic carriers. In both siblings, no uterus was visible on ultrasound and in laparoscopy. Relocation and fixation of the gonads into the labioscrotal region was performed to allow sonographic monitoring, which is so far without pathological findings.

Psychosocial care occurred initially low-frequently and was intensified over time. The parents chose female sex of rearing for both siblings, though virilization is expected during puberty due to testosterone production of the gonads.

By blocking puberty, GnRH-analogues open a time frame for further reflection about gender identity. We recently started Triptorelin 3.75 mg i.m./28 days in pat.1 at the age of 11 years due to slightly rising gonadotropins and testosterone. Further induction of puberty could be oestrogen-dominant or biologically androgen-dominant (+DHT transdermal).

Deciding about partly irreversible and life-changing therapy strategies is a challenge as for a prepubertal child as for parents. Our experience points towards the importance of patient participation, peer counselling and exchange with self-help groups. Essentially integrated continuous psychosocial care should recognize the following aspects: diagnosis coping, body acceptance, dealing with identity, psychosocial health status, sexuality and fertility.

To summarize, personalized care including the implementation of psychosocial support is essential for people with disorders of sex development, such as 5α-reductase deficiency.

P2-277

Study of the epidemiological, clinical and metabolic markers during an anomaly of sexual differentiation in children

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The anomalies of sexual differentiation correspond to congenital chromosomal, gonadal or phenotypic atypia of sexual development that group together pathologies with an undifferentiated or poorly differentiated aspect of the external genitalia and/or internal, or a state of mismatch between external genitalia and internal organs genitalia.

The objective of this work is to describe the epidemiological, clinical and metabolic biomarker profiles in patients with abnormalities of sexual development.

Material and Methods: This is a descriptive cross-sectional study of 80 cases of dsd who are followed in

endocrinology -Pediatric consultation between 2013 and 2017.

Results: The frequency of gonosomal abnormalities is 10%, that of XY anomalies of sexual differentiation is 74% and that of XX anomalies of sexual differentiation is 16%.

Biomarker results show an elevation of testosterone in 9/61 patients and a decrease in 38/61 patients. 17OHP is elevated in 6/11 patients and low in 1/11 patients. Pelvic ultrasound and genitography were abnormal in 22/29 and 7/15 patients, respectively. The diagnosis of congenital adrenal hyperplasia was made in 20 patients, LH receptor abnormality in 15 patients and testicular regression syndrome in 15 cases, Hypospadias in 9 cases, Turner syndrome in 7 cases, ovotestis in 5 patients, gonadal dysgenesis in 4 cases, hypogonadotropic hypogonadism in 3 cases, Klinefelter's syndrome and deficiency of testosterone secretion in 1 patient.

Conclusion: Our study shows an important frequency of anomalies of sexual differentiation, hence the interest of a systematic neonatal examination of external genitalia organs and of a multidisciplinary management of any anomalies of sexual differentiation in order to allow an adequate orientation and a better vital prognosis.

P2-278

Delayed puberty by anomalies hypo-gonadotropic hypogonadism, hyper-gonadotropic hypogonadism and puberty induction

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Introduction: Delayed puberty is defined as the absence of the development of sexual characteristics beyond the age of 14 for boys and 13 for girls.

To better understand this pathology, we conducted a retrospective study over a period of 7 years; between 2013 and 2020, involving 11 patients with a delayed puberty, followed by a pediatric endocrinology consultation at the children's hospital Ibn Sina in Rabat.

Patients: Our patients are divided into 18.2% of girls and 81.8% of boys with a sex ratio of 4.5 (Boys/Girls). The average age for recognizing a delayed puberty is 14 years for girls and 15 years for boys. Statural delay is found in 72.7% of patients with a delayed puberty. The latter is severe in 18.1% of the cases (-4DS). Complementary examinations carried out for our patients led to the following diagnoses:

Simple pubertal delay in 3 patients; 3 patients have hypergonadotropic hypogonadism;

5 patients présentent un hypogonadisme hypo-gonadotrope. 5 patients were treated with sexual androgens and 3 of them showed a marked improvement in puberty.

Conclusion: Delayed puberty is a multi-factorial process whose diagnosis is based, firstly on the clinic but also on the realization of the hormonal assessment, the bone age, as well as other biological and radiological examinations. Moreover, the pubertal induction by sexual androgens is the cornerstone of the treatment of delayed puberty.

Thyroid

P2-279

Evaluating the role of circulating dendritic cells in methimazole-treated pediatric Graves' disease patients

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Graves' disease (GD) is hyperthyroidism associated with organ-specific autoimmune inflammation. GD occurs more frequently in adults than in children, however, pediatric patients are a therapeutic challenge due to cycles of remissions and relapses requiring constant monitoring at every stage of treatment administered. Dendritic cells (DCs) are considered a link between innate and adaptive immunity. DCs as antigen-presenting cells (APCs) are involved in antigen presentation to T lymphocytes, thereby, initiate shift towards effector cells. In accordance, DCs participates also in the modulation of tolerance to specific antigens. To date, the data on DC role in Graves' pathological processes are scarce. Therefore, here we evaluated frequencies and role of circulating DCs in GD pediatric patients treated with methimazole. Flow cytometric analysis was implemented to evaluate three subsets of dendritic cells and their correlation with clinical GD-related parameters. We found significantly higher levels of DC subsets in patients at diagnosis. Furthermore, methimazole treatment seemed to effectively reduce subsets of DCs which, in addition, were found to differentially correlate with thyroid function. Our study shed a new light on DCs role in pediatric GD pathomechanism. Further studies are required for mechanistic assessment of DCs exact role in disease progression and influence on thyroid function.

P2-280

From overt hyperthyroidism to normal thyroid function in TSH receptor activating mutations: reports of two families with novel pathogenetic variants and suggestion of a phenotypical sexual dimorphism

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Introduction: Familial non-autoimmune autosomal dominant hyperthyroidism (FNAH) is a rare cause of childhood hyperthyroidism caused by an activating variant of the thyroid stimulating hormone receptor (TSHR) gene. This disorder may occur as a result of an autosomal dominant inheritance or sporadically through de novo variation. The severity of hyperthyroid symptoms is variable and phenotype differences have been described in subjects harbouring the same mutation. We hereby describe two families bearing heterozygous variants of first description in the TSHR gene, who presented with FNAH of different severity.

Case Presentation: The first family presented a novel mutation in heterozygosis located on exon 10 of the TSHR gene (p.N670H, c.2008A>C) affecting two siblings and their mother. The girl (5.8 years old) complained tachycardia and nervousness and showed a regular growth at the higher percentiles. Investigations revealed overt primary hyperthyroidism (TSH 0.01 mcUl/ml, FT4 2.87 ng/dl

(0.7-1.7), FT3 7.46 pg/ml (2-4)), with negative thyroid antibodies and normal ultrasonography. Patient started treatment with methimazole allowing satisfactory thyroid control. The patient's brother (13 years old) presented tachycardia and mild FNAH (TSH 0.05 mcIU/ml, FT4 18.8 pmol/l (8-17), FT3 6.2 pg/ml (2.5-5.3)), with normal thyroid ultrasonography. Methimazole therapy was started with rapid achievement of hormonal and clinical control. At puberty, the need for methimazole progressively decreased until withdrawal. Their mother underwent thyroidectomy for thyroid nodule and is currently on L-thyroxine treatment.

The second family presented a heterozygous variant in the TSHR gene of first description (p.C636G, c.1906T>G), affecting two twins and their mother. The girl (16.6 yrs) revealed overt FNAH (TSH 0.02 mcIU/mL, FT4 1.67 ng/dl (0.83-1.43), FT3 5.18 pg/ml (3-4.7)), with normal thyroid ultrasound. On methimazole she achieved stable euthyroidism. After a self-discontinuation of treatment, hyperthyroidism recurred and methimazole was reintroduced with rapid hormonal control.

In this family as well, the male was affected by a milder thyroid dysfunction, with initial subclinical hyperthyroidism (TSH 0.25 mcIU/mL, FT4 1.11 ng/dl (0.83-1.43), FT3 4.57 pg/ml (3-4.7)) and remission at puberty. To date, he has never needed anti-thyroid therapy. In both siblings, thyroid scintigraphy (99-Tc) showed a diffuse uptake. Their mother reported hyperthyroidism treated with radioablation and subsequent hypothyroidism on L-thyroxine therapy.

Conclusion: We present two different novel variants of TSHR gene, inherited in an autosomal dominant pattern, with phenotypic variability with respect to the patient's gender. Functional studies are ongoing to substantiate this hypothesis.

P2-281

Effects of therapy on Th1, Th17, Th22 and Bregs in pediatric patients with Graves' disease

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Introduction: The precise pathogenesis of Graves' disease (GD) still remains unclear, especially in the field of immunological aspects. Thyroid infiltration by reactive T and B lymphocytes plays a crucial role in the course of autoimmune thyroid diseases (ATD). Previous pattern of inflammation process was characterized by the presence of two antagonistic groups of T effector or also called-helper cells: Th1 and Th2. Recently, more attention is paid to Th17, relatively newly developed Th22 and B regulatory cells (Breg). This subject is rarely undertaken in the context of the children population.

Aim: The aim of this study was to analyze differences in level of Th1, Th17 and Th22 and assess correlation between T effector and B regulatory cells (Breg) in GD pediatric patients. Additionally, we explored effects of therapy with methimazole on these populations.

Material and Methods: A total of 22 children with active GD were involved in the investigation. The control group consisted of 31 euthyroid healthy children. Peripheral blood was collected from GD patients at three time-points: at the admission (before treatment), after 3 months and 1 year of the methimazole implementation. The expressions of the immune cell populations were analysed by four-color flow cytometry using a FASC Canto II cytometer (BD Biosciences).

Results: We reported higher levels of Th1, Th17 and Th22 within CD4+ lymphocytes and as absolute cell numbers in GD patients at the diagnosis. There was no significant difference in cells populations in the course of anti-thyroid treatment. Furthermore, we found positive correlation between levels of Th17 and Th22 and higher fT3 concentration before therapy initiation. Finally, we observed decline of mutual dependencies between T helper cells and B regulatory cells in GD patients compared to healthy controls, where there is a balance of pro- and anti-inflammatory lymphocytes.

Conclusions: Our data discusses the potential role of chosen subsets of T effector and B regulatory cells in pediatric GD development. Presented results confirm that in the course of ATD, immunological homeostasis is disturbed and certain lymphocytes are superior to others what may be used as a ground for new treatment options in the future.

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Papillary Tyhroid Carcinoma in Two Siblings With Congenital Famial Hypothyroidism

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Background: Cases diagnosed with congenital hypothyroidism are considered to be at risk of thyroid nodule formation and subsequent thyroid carcinoma due to TSH overstimulation. Few cases has been reported hitherto. We are presenting two siblings diagnosed with congenital hypothyroidism due to dyshormogenesis who developed thyroid papillary carcinoma during follow up.

Case Presentation: Case 1 was born at term as the first child of consanguineous parents. She was diagnosed with congenital hypothyroidism and on treatment with L-T4. She was admitted to our clinic at the age of 20 months. Tyhroid ultrasonography showed no pathogenesis. Perchlorate test was interpreted as organification defect. Genetic analysis revealed homozygous c.1477 G>A mutation in the TPO gene. L-T4 dose was adjusted acording to blood tests performed at regular intervals. Ultrasonographic follow-up was annually. At 17 7/12 years of age thyroid USG revealed an ovoid, hipoechoic 4*2 mm solid nodule, with punctual echogenities, on the right lobe and an ovoid, 7,5*5,3 mm, solid nodule with smooth margin on the left lobe. Pathological examination of the fine needle aspiration sample from the nodule on the left lobe showed atypia with unknown significance. Thyroid gland was totally resected. Histopatological examination of nodule on the left lobe revealed papillary microcarsinoma. Second sibling of the family was on L-T4 treatment due to diagnosis of congenital hypothyroidism at 13th day of life. Thyroid funcitons were followed with

regular blood tests and thyroid USG annually. Genetic testing was compatible with that of elder sibling. At 7 9/12 of age, thyroid USG revealed a solid, 6-7 mm nodule on right lobe. It turned out to be a degenerated, cyctic, hypoechoic nodule with diameters of 11*6 mm. Pathological examination of the fine needle aspiration sample from the nodule showed atypia with unknown significance. Bilateral total thyroidectomy was performed. Papillary thyroid carcinoma was the diagnosis on pathological examination of the sample (T1bN0M0). Genetical analysis showed no BRAF mutation. Patient received radioactive iodine treatment. She is on follow-up without any morbidity.

Result: We wanted to emphysize the risk of thyroid carcinoma development in cases with congenital hypothyroidism due to familial dyshormonogenesis. Thereof, we believe regular follow-up of nodule development with thyroid USG is necessary in congenital hypothyroidism.

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Identification of predictors of transient and permanent congenital hypothyroidism

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Introduction: Congenital hypothyroidism (CH) is classified as permanent CH (PCH) if levothyroxine (LT4) is life-long required, or as transient CH (TCH) if after LT4 discontinuation thyroid function remains normal. Early detection of TCH allows early discontinuation of LT4.

Purposes: To identify predictors of TCH and PCH, and their cut-off value.

Subjects and Methods: Retrospective study of patients aged >3 years diagnosed of CH from 1993.

Exclusion criteria: ≤32 weeks of gestation and birth weight ≤1500g.

Patients are classified as PCH in case of high TSH after LT4 discontinuation, or compatible thyroid imaging (athyreotic or ectopic gland).

Result: Gestational age, birth weight, TSH and fT4 at age 6 and 12 months do not show significant differences between TCH and PCH groups.

Conclusions: The strongest predictors of PCH are LT4 dose ≥3.15 μg/kg/day at age 12 months, and LT4 dose ≥2.42 μg/kg/day at age 3 years.

While screening TSH <4.61 mIU/l, diagnosis TSH <23.6 mIU/l, diagnosis fT4 ≥1.77 ng/dl, starting LT4 dose <7.81 μg/kg/day, LT4 dose <3.1 μg/kg/day at age 6 months, LT4 dose <2.25 μg/kg/day at age 12 months and LT4 dose <1.4 μg/kg/day at age 3 years individually predict TCH.

These predictors allow to identificate which patients may benefit for an ealy LT4 discontinuation.

N=114	PCH (n=92, 80.7%)	N	TCH (n=22, 19.3%)	N	P	-Cut-off value (ROC area) -Cut-off value with specificity >95% for PCH/TCH
Screening TSH (mIU/l)[b]	101 (23.7-180)	61	15.3 (12.7–18.7)	13	<0.001	≥18.8 (0.83) ≥54.8/<4.61
Diagnosis TSH (mIU/l)[b]	151 (52.28–425)	87	39 (13.86–59.3)	21	<0.001	≥59.3 (0.85) ≥99.5/<23.6
Diagnosis fT4 (ng/dl)[b]	0.495 (0.25–1.06)	84	1.14 (0.75–1.61)	20	<0.001	≥ 0.95 (0.76) <0.36/≥1.77
Thyroid imaging[a]						
- Apparent aplastic or hypoplastic	24 (27.59%)	87	2 (12.5%)	16	<0.001	
- Ectopic	41 (47.13%)					
- In situ	16 (18.39%)		11 (68.75%)			
- Enlarged	6 (6.9%)		3 (18.75%)			
Starting LT4 dose (μg/kg)[c]	12.91 (3.74)	79	9.81 (3.44)	21	<0.001	≥10.72 (0.74) ≥13.81 / <7.81
6 months LT4 dose (μg/kg/day)[b]	4.47 (3.75–5.33)	75	3.11 (2.36 – 3.73)	14	<0.001	≥3.74 (0.83)
- <3 μg/kg/day[a]	3 (4%)		6 (42.86%)		<0.001	≥5.12/<3.1
12 months LT4 dose (μg/kg/day)[b]	4.3 (3.7–5.19)	79	2.4 (1.5–2.88)	17	<0.001	≥3.15 (0.92)
- <3μg/kg/day[a]	12 (15.19%)		13 (76.47%)		<0.001	≥3.87/<2.25
3 years LT4 dose (μg/kg/day)[b]	3.73 (3–4.44)	37	1.7 (1–2.08)	19	<0.001	≥2.42 (0.91)
- <3μg/kg/day[a]	8 (25.8%)		18 (94.7%)		<0.001	≥2.5/<1.4

[a] Frequency
[b] Median (interquartile range)
[c] Mean (SD)

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Prevalence of pediatric thyroid cancer in Latvia

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Introduction: Thyroid cancer is rare in the pediatric population, but the incidence is increasing every year.

Thyroid nodules are known to be less common in children than in adult, but it is one of the most common endocrine malignancies in the pediatric population.

The tumor can develop at any age, but is more common in adolescence and is the second most common tumor in adolescents.

Differentiated thyroid carcinoma includes two different types, papillary thyroid carcinoma and follicular thyroid carcinoma. Both of these type develop from thyroid cells, which normally produce thyroid hormone.

Papillary thyroid cancer is most common type of cancer in children, grows very slowly.

Follicular thyroid cancer is less common and spreads to the neck through blood vessels, causing the cancer to spread to other parts of the body, making the disease more difficult and uncontrollable.

Medular - rare form of thyroid cancer develops in cells that produce calcitonin. Cancer aggression is spread to other parts of the body. In the pediatric population is usually associated with specific congenital genetic conditions (MEN2).

Objective: Collect and evaluate data on patients with thyroid cancer. To find out the prevalence of cancer type in the pediatric population, between the sexes and in Latvia in general.

Identify and summarize the most common clinical symptoms in children with different types of thyroid cancer. Evaluate the long-term effectiveness of therapy.

Methods: Data on children with a confirmed diagnosis of thyroid carcinoma in a pediatric clinical hospital in Latvia were collected. Patients were selected for period from 1990 to 2022. There were 25 case of patients with a confirmed diagnosis. Including 15 girls and 10 boys. The population of diagnosed patients was compared with other countries, the most common type of cancer and the distribution by age groups.

Results: 60% of diagnosed tumor confirm papillary tumor on biopsy and only 16% of all cases are detected by MEN 2. The youngest patient has reached the age of 5, the oldest is 17 years. In 75% of patients, TIRAD 4-5 is detected on primary ultrasonography.

Conclusion: Thyroid tumors are a rare pathology in the pediatric population in Latvia. The number of patients with thyroid cancer is growing every year. The statistics are worsened by the average age at which a thyroid tumor is diagnosed. Pacients are delayed to confirm the diagnosis due to non-specific clinic. Tirad 4-5 of papillary carcinoma is stastically more common.

P2-285

Iodine: Double edged sword in hypothyroidism

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Iodine is the most important element in thyroid function. Its deficiency and excess can cause hypothyroidism. Our location has been known as the iodine deficiency area for the last 20 years.

In this study, we aimed to investigate thyroid dysfunction and assess its relationship with iodine levels in the neonatal period.

Method: One hundred and seventy newborns were included in the study. Infants were selected from patients referred to for neonatal heel blood screening in the last 2 years. At the beginning of the study, their weight, height, head circumference, thyroid function (TF), thyroglobulin (Tg) and urinary iodine excretion (UIL) were evaluated. According to their TF, the three groups were separated as congenital hypothyroid (CH), subclinical hypothyroid (SH) and euthyroid (E), and compared.

Table 1. Statistical comparison of laboratory data according to thyroid dysfunctions

	Congenital hypothyroidism (n= 59)	Subclinical hypothyroidism (n= 31)	Euthyroidism (n= 80)	
Laboratory data	Median±SD (min-max)	Median±SD (min-max)	Median±SD (min-max)	p value
UIE (μg/L)	160.0 ± 240.3 a (10-1160)	110.0 ± 90.8 b (10-390)	100.0 ± 140.5 b (10-760)	0.004*
TSH (μIU/mL)	55.8 ± 33.9 a (9.55-100)	12.9 ± 2.9 b (10.0-20.6)	5.2.0 ± 2.2 b (1.2-9.4)	0.001*
fT3 (pg/mL	4.0 ± 1.1 a (1.0-6.7)	4.7 ± 1.3 b (3.4- 8.5)	4.6 ± 0.6 b (3.2-6.4)	0.001**
fT4 (ng/dL)	0.8 ± 0.4 a (0.1- 1.7)	1.3 ± 0.2 b (2.0-1.0)	1.4 ± 0.2 b (0.9-2.1)	0.001**
Tg (ng/mL)	300.0 ± 302.8 a (0.3-2118.0)	145.0 ± 107.4 b (39.4- 500.0)	85.5 ± 103.0 b (2.2-539.0)	0.001*

*Kruskall–Wallis test.

** One-way ANOVA test.

Results: Eighty-four patients (49.4 %) were male. The ratios of CH, SH and E were 34.7%, 16.7% and 47.1%, respectively. In terms of anthropometric parameters, there was no difference. As expected, TSH, free T3 and T4, Tg levels were significantly different in the CH groups than in the others. Surprisingly, UIE values were the highest in the CH group. Iodine levels according to diagnoses were given in Table 1.

In the CH, SH and E groups, while the ratio of the iodine excess was 37.3%, 20% and 21%, iodine deficiency rate was 23.7%, 40% and 46.9%, respectively.

Conclusion: Although iodine deficiency is still seen as a problem in our region, iodine excess also causes congenital hypothyroidism at an increasing rate.

Post hoc test results are indicated by character (ab). The same character indicates that there is no difference and different character indicate that there is a significant difference.

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A Case of Sjogren's Syndrome with systemic involvement combined with exacerbated hyperthyroidism improved after glucocorticoid treatment

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Background: Sjogren's syndrome is a systemic autoimmune disease, and it is rare in pediatric population. Primary symptoms are dry mouth and dry eyes. However, it may present with systemic manifestations, involving lungs, liver, kidneys, vasculature, and blood. We report a case of Sjogren's syndrome with systemic involvement in a child with Graves' disease.

Case Report: A 9-year-old 11-month-old girl presented to the emergency department with complaints of fever for 2 days. She was diagnosed with Graves' disease a year ago and has been treated with 10 mg/day of methimazole. Her laboratory finding showed leukopenia and mild elevation of pancreatic enzymes. And hyperthyroidism was exacerbated.

On post admission day 4, fever continued, and neck swelling was observed. Ultrasonography on her neck revealed diffuse swelling of the both parotid glands with numerous tiny calcific foci, suggesting chronic sialadenitis such as autoimmune parotitis.

Further evaluation was performed considering Sjogren's syndrome as the cause of autoimmune parotitis. She complained of dry mouth and dry eyes, and ophthalmic examination showed abnormal Schirmer's test. Laboratory finding showed positive Anti-Ro/SS-A antibody and antinuclear antibody. Bone marrow aspiration was unremarkable. Her salivary scan showed decreased wash-out in the bilateral parotid and submandibular glands with normal uptake, suggesting duct stricture or obstruction.

She was diagnosed with Sjogren's syndrome with systemic involvement, and prednisolone (2mg/kg daily) and pilocarpine was started. The fever subsided, and hyperthyroidism with improved normalized.

Conclusion: Systemic involvement of Sjogren's syndrome combined with hyperthyroidism in children is rare and glucocorticoid could be the choice of treatment. In patients with an autoimmune disease, the possibility of developing another autoimmune disease should be considered.)

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Prader Willi Syndrome with Cribiform Papillary Thyroid Carcinoma. A case to share

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Cribiform Papillary Thyroid Carcinoma has low prevalence. Our objective is to present a case and to emphasize future implications.

We present a female 14.9 years old patient with PWS (del 15 q11-13 by methylation test) with a history of asthma, hepatic steatosis, increased Waist-to-Height ratio, HbA1c 5.86 % and C-Peptide 3.64 ng/mL. She had primary hypotiroidism since 7 years old treated with 25 mcg/ day of levothyroxine and impaired fasting glucose since 10 years old with a BMI = 24.2 (+ 2.4 SDS). She was treated with metformin 500 mg / day since 11 years. At 11.7 years she presented an acute asthma episode requiring systemic steroid therapy followed by a diabetic ketoacidosis with glycemia = 16.7 mM/L and HbA1c 8 %. Since then she was treated with glargine and aspartic insulin with favorable metabolic response.

At 13.6 years old thyroid ultrasound showed the right lobe with an increased size, with two heterogeneous nodules, one of 14 mm and the other of 15 mm. They had a hypoechoic halo and and peripheral vascularization. Three lymph nodes were also detected, with a normal left lobe. Fine needle aspiration puncture showed a positive neoplastic citology Bethesda 5. Total thyroidectomy was performed, showing a Cribiform Morular Papillary Carcinoma, with multifocal intrathyroid extension and a vascular embolus in the thyroid capsule. Inmunohistochemistry: TTF1, PAX8, AE1 / AE3, CK7, S100 positive, Calcitonin, CK20, CEA negative, Bethacatenin intense positive in the tumor.

Given the patients history, we decided to study Familial Adenomatous Polyposis, an autosomic dominant syndrome, with a variable degree of penetrance which characterizes by the early development of hundreds of polyps through the colon and rectum. 70 to 90 % of cases are due to a mutation in the APC tumor suppressor gene. It also has extra intestinal manifestations including Thyroid carcinoma in 2 % of cases, mostly of Cribiform variant.

Our patient´s grandmother died because of a colon carcinoma.

We performed a genetic study of the patient and found an uncertain meaning variant in MUTYH gene (c.658A>G/p. lle220val), that plays a significant role in ADN reparation and might be associated with familial poliposis.

According to our knowledge this is the first case of Cribiform Papillary Thyroid Carcinoma associated with PWS. It remains to be ruled out other types of carcinoma development in the future.

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Case Report: the rare case of pediatric myxedema due to an unrecognized chronic autoimmune hypothyroidism

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Hypothyroidism is the most common thyroid disorder in children. It usually presents with nonspecific symptoms, that can be mild and occur slowly over time, compromising a timely diagnosis, with possible effects on pituitary gland, multiple organs and growth. In case of long-standing unrecognized hypothyroidism, myxedema or myxedema coma can occur, rare but severe conditions.

This case report describes an adolescent presenting with extensive trunk and neck swelling. After excluding the main renal, gastrointestinal, and cardiac causes of edema, the ultrasound study showed a thickening of subcutaneous tissue and an enlarged thyroid, with ultrasound signs of thyroiditis. Blood exams showed extremely low FT4 concentrations (0.6 pg/ml), markedly increased TSH (>1000 IU/ml) and positive anti-thyroid peroxidase and anti-thyroglobulin antibodies. The condition was consistent with myxedema due to chronic autoimmune hypothyroidism. Other associated symptoms appeared mild, but significant neglected growth delay was present. Pituitary hyperplasia, hyperprolactinemia, increased serum creatinine and pericardial effusion were found. A prompt levothyroxine treatment allowed to reach an improvement of clinical status and edema regression in 2 weeks, a normalization of FT4 in 3 weeks and of TSH and creatinine in 2 months. Furthermore, Magnetic Resonance Imaging control at 6 months showed a complete regression of pituitary hyperplasia. Ongoing endocrinological follow-up will monitor growth, although current height and pubertal stage suggest a possibly compromised final height.

The diagnostic delay could be linked to the apparent good health of the boy, not requiring pediatric evaluations, and to the underestimation of the growth delay, in presence of a family history of pubertal delay. This report suggests the importance of pediatric follow-up in adolescence, a critical period for identifying endocrine conditions which, if not diagnosed, can lead to severe clinical manifestations and even long-term sequelae.

P2-289

Retrospective assessment of malignant thyroid nodules in a group of polish children and adolescents involving elastography

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Introduction: Thyroid nodules occur in 1.8% children which is not so often in comparison to adults (19–68%), but in children they appear to be at higher risk of malignancy (22–26% vs.5–10% respectively). It has been shown that the probability of thyroid nodules malignancy correlates with the presence of characteristic ultrasonographic features. Elastography - the noninvasive ultrasound imaging technique based on estimation of the tissue flexibility - seems to improve differential diagnosis of thyroid nodules. In adults benign thyroid nodules are flexible in elastography whereas low flexibility is characteristic for malignant lesions.

Aim of Study: The purpose of the study was to assess the application of strain elastography in the management of thyroid nodules in children and adolescents from Department of Pediatrics, Endocrinology, Diabetology with Cardiology Unit, Medical University of Bialystok.

Materials and Methods: Out of 165 pediatric patients with thyroid lesions enrolled to the study, seventeen suspected thyroid nodules with Bethesda III, IV, V and VI were qualified to further retrospective analysis. Elastography parameters were acquired with Toshiba Aplio MX SSA-780A system and the result was presented as a strain ratio (SR) which indicates the deformation of the region of the nodule in comparison to the deformation of the region of the healthy tissue as a reference.

Results and Conclusions: The strain ratio in the group of thyroid nodules diagnosed eventually as malignant (histopathology) was significantly higher than in benign nodules (6.07 vs. 3.09, $p = 0.036$). Our results suggest that application of the elastography in differential diagnosis of thyroid nodules in children may be a suitable method. In case of suspicion of malignancy it may help to make a clinical decision about the need for further invasive diagnosis of thyroid nodules in children.

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Acquired Hypothyroidism in Children: Hypertrichosis as unusual presentation. A Case Report

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Introduction: Thyroid diseases are among the most common endocrine disorders affecting children and adolescents. These conditions are often associated with a wide range of skin disorders such as xerosis, mixedema, hypohidrosis, eczema, and more rarely hypertrichosis.

Case: A 5-year-old female child was referred to our clinic due to short stature, Cushingoid appearance and marked hypertrichosis. At birth length and weight were normal and psychomotor development was regular. Her parents were healthy, non-consanguineous, of Moroccan origin. Her family history revealed no endocrine diseases. Parents reported a 3-months history of mood tone depression.

Her physical examination revealed short stature (height -2.85 SDS, ref. WHO 2006) and a BMI above the 90th centile (ref. WHO 2006). She also presented a noticeable hypertrichosis on trunk and limbs whithout development of pubic or axillary hair and breast. External genitalia were normal. Bone age was delayed (3 years according to Greulich & Pyle's atlas).

Blood samples revealed normal levels of IGF-1, testosterone, DHEAs and androstenedione, with slight increase of prolactin (32 ng/mL, reference range: 3-25 ng/mL). Serum and urinary cortisol as well as basal and after stimulus 17-OH progesterone were normal.

Thyroid hormones profile revealed fT4 0.039 ng/dL (reference range: 0.9–2.6 ng/dL), TSH >1350 mU/L (reference range: 0.8–6.4 mU/L). Autoantibodies levels were elevated (anti-thyroid peroxidase antibodies 217 U/L and anti-thyroglobulin antibodies 246 U/L).

Sodium-L-Thyroxine was given (2 μg/kg/day) and the thyroid function tests became normal (free T4 1.6 ng/dL, TSH 6.48 mU/mL) within 21 days. During three months her hypertrichosis improved progressively.

Discussion: Hashimoto's thyroiditis is the most common thyroid disease of children and adolescents. It may be characterized by euthyroidism, the most common initial pattern (about 52% of patients), overt hypothyroidism (22.2%) or subclinical hypothyroidism (19.2%). Hypertrichosis or hirsutism as manifestations of juvenile hypothyroidism has been described first time by Perloff, that demonstrated a good response to thyroxine replacement therapy in four children as in our case. However, data on association between hypothyroidism and hypertrichosis in pediatric age are still limited and the pathophysiology of this relationship is difficult to explain.

Conclusions: A full assessment of thyroid function must be carried out in all cases of child hypertrichosis.

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Graves' disease outcome in children and adolescents

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Background: Graves' disease is a rare autoimmune disorder in children. Its incidence is 0.1/100,000 person-years in young children and 3/100,000 person-years in adolescents. It is related to the production of TSH-stimulating autoantibodies occurring on a particular genetic predisposition. The particularity of Graves' disease in children is the risk of relapse after medical treatment, which is more frequent than in adults with a frequency of around 30%. Radio iodine treatment is a good alternative in children over 5 years old.

Aim: The aim of this study is to assess the modalities of management of Graves' disease in children and adolescents at the endocrinology department of the central hospital of Army

Method: between 2009 and 2022, nineteen children and adolescents were treated for Graves' disease. Two patients have a history of type 1 diabetes and two children have Down syndrome. All patients underwent a clinical evaluation, an assay of Thyroid Stimulation Ultrasensitive Hormone (TSHus) and peripheral thyroid hormones. A cervical ultrasound is carried out as well as an assay of anti TSH receptor antibodies (TRAK).

Results: The average age is 11.76 years [3-18] years. The most frequent reason for consultation was cervical mass in 80%, signs of thyrotoxicosis 71.4% and exophthalmos 26.3%. TSH is slowed down and FT4 high in all patients. Thyroid stimulating immunoglobulin's were high in 71.4% of patients. Goiter was constant; its volume exceeds 30 cc in 2 patients. All patients received initial medical treatment (Carbimazole) at an average dose of 0.84 mg / kg / day without exceeding 30 mg / day. Long-term medical treatment is the most adopted attitude in our department in 68,4% of patients with an average duration of treatment of 44 months [3-96]. Two patients underwent a total thyroidectomy and four patients receive radio iodine treatment after two relapses under medical treatment with hypothyroidism secondary to radical treatment.

Conclusion: Graves' disease is a rare reason of consultation and admission in our department. The diagnosis was easily done in all patients. Long-term medical treatment is the most adopted attitude with general good observance and obtaining of remission in 21% of patients. Radical treatment was proposed in voluminous goiter and in case of failure of long term medical treatment.

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Assessment of thyroid function in steroid resistant nephrotic syndrome patients

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Introduction: There is a known interaction between kidney and thyroid functions for years. In steroid resistant nephrotic syndrome (SRNS), protracted proteinuria is a characteristic feature of SRNS that leads to loss of thyroxine binding globulin and albumin resulting in low level of thyroid hormones. Furthermore, the long duration of proteinuria in patients with SRNS might damage the renal tubules leading to reduced absorption of low molecular weight proteins that could exhaust the thyroid reserve leading to overt hypothyroidism. Thus, SRNS patients have variable thyroid function range. There is scarcity of data on the prevalence of thyroid dysfunction in these children. Therefore the present study will be conducted to investigate the frequency of subclinical and possible overt hypothyroidism in SRNS.

Objectives: This study aimed at assessing thyroid function (TSH, total T4, FT4, total T3, FT3) in those patients with SRNS and correlate the levels of thyroid hormones with the clinical and laboratory findings of the patients and the duration of illness. Besides, it aimed at determining the frequency of subclinical and overt hypothyroidism in SRNS patients.

Methods: A comparative cross sectional hospital-based study was used to evaluate the thyroid status of children with SRNS who are attending the nephrology clinic of Alexandria University Children's Hospitals. Fifty children with SRNS and equal number of age and sex matched healthy controls were enrolled in this study. Demographic data and thorough clinical examination were fully done for two groups. Renal profile and thyroid function tests were done for them too.

Results: Mean age for the SRNS and control groups was 7.93 ± 3.43 and7.58 ± 2.77 respectively. There was statistically significant correlation between the two groups according to anthropometric measurements and systolic and diastolic blood pressure. The mean TSH level was significantly higher in children with SRNS than the control group. The prevalence of non auto-immune subclinical hypothyroidism was 54 % among SRNS group with no detected thyroid dysfunction in the control group. No cases with overt hypothyroidism were detected among the two groups.

Conclusion: A significant number of SRNS children showed subclinical non-autoimmune hypothyroidism in comparison to healthy controls. It was noticed especially with those who suffered from protracted course of proteinuria. Thus, testing thyroid functions must be done on regular basis in SRNS patients for early diagnosis of subclinical or even overt hypothyroidism and early treatment accordingly.

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The importance of thyroid function tests in precocious menarche: Van Wyk Grumbach syndrome

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Introduction: Van Wyk Grumbach Syndrome (VWGS) is characterized by untreated severe hypothyroidism, isosexual precocious puberty, multiple ovarian cysts and delayed bone age. The disorder is most likely due to complex interactions of the hormonal axis; (1) excess TSH stimulates the FSH-receptor, (2) pituitary enlargement and hyperstimulation, (3) secondary ovarian hyperstimulation. Although it is extremely rare, it is important to recognize before the unnecessary ovarian surgeries because of its curability with a simple thyroid hormone replacement. Here, we reported a case presented with precocious menarche and diagnosed as VWGS.

Case: A 5-year-and-3-month-old female was presented with menarche. There was no history of trauma or bleeding disorders or family history of precocious puberty. Her parents reported fatigue, constipation, intolerance to cold and lack of appetite. She was born as the first child of healthy unrelated parents by normal vaginal delivery after uneventful pregnancy. In her family history, mother was being treated for autoimmune thyroiditis. On physical examination, weight was 18.5 kg (-0.1 standard deviation score (SDS)), height was 105 cm (-1.1 SDS). She was lethargic and pale. She had puffiness of face, dry brittle hair, depressed nasal bridge and short fingers. Her breast development was compatible with Tanner stage 3 without axillary or pubic hair. She had no goiter. Other systemic physical examination features were unremarkable. Initial laboratory investigations had shown normal electrolytes, renal and liver functions. She had macrocytic anemia with a hemoglobin level of 9.7 g/dl (N, 10.2-12.7). Hormonal evaluation revealed high TSH, anti-TPO, anti-TG, low free T4, suggesting Hashimoto thyroiditis and also increased FSH, estradiol, prolactin. Her bone age was compatible with 3 years and 6 months according to The Greulich and Pyle atlas. Ultrasonographic examination of the thyroid revealed thyroiditis with enlargement of the thyroid volume. Pelvic ultrasonography and MRI revealed pubertal uterus (41x20x25 mm) with an endometrial thickness of 7 mm, enlarged left ovary with multiple follicles, and multicystic mass with a size of 42x24x30 mm in the right ovary location. In summary, she had severe hypothyroidism, isosexual precocious puberty with delayed bone age and massive ovarian cysts. With these findings, a diagnosis of VWGS was considered and oral L-thyroxine replacement was started. Following thyroxine replacement, all abnormalities resolved and the multicystic mass structure in the ovaries disappeared completely.

Conclusion: The diagnosis of VWGS should be kept in mind because simple L-thyroxine replacement completely resolves symptoms and abnormalities and prevents unnecessary investigations for malignancies and surgeries.

P2-294

Hypothyroidism presenting with left sided Brown's syndrome

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An 11-year-old female presents with a 6-week history of double and blurred vision associated with headaches and neck swelling. Thyroid function tests demonstrated antibody negative hypothyroidism and connective tissue disorder screening was negative. The patient was commenced on thyroid hormone replacement (levothyroxine). 5 days later, she re-presented with strabismus and progressive diplopia. Intracranial imaging was performed to rule out space occupying masses. A diagnosis of left sided Brown's syndrome secondary to hypothyroidism was made. Initial treatment consisted of conservative management with a Fresnel prism whilst continuing levothyroxine to reach euthyroid status. Patient has remained clinically stable since presentation with no further recurrence of symptoms.

Further tests after her first presentation included thyroid antibody and connective tissue disorder screening, an adrenocorticotrophin stimulating test and glucose levels which were all normal. Importantly, anti-thyroid peroxidase antibodies were not detected. An ultrasound scan described findings consistent with a diffuse goitre. Computerised tomography performed at the time of her second presentation and a follow-up magnetic resonance image of the brain was reported as normal with no evidence of a mass lesion. Specifically, there were normal appearances of the extra-ocular muscles.

A repeat thyroid ultrasound 3 years 8 months from first presentation demonstrated a mildly enlarged thyroid gland with a heterogenous texture and increased vascularity consistent with thyroiditis.

Brown's syndrome is characterised by the inability to elevate the affected eye in adduction due to a mechanical restriction of the superior oblique muscle tendon. Most commonly a congenital condition, acquired cases are usually caused by surgery, trauma or disorders associated with inflammation such as sinusitis, system lupus erythematosus or juvenile rheumatoid arthritis. (1,2)

This is the first published case where Brown's syndrome formed part of the clinical presentation of antibody negative hypothyroidism.

P2-295

Girl with thyroid hormone resistance: A case report

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The syndrome of thyroid hormone resistance (THR), is an inherited condition that occurs in 1 of 40,000 live births characterized by a reduced responsiveness of target tissues to thyroid hormone due to mutations on the thyroid hormone receptor.

We report the case of a girl who presented at 18 months of age with growth retardation persistent tachycardia and chronic diarrhea, serology testing for coeliac disease was negative. Serum levels of total and free T4 and T3 were elevated associated with inappropriately normal TSH levels. Auto-antibodies against thyroid peroxidase (TPO) and TRAC were negative. The diagnosis of THR Diagnosis was based on persistent elevations of serum free T4 and T3 levels in the absence of TSH suppression despite a treatment with antithyroid drugs. The treatment was stopped under clinical follow-up. The confirmation with genetic testing and family screening is planned.

Due to their nonspecific symptomatic presentation, these patients can be misdiagnosed if the primary care physician is not familiar with the condition. The treatment decision depends on the individual characteristics of each patient.

P2-296

Factors related to permanent congenital hypothyroidism

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Purpose: The purpose of this study was to retrospectively analyze the clinical, laboratory, imaging findings (sonography and Tc99m-pertechnetate scanning) in patient with congenital hypothyroidism (CH) who completed 3 years of LT4 medication.

Method: 86 patients with congenital hypothyroidism were retrospectively reviewed. Medical history, laboratory, radiologic finding at the time of CH diagnosis were evaluated. Correlation between permanent CH and factors was analyzed by independent t test and chi-squared test.

Results and Conclusion: Permanent hypothyroidism was associated with TSH levels at the time of CH diagnosis, term infants, thyroid dysgenesis. Thyroid sonography was more likely to predict prognosis than scintigraphy. Half of the patients with thyroid hypoplasia and enlarged thyroid had normal thyroid function after 3 years of treatment.

P2-297

Discrimination between transient and permanent congenital hypothyroidism in patients with eutopic thyroid gland

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Introduction: Congenital hypothyroidism (CH) is diagnosed with neonatal screening and treated early in the neonatal period. Among these patients, transient congenital hypothyroidism (TCH) is included and requires re-evaluation. In this study, we aimed to identify factors that would allow discrimination between permanent and transient hypothyroidism in patients with eutopic thyroid gland.

Methods: We retrospectively analyzed medical records of 77 patients with congenital hypothyroidism and with eutopic thyroid gland. All subjects were treated with levothyroxine and underwent re-evaluation after 3 years of age.

Results: Thirty subjects were permanent CH (PCH) group, and 47 subjects were TCH group. Clinical parameters including TSH and free T4 (fT4) at initial diagnosis were not significantly different between two groups. At re-evaluation after drug discontinuation, TSH and fT4 levels were all significantly different between two groups ($P<0.01$). The optimal cut-off value on the receiver operating characteristic (ROC) curve for permanent prediction with TSH level was greater than 9.2 μIU/mL (sensitivity of 83% and specificity of 94%). The optimal cut-off value on the ROC curve for transient prediction with fT4 level was greater than 1.13 ng/dL (sensitivity of 68% and specificity of 80%).

Conclusion: Thirty patients (40%) with CH and eutopic thyroid gland needed to continue levothyroxine therapy after re-evaluation. TSH and fT4 levels at re-evaluation might have a predictive role in differentiating TCH from PCH in patients with eutopic thyroid gland.

P2-298

Complicated Hypothyroidism in a Child with Trisomy 21

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Introduction: Hypothyroidism is the commonest endocrine disorder which associates with Trisomy 21. It affects the physical and intellectual development of children. It can be either congenital or acquired.

Case Report: 9 years old boy diagnosed patient with Trisomy 21; presented with the complaint of bowel not opened for 3 weeks and grossly distended abdomen.

On the day of admission, he had low-grade fever and settled within 24 hours. He didn't have any systemic symptoms of hypothyroidism and cardiac symptoms other than the distended abdomen and constipation,

He was the 4th born child to non-consanguineous parents. Term baby delivered by an emergency cesarian section due to maternal Pregnancy induced hypertension. Birth weight was 1.5Kg. He had Duodenal Obstruction due to annular pancreas and undergone Duodenoduodenostomy on day 4 of life. He had restricted PDA without Pulmonary Hypertension. At birth, his TSH was normal.

He is having speech and intellectual development delay. Development age compatible with 4 years.

TSH was normal until 4 years of age. Defaulted follow-up afterward.

On examination, he had typical features of Trisomy 21 and short stature (< 5th Centile), mild pallor and coarse skin. No respiratory distress. CVS, Respiratory system and CNS examinations were normal. Abdominal examination was normal except the distended abdomen.

Investigations showed mild anaemia. Serum free T4 0.1ng/dl and TSH >100micIU/ml. Liver functions were deranged. Renal functions normal.

USS Neck, small sized Thyroid gland. USS abdomen normal. 2D ECHO showed moderate size circumferential pericardial effusion without cardiac tamponade.

Due to the acute presentation, he has undergone Anal stretch and Rectal biopsy. Histology showed ganglion cells. He was started on High dose Thyroxin 100 micg/day. Pericardiocentesis done. Sterile pericardial fluid.

Discussion: Our patient had most of the complications related to uncontrolled/untreated hypothyroidism. He had severe constipation which need surgical management, delay in speech and intellectual development, short stature and asymptomatic pericardial effusion.

Early recognition and treatment with thyroid hormone replacement and prevent the need for unnecessary invasive procedures and treatment and complications

Periodic follow-up with Thyroid function test is essential for a better outcome of a child with Trisomy 21.

P2-299

Chronic urticaria associated with Hashimoto's thyroiditis: A case report

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Introduction: Thyroid autoimmunity in chronic urticaria is a growing process and maybe manifested before concomitant with, or several years after the appearance of the urticaria. The association of chronic urticaria with autoimmune thyroid disease has frequently been reported in adults. Limited cases have been reported in children.

Case Report: Here we describe an eleven years old girl. Who was born to non-consanguineous parents. She has a history of recurrent urticarial lesions for 1.5 years over the face, trunk and extremities. She did not respond to antihistaminic drugs. Subsequently, she was diagnosed with hypothyroidism and she was started L-thyroxin. The patient presented with generalized wheals, redness and itching of the face, trunk and extremities. Oedema of the face and extremities. The thyroid gland was not palpable. Systemic examination was unremarkable. Laboratory assessment revealed: TSH: 3.5 µIU/ml (0.7-6.4), FT4: 1.7 ng/dL (0.8-2), FT3: 3.1 pg/ml (2.4-7). Anti-Thyroglobulin antibodies: 41.6 IU/ml (2.4 -7), Anti- thyroperoxidase antibodies: 188 IU/ml (0 -34) and high IgE.

Conclusion: Screening for thyroid function may be useful in all the patients with chronic urticarial.

P2-300

Thyroid function and congenital heart defects in children with down syndrome at hasan sadikin general hospital, Bandung, Indonesia

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Introduction: Down Syndrome (DS) is a genetic disorder that has a high mortality rate and a large number of comorbidities such as hypothyroidism and heart disease. Thyroid hormones have significant effects on cardiovascular. This study aims to describe thyroid function and congenital heart defects in Down Syndrome children at dr. Hasan Sadikin General Hospital.

Methods: This is a cross-sectional study. The inclusion criteria are patients younger than 18 years of age at dr. Hasan Sadikin General Hospital Bandung during January 1st, 2015 – December 30th, 2019, clinically and confirm karyotyping diagnosed with DS, and had an examination of thyroid function and echocardiography. The data collected were sex, age, nutritional status, thyroid function, and heart abnormalities based on echocardiography.

Results: The characteristics of research subjects were male (63.6%); age 3–5 years (41.6%). There was a significant statistical difference in thyroid function (p=0.005) based on TSH levels before therapy (5.7 IU/L) and during therapy (0.7 IU/L). A total of 29% of subjects experienced tricuspid regurgitation (TR). The most common type of heart defect was PDA (30.0%).

Conclusion: This study showed the prevalence of thyroid dysfunction and heart abnormalities in patients with DS. As much as 65% of the total patients had thyroid dysfunction, and mostly hypothyroidism, with thyroid scintigraphy indicated dyshormonogenesis. The most common heart defect was PDA. Cardiac function in patients with DS and heart defects was still within normal limits.

Keywords: Down syndrome, congenital heart defects, hypothyroidism, tricuspid regurgitation

Late Breaking

P2-301

Analysis of Factors Affecting Bone Mineral Density in Children and Adolescents with systemic lupus erythematosus

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Background: Children and adolescents with chronic disease are at risk of developing bone fragility. In particular, low bone mineral density (BMD) is increasingly recognized in pediatric patients with glucocorticoid treated rheumatic disease. The purpose of this study was to evaluate the clinical characteristics of children and adolescents with systemic lupus erythematosus (SLE), and to analyze the factors associated with a lower BMD in these patients.

Methods: Children and adolescents diagnosed with SLE who had received GC treatment were included. Clinical and laboratory data including anthropometry, GC exposure, other anti-rheumatic drug treatment, biochemical markers related to bone metabolism, serologic markers of disease activity in SLE, lateral thoracolumbar (D-L) spine radiography, and BMD were collected. Lumbar spine bone mineral density (LSBMD) was measured by Dual-energy x-ray absorptiometry (DXA). The correlation between BMD and anthropometry, steroid and anti-rheumatic treatment, biochemical variables was investigated.

Results: A total of 30 patients with median age of 17.5 years (range 12 -25years) were included. Of the 29 patients who had DXA done, 7 patients had LSBMD z score lower than -2.0, and diagnosed as osteoporosis. SLE patients with osteoporosis were compared with those with a z score higher than -2.0. These patients had longer GC exposure, higher cumulative GC dose, longer hydroxychloroquine exposure. The main factor correlated with a low BMD was duration of GC exposure. BMD was positively correlated with height and weight at diagnosis. Bone metabolic markers and serologic markers of disease activity in SLE had no significant correlation with BMD.

Conclusion: Children and adolescent SLE patients with OP had longer GC exposure, higher cumulative GC dose compared with those with LSBMD z score higher than -2.0. The main factor correlated with a low BMD was duration of GC exposure. Therefore, efforts should be made to reduce the duration of GC exposure and reduce medication to the lower possible maintenance dose. Since longer treatment duration affects BMD, close monitoring during the treatment period is recommended to prevent further loss of bone mass in pediatric SLE patients.

P2-302

Pseudohypoparathyroidism- Presented with a convulsion

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Introduction: In Pseudohypoparathyroidism (PHP), parathyroid glands are normal or hyperplastic and they can synthesize and secrete parathyroid (PTH) hormone. Serum immunoreactive PTH are elevated even when the patient is normocalcemic. Neither endogenous nor administered PTH raises the serum Ca or lowers the levels of P. Depending on the phenotypic and biological findings, PHP is classified into various types.

Case Report: 9 years old girl Presented with 2nd episode of a convulsion while walking. It was not associated with fever. 1st convulsion occurred 6 months before with similar semiology and was awake at that time also.

2nd born child to healthy non consanguineous parents with birth weight of 2.5kg. She is having bronchial asthma since 5years of age, and it is under control. No delay in achieving development milestones. Recently noted poor school performances were there.

On examination, found to have short stature (<-2SD). Afebrile, alert, no neurocutaneous manifestations, no subcutaneous nodules. There was shortening of bilateral 1st and 4th fingers. CNS including fundi, CVS, Respiratory system and abdominal examination was normal.

Investigations: CBC, Liver and Renal profiles were normal. Serum Ca was low (1.43 mmol/L) and serum P was elevated (3mmol/L). Serum PTH was markedly elevated (750 pg/ml). Xray hands showed bilateral shortening of 1st and 4th metacarpal bones. Bone age was compatible with the chronological age. EEG excluded the possibility of epilepsy.

Non contrast CT brain; bilateral symmetrical calcifications of basal ganglia, thalami and sub cortical white matter in the frontal and parietal lobes. There was no evidence of nephrocalcinosis. Ocular calcifications were excluded.

Started her on CaCO3 and 1alfa cholecalciferol.

Discussion: With the history and examination, other than finding a cause for afebrile convulsion, we worked on short stature as well. With that we evaluated our patient on short stature. Her afebrile convulsions, decline in school performances and short stature were nicely explained with the final diagnosis of Pseudohypoparathyroidism. The learning point was evaluation of a patient with a good clinical history and examination will guide to a proper diagnosis. After starting treatment, there was an improvement in her school performances as well as an improvement in her biochemical parameters.

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P2-303

Donohue syndrome in a Turkish infant: Mild clinical course despite severe genetic mutation

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Donohue syndrome (DS) is a rare and often lethal autosomal recessive disease. Its prevalence is estimated less than one in a million live births. Mutations in the insulin reseptor (INSR) gene cause rare severe INSR-related insulin resistance syndromes such as DS. It is characterized by severe insulin resistance (hyperinsulinemia, fasting hypoglycemia and postprandial hyperglycemia), intrauterine and postnatal growth retardation, hypotonia, organomegaly including heart, liver, kidneys and ovaries, developmental delay, hypertrichosis, reduced subcutaneous fat and prominent nipples. Patients with DS have typical facial dysmorphism with thick lips, broad nose, proptosis, large and low set ears.

We report the case of surviving Turkish boy with DS who had typical facial dysmorphism, lipoatrophy, muscle wasting, nipple hypertrophy, macropenis and generalized hypertrichosis. Echocardiogram showed consentric left ventricular hypertrophy in his cardiological examination. He had homozygous mutation in exon 4 of the INSR gene (c.1049C>T / p.Ser350Leu). Both parents were found heterozygous for the mutant allele. There are currently no effective treatments for DS. Management aims to normalize blood glucose. Metformin treatment was started to normalize blood glucose (30 mg/kg/day initial dose) but discontinued at the first week due to the fasting hypoglycemia. During his follow-up, hyperglycemia exceeding 200 mg/dL was rarely observed and he had no hypoglycemia without treatment. Since his condition was stable, he was discharged from the hospital with frequent oral feeding at the second month of his life. At the last visit in our outpatient department, the patient was 16 -month old. His weight gain and height velocity were sufficient. His left ventricular hypertrophy didn't get worse in monthly cardiological follow-up.

Although our patient has a severe phenotype, on the contrary, he has a mild clinical course. This condition may be explained by the degree of insulin resistance and residual binding capacity. In conclusion, it is very important to perform preimplantation genetic diagnosis and provide genetic counseling to families with a risk of having an affected child with these syndromes. Identification of this mutation will help families planning future pregnancies and having healty children.

P2-304

Diabetic ketoacidosis associated with hypertriglyceridemia in the pediatric age group – A case report

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Introduction: Diabetic ketoacidosis (DKA) is a potentially fatal hyperglycemic emergency primarily associated with type 1 diabetes mellitus (T1D). The association between DKA and severe hypertriglyceridemia has already been previously discussed with a prevalence ranging between 7.1%-25%, with pancreatitis present in the majority of cases. Epidemiological data in the pediatric age are scarce and not well established. Its etiology is not yet fully known. The "cryptic triangle" (DKA, hypertriglyceridemia and pancreatitis) is a rare and serious condition.

Objective: To report a case of DKA associated with severe hypertriglyceridemia without acute pancreatitis.

Case Description: Female patient, 13yo, previously healthy, diagnosed with T1D and severe DKA. A lipemic sample was identified and hypertriglyceridemia (7110 mg/dL) was confirmed. At hospitalization, levels of serum amylase, lipase and imaging exams did not suggest pancreatitis. The patient was discharged using simvastatin (20 mg/day), and a basal-bolus insulin regimen (0.8 IU/kg/day).

Discussion: Hypertriglyceridemia can lead to acute pancreatitis and, consequently, to DKA by destroying pancreatic beta cells. However, it can also be a consequence of DKA, as the lack of insulin leads to an increase in triglycerides, which in turn could lead to acute pancreatitis. The association between DKA and hypertriglyceridemia occurs due to lack of insulin, leading to enlarged lipolysis, increased production of VLDL by the liver due to increased hepatic fatty acid flow, which, in addition to ketogenesis, can be secreted as VLDL. In addition, VLDL clearance is decreased by inhibiting lipoprotein lipase activity, responsible for hydrolyzing triglycerides into fatty acids, in peripheral tissues. Two main mechanisms for pancreatitis due to changes in lipid metabolism resulting from DKA are suggested: (a) fatty acids when carried by albumin are not toxic, but if they are in large quantities, endothelial lipase degrades the fatty acids and increases the pancreatic lysolecithin activity; (b) chylomicrons would damage the distal pancreatic circulation, inducing ischaemia and altering the acinar function, in addition to exposing the tissue to triglycerides and activating pancreatic lipase. The differential diagnosis between DKA associated or not with acute pancreatitis is challenging due to the overlapping symptoms and laboratory tests. DKA is a severe complication of T1D and its association with other disorders can worsen the prognosis.

Conclusion: There is a paucity of data in the literature about treatment recommendations for acute hypertriglyceridemia, with most case reports using fibrates for handling it. The triad hypertriglyceridemia, DKA and pancreatitis is associated with increased mortality and complications.

P2-305

Poor Infant Feeding Practices and Type 1 Diabetes Mellitus: Any Correlation?

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Background: Type 1 diabetes mellitus (T1DM) is a chronic immune mediated condition where autoimmunity against pancreatic beta cell is triggered by many environmental factors in genetically susceptible person. Association of poor infant feeding practices as potential risk factor for developing T1DM is still debatable.

Objective: The aim of this study is to look for association of infant feeding malpractices with type 1 diabetes mellitus in developing countries.

Methodology: It is prospective observational case control study conducted at Paediatric Endocrinology and Diabetes Clinic of Hameed Latif Hospital, Lahore. Total 60 children, aged 1-18 year were included, with 30 known T1DM (case) and 30 healthy non-diabetic (control). Different infant feeding malpractices such as lack of exclusive breastfeeding for 6 months, introducing cow milk before 1 year of age and early weaning (before 6 months of age) were noted in both groups. These risk factors were statistically assessed for their association with T1DM by Chi square test with p value <0.05 considered significant.

Results: Lack of exclusive breastfeeding for first 6 month of life does not seem to be associated with T1DM (p=0.532). Introducing cow milk before 1 year of age and early weaning (before 6 month of age) seems to be a significant risk factor for T1DM with p values of 0.02 and 0.045 respectively.

Conclusion: Introduction of cow milk in infancy and early weaning seems to be an important risk factor in developing type 1 diabetes mellitus. However, further studies with large cohort are needed to confirm this association.

P2-306

Clinical Spectrum of Associated Autoimmune Conditions in Children with Type 1 Diabetes Mellitus (TIDM) in Developing Countries

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Background and Aim: Type 1 diabetes mellitus (TIDM) is not an inherited condition and 80% of children with T1DM have no family history of diabetes. It is associated with other autoimmune conditions with hypothyroid being the most common followed by celiac disease. However, most of this data is from developed countries. The aim of this study is to determine the incidence of different autoimmune conditions in T1DM and to look for the clinical pattern of autoimmunity in families of T1DM in developing countries.

Methodology: Retrospective review of all T1DM children presented in Paediatric Endocrine and Diabetes Clinic of a tertiary care hospital over last 1 year.

Results: Total 47 cases (25 females) were included. Mean age of diagnosis of T1DM was 6.3 year (8m – 14 years). Mean duration of diabetes was 1.8 year (2 m – 8.5 years). Parental consanguinity was found in 21 cases (44.7%).

Total 6 cases (12.8%) were having other autoimmune conditions with celiac disease being the most common (n=6), followed by hypothyroidism (n=1) and autoimmune hepatitis (n=1). Family history of autoimmune condition was found in 18 cases (38.3%) with T1DM being the most common (n=8), followed by celiac disease (n=4), hypothyroidism (n=4), vitiligo (n=2), hyperthyroidism (n=1), nephrotic syndrome (n=1), and rheumatoid arthritis (n=1).

7 cases (14.9%) of cohort had a sibling with autoimmune condition (T1DM=4, celiac=2, and nephrotic syndrome =1). Mother with known autoimmune condition was found in 7/47 cases (14.9%), with T1DM being the most common (n=5), followed by hyperthyroidism (n=1), hypothyroidism and vitiligo (n=1). There are 4 cases (8.5%) where father was having pre-existing autoimmune condition (T1DM=2, hypothyroidism=1, vitiligo=1). Detailed extended family history showed 9 cases (19.2%) of our cohort had autoimmunity in extended family (6 cases from paternal side, 3 from maternal).

Conclusion: Children with T1DM in developing countries seems to have 12.8% incidence of other autoimmune diseases with celiac being the most common. Autoimmune conditions in family were found in 38.3% with T1DM being the most common condition.

P2-307

Hypoglycemia as a result of skewed thiopurine metabolism in two pediatric patients

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Introduction: 6 Mercaptopurine (6MP) is a cornerstone of maintenance therapy in pediatric acute lymphoblastic leukemia (ALL). Fasting hypoglycemia is a rare side effect of 6MP therapy that has been observed in children being treated for ALL. We present two pediatric patients who developed symptomatic, fasting hypoglycemia during maintenance therapy.

Case Description: A 7-year-old male with standard risk B ALL receiving maintenance therapy presented after an overnight fast with lethargy, slurred speech, and emesis and was found to have a serum glucose of 24 mg/dl. Symptomatic hypoglycemia resolved after infusion of D10W. The patient had been receiving escalating doses of 6MP and methotrexate in an attempt to achieve adequate myelosuppression over the preceding months, and had been complaining of intermittent nausea and vomiting. 6-Thioguanine nucleotide (6TG) was measured at 298 pmol/8x 10E8 RBCs and 6-methylmercaptopurine (6MMP) 33,100 pmol/8x 10E8 RBCs.

An 8-year-old male with relapsed B ALL in second remission receiving maintenance therapy presented after an overnight fast with lethargy, weakness and diaphoresis and was found to have a serum glucose of 39. Symptomatic hypoglycemia resolved after infusion of D10W. The patient also had symptoms of an upper respiratory infection and was found to be infected with rhino/enterovirus. 6TG was measured at 182 pmol/8x 10E8 RBCs and 6MMP 21,051 pmol/8x 10E8 RBCs.

Both patients underwent a diagnostic fast, during which no further episodes of hypoglycemia were noted, making a primary endocrinological disorder unlikely as the cause of their hypoglycemia. Thyroid studies were normal. Both patients had markedly elevated 6MMP levels.

Discussion: 6MP is metabolized to 6TG which is myelosuppressive and reduces the risk of re-emergence of the leukemic clone, and 6MMP which can increase the risk for hepatotoxicity and hypoglycemia. Although the exact mechanism remains unknown, it is theorized that elevated 6MMP levels disrupt the conversion of alanine to pyruvate in the liver, consequently impairing gluconeogenesis. 6MMP levels >5700 pmol/8x10E8 RBCs are associated with hepatotoxicity. Strategies to mitigate this unusual side effect include modifications of 6MP administration such as morning or twice daily administration, or adding allopurinol to decrease the formation of 6MMP and increase the formation of 6TG.

Conclusion: Fasting symptomatic hypoglycemia may occur in pediatric patients receiving 6MP. While uncommon, 6MP related hepatotoxicity may lead to pauses in chemotherapy and limit the tolerated doses of 6MP thereby increasing the risk for relapse. Evidence-based strategies which lessen 6MP associated toxicities during maintenance therapy for ALL are needed.

P2-308

LAL-D: KNOW IT TO RECOGNIZE IT

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Introduction: Lysosomal Acid Lipase Deficiency (LAL-D) is a rare and systemic condition, secondary to LIPA gene mutations, responsible for lysosomal accumulation of cholesterol esters and triglycerides. Clinical manifestations are heterogeneous in terms of age of onset, severity and biochemical and radiological findings. Dyslipidemia, hepatomegaly and hepatosteatosis with hypertransaminasemia are the most common features. There is significant evidence of increased risk of premature atherosclerosis and cardiovascular disorders related to the alteration of lipid profile. This case report documents the difficulty in diagnosing LAL-D especially in the context of common clinical pictures associated with obesity-related metabolic syndrome.

Case Report: F. is a 12-year-old child in follow-up for obesity (weight 83 kg, height 164 cm, BMI 30.8 kg/m2, BMIz +2.94), metabolic syndrome, severe hepatosteatosis and familial hypercholesterolemia (total cholesterol 265 mg/dl, LDL-C 191 mg/dl, HDL-C 27 mg/dl) related to LDLR (low density lipoprotein receptor) gene heterozygous mutation, in dietary-nutritional and pharmacological treatment with pravastatin. Father with ill-defined liver cirrhosis awaiting transplant. In the suspicion of hypertransaminasemia (AST 60 U/L, ALT 129 U/L) secondary to statin toxicity, this therapy was temporarily suspended. Clinical picture substantially unchanged after 6 months, with persistently elevated transaminases (AST 55 U/L, ALT 144 U/L), appeared compatible with MAFLD (metabolic associated fatty liver disease) aggravated by the condition of familial hypercholesterolemia. The persistence of hypertransaminasemia during observation time, the familiarity for evolutive liver diseases and the severity of steatosis documented by ultrasound, required the exclusion of other causes of liver disease (infectious, autoimmune, metabolic/genetic, nutritional/intestinal, toxic, muscular). In particular, the coexistence of hypertransaminasemia (ALT >1.5 nv), dyslipidemia (LDL> 190 mg/dl, HDL <40 mg/dl) and hepatosteatosis suggested the diagnostic suspicion of LAL-D. Enzyme activity was reduced in dried blood spot (DBS) screening test, so molecular testing was performed to look for mutations in the LIPA gene, which is currently underway.

Conclusion: Although signs and symptoms common to other diseases make identification challenge, LAL-D should be considered in the differential diagnosis of familial forms of dyslipidemia, metabolic syndromes with hepatosteatosis and hypertransaminasemia and pediatric diseases presenting with dyslipidemia and liver storage of intracellular products. The trend, variably progressive, leads to fibrosis, cirrhosis and liver insufficiency. The current availability of DBS screening test may consent an early identification of LAL-D and an improved prognosis thanks to possibility of enzyme replacement therapy with sebelipase alfa to improve lipid profile, liver enzymes and hepatomegaly.

P2-309

Three cases of Latent Autoimmune Diabetes in Youth in Korean Obese Adolescents

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Introduction: LADY (latent autoimmune diabetes in youth) have been proposed in younger type 2 DM with presence of beta cell autoantibodies like LADA in adult. LADA patients showed greater complication risk in the later course of disease compared with type 2 DM. When we see the LADY and the LADA in an age-related continuous spectrum, LADY will have more adverse results than type 2 DM. And a large number of LADY is expected as diabetes related autoimmunity in youth has been reported greater than in adults. In Korea, the presence of autoantibodies among patients with type 2 DM in the age of children and adolescents was reported near one-third and the positive rate was higher in the younger age group. The incidence of prediabetes and type 2 DM among childhood and adolescence is increasing along with the increase of obesity and high autoimmunity with beta cell autoantibodies are expected. However, there are no criteria or clinical guidelines for diagnosing and management these children and adolescents.

Case: Here, we present three cases of obese adolescents with type 2 diabetes or prediabetes with beta-cell autoantibodies. Their clinical characteristics were examined in detail; average height z-score was 0.92, weight z-score 3.37 and BMI z-score was 3.62. Insulin resistance symptom such as acanthosis nigricans showed in all three patients. They are under currently monitoring and continuing life style intervention with two of them are receiving oral hypoglycemic agent.

Conclusion: As more LADY patients with prediabetes or type 2 DM are expected, more efforts for early detection of diabetes progression risk associated autoimmune markers in adolescent population are needed. Long-term studies of beta-cell function monitoring and identification factors which accelerate the clinical courses should be followed.

P2-310

GH treatment in a girl with Acrodysostosis type 2 due to Novo Mutation in PDE4D gene

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Acrodysostosis (ACRDYS) (MIM 101800) is a rare autosomal dominant condition affecting skeletal growth and resulting in primary skeletal dysplasia. Two types of ACRDYS have been described and characterized by distinct references on OMIM database. ACRDYS is similar and often confused with PHP1A, but caused by mutations downstream of the genes involved in PHP1A.

Most of the patients have de novo variants. Both types of ACRDYS present with similar skeletal abnormalities (disproportional short stature with shorter extremities, facial dysostosis, brachydactyly with cone shaped epiphyses, scoliosisor kyphosis) and variable degree of hormone resistance. Patients with ACRDYS 1 present more often with normal intelligence, less facial dysostosis and hormonal resistance to multiple hormones, whereas patients with ACRDYS2 present more often facial dysostosis, neurological abnormalities and intellectual diabilities and no hormonal resistance (3)

We report a patient, who has clinical features of acrodysostosis type 2 and a molecularly confirmed novel pathogenic variant in the PDE4D gene who received GH therapy because of falling growth rate and mildly low GH levels. GH therapy was initiated at 0.2 mg/kg/week – a mid-range dose for children with GHD. Three months later, her serum IGF-1 levels rose from 164 to 312ng/ml. After 1.5 years of treatment her growth velocity increased from 2.3cm/year to 6cm/year. Not any adverse reactions have been observed so far.

P2-311

A novel 2q12 duplication causes intellectual disability and short stature in a Turkish family

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Copy-number variation (CNV) is a kind of malfunction of DNA polymerase to produce extra genetic material which leads to more number of repeats in genes. CNVs have been associated with different clinical phenotypes, such as learning disabilities, short stature, and intellectual disability. The chromosomal microarray analysis is an effective diagnostic method for identifying new CNVs and understanding their clinical effects. In this case report, a variation that has not been reported previously in the literature is presented. This case report will contribute to increasing the knowledge. The CNV (arr [hg19] 2q12.1q12.3 (103,368,824-107,946,062) x3) detected in the index case was also detected in her father and male sibling

P2-312

Karyotype-phenotype correlation and associated problems in patients with Turner Syndrome: a single center Turkish experience

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Background: Turner syndrome (TS) is a genetic disorder related to complete or partial absense of the second X chromosome. TS is characterized by short stature, multiple skeletal anomalies, gonadal failure, autoimmune diseases and multiple congenital organ anomalies. This study aimed to determine phenotype and karyotype correlation and define the frequency of associated problems in TS patients.

Methods: Our retrospective study included 33 TS patients who were evaluated in Pediatric Endocrinology Clinic of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, Turkey between 2010-2020 years.

Results: Mean diagnosis age was 8.1±4.5 years. The most frequent presenting complaint was short stature (87.9%). Cardiovascular pathologies were the most common congenital anomalies (39.4%). This was followed by renal anomalies (36.4%), dermatologic (15.2%), orthopedic (15.2%), ophthalmologic (12.1%) and audiological (12.1%) problems. The incidence of autoimmune disease was 51.5%. The most frequent autoimmune disease was Hashimoto's thyroiditis (45.5%). Growth hormone treatment was given to 29 patients (87.9%). The mean age of GH treatment initiation was 9.6±3.6 years. The mean duration of GH treatment was 4.8±2.7 years. Twenty-seven cases (81.8%) were reached the final height. The mean final height of these patients was 145.5±5.9 cm. According to karyotype groups, renal anomalies were found significantly higher in the monosomic group (p:0,008). Also autoimmune diseases were found significantly higher in the structural group (p:0,026).

We could only reached 12 out of 19 TS patients aged 18 years. 11 of these patients (91.7%) had regular menstruation with oral contraceptive drugs. There was no case who got married or had children. When their educational status was questioned, it was learned that there were 4 students (33.3%) at university. Two patients (16.7%) were graduated from university, 4 patients (33.3%) were high school students and 2 patients (16.7%) were graduated from high school. Only 2 out of 33 patients (6.1%) had mild mental retardation.

Conclusions: Determining the phenotype-karyotype correlation and defining the frequency of associated problems in TS can help increase awareness and early diagnosis of TS. Early diagnosis will improve quality of life in TS patients and could prevent associated problems that may appear during adulthood.

Keywords: Turner syndrome, karyotype-phenotype correlation, associated problems

P2-313

A rare cause of precocious puberty: Hepatoblastoma

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Background: Neoplastic causes of precocious puberty include brain, gonadal, adrenal and germ cell tumors; hepatoblastoma (HB) is only rarely noted [1,2]. HB, is a rare primary hepatic tumor of childhood [3]. It is accompanied by raised levels of alpha-fetoprotein (α-FP). Rarely, beta-human chorionic gonadotropin (β-hCG) levels are elevated, resulting in peripheral precocious puberty (PPP).

Clinical Case: We present a case of rapidly progressive precocious puberty over a one-month period in an otherwise healthy 3-year-old boy. Serum concentrations of α-FP, β-hCG and testosterone were significantly elevated, while follicle-stimulating, and luteinizing hormone levels were suppressed. Imaging was obtained in view of significantly elevated tumor markers. CT of chest and abdomen confirmed a large right-sided hepatic tumor with two metastatic lung nodules. The child underwent liver biopsy confirming hepatoblastoma. He started chemotherapy, and on follow up eventually tumor size did significantly shrink and lung metastasis completely disappeared. Repeat β-hCG was within normal limits after 3 months of chemotherapy. He then underwent right lobectomy and histopathology confirmed it to be hepatoblastoma epithelial type.

Conclusion: β-hCG-secreting HB is an uncommon cause of isosexual precious puberty. β-hCG binds to LH receptors in the testes stimulating testosterone production.

Precocious puberty in boys invariably has an underlying pathologic cause and requires prompt and thorough investigation. Urgent, comprehensive evaluation including baseline hormonal labs with tumor markers to determine central or peripheral cause, and comprehensive imaging are required.

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P2-314

A case of permanent congenital hypothyroidism with *NKX2-1* mutation and optic nerve thickness

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Congenital hypothyroidism can be caused by the wrong formation of the thyroid gland or the defect in the synthesis of thyroid hormone. Among the candidate genes, defect in the gene *NKX2-1* can be presented as thyroid, lung, or brain dysfunction.

An eight-year-old boy was diagnosed as congenital hypothyroidism at the age of 16 days. He was referred to our Pediatric Endocrinology Clinic due to elevated TSH level (36.28uIU/mL). Serum total T3 and free T4 were 125 ng/dL and 1.2 ng/dL. Thyroid sonography showed normal positioned thyroid gland with normal echogenicity. Medication with L-thyroxine started immediately. After 2 months of treatment, he moved to other place and came back to our clinic when he was 26 months, when he had global developmental delay. Serum total T3, free T4, and TSH levels were 161.4ng/dL, 1.23ng/dL, and 22.97uIU/mL, respectively at the time. L-thyroxine dose was increased based on the result of thyroid function test. Because he manifested clinical symptoms involving both thyroid and brain, whole exome sequencing was performed, which revealed likely pathogenic variant in the gene *NKX2-1*. His mother who has tic-like movement also had same mutation. On Brain MRI, there was no abnormal finding in the basal ganglia, however optic nerve thickness was detected. Ophthalmologic consultation and regular follow-up of brain MRI were performed with continuous treatment with L-thyroxine.

Here we report a case of congenital hypothyroidism with *NKX2-1* mutation in an 8-year-old boy with developmental delay and optic nerve thickness.

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