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Single-Center Experience in Patients with Mixed Gonadal Dysgenesis

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What is already known on this topic?

- *MGD is a rare chromosomal DSD with a very diverse phenotype, ranging from a normal male phenotype to an almost female phenotype. The growth pattern of children with MGD has not been sufficiently defined.*

What this study adds on this topic?

- *Since it is a rare disease, there are very few descriptive studies on this subject. This study provides insight into treatment strategies and contributes to the literature by offering information on the phenotypic diversity, follow-up, and treatment of this rare disease group.*

ABSTRACT

Objective: Mixed gonadal dysgenesis (MGD) is an uncommon chromosomal Disorder of Sexual Development (DSD). There is insufficient information regarding clinical findings and growth patterns. This study aimed to provide more information about mixed gonadal dysgenesis, which has not yet been sufficiently defined.

Materials and Methods: Data from 10 patients diagnosed with mixed gonadal dysgenesis were retrospectively reviewed. Clinical presentations, complaints at admission, imaging, genetic results, and treatments received by the patients were examined. Gonadal status and the gender of the patients were reared and evaluated by a multidisciplinary council decision. If received, growth hormone treatment doses and height gains were examined.

Results: The patients' ages at admission range from 6 months to 17.5 years. The median height SDS of the patients was −0.75 (2.73), the mean body weight SDS was −0.49 (±1.46), and the mean body mass index (BMI) SDS was 0.26 (±0.97). The complaints at admission varied, including ambiguous genitalia, short stature, and absence of menstruation. Some patients are completely in the female phenotype, while some are inadequately virilized male phenotype. External Masculinization Score (EMS) ranges from 1 to 6.5. The decision to raise 6 patients as female and 4 patients as male was made by a multidisciplinary council. Growth hormone treatment was administered to patients raised as female and diagnosed with short stature. The height SDS gain in treated patients was 0.42 (±0.49).

Conclusion: Due to its rarity and varied clinical presentation, our knowledge about mixed gonadal dysgenesis is limited. Therefore, early diagnosis and individualized treatment plans are crucial for this patient group.

Keywords: Ambiguous genitalia, disorders of sexual development, growth hormone, mixed gonadal dysgenesis, short stature

INTRODUCTION

Mixed gonadal dysgenesis (MGD) (45X,46XY) is a term used to describe chromosomal mosaicism and is classified under chromosomal disorders of sexual development (DSD) since the Chicago Consensus.[1] Patients with MGD have mosaic 45,X and aberrant chromosomes in 46,XY cells and may have dysplastic streak gonads or normal ovaries/testes. The 45X/46XY mosaicism phenotype is very heterogeneous. It can manifest in newborns due to ambiguous genitalia or in adolescents due to short stature or inability to menstruate.[2] A long-term and most appropriate management approach should be planned for patients with MGD, considering childhood, adolescence, and young adulthood. Planning should take into consideration gender identity, gonadal management, fertility, social adaptation, and hormonal therapy if gonads have been removed. Mixed gonadal dysgenesis typically leans towards early gonadectomy. However, some opinions argue that it may be appropriate to preserve the gonads and monitor them until the patient is old enough to decide.[3]

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Gender assignment for cases should be determined as early as possible, involving various disciplines such as child psychiatry, forensic medicine, ethics, pediatric surgery, pediatric endocrinology, and relevant fields. In selected cases, growth hormone therapy improves adult height, especially in short girls.[4] Early diagnosis is important for both gender assignment and growth hormone therapy. Chromosome analysis is also recommended for boys with short stature of unknown cause.[5] It is stated that growth hormone is not very satisfactory in the long term in men diagnosed with MGD.[4]

The objective of this analysis is to examine the general clinical characteristics, follow-up, growth pattern, and treatment strategies of patients diagnosed with MGD.

MATERIALS AND METHODS

Patient Selection and Follow-up Information

Ten children diagnosed with MGD were evaluated at a single institution between 2000 and 2022. The children were followed up by a pediatric endocrinology/pediatric psychiatry/pediatric surgery team.

The records of 10 patients were reviewed, including findings at presentation, laboratory results, karyotypes, imaging findings, and pathology results. Karyotype analysis was performed on cultured lymphocytes, with at least 20 cells analyzed per patient. The patients' ambiguous genitalia condition was evaluated based on the external masculinization score (EMS).[6]

The gender assignment of the patients, along with surgical and medical treatments, was examined. During follow-up, growth velocity, final heights, puberty signs, and necessary additional treatments were evaluated.

Statistical Analysis

The SPSS version 23.0 (IBM SPSS Corp.; Armonk, NY, USA) program was used for statistical analysis. Categorical measurements were presented as numbers and percentages, and continuous measurements as mean ± SD or median interquartile range (IQR).

Ethics

The cases were evaluated considering the Declaration of Helsinki. The study was approved by the Akdeniz University Ethics Committee (Approval date: May 16, 2023; Approval no. 70904504/347).

RESULTS

The median age at the presentation of the patients was 1.50 (11.50) years, with ages ranging from 6 months to 17.5 years. The median height SDS of the patients was −0.75 (2.73), the mean body weight SDS was −0.49 (±1.46), and the mean body mass index (BMI) SDS was 0.26 (±0.97). Five patients presented with ambiguous genitalia, 4 had short stature, and 1 had amenorrhea. None exhibited Turner stigmata and additional anomalies. Five patients had a completely female phenotype, and 5 had an insufficiently virilized male phenotype. External masculinization scores (EMS) ranged from 1 to 6.5. Seven patients underwent laparotomy and gonadal biopsy. Four patients had bilateral streak gonads, 2 patients had 1 streak and 1 dysplastic gonad, and 1 patient had 1 dysplastic gonad and 1 testis.

Table 1. Clinicopathologic and Cytogenetic Features of 45,X/46,XY Patients

Patient No	Age (Years)	Symptoms	EMS	Prader	Puberty	Karyotype	Gonads	Müllerien Structures	Gender
1	17.5	Amenorrhea	1	1	T3P4	45X(27)/47X,+mar1,+ mar2 (16)/ 46x,+mar (7), SRY+	Streak/streak	+	Female
2	12	Short stature	1	1	T1P1	45X(9)/46,XY (41)	Streak/streak	+	Female
3	9	Short stature	1	1	T1P1	45X(%84)/46,XY(%16)	Streak/dysplasic	+	Female
4	5.5	Short stature	1	1	T1P1	45,X(%8),46,XY(%92)	Streak/streak	+	Female
5	11.5	Short stature	1	1	T1P2	45X(32)/46XY(18)	Streak/streak	+	Female
6	0.5	Ambiguous genitalia	3	3	T1P1	45X(%60)/46,XY (%40)	Streak/dysplasic	-	Female
7	0.5	Ambiguous genitalia	6,5	4	P1	45,X(24)/46,XY(6)	NA	-	8
0.9	Ambiguous genitalia	5	3	P1	45,X(%76)/46,XY(%24)	Testis/dysplasic	-	Male	9
0.6	Ambiguous genitalia	4	3	P1	45X(%90)/46,XY(%8)/ 47XXY (%2)	NA	-	Male	10
3.5	Ambiguous genitalia	3	3	P1	45 X (%90), 46 XY(%8), 47 XYY(%2)	NA	-	Male	

DSD, disorders of sexual development; EMS, external masculinization score.

All had 1 cell line with a 45,X karyotype and a second cell line containing Y chromosomal material. Based on the multidisciplinary council's decision (pediatric endocrinology, pediatric psychiatry, and pediatric surgery), 6 patients were reared as girls and 4 as boys (Table 1).

Clinical Characteristics in Female Children

Four X/XY female children presented with short stature, 1 with amenorrhea, and 1 with ambiguous genitalia. The urogenital examination of 5 patients revealed Prader stage 1, and their EMS score was 1. One patient was at Prader stage 3 with an EMS score of 3. In 4 patients raised as girls, short stature was observed. These patients were treated with a growth hormone dose of 45 mcg/kg/day, similar to Turner syndrome. One of the girls did not have short stature, and 1 patient was not attending follow-up appointments. All these patients had already undergone gonadectomy. Before growth hormone treatment, the mean height SDS of the patients was −3.12 (±0.61) and their mean age was 8.95 (±3.47) years. The growth hormone stimulation test peak responses were below 7 mIU/L. Patients' growth hormone doses were adjusted according to their IGF-1 levels. The median IGF-1 SDS during the treatment period was 1.50 (0.53). Patients received growth hormone treatment for an average of 4.97 (±3.46) years. The height gain was 29.4 (±14.67) cm, and the height SDS gain was 0.42 (±0.49) (Table 2). Additionally, hormone replacement therapy (HRT) was administered to 6 patients for pubertal induction. Hormone replacement therapy initially started with induction using estrogen, followed by a combination of estrogen and progesterone.

Clinical Characteristics in Male Children

No short stature was observed in male children at admission or during follow-up. The final height of the male children could not be determined because some discontinued follow-up. Only 1 patient underwent a gonadal biopsy; 1 gonad was testis, and 1 gonad was dysplastic. No patients underwent gonadectomy. X/XY male children were monitored for malignancy with scrotal ultrasound. Gonadoblastoma did not develop in any patient during follow-up (Table 1).

DISCUSSION

In this article, we present our experience in diagnosis, gender assignment, and management of 10 45,X/46,XY DSD children. The importance of this study arises from the relatively large number of patients with such a rare clinical condition.

Weidler et al[3] suggested an individualized treatment plan for patients diagnosed with MGD. Patients with mild undervirilization and ambiguous genitalia have been considered for orchiopexy, regular self-examination or ultrasound annually, and biopsy (1 prepubertal biopsy and 1 postpubertal biopsy). Patients with female phenotypes are considered for elective gonadectomy.

The risk of gonadal malignancy in patients with MGD has been described to be 10%-15%.[7,8] Some reports suggest a malignancy risk as low as 2%, while others report a high value such as 35%.[9,10] Manuel et al[10] have defined this risk as 2% at the age of 10 years, 5% at the age of 14 years, 16% at the age of 20 years, and 27.5% at the age of 30 years. Therefore, prophylactic gonadectomy was performed on 6 patients who were reared as girls. The other 4 patients, who were reared as males, were planned to be followed up with intermittent examinations (every 3 months) and ultrasound (every year). We did not have any patients who developed gonadal malignancy during our follow-up. However, some patients have been lost to follow-up during monitoring, so their long-term outcomes are unknown.

Seven patients underwent gonadal biopsy. Four patients had bilateral streak gonads, 2 patients had 1 streak and 1 dysplastic gonad, and 1 patient had 1 dysplastic gonad and 1 testis. The gonadal histology did not vary according to the patient's karyotype results, and a low degree of masculinization at birth in females with MGD does not seem to exclude the possibility of testicular tissue with carcinoma in situ.[11] Therefore, a biopsy should be performed during follow-up in patients with MGD.

In patients with MGD, there is a percentile loss starting from infancy due to decreased growth velocity.[4] They also cannot make the pubertal growth spurt.[8] Karyotyping can be performed in all boys with short stature to avoid missing the diagnosis of MGD.[5] This is more likely due to SHOX haploinsufficiency, not GH deficiency.[12,13] Growth hormone treatment enhances adult height in girls and boys.[4,5] These patients are recommended GH treatment at supraphysiological doses, as in Turner syndrome and SHOX haploinsufficiency.[5] Our female patients with MGD also benefited from GH treatment and had height SDS gain. However, there was no short stature in boys with MGD.

All female patients with MGD require HRT at puberty due to gonadectomy. Boys with MGD may enter puberty spontaneously but subsequently need HRT.[11] We gave HRT to 6 female patients with MGD during puberty. The others were lost to follow-up. Therefore, pubertal follow-up could not be done.

Among the limitations of the study, we can list the small number of patients due to a rare genetic disorder. Another limitation

Table 2. General Characteristics of Patients with Growth Hormone Therapy

Patient No.	GH ST	GH Onset Age	Duration of GH Treatment (Year)	GH End Age	BT Height SDS	AT Height SDS	SDS Gain	Height Gain (cm)	Final Height
2	1.9	11.6	2.4	14	−3.6	−3.5	0.1	17.2	140.1
3	2.1	9.1	4.5	13.6	−2.7	−2.2	0.5	31	147
4	0.7	4	10	14	−2.5	−2.5	0	49.5	145.5
5	1.6	11.1	3	14.1	−3.7	−2.6	1.1	19.9	142.5
Mean	1.57 ± 0.61	8.95 ± 3.47	4.97 ± 3.46	13.92 ± 0.22	−3.12 ± 0.61	−2.7 ± 0.55	0.42 ± 0.49	29.4 ± 14.67	143.77 ± 3.08

AT, after treatment; BT, before treatment; GH ST, growth hormone stimulation test; GH, growth hormone.

is that the recommended ideal count of 100 metaphases in chromosome analysis cannot be achieved in some patients. Additionally, we were only able to evaluate patients who presented symptoms and sought treatment from us. These data do not generalize to those who are asymptomatic and undiagnosed. Ultimately, there is a need for studies involving a larger number of patients.

As a result, MGD, due to its rarity and potential presentation with various symptoms, can be challenging to diagnose. It is important to keep this condition in mind for an accurate diagnosis. Owing to its various clinical presentations, management should be individualized for each patient.

CONCLUSION

Mixed gonadal dysgenesis is a genetic anomaly about which we have limited information due to its rarity. The phenotype may present as a female appearance or ambiguous genitalia. The age at admission and complaints may vary. Gender determination and treatment planning are challenging. Therefore, early evaluation by multidisciplinary teams is necessary.

Ethics Committee Approval: This study was approved by the Ethics Committee of Akdeniz University (approval No: 70904504/347, date: May 16, 2023).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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