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Distal Metatarsal Osteotomy in Hallux Valgus Surgery: Chevron Osteotomy

Doğar F, Ozan F, Gürbüz K, Ekinci Y, Bilal Ö, Öncel ES



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Etiology of Overt or Subclinical Hyperthyroidism and Iodine Status in Older Than Sixty Years

60 Yaş ve Üzeri Hastalarda Aşikar ya da Subklinik Hipertiroidi Etyolojisi ve İyot Durumu

Hipertiroidi, İyot, Yaşlı / Hyperthyroidism, Iodine, Elderly

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Özet

Amaç: Tiroid disfonksiyou yaşlı populasyonda mortalite ve ve morbiditeyle ilgili olarak yaygın olarak görülmektedir. Graves Hastalığı tüm hipertiroidizmin nedenleri arasında en sık görülendir. TMNG ise yaşlı popülasyonda daha sık görülmektedir. Tiroid hormonu sentezi için iyot temel moleküldür. Tiroid bezi içersinde iyota oldukça duyarlı olan otonomi kazanmış alanlar oluşabilir. Çalışmamızda 60 yaş ve üstündeki hastalarda hipertiroidi etiyolojisini araştırmayı planladık. Gereç ve Yöntem: Bu çalışmaya 60 yaş ve üstü aşikar ve subklinik hipertiroidi tanısı olan 100 hasta dahil edildi. Hastaların demografik ve klinik özellikleri kaydedildi. Tüm hastaların Anti-tiroid antikorları, tiroid ultrasonografileri ve tiroid sintigrafik incelemeleri yapıldı. Tüm hastaların 24 saatlik idrarda iyot atılımı incelendi. Bulgular: Çalışmaya katılan 81 hasta (%81) aşikar, geriye kalan 19 hasta (%19) ise subklinik hipertiroidi olarak değerlendirildi, bu hastalarda ortalama yaş 70.48 ± 6.16 (60-88 arası) olarak saptandı. İyot maruziyeti 30 hastada mevcuttu ve 11 hastada ise JBP görüldü. En yaygın hipertiroidi nedeni TMNG (%29.2) idi, 8 hastaya herhangi bir tanı konulamadı ve bu hastalar nondiyagnostik (ND) olarak tanımlandı. Tartışma: Bu çalışma yaşlı popülasyonda tirotoksikozun sebeplerinin araştırıldığı ilk çalışmadır. Sonuçlarımız bu popülasyonda TMNG'nin en sık neden olduğunu göstermiştir. JBP olan hastaların öykülerinde iyot maruziyeti mutlaka vardır. Bu sebeple özellikle radyokontrast madde kullanımı olan yaşlı popülasyonda bu durum dikkatli bir şekilde değerlendirilmelidir.

Anahtar Kelimeler

60 Yaş Üstü; Hipertiroidi; Subklinik Hipertiroidi

Abstract

Aim: Thyroid dysfunction is common among older people associated with morbidity and mortality. Overall, the most common cause of hyperthyroidism is Grave's Disease (GD). In the older population however, Toxic Multinodular Goitre (TMG) is more common. Iodine is an essential molecule for thyroid hormone synthesis. This may be due to the presence of autonomic areas with a higher sensitivity to iodine in the thyroid gland. The aim of this study was to detect the etiology of hyperthyroidism among cases older than 60 years. Material and Method: The study included 100 patients ≥60 years or older with hyperthyroidism. Demographic and clinical features of the patients were recorded. All patients were tested for anti-thyroid autoantibodies and underwent thyroid ultrasonographic (USG) and scintigraphic examination. Iodine exposure was detected in 24-hour urine specimens. Results: Eighty-one patients (81%) had overt and the remaining 19 (19%) had subclinical hyperthyroidism and the mean age was 70.48 ± 6.16 (range 60-88). Thirteen patients had recent exposure to iodine and 11 had Jod Basedow Phenomenon (JBP). The most common disease was TMNG (29.2%) and 8 patients had no definitive diagnosis; they were designated nondiagnostic (ND). Discussion: This is the first study that investigates the causes of thyrotoxicosis amoung older people in our country. The results indicated that TMNG was the most common cause. JBP cases had a history of exposure to iodine. For this reason, radiocontrast use in older people should be carefully evaluated with this respect.

Keywords

Older Than 60 Years; Hyperthyroidism; Subclinical Hyperthyroidism

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Introduction

Hyperthyroidism is the exposure of tissues with increased concentrations of thyroid hormones [1]. Hyperthyroidism is more common among women than in men [2]. The most common symptoms of hyperthyroidism are anxiety, nervousness, weakness, weight loss despite increasing appetite, intolerance to heat, sweating, tremor, palpitation, insomnia, increasing frequency of stools, oligomenorrhea and amenorrhea in women and gynecomastia and erectile dysfunctions among men [3].

The most common three causes of hyperthyroidism are Graves Disease (GD), Toxic Multinodular Goiter (TMNG) and Toxic Nodular Goiter (TNG). Graves Disease accounts for 60-90% of all hyperthyroidism cases [4]. However, the frequency of TMNG increases among older cases. Somatic mutations were detected in the thyroid stimulating hormone (TSH) receptor gene in 20-80% of patients [5-6]. Excessive iodine may cause hyperthyroidism in individuals who live in endemic goiter regions or in the presence of autonomic nodules in the thyroid gland; this is called Jod Basedow Phenomenon (JBP) [7]. Iodine exposure may be detected by examining 24-hour urine samples in such patients [8].

The definitive diagnosis of hyperthyroidism in the aged population is important because it is a major cause of morbidity and mortality. The classic symptoms of thyroid dysfunction are usually absent or may be overlooked in older patients, making the diagnosis and subsequent management challenging. However, there is no study on the etiology of hyperthyroidism among the older population in Turkish population. In this study, we aimed to determine the etiology of hyperthyroidism among individuals ≥60 years.

Material and Method

Patient selection: Thyroid function tests (TFT) were done in individuals ≥60 years. The study group included 100 patients with hyperthyroidism with high levels of sT3 and sT4 and low levels of TSH and subclinical hyperthyroidism cases with normal levels of sT3 and sT4 and TSH levels <0.10. Gender, age, history and symptoms-sweating, tremor, nervousness, palpitation, weight loss, insomnia-were recorded.

Laboratory tests: Laboratory tests included fasting glucose (FG), creatinine (Cre), alanin aminotranspherase (ALT), hemoglobin (Hb), white blood cells (WBC), plateletes (Plt), ATPO, ATG, and TRAb (Serum samples were centrifuged at 3000 rpm for 10 minutes and radioimmunoassay technique was utilized using the Brahms kits. Normal range for TRAbs was considered 0-10 u/l; levels over 10 u/l were considered positive) as well as thyroid function tests (TFT). Iodine level in 24-hour urine samples was detected by Sandell-Kolthoff method spectrophotometrically. The results were categorized as severe deficiency for <20 µg/l, intermediate deficiency for 20-50 µg/l, mild deficiency for 50-100 µg/l, normal iodine intake for 100-200 µg/l, higher than normal iodine intake for 200-300 µg/l and excessive iodine intake for >300 µg/l. All patients underwent thyroid ultrasonographic examination and scintingraphy. Thyroid USG examined the size and the parenchymal structure of the thyroid gland and the presence of nodules. Thyroid scintigraphy revealed the shape and the contours of the thyroid gland and the uptake of technetium by the gland.

Statistical analysis:Statistical analysis was run by SPSS version 15.0. Continuous variables were expressed as arithmetic mean ± standard deviation, categorical variables were expressed as percentages. Continuous variables were compared with One-way ANOVA and chi-square test was used for categorical variables. A p value <0.05 was considered statistically significant.

Results

This study included 100 patients with overt hyperthyroidism or subclinical hyperthyroidism with TSH levels < 0.1. Of the patients, 43 were male and 57 were female. Eighty-one patients (81%) had overt and the remaining 19 (19%) had subclinical hyperthyroidism and the mean age was 70.48 ± 6.16 (range 60-88). Thirteen patients had recent exposure to iodine. The mean levels of various biochemical parameters were T3 4.33 ± 2.91 ng/dL, sT4 1.80 ± 1.03 ng/dL, TSH 0.04 ± 0.10 µ/mL, cre 1.09 ± 1.02 mg/dl, FG 119.12 ± 57.29 mg/dl, ALT 22.08 ± 12.75 u/l, WBC 7,27 ± 2.32 103/µL, HB 13.3 mg/dl, PLT 238 x103/µL. The mean amount of iodine in 24-hour urine samples was 200.62 ± 138.30 µg/day (Table-1)

Table 1. Laboratory values of all patients Laboratory values of all patients

Gender (M/F)	43/57
Age (Years)	70.48 ± 6.16 (60-88)
White Blood Cell (103/Ml)	7.27 ± 2.32 (1.28-1.41)
Creatinine (mg/dL)	1.09 ± 1.02 (0.5-8.3)
Alanine Transaminase (U/L)	22.08 ± 12.75 (22-76)
Free T3 ((ng/dL)	4.33 ± 2.91 (1.79-22)
Free T4 ((ng/dL)	1.80 ± 1.03 (0.6-6)
TSH (µlU/mL)	0.04 ± 0.10 (0-0.9)
Urine iodine amount (µg/day)	200.6 ± 138.3 (26-750)

Data were expressed as mean ± Standard error.

The most common condition was TMNG. Patients were categorized in five groups. The first group TMNG included 29, the second group GD included 25, the third group TNG 24, and the fourth group JBF 14 patients. The remaining 8 patients were included in the fifth group designated Nondiagnostic (ND). The overall results were shown in (Table 2).

Table 2. Etiology of the hyperthyroidism in the study group

Etiology	N (%)
Toxic Multinodular Goiter	29
Grave's Disease	25
Toxic Nodular Goiter	24
Jod Basedow Phenomenon	14
Non-diagnostic	8

The most common symptom was intolerance to heat in 79 patients. The clinical features of the patients according to causes of hyperthyroidism were shown in (Table 3). Comparison of laboratory parameters among patient groups did not reveal any significance for FG, Cre, ALT, WBC, Plt, Hb, sT3, sT4 and TSH. Grave's disease was diagnosed in 7 out of 10 patients with ATPO antibodies, in 9 patients out of 12 with ATG antibodies and all 6 patients with TRAb antibodies. Grave's disease was correlated with ATPO (p<0.01), ATG (p<0.001) and TRAb (p<0.001) (Table 4). Jod Basedow Phenomenon was pres-

Table 3. Clinical features of the patients with hyperthyroidism according to etiology

Features (Present/absent)	TMNG n=29	GD n=25	TNG n=24	JBP n=14	ND n=8
Symtoms	26/3	24/1	19/5	2/12	5/3
Sweating	21/8	21/4	18/6	10/4	5/3
Palpitation	18/11	16/9	10/14	6/8	2/6
Weight loss	8/21	6/19	4/20	3/11	0/8
Insomnia	5/24	5/20	4/20	1/13	0/8
Tremor	7/22	9/16	5/19	1/13	1/7
Intolerance to heat	25/4	22/3	17/7	10/4	5/3
Nervousness	4/24	9/16	3/21	3/11	0/8
Fever	0/29	1/24	0/24	0/14	0/8
Visual problems	0/29	0/29	0/24	0/14	0/8
Ophtalmopathy	0/29	5/20	0/24	0/14	0/8

Table 4. Comparisons of the laboratory parameters

	TMNG n=29	GD n=25	TNG n=24	JBP n=14	ND n=8
Age	70.2±4.8	68.5±7.3	73±5.6	68±5.8	74±5.3
Gender (M/F)	9/20	11/14	13/11	7/7	3/5
Creatinine (mg/dL)	1.2±1.7	0.9±0.5	0.93±0.1	1.25±0.8	1.17±0.2
ALT (U/L)	20.1±13	23.8±13.5	20.7±10.5	23.1±14.1	25.7±14.1
FreeT3 (ng/dL)	4.7±2.4	5.2±4.8	4±1.04	3.1±1.3	3.08±0.7
Free T4 (ng/dL)	1.7±0.9	2.2±1.2	1.5±1	1.8±0.8	1.3±0.3
TSH(µI/mL)	0.03±0.06	0.02±0.04	0.03±0.05	0.07±0.05	0.14±0.3
AntiTPO (+/-)	2/27	7/18	0/24	1/13	0/8
AntiTG (+/-)	0/29	9/16	1/23	2/12	0/8
TRAb (+/-)	0/29	6/19	0/24	0/14	0/8
Subclinical hyperthyroidism	5/29	3/25	8/24	2/14	1/8
Overt hyperthyroidism	24/29	22/25	16/24	12/14	7/8
WBC (103/µL)	7.04±2.1	7.02±2.2	7.18±1.9	8.65±3.1	6.81±1.9

TMNG, Toxic Multinodular Goiter; GD, Grave's Disease; TNG, Toxic Nodular Goiter; JBF, Jod Basedow Phenomenon; ND, Nondiagnostic, ALT, Alanine Transaminase FT3, free triiodothyronine FT4 free tetraiodothyronine; TSH; Thyroid Stimulating hormone, WBC, White Blood Cell; AntiTPO, Anti Thyroid Peroxidase antibody; AntiTG Antithyrogloguline Antibody TRAb TSH receptor antibody

ent in 11 out of 13 patients with iodine exposure. Jod Basedow Phenomenon significantly correlated with iodine exposure (p<0.001). The mean amount of iodine in 24-hour urine samples was 172.86 ± 129.77 TMNG, 171.24 ± 103.54 for GD, 159.95 ± 93.42 for TNG, 382.71 ± 16.01 for JBP and 196.37 ± 103.45 for ND. JBP significantly correlated with the amount of iodine in urine (p<0.001) (Table-5).

Discussion

Thyroid dysfunction is a common condition in old age with significant morbidity and mortality [9-10]. The classical symptoms of hyperthyroidism are vague in older patients. Such patients usually present with cardiopulmonary symptoms and complications such as tachycardia, AF, respiratory distress and cardiac failure [11]. Thus, thyrotoxicosis should be diagnosed early and accurately and treated appropriately to prevent complications.

It is well-established that GD is the most common cause of hyperthyroidism [4-12]. On the other hand, TMNG is more common among elderly. However, there is no other study investigating the causes of thyrotoxicosis among older individuals. In a study from Turkey including 116 patients with thyroid dysfunction, where almost half of the patients (50/116) were over 65 years, diagnosis was overt hypothyroidism in 0.4%, subclinical hypothyroidism in 8.5%, subclinical hyperthyroidism in 30%, and overt hyperthyroidism in 16%. However, the study did not investigate the causes of hyperthyroidism [13]. In a report from Denmark including 2 027 208 patients, 1682 were diagnosed with overt hyperthyroidism. All patients underwent thyroid scintigraphy and were investigated for thyroid autoantibodies [14]. The results revealed that 44.1% of patients had TMNG, 37.6% GD, 5.7% TNG, 5.4% mixed type (TRAb positive, scintigraphic multinodular), 2.3% subacute thyroiditis, 2.2% postpartum thyroiditis, 0.8% amiodarone-associated hyperthyroidism and 0.7% lithium-associated hyperthyroidism. Although the coverage rate was high in the study, 24-hour urine samples were not tested for iodine. Thus, JBP diagnosis might have been missed in middle- and old-aged patients who live in endemic goitre regions. In addition, the study included patients with overt hyperthyroidism with high sT3 and sT4 levels and low TSH levels. However, in elderly patients, systemic diseases or stress that decreases serum T3 levels may inhibit the T3 response to hyperthyroidism. Thus, the exclusion of subclinical hyperthyroidism patients from the study could have influenced the results of the study.

In our study, 24-hour urine samples were tested for iodine levels in all patients. Iodine is an essential molecule for thyroid hormone synthesis. The dietary amount of iodine should be 150 µg/day. Only 20% of the iodine ingested with food is taken by the thyroid gland and the rest is excreted with urine. The mean level of iodine in our study was 200.62 ± 138.30 µg/day. This suggests excessive dietary iodine intake in our country where the major source is likely to be salt. Another important finding

Table 5. Iodine status of the patients

		TMNG n=29	GD n=25	TNG n=24	JBP n=14	ND n=8
Iodine exposure (n)		0	1	1	11	0
Urine iodine (µg/day)		172.8±129.7	171.2±103.5	159.9±93.4	382.7±162	196.3±103.4
		7		4	2	4
Urine iodine	<150	19	13	15	1	
	150-200	3	6	3	6	
	200-300	3	3	3	4	
	>300	4	3	3	10	1

of the study was the high number (14 cases) of JBP cases where 11 had a history of exposure to radiocontrast substance. Radiocontrast use in older people should be carefully evaluated with this respect. The high number of JBP, TMNG and TNG patients is parallel to the results of a study from Denmark. This may be due to the presence of autonomic areas with a higher sensitivity to iodine in the thyroid gland of our study patients who spent their childhood and early adulthood in Isparta-where the study was run-which is an endemic goiter region.

Blood samples were collected from each patient for TRAb test. As mentioned above, there are two TRAbs-stimulator and inhibitor. While stimulator TRAb is specific for GD, inhibitor antibodies may also be present in Hashimato disease, type-1 diabetes, primary biliary cirrhosis, Sjogren's syndrome, autoimmune hepatitis, systemic lupus erythematosus, and myastenia gravis patients [15]. Among 100 patients included in our study, 6 were positive for TRAb; they all had GD. Thus, the false positivity rate for this antibody specific for GD was zero. In addition, TRAb was positive in all five patients with ophtalmopathy. Reports from other countries suggest that TRAb is specific for GD [16]. In addition, they have a major role in the pathogenesis of graves ophthalmopathy and pretibial myxedema [17-18]. From another perspective, TRAb was positive only in 6 out of 25 patients (25%) with GD. Other studies reveal discrepant results with TRAb positivity in more than 90% of GD patients [19-20]. This may be due to the use of different measuring methods and reference ranges. It may also be due to the reduction in serum levels with old age.

While the most common symptom was intolerance to heat, sweating, weight loss, and tremor, 14 patients were asypmtomatic. Similar results were obtained in 2/3 of studies investigating hyperthyroidism symptoms in the elderly population [11-21]. We had mentioned that symptoms such as sweating, intolerance to heat and tremor were milder in older patients due to increasing sympathetic activity and respiratory distress and weight loss would be more common compared to younger patients. However, the high number of asymptomatic patients overlaps with the novel concept of apathetic hyperthyroidism. Thus, we suggest physicians to take a detailed history and test for TSH levels in older patients regardless of the reason for their hospital visit.

Eight patients were undiagnosed in our study. Their mean iodine level was 196.37 ± 103.45 µg/day, ATPO, ATG, and TRAb were negative and they showed medium technetium uptake in the scintigraphic examination. If we could have done the RAIU test in those patients, a much more accurate interpretation of their conditions would have been possible. However, it was not possible to purchase the test due to budget limitations.

In conclusion, this is the first study that investigates the caused of thyrotoxicosis in our country. The results indicated that TMNG was the most common cause. However, the small number of patients was the major limitation of the study. Further large-scale studies including the radioactive iodine uptake test are required.

Competing interests

The authors declare that they have no competing interests.

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Machine Learning Techniques in Diagnosis of Pulmonary Embolism

Pulmoner Emboli Tanısında Makine Öğrenmesi Teknikleri

Acilde Yapay Zeka / Artificial Intelligence in Emergency

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Özet

Amaç: Pulmoner emboli (PE), tanıda klinik şüphe ve tanısal laboratuvar ve görüntüleme sonuçlarının yüksek öneme sahip olduğu, yüksek mortalitesi olan bir hastalıktır. Bazı vakalarda antikoagülasyon ve fibrinolitik tedavilere kara vermek zor olmakta ve bu nedenle erken tanı acil tıp açısından önem arz etmektedir.Gereç ve Yöntem: Çalışma Ocak 2010 ve Ekim 2013 arasında acil servise nefes darlığı ve göğüs ağrısı da dahil olmak üzere akciğer şikayetleri ile başvuran 201 hastanın retrospektif kayıtlarına dayanarak tasarlanmıştır. Makine öğrenmesi teknikleri PE tanısında başarı hesaplanması için kullanıldı. Bulgular: PE tespiti için sınıflandırma ağacı yönteminin başarı oranının (%95), KNN sınıflaması (% 75) ve Naive Bayes Sınıflandırmasına (% 88.5) göre daha yüksek olduğu saptandı. Tartışma: Özellikle tanı konmasının zor olduğu hastalarda ve tetkiklerin kısıtlı olduğu acil servislerde, Sınıflandırma ağacı ve Bayes yöntemi gibi makine öğrenmesi teknikleri teşhis veya pulmoner emboli olasılığını tanımlamak için seçilebilir.

Anahtar Kelimeler

Pulmoner Emboli; Makine Öğrenmesi; Yapay Zeka

Abstract

Aim: Pulmonary embolism (PE), is a high mortality disease which clinical suspicion and a variety of diagnostic laboratory and imagingresults have a high importance in diagnose. Anticoagulation and fybrinolytic treatments are hard to decide in some cases therefore early diagnose is important in emergency medicine.Material and Method: The study was designed retrospectively based on the records of the 201 patients who were presenting to Emergency Department with pulmonary complaints including dyspnea and chest pain between January 2010 and October 2013. Results: Machine learning techniques were used for calculating the success in diagnosing PE. The success rate of the classification tree method for detection of PE was 95%, which was higher than that of KNN classification (75%) and Naive Bayes Classification (88.5%). Discussion: Classification tree and Bayesian method can be selected ones to diagnose or define possibility of pulmonary embolism in emergency centers with limited study tests and for the patients difficultly diagnosed.

Keywords

Artificial Intelligence; Machine Learning; Pulmonary Embolism

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Introduction

Pulmonary embolism (PE), is a high mortality disease as blockage of pulmonary artery blood flow of the main branches or sub-branches by a thrombus. It is an urgent cardiovascular disease, and the most common cause is venous thromboembolism (VTE)[1,2]. Mortality of pulmonary embolism in patients with timely diagnosis and have appropriate prophylaxis and treatment, 2-10%, which of 2/3 the incorrect diagnosis or concomitant disease is present mortality up to 30% [1, 3]. The most commonly used laboratory methods to assist in establishing the diagnosis of pulmonary embolism is d-dimer but reliability is low. In radiological imaging, electrocardiography, echocardiography, computed tomography, ventilation-perfusion scintigraphy and pulmonary angiography can be used at specific standard. Pulmonary angiography is of limited use in emergency conditions. Clinical suspicion a variety of diagnostic laboratory and imaging results have a high importance. Anticoagulation and fybrinolytic treatments are hard to decide in some cases therefore early diagnose is important in emergency medicine.

Machine learning is a scientific discipline that deals with design and development processes of command indices to be used for transforming inputs into outputs and enables learning based on data types such as sensor data or database of the computers. It plays a role in gaining skills of perceiving complex patterns and making rational decisions based on data. Learning strategies include supervised learning, unsupervised learning, learning through problem solving, learning via neural networks, and genetic algorithms [4]. Medical use of machine learning is recently in define possibility and diagnosis.

In our study, it is planned to creation of artificial intelligence technique in diagnosing pulmonary embolism using machine learning methods. Medical history, physical examination, biochemical markers and imaging techniques of 201 patients with pulmonary complaints admitted to Mersin University Medical Faculty Hospital Emergency Department between January 2010 - October 2013 were recorded.

Material and Method

Our study was approved by the ethics committee of Gazi University. The study was designed retrospectively based on the records of the 201 patients who were presenting to Emergency Department with pulmonary complaints including dyspnea and chest pain between January 2010 and October 2013.. Based on the tests and examinations performed in the Emergency Department, the patients were grouped into two categories as “pulmonary embolism present” and “pulmonary embolism absent”. Age, sex, risk factors, d-dimer level, echocardiography findings, Doppler findings, and thoracic CT findings of the patients were recorded. The subjects were randomly assigned to education and test groups and the diagnostic accuracy (success) was assessed using MATLAB R2012b.

Results

Classification methods and success rating

Data of a total of 201 patients were used to diagnose PE. To construct a decision tree, 161 (80%) samples were assigned to education group and 40 (20%) to the test group. These samples were evaluated with success rating by using 3 separate machine learning method classification tree (CTREE), Naïve Bayes Theorem (NB), K nearest neighbor (KNN) in order to make PE diagnosis [5-8]. Accuracy (the number of correctly classified positive or negative samples), error ratio (the number of incorrectly classified positive or negative samples) as well as sensitivity (True positive ratio) and specifity ratio (False positive ratio) were calculated with the following formula :

True positive ratio = True positive / True positive + False negative

False positive ratio= False positive / True negative + False positive

Experimental Study

CTREE

In this part, presence of PE was classified using the classification tree. The algorithm formed by the decision tree operates with 95% success rate for detection of PE. The algorithm is shown on Figure 1, Figure 2.

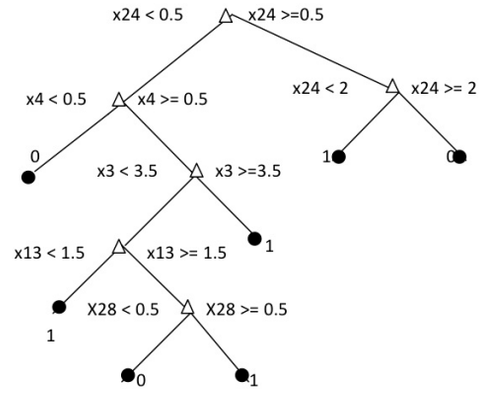


Figure 1. Algorithm of classification tree

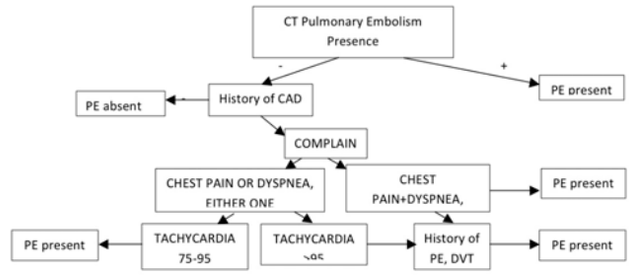


Figure 2. Algortihm of classification tree symptoms and findings with definitions (CT: Computer tomography, CAD: Coronary artery disease, DVT: Deep venous thrombosis)

In the classification study performed with the decision tree on 40 test data the complexity matrix was obtained as shown on Table 1. CTREE correctly identified 28 of 29 PE patients in the test data while it misclassified 1 of them as negative for PE. It also correctly identified 10 of 11 healthy subjects in the test data. Its sensitivity was found 96.5% and its specifity was found 90.9%.

Table 1. Complexity matrix for classification according to Classification Tree Method

		Pulmonary Embolism		
		Present	Absent	Total
CTREE	Present	28	1	40
	Absent	1	10	

KNN METHOD

The success rate of the K nearest neighbor method for detection of PE was 75%, which was lower than that of the decision tree (K=6)(Table 2). Its sensitivity was 77.1% and specifity was 60%. It was determined that the success rate was reduced to 72.5% with K=5.

Table 2. Complexity matrix for classification according to KNN Method

		Pulmonary Embolism		
		Present	Absent	Total
KNN	Present	27	2	40
	Absent	8	3	

NAİVE BAYES CLASSIFICATION METHOD

The success rate of the Naive Bayes Classification Method for detection of PE was 88.5%, which was higher than that of KNN classification. The classification was done on 201 test data. The complexity matrix of this classification was shown on Table 3. With the classification NBO, 134 cases in the test data were true positive and 11 cases were true negative. However, 12 of patients were false negative while 44 of them were false negative. The sensitivity and specifity of the method were found 91.7% and 80%, respectively.

Table 3. Complexity matrix for classification according to Naive Bayes Method

		Pulmonary Embolism		
		Present	Absent	Total
NBO	Present	134	11	201
	Absent	12	44	

Conclusion

The average of annual incidence in United States of America (USA is 1/1000 approximately. The European Union of Cardiology issued a study report of annual number of new cases of PE for Italy, Wales and France as 60000, 65,000 and 100,000 respectively [2]. In USA, annual insidance of pulmonary embolism is estimated as 600,000[9]. These results clearly show its inadequacy of PE in our country. But in recent years due to advances in the imaging and diagnosis of PE is increasing [10,11]. Rapid diagnosis and treatment of pulmonary embolism in the emergency department substantially reduce mortality and morbidity rates. Specific examination of pulmonary embolism, due to lack of laboratory and imaging findings, risk classification is determined. Purpose of determining the probability scores based on risk stratification, treatment approaches for these patients is formed.

This score is most frequently known Wells scoring, “Canadian” scores, also known as the modified Geneva score of patients with clinical probability low, medium and high risk group classification and laboratory investigations along with the evaluation[12-14].

Diagnostic aids that hasten diagnosis and increase diagnostic accuracy have been developed in the form of artificial neural networks and machine learning algorithms. Particularly, studies on imaging methods corroborated by artificial intelligence have been increased in recent years. Bouma et al found in a study that a system educated by 38 data sets created by contrast-enhanced computed tomography images had a sensitivity of 63%[8]. By forming knowledge-based artificial neural networks (KBANN), Serpen et al classified pulmonary embolism diagnosis with the modified criteria of prospective investigation of pulmonary embolism diagnosis (PIOPED) in an attempt to compare the performance of this method with those of other methods such as Bayes and decision Tree, and reported successful results [15]. Differently from PIOPED study(54.5%) , our study has a success rate of %88.5 with Naive Bayes method. Blackmon et al in another study (CAD) for pulmonary embolism diagnosis reported that computer-assisted tomography interpretation help inexperienced healthcare personnel make diagnosis and increased false positivity, albeit to a lesser extent[16]. Falsetti et al compared Wells and Geneva scores with artificial neural networks and found better results for diagnosis with artificial neural networks[17].

Similar with literature, we found same accuracy with the study of Luciani et al (88.6%)[18]. Sensitivity of 91.6% and specifity of 86.6% was similar to our study 91.7% and 80%, respectively. As in this study, no pulmonary angiography used to diagnose in the first place, Luciani et al also found 83.6%, sensitivity 88.8% and specificity 79.6% in the subgroup that pulmonary angiography was not used[18].

Pulmonary embolism has a high mortality rate and its symptoms are occasionally diagnosed in emergency services. Machine learning systems can be used especially in diseases diagnosed with clinical scores. These methods can help physicians that have no advanced diagnosing techniques as V/P sintigraphy, angiography in emergency medicine Classification tree and Bayesian method can be selected ones to diagnose or define possibility of pulmonary embolism.

Competing interests

The authors declare that they have no competing interests.

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A Ten Year Analysis of Fatal Peripheral Vascular Injuries Autopsy Study

Ölümcül Periferik Damar Yaralanmalarının 10 Yıllı Analizi

Periferik Vasküler Yaralanmalar / Peripheral Vascular Injuries

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Özet

Amaç: Periferik damar yaralanmaları genellikle ölümcül yaralanmalara eşlik eder. Erken tanı ve müdahale periferik damar yaralanmalarında olumlu sonuç alınması için hayati önem taşımaktadır. Bu çalışmada 2003-2012 yılları arasındaki dönemde ölüme neden olan periferik damar yaralanmaları değerlendirildi. Gereç ve Yöntem: 2003-2012 yılları arasındaki 10 yıllık dönemde Eskişehir'de otopsi ve ölü muayenesi yapılan 2845 olgu retrospektif olarak değerlendirildi. Çalışmaya dahil edilen olguların yaş ortalamasının 32,5±7,9 olduğu ve olguların en sık 30-39 yaş grubunda olduğu saptandı. Olguların %89,2'sini erkekler oluşturmaktaydı. Ölümlerin en sık sebebinin %83.8 ile cinayetti. En sık yaralanan periferik damarın 29 olguyla femoral arter olduğu belirlendi (%78,4). Çalışmada 33 olgunun (%89.3) olay yerinde hiçbir tedavi almadan öldüğü belirlendi. Tartışma: Çalışmamıza göre periferik damar yaralanmaları en sık kesici-delici alet yaralanmasına bağlı olarak meydana gelmektedir. Yaralanmaların, erken müdahale edildiği takdirde mortalitesi düşüktür. Yapılan otopsi sadece ölüm nedenlerinin değil, ihmal veya malpraktis iddialarına neden olan tedavi sürecinin aydınlatılması açısından da oldukça önemlidir.

Anahtar Kelimeler

Vasküler Yaralanma; Otopsi; Femoral Arter

Abstract

Aim: Peripheral vascular injuries are usually associated with fatal injuries. Early diagnosis and intervention are so vital for improving a favorable outcome for traumatic vascular injuries. As a preventable cause of death, we aimed to evaluate peripheral vascular injuries in overall deaths in ten year period, 2003-2012. Material and Method: A retrospective evaluation was made of 2845 death cases which had post-mortem examination and autopsy from the 10-year period of 2003-2012 in Eskisehir, Turkey. The mean age of the cases included in the study was 32.5±7.9 years with the highest rate of cases occurring in the 30-39 years age group. Males constituted 89.2% of the victims. The most frequent manner of death was homicide 83.8%.The femoral artery was the most commonly injured vessel 29 cases (78.4%). In this study it was identified that, 33 patients (89.3%) died before any medical intervention could be performed. Discussion: Our study shows that, peripheral vascular injuries most commonly caused by sharp objects. The injuries have a low mortality rate when early intervention is made. Autopsies are conducted is very important to explain not only the cause of death but also the treatment process, which would clear the cases of any potential malpractice or negligence claims.

Keywords

Vascular Injury; Autopsy; Femoral Artery

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Introduction

Peripheral vascular injures defined as vessels in the upper extremity such as axillary, brachial and branches and vessels in the lower extremity such as femoral, popliteal and branches account for 40% to 75% of all vascular injuries treated in trauma centers [1-2]. In forensic medicine practice, peripheral vascular injuries are usually associated with fatal injuries of head or torso. Isolated fatal peripheral vascular injuries involving upper and lower extremities including vessels such as femoral, popliteal, brachial, ulnar and radial veins and arteries are uncommon [3]. Although peripheral vascular injuries are common injuries, mortality is largely preventable through early intervention and effective treatment [3-5]. These kinds of injuries arising from blunt trauma are particularly more difficult to diagnose than those occurring from penetrating trauma [6,7].

In the cases of peripheral vascular injuries, the vessel causing death has to be detailed in terms of criminal investigation. If the patient was treated, the compatibility of the hospital records with the autopsy findings must be checked.

In this study, fatal peripheral vascular injuries covering a ten-year period in Eskisehir were retrospectively analyzed and compared with the literature.

Material and Method

A retrospective evaluation was made of 2845 death cases which had post-mortem examination and autopsy covering the 10-year period of 2003-2012 in Eskisehir. Peripheral vascular injury was identified as the sole cause of death in 37 cases (1.3%). In this study, isolated peripheral vascular injuries were examined. Multiple trauma cases and/or other any fatal traumas involving head or torso including peripheral vascular injuries were excluded from the study Thus the study is limited to isolated peripheral vascular injuries as the sole mechanism of death.

Cases were evaluated in terms of age, gender, origin of the event, injury type, location of injury, place of death and vascular injury that caused death. All statistical analyses were performed by using the SPSS 16.0 (SPSS Inc., Chicago, IL, USA) statistical package.

Results

1.3% (n=37) of the medicolegal deaths covering ten year period in Eskisehir were found to be due to peripheral vascular injury. 89.2% (n=33) and 10.8% (n=4) of the cases were male and were female respectively (p<0.001).

The mean age of the cases included in the study was 32.5±7.9 years (range, 19- 56 years) with the highest rate of cases occurring in the 30-39 years age group (n=18, 48.6%) (Figure 1).

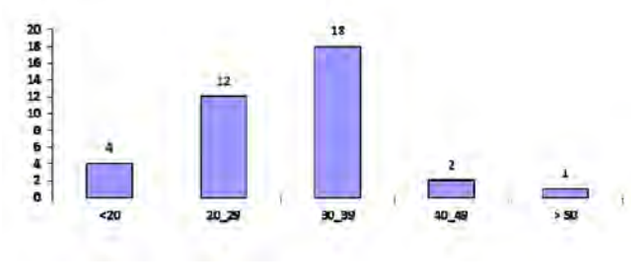


Figure 1. The range of the cases according to age groups.

The assessment of the injury type and origin is presented in Table-1. Sharp object injuries were determined to be the most common type (n = 21, 56.8%). The most common origin of the injury was homicide (n=31, 83.8%). 64.5% of the homicide cases were caused by sharp objects. 12 cases were caused by firearms and all those injuries were caused by handguns. 4 cases (10.8) were due to accidents, 2 of those were due to car accidents, 1 case was due to a train accident and 1 case was due to glass cut which happened at a furniture factory.

Table 1. The Range of Injuries According to Age and Origin

Type of Injury	Homicide		Suicide		Accident		Total	
	n	%	n	%	n	%	n	%
Sharp Object	20	54.1	1	2.7	-	-	21	56.8
Firearms	11	29.7	1	2.7	-	-	12	32.4
Train Accident	-	-	-	-	1	2.7	1	2.7
Car Accident	-	-	-	-	2	5.4	2	5.4
Glass Cut	-	-	-	-	1	2.7	1	2.7
Total	31	83.8	2	5.4	4	10.8	37	100

34 cases (91.9%) and 3 (8.1%) of fatal peripheral vascular injuries involved lower extremity and upper extremity respectively. Of the lower extremity cases, 55.9% (n=19) and 44.1% (n=15) were left sided and were right sided respectively.

It was identified that autopsy was performed in all cases and injured peripheral vessels were described. The range of fatally injured peripheral vessels is presented in Table-2. Femoral artery was the most commonly injured vessel (n=29, 78.4%). Femoral vein injury was accompanied by 86.2% (n=25) of the femoral artery injuries. In 2 cases (75%) of upper extremity injuries, brachial artery injury was accompanied by brachial vein injury. Coexistence of injury of ulnar artery, ulnar vein, radial artery and radial vein were observed in 1 case (25%).

Table 2. Injured Vessels

Extremity	Injured Vessel	n	%
Lower Extremity	A.Femoralis	29	78.4
	V.Femoralis	25	67.6
	A.Poplitea	5	13.5
	V.Poplitea	2	5.4
Upper Extremity	A.Brachialis	2	5.4
	V.Brachialis	2	54
	A.Ulnaris	1	2.7
	V.Ulnaris	1	2.7
	A.Radialis	1	2.7
	V.Radialis	1	2.7

In 8 cases (21.6%) bone fracture accompanied the vascular injury. 3 cases were due to blunt trauma, 2 of those were due to traffic accidents and 1 case was due to a train accident, while 5 cases were due to firearms injuries. Lower extremity was involved in all cases with blunt trauma and 4 cases involved the lower extremity while 1 case involved the upper extremity in the firearms injuries.

It is identified that 1 patient (2.7%) died in hospital, 33 (89.2%) died at the scene and 3 (8.1%) died on the way to hospital. The patient died in the hospital was determined arrest upon arrival

to the emergency department and was pronounced dead after 30 minutes. The mechanism of death in all cases was hypovolemia due to external bleeding.

Discussion

With early intervention and effective treatment, peripheral vascular injuries have a low mortality rate [3-8]. Today, peripheral vascular injuries are accepted as treatable injuries [6-10]. In a study of a ten-year period in Bursa, it was reported that only 0.9% (n=63) of all medicolegal deaths were due to peripheral vascular injury [3]. Similarly, it was identified that 1.3% (n=37) of all medicolegal deaths were due to peripheral vascular injury in the current study covering a ten-year period in Eskisehir.

Deaths due to peripheral vascular injury are more common among males, as in all trauma cases [3-5,11-13]. In a study from Pakistan, it was reported that 86% (n=49) of cases were male, whereas only 14% (n= 8) of cases were female [13]. In a study from Bursa, it was reported that 90.5% of the cases (n=57) were male [3]. In the current study, 89.2% (n=33) of the peripheral vascular injury cases were identified as male and 10.8% (n=4) were female.

In literature, it has been stated that peripheral vascular injuries are more prevalent in young age groups [3, 11-14]. Studies have reported the average age of cases to be 29.4 years in Pakistan [4], 35.6 years in Bursa [3] and 28.9 years in Malatya [16]. In this study, the identified average age was 32.5±7.9 years and the highest rate of cases occurred in the 30-39 years age group (n=18, 48.6%).

In studies on peripheral vascular injuries, sharp object injuries have been determined as the most common injury type [3-5, 13-19]. In the United States, sharp object wounds account for 30% of penetrating peripheral vascular injuries but are a much more common cause in countries in which firearms are more difficult to obtain [20]. In the Bursa study, 58.7% of the cases were reported to be caused by a sharp object [3]. It was determined in accordance with the literature in the current study that injury cases due to a sharp object were the most common type (n=21, 56.8%), 12 injury cases were caused by firearms, the most common origin of injury was homicide (n=31, 83.8%), 64.5% of the homicide cases (n=20) were caused by sharp objects, 35.5% of the homicides (n=11) were caused by firearms and all firearms injuries were caused by handguns.

Although it is easy to diagnose the injury in penetrating traumas, it is more difficult to diagnose in blunt traumas [6,7]. It has been emphasized in studies that bone fractures usually accompany peripheral vascular injuries caused by blunt traumas [21-24]. In a study from Thailand which included 33 blunt traumas, it was reported that bone fractures accompanied the vascular traumas in 26 cases (86.7%) [22]. In the current study, it was identified that the vascular injuries caused by 3 blunt traumas (8.1%) occurred in 2 car accidents and 1 train accident. In all these cases, bone fractures accompanied the vascular traumas. In the car accident cases, femoral bone fractures were accompanied by injuries of femoral artery and vein. In the train accident, it was identified that there was a crush injury involving lower extremity which included a comminuted fracture in the femoral bone which was accompanied by femoral artery and vein ruptures [22].

Studies have emphasized that peripheral vascular injuries can be treated with early intervention [19,21-25]. It was determined in accordance with the literature that 33 cases (89.2%) died at the scene, 3 patients (8.1%) died on the way to the hospital, and only 1 patient who was determined arrest upon arrival to the emergency department died in the hospital.

Injuries were identified to be most common in the left extremity (n=19, 55.9%). Other studies have also identified that peripheral vascular injuries are most frequently seen in the left extremity [3,4,14,18]. Since the majority of injuries have been caused by a sharp object [3-7,11-17] and attackers are usually right handed, the injuries generally involve left extremity. Associated with that is the high rate of injury to the femoral artery (n=29, 78.4%) and femoral vein (n=25, 67.6%). It has been reported that femoral artery and vein injuries are commonly encountered in fatal peripheral vascular injuries [3,4,8,18].

Peripheral vascular injuries are most commonly caused by sharp objects. The injuries might have a low mortality rate when early intervention was made. In this study it was identified that 33 patients (89.3%) died before any medical intervention could be performed. All the death cases were autopsied where peripheral vascular injuries were described and it was identified that none of the patients had the chance of surgical intervention. It is crucial for performing autopsies in terms of clarifying not only the cause of death but also the treatment process and any potential malpractice or negligence claims.

Competing interests

The authors declare that they have no competing interests.

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Comparison of Catether Angiography with Magnetic Resonance Angiography in the Diagnosis of Renal Artery Stenosis

Renal Arter Stenozunda Kateter Anjiografi ile Manyetik Rezonans Anjiyografi Bulgularının Karşılaştırılması

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Özet

Amaç: Tüm hipertansiyonlu olgular göz önüne alındığında, bunların %1–5'inde neden renal arter stenozudur (RAS). Renovasküler hastalığın erken tanı ve tedavisi, renal fonksiyonların korunması bakımından önemlidir. RAS yönünden klinik kuşku taşıyan hasta dağılımında RAS varlığı açısından yüksek doğrulukta araştırma yapmaya olanak veren, non-invaziv, güvenli ve kolay uygulanabilir yöntemler tercih edilmelidir. Gereç ve Yöntem: Ocak 2007 ile Aralık 2011 tarihleri arasında RAS ile uyumlu ya da RAS açısından kuşkulu klinik, fizik muayene ve laboratuar bulguları nedeniyle 4 ayrı merkezde yapılan MRA'da RAS saptanan ve sonrasında kliniğimizde DSA yapılan ve verilerine ulaşılabilen 17-83 yaşları arasında (Ortalama yaş 47,97), 30'u (%42,9) erkek, 40'ı (%57,1) kadın toplam 70 hasta çalışmaya dahil edildi.70 hastada toplam 149 ana renal artere ait MRA ve DSA bulguları retrospektif olarak değerlendirildi. Bulgular: MRA'da 149 renal arterin 89'unda RAS saptanırken DSA'da gerçekte 49 tanesinde RAS olduğu tespit edilmiştir. MRA'nın RAS'ı saptamadaki duyarlılığı %87.8 seçiciliği %54'tür. Duyarlılık literatürle benzer olmakla birlikte seçicilik daha düşük bulunmuştur. Bunun nedeni MRA'nın teknik sınırlamaları ve artefaktlarına bağlıdır. Çalışmada 70 hastada (139 renal ünite) DSA'da 78'i sağ 71'i sol olmak üzere toplam 149 ana renal arter saptanırken, MRA'da 72'si sağ, 68'i sol olmak üzere toplam 140 ana renal arter izlenmiştir. Yine MRA'da toplam 1 hastada 1 adet aksesuar renal arter saptanabilirken DSA'da 12 hastada 17 adet aksesuar renal arter saptanmıştır. Aksesuar arterlerin ve aksesuar arterler kadar ince kalibrasyondaki renal arterlerin saptanması ve bu arterlerdeki stenozların doğru tanınma oranı halen düşüktür. Bunun başlıca sebebi ince kalibredeki arterlerde görüntü rezolüsyonunun sınırlayıcı faktör olmasıdır. Tartışma: Nefes tutmalı 3 boyutlu kontrastlı renal MRA, özellikle otomatik enjektör kullanımı ile bolus zamanlaması yapılarak elde olunduğunda, tekniğin sınırlılıkları ve artefaktlarının bilinip bunların ışığında değerlendirme yapıldığında ve bu sınırlılıklar ile artefaktları minimuma indirecek önlem ya da teknikler kullanıldığında yüksek doğrulukta renal arter stenozlarını belirleyebilen gereksiz radyasyon alımına sebep olan invaziv anjiografik görüntülemelerin önüne geçen noninvaziv bir yöntemdir. Özellikle sensitivitesinin oldukça yüksek oranlarda olması bu tekniğin RAS taramasında güvenle kullanılabileceğini göstermektedir.

Anahtar Kelimeler

Hipertansiyon; Renal Arter Stenozu; Manyetik Resonans Anjiografi; Dijital Çıkarımlı Anjiografi

Abstract

Aim: Renal artery stenosis (RAS) is a cause of 1-5% of all cases of hypertension. The early diagnosis and treatment of renovascular disease is important in terms of the protection of renal function. Noninvasive, safe, simple and accurate imaging methods should be preferred in the diagnosis of RAS. Material and Method: Seventy patients aged between 17-83 years (average age 47.97 years), including 30 males (42.9%) and 40 females (57.1%) that were diagnosed with RAS by Magnetic Resonance Angiography (MRA) were included in the study. The MRA examinations were performed in 4 different centers between January 2007 and December 2011. Physical examination and laboratory findings of all patients were consistent with RAS. Following the MRA evaluation, the Digital Subtraction Angiography (DSA) examinations of all cases were performed in our clinic. A total of 149 main renal artery MRA and DSA findings from 70 patients were evaluated retrospectively. Results: While 89 out of 149 renal arteries were diagnosed with RAS by using MRA, 49 of them were diagnosed by using DSA. In the diagnosis of RAS the sensitivity and selectivity of MRA were 87.8% and 54%, respectively. Comparison with the literature showed that while sensitivity of MRA was similar to the literature, although the selectivity was lower, which might be due to the technical restrictions and artifacts of MRA. In this study we examined 149 main renal arteries in 70 patients by using DSA. Seventy-eight of were right and seventy-one were left renal arteries. Meanwhile, the evaluation with MRA revealed a total of 140 main renal arteries. Seventy-two of these were right, while sixty-eight were left renal arteries. The MRA showed 1 accessory renal artery in 1 patient, whereas DSA showed 17 accessory renal arteries. The detection and correct evaluation of the degree of stenosis of accessory arteries and finely calibrated renal arteries that are similar to accessory arteries is still low. The main reason for this is the relatively low image resolution as a restrictive factor in thinner arteries. Discussion: Breath-hold three-dimensional (3D) contrast enhanced renal MRA is a noninvasive method preventing invasive angiographic examinations that cause unnecessary radiation exposure. MRA can also determine renal artery stenosis with high accuracy, especially with the use of an automatic injector and bolus timing. However, one should be aware of the limitations and artifacts of the technique and precautions should be used to minimize these artifacts. In conclusion, MRA can be used in the screening of RAS confidently because the sensitivity of this method is considerably high.

Keywords

Hypertension; Renal Artery Stenosis; Magnetic Resonance Angiography; Digital Subtraction Angiography

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Introduction

Hypertension is a major public health problem affecting approximately one fifth of the world population [1]. Renal artery stenosis (RAS) is a cause of hypertension in 1-5% of patients [2-5]. Renovascular hypertension (RVH) has been reported to affect 15-30% of cases whose clinical data support renovascular disease [6, 7]. Early diagnosis and treatment of renovascular disease is important for the preservation of renal function. Non-invasive, safe and easily applicable methods that allow detection of RAS with high accuracy should be preferred in patients whose clinical findings are suggestive of this disease entity [1].

In our study, we evaluated the three-dimensional contrast-enhanced magnetic resonance angiography (MRA) and digital subtraction angiography (DSA) images of patients whose clinical findings suggested RVH. The images were taken in our clinic as well as in other clinics. We aimed to investigate the comparative diagnostic value of these methods and to determine which method is superior.

Material and Method

Seventy patients, including thirty (42.9%) males and forty (57.1%) females with a mean age of 47.9 years (17-83 years) and whose RAS were detected using MRA and DSA were included in the study (Figure). A total of 149 main renal artery

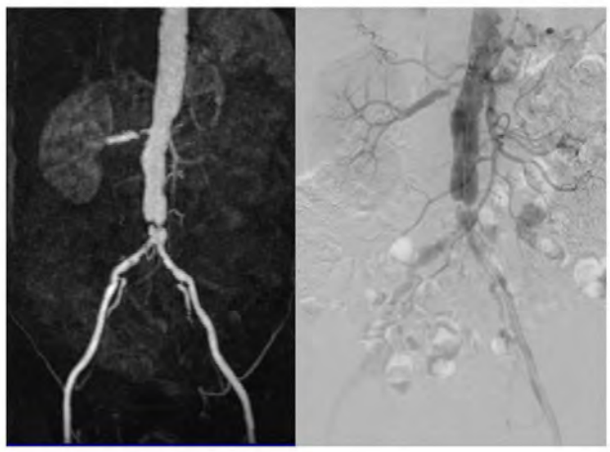


Figure. MRA and DSA images of right renal artery stenosis.

MRA and DSA findings were retrospectively evaluated in the 70 patients. The DSA imaging was performed by using a TOSHIBA Infinix (Toshiba Inc., Tokyo, Japan) angiography device. First, abdominal angiography was performed using the Seldinger method and entering through the femoral or axillary artery and then the renal arteries were selectively catheterized and displayed. Prior to the procedure, the patients' blood pressure was measured and it was investigated whether the patients had bleeding diathesis. Patients were informed about the procedure and their informed consents were obtained. Angiograms were evaluated by a radiologist specialized in this field. The patients' renal parenchymal staining, number of main renal arteries, number of accessory renal arteries, presence of stenosis, location of stenosis, degree of stenosis, etiology of stenosis, and presence of lesions in other vessels within the image range were investigated. In cases of necessity (stenosis of 50% or above), endovascular therapy was done in patients with RAS in the same or at a later session. The MRA imaging was carried out in four different centers. The 1.5 T imaging device (Magnetom Avanto, Siemens, Erlangen , Germany) body total imaging matrix (TIM) coil was used for MRA imaging in our center (Center 1). The breath-hold contrast-enhanced 3D-FSGR (fast spoiled gradient-recalled) sequence MRA imaging was performed by using a 1.5 T device (Intera, Philips, Netherlands) with Q body matrix coil in Center 2, Magnetom Maestro (Siemens, Erlangen, Germany) in Center 3, and in Center 4. In our center the injection of contrast material was performed by using an MR compatible automatic injector (Ulrich, Ulm, Germany), while in other centers the injections were performed manually. The maximum intensity projection (MIP) and 3D images were reconstructed from raw images.

Image Analyses

Three radiologists experienced in the area reported the MRA finding in Center 1. The MRA findings were evaluated based on the raw images and MIP and 3D images reconstructed from those raw images and the results were recorded.

First, we evaluated anatomical localization, size, number and parenchymal signal intensity of the bilateral kidneys. Then, the main renal artery was evaluated in terms of the origin, number, the presence of stenosis, the localization of the stenosis (proximal, middle, distal and long segments), the etiology of stenosis (atherosclerosis, fibromuscular dysplasia (FMD)) and the degree of stenosis. Finally, the presence of accessory renal arteries, and if present the number and presence of stenosis in the accessory renal arteries were determined.

Statistical Analyses

The data was analyzed using SPSS 20. Descriptive statistics such as frequency distribution, mean, standard deviation, and median were used to define the sampling. The distribution of MRA and DSA methods according to the number, presence of stenosis, stenosis segments and the degree of stenosis in the renal arteries was determined separately. In addition, sensitivity and specificity of MRA and DSA methods in terms of RAS were investigated.

Results

1. Comparison of MRA and DSA regarding detection of renal artery numbers and variations

The evaluation of 70 patients with DSA revealed 149 main renal arteries including 78 right and 71 left, while evaluation with MRA showed 140 main renal arteries 72 of which were right and 68 were left.

In 10 patients whose MRA imaging was done in our clinic (Center 1) both the MRA and DSA imaging showed a total of 23 renal arteries: 13 on the right and 10 on the left. The right renal artery in one patient and the left renal artery in another were observed in both tests. The patient whose right renal artery was not seen had a history of right nephrectomy, while the patient whose left renal artery was not seen had a history of severe hypoplasia of the left kidney. In one patient, the MRA detected three right renal arteries, while the DSA detected four.

Furthermore, the MRA did not detect any left renal arteries in two patients; however, the DSA detected two left renal arteries in one of those patients and one renal artery in another patient. The MRA did not detect any right renal arteries in one patient, while the DSA detected one renal artery in the same patient. Moreover, in 3 patients the MRA detected one right renal artery; meanwhile the DSA detected two right renal arteries in those patients. In another patient, 1 right main renal artery was seen by MRA, while 3 right main renal arteries were observed by using DSA. The MRA detected double main renal artery in one patient, but the DSA detected only one main renal artery in the same patient. Double right renal artery in one patient and double left renal artery in another patient was observed using both methods. Both methods showed left kidney hypoplasia in 2 out of 70 patients, right kidney hypoplasia in 4 patients and nephrectomy of the right kidney in 1 patient. Furthermore, both methods showed that in one patient the left kidney had a left iliac fossa and pelvic localization and that the left main renal artery emerged from the left internal iliac artery.

Early branching variation in the right main renal artery was observed in one patient in both methods. The MRA detected 1 accessory renal artery in 1 patient, while the DSA detected a total of 17 accessory renal arteries in 12 patients, 1 accessory renal artery in 8 patients, 2 in 3 patients, and 3 in 1 patient. The accessory renal artery detected in MRA was also observed in the DSA.

2. The sensitivity and selectivity of MRA in diagnosis of RAS

We compared the MRA with DSA in terms of the number of renal arteries in order to determine the sensitivity and specificity of MRA in the detection of RAS. While the MRA detected RAS in 89 of the 149 renal arteries, the DSA detected 49 RAS. These 43 RAS detected in both MRA and DSA were considered true positives. On the other hand, 46 out of 89 RAS detected by MRA were found to be normal renal arteries in DSA (false positive). Moreover, neither of the tests detected RAS in 54 of 149 renal arteries (true negatives), while 6 out of 49 RAS detected by DSA were evaluated as normal renal arteries in MRA (false negative) (Table 1).

Table 1. Comparison of the renal arteries with RAS in MRA and DSA

			DSA		Sum
			RAS (-)	RAS (+)	
MRA	RAS (-)	Number	54	6	60
		%	54.0%	12.2%	40.3%
	RAS (+)	Number	46	43	89
		%	46.0%	87.8%	59.7%
Sum		Number	100	49	149
		%	100.0%	100.0%	100.0%

MRA: Magnetic Resonans Angiography, DSA: Digital Substraction Angiography, RAS: Renal Artery Stenosis

The MRA identified bilateral RAS in 21 out of 70 patients, while the DSA detected bilateral RAS in 9 patients (true positive), unilateral RAS in 6 patients and normal renal artery in 6 patients (false positive). Moreover, the MRA identified that 47 patients had unilateral RAS, however the DSA confirmed only 16 of those patients (true positive), while 27 patients were shown to have normal renal arteries (false positive) and 4 patients were shown to have bilateral RAS (false negative). Neither of the tests detected RAS in 1 patient (true negative). According to these results, sensitivity, selectivity and accuracy of MRA in the detection of RAS were 87.8%, 54% and 65%, respectively.

In our clinic we used an automatic injector, while other clinics did the injections manually. Therefore, we determined the contribution of the use of an automatic injector on the MRA's diagnostic value by calculating sensitivity, selectivity and accuracy separately and these values were found to be 100%, 90% and 95.6%, respectively.

3. The comparison of MRA and DSA in terms of degree and localization of RAS

The DSA determined varying degrees of main renal artery stenosis in 49 patients. Mild stenosis was detected in 18 renal arteries, moderate in 12, severe in 16, and occlusion was detected in 3 renal arteries. Among 18 renal arteries that were identified to have mild stenosis by DSA, MRA showed mild stenosis in 10, moderate stenosis in 5 and normal renal artery in 3. Among 12 renal arteries that were identified as having moderate stenosis by DSA, MRA showed moderate stenosis in 8, severe stenosis in 2, occlusion in 1, and a normal renal artery in 1. Moreover, out of the 16 renal arteries that were determined to have severe stenosis by DSA, 14 were identified to have severe stenosis by MRA as well, but 2 of them were defined as normal. The MRA detected an occlusion in 3 renal arteries, while DSA determined that 2 of them had severe stenosis while 1 had moderate stenosis. In addition, among the 98 renal arteries that were determined to be normal by DSA, 52 were determined to be normal by MRA as well. However, DSA showed mild stenosis in 32, moderate stenosis in 8, severe stenosis in 3, and occlusion in 3 renal arteries.

The evaluation of stenosis localization in 89 patients who were identified to have RAS by using MRA showed ostial or proximal 1/3 localization in 61 renal arteries, central renal artery localization in 13 renal arteries, only distal 1/3 localization in 11 renal arteries and long segment localization in 4 renal arteries. On the other hand, in 49 patients identified to have RAS by using DSA, the stenosis localization was as follows: ostial or proximal 1/3 localization in 42 renal arteries, central artery localization in 5 renal arteries, distal localization in 1 renal artery and long segment localization in 1 renal artery.

4. Comparison of MRA and DSA in terms of RAS etiology and age

Out of a total of 49 RAS cases, 43 cases (88%) had atherosclerosis and 6 cases (12%) had FMD. The comparison of stenosis locations with the etiology showed atherosclerosis in 42 cases with ostial-proximal 1/3 segment localization and 1 case with long segment localization, and FMD in 6 cases with middle 1/3 and/or distal segment localization (Table 2).

The evaluation of age distribution of 49 renal artery cases with RAS revealed that 9 cases were in the 17-39 years age group, 20 cases were in 40-62 years age group and 20 cases were in 63-85 years age group. Forty-three of them (87.7%) had atherosclerosis, while 6 (12.3%) had FMD in their etiology (Table 3).

Table 2. Ethiology of RAS according to the localization of the pathology.

Stenosis Localization	Stenosis		Sum
	Atherosclerosis	FMD	
Proksimal	42	0	42
Middle	0	5	5
Distal	0	1	1
Long segment	1	0	1
Sum	43	6	49

FMD: Fibromuscular Dysplasia

Table 3. The distribution of RAS according to age groups

		Age groups			Sum
		17-39	40-62	63-85	
DSA	RAS (-)	41	32	18	91
	RAS (+)	9	20	20	49
Sum	50	52	38	140	

DSA: Digital Substraction Angiography, RAS: Renal Artery Stenosis

5. The Percutaneous Transluminal Angioplasty (PTA) Rates in RAS

The Percutaneous Transluminal Angioplasty (PTA) procedure was performed in 22 (28%) of the 49 RAS detected patients. PTA was recommended in another 4 patients (8.1%), but the procedure could not be carried out in our clinic for patient-related reasons. Balloon angioplasty alone was applied to 7 patients (32%) that underwent PTA, while the combination of balloon angioplasty and stenting was applied to 15 patients (68%). The PTA procedure did not result in any complications in any of the patients. Additionally, all patients were discharged after 24 hours of observation. Bilateral balloon+stent angioplasty was applied to 3 patients who underwent PTA and unilateral balloon+stent angioplasty was applied to 13 patients. Stent restenosis was observed during the follow-up of one of the patients who underwent PTA and therefore an in-stent balloon angioplasty procedure was applied during the second PTA and in-stent lumen patency was achieved again.

Discussion

Renal artery stenosis (RAS) is a pathology that may cause hypertension, renal ischemia, and end-stage renal failure. The threshold value of RAS that results in hypertension or ischemic injury is not known and varies from patient to patient [8,9,10]. Narrowing of 50-60% of the luminal diameter is considered significant in terms of hemodynamics (10). The most common cause of RAS is atherosclerosis followed by FMD. Early detection of RAS is important in order to prevent permanent damage. Currently, interventional radiological methods are used for treatment of RAS [11]. Although DSA is a gold standard in the diagnosis of RAS, this method is invasive, includes radiation and requires the use of nephrotoxic iodinated contrast agents and thus cannot be used as a screening method. Many tests have been used in the detection of RAS in the past. Among these methods are Doppler ultrasonography and Captopril scintigraphy that investigate functional effects, while techniques such as BTA and 3D-MRA provide morphological information [12]. In recent years, there have been some studies suggesting that MRA could provide functional information [11, 13].

MRA is a noninvasive technique used to display many arterial systems in the body. The conventional MRA methods such as time-of-flight (TOF) and phase contrast (PC) have been previously used to display renal arteries trending towards RAS. Gedroye et al. have reported that the 3D-PC reconstruction method's sensitivity was 84% and specificity was 91% [14]. Although PC MRA provides high quality images, it has several disadvantages such as long procedure time, limitation in the volume that will be examined and difficulty in showing accessory arteries [15, 16]. Servois et al. have reported the 2D-TOF method's sensitivity and selectivity as 70-85% and 78-86%, respectively [17]. The combination of both techniques increases the sensitivity and selectivity values to 87% and 97% [18]. The disadvantage of the TOF technique is signal loss resulting from the movement of protons in different directions in the arteries when the normal laminar blood flow profile is perturbed. This signal loss is evident in low caliber distal portions of vessels and twisted portions of the renal arteries or in the turbulent flow that develops secondary to stenosis [19]. In order to eliminate this problem Prince et al. have suggested using high doses of gadolinium to increase the signal intensity of blood in the displayed volume and reported seeing increased signal in the aorta and its branches in the 3D-TOF sequence [20]. The studies that have used this method have reported seeing increases in sensitivity and specificity (94% and 98%, respectively) [21]. The most important technical feature of this technique was using intravenously injected paramagnetic agents that decreases the blood's T1 relaxation time and thus creates significant contrast difference between the blood and the surrounding tissues. Another important feature of the technique is that it provides images in a very short time (expressed in seconds) during the time when the paramagnetic agent passes through the desired vascular system for the first time [22].

There are many studies in the literature that have used various techniques and some studies have reported contrast-enhanced 3D-MRA's sensitivity and specificity as 88-100% and 90-94%, respectively (11, 23). Thanks to these high rates, the contrast-enhanced 3D-MRA has become a routinely used effective non-invasive screening method to determine proximally located atherosclerotic lesions that are the most common cause of RAS. In our study, the sensitivity of MRA was detected as 87.8%, which was consistent with the values presented in the literature. However, the selectivity, which is the ability to distinguish non-RAS cases, was determined to be 54%, which is lower than values reported in the literature. Various factors might have resulted in a low selectivity. First, the difficulty in the evaluation of stenosis and failure to provide adequate saturation due to spatial pre-saturation in the lumen of finely calibrated veins and a decrease in gadolinium T1's shortening effect may explain these results. Second, improper stenosis diagnosis due to inability to achieve adequate arterial contrast as a result of timing error or due to venous contamination is another possibility. Third, an incorrect stenosis diagnosis due to loss of signal associated with de-phasing artifact in twisted veins or in normal veins with impaired laminar flow could be another reason for the results. Another reason includes the MRA's technical limitations and artifacts such as movement artifacts due to patients' inability to hold their breath. In addition, the inhomogeneity of the properties of devices used for MRA imaging in different centers as

well as the different parameters used in the imaging procedure were important contributors to low selectivity. It is important to know MRA's technical limitations and artifacts for a proper diagnostic approach, to take measures to address these artifacts and limitations in patients with RAS, to take more careful assessment, and if needed to evaluate the patient with other noninvasive techniques such as Color Doppler Ultrasound.

Recent developments in rapid gradient echo imaging and echo-planar technology lead to significant shortening in the examination time and routinely used surface coils have improved the signal/noise ratio and thus increased image quality. This has allowed for the visualization of even very fine caliber accessory arteries [24]. In studies that used MRA to detect RAS, the rate of accessory renal artery detection was between 10-42%. A study by Thornton et al. reported detecting 19 accessory renal arteries in 60 patients [19]. Cobelli et al. have identified a total of 13 accessory renal arteries in 45 patients [25]. In our study, the MRA detected 1 accessory renal artery in 1 patient, while the DSA detected a total 17 accessory renal arteries in 12 patients: this included 1 in 8 patients, 2 in 3 patients, and 3 in 1 patient. The accessory renal artery detected in MRA was also observed in DSA. In conclusion, the rate of detection of accessory renal arteries with MRA was 6% in this study, which is below the rate reported in the literature. However, the detection of accessory arteries and thin renal arteries as accessory arteries and the rate of accurate detection of stenosis in renal arteries were still low. The main reason for this is that image resolution is a limiting factor in small caliber arteries. The decrease in spatial pre-saturation and the shortening effect of gadolinium T1 in the lumen of the small caliber arteries prevents adequate saturation thus making it difficult to evaluate stenosis [24]. For the same reason in our study, 9 out of 149 renal arteries observed by DSA were not detected by MRA. In addition, 6 renal arteries (5 left and 1 right renal arteries) that were visualized as normal by MRA were determined to have RAS of various degrees located in the proximal segment by DSA (false negative).

Stenosis in intrarenal and segmental branches is extremely rare and often seen in young non-azotemic hypertensive patients or in patients with FMD. In our study, the DSA detected segmental stenosis in one patient, however it was not observed in MRA. Difficulties in the diagnosis of such stenosis have been described before. Therefore, although MRA seems to be normal in younger patients or in patients with possible distal or segmental renal artery involvement such as FMD, if there is a clinical suspicion for RAS it is recommended that the patient undergoes DAS [24].

The most common artifacts beside the technical limitations described above often occur due to timing errors. Capturing the intravenously injected contrast agent in the desired vascular system in the arterial phase is essential for a quality image. While early arterial injection cannot achieve adequate signal, late injections lead to contrast of systems related to venous return that superposition with arteries thus making it difficult to evaluate the results. This problem can be overcome by using automatic injector systems with automatic triggering programs that enable contrast agent injections and ensures capturing of the contrast agent in the arterial phase of the desired vascular system. In our study, although the automatic triggering software was used in all centers, the automatic injection system was used only in our clinic (Center 1), while in other centers the contrast material injection was done manually. Performing contrast agent injections manually instead of with automatic injections resulted in timing errors and venous superposition due to enhancement of venous structures, especially the left renal vein in younger patients with rapid circulations. This was likely the reason why MRA detected RAS in 46 of the 149 renal arteries, while DAS showed that those 46 renal arteries were normal (false positive). In our clinic (Center 1) MRA was performed by using an automatic injector and showed 1 stenosis in a total of 23 renal arteries, but this was not confirmed by DSA (false positive). The MRA's sensitivity, specificity and accuracy in detecting RAS were determined to be 100%, 90% and 95.6%, respectively. The important point here is that if the venous return had occurred the evaluation should be done not only based on MIP and 3D images but these findings should also be correlated with raw images, and the possibility of arteriovenous malformation should be especially considered in patients with unilateral venous return [22, 26].

Respiratory artifacts might have been among another limitation for 46 false positives detected in our study. Double-contour appearance and the loss of sharpness in the orifice level in particular associated with an inability to provide optimal breath-hold lead to a false stenosis appearance [26]. In our study, a total of 46 false positives were detected: 19 in the proximal segment, 8 in the middle segment, and 10 in the distal segment. These false stenosis appearances were due to respiratory artifacts, timing errors and de-phasing artifacts associated with turbulent flow at the orifice level especially in cases with stenosis observed in the proximal segment. In order to bring breathing artifacts within the limits so that they won't disrupt the diagnostic quality before the examination, patients should be evaluated for the presence of obstructive or restrictive lung pathologies. Moreover, patients should be evaluated in terms of how long they can hold their breaths and if that period is short the sequence parameters should be adjusted to shorten the examination time. In addition, in patients who are without pulmonary diseases, it would also be useful to give breath-hold training prior to the procedure [27, 28].

Another observation in our study was the exaggerated loss of signal that occurred at the level of stenosis that blocked the accurate determination of the degree of stenosis. Although contrast-enhanced examination largely prevents signal loss, some amount of de-phasing, i.e. signal loss, occurs in severe stenosis or in regions with turbulent flow such as orifice level [26-29]. Indeed, in our study MRA showed moderate stenosis in 5, severe stenosis in 2 and occlusion in 1 renal artery, while the DSA determined those 5 moderate stenoses as mild, 2 severe stenoses as moderate and 1 occlusion as moderate stenosis and we believe that the reason for this was that the signal loss exaggerated the degree of stenosis. Therefore, one must be aware of de-phasing artifact in signal losses observed as localized narrowing of the lumen, especially in orifice levels [11, 30].

In many studies in the literature, it has been reported that atherosclerosis involves the proximal branches of the renal arteries, while FMD occurs in the middle, distal, and intrarenal branches of renal arteries. In our study, atherosclerosis was

present in 43 out of 49 (87.7%) detected RAS and in 42 (97%) of those the involvement was observed in the proximal 1/3 and 1 (3%) was observed in the long-segment of the renal artery. Moreover, there were 6 patients with FMD (12.3%) and in 5 (83%) of them the involvement was in the middle and distal 1/3, and 1 case (17%) was only in the distal 1/3. The distribution of our cases according to the etiology of stenosis localization was consistent with other studies in the literature.

In our study, RAS was detected in 36 out of 70 patients (51.4%) by using DSA, which is the gold standard in detection of RAS. Twenty-two (61.1%) of those patients were males and fourteen (38.9%) were females. The RAS was detected in 49 renal arteries and 40 of those (81.6%) were detected in patients between 40-85 years of age, while 9 of them (18.4%) were detected in patients between 17- 39 years of age. These findings are in line with the literature. In addition, the evaluation of etiology-gender distribution showed that among 49 patients with RAS, FMD was detected in 6 patients: 5 males and 1 female. Additionally, atherosclerosis was detected in 43 patients: 17 males and 13 females. The results of atherosclerosis-gender distribution showed similarity with the literature, but the results of the FMD distribution, which is usually more common in the female population, did not match the literature.

Conclusion

MRA is highly sensitive in the diagnosis of RAS, limits the use of contrast agents, is less invasive than DSA and can safely be used in the diagnosis and screening of hypertension.

Competing interests

The authors declare that they have no competing interests.

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Comparison of B.melitensis and B.abortus Bacteremias with Respect to Diagnostic Laboratory Tests

Laboratuvar Tanı Testleri Açısından B.melitensis ve B.abortus Bakteriyemilerinin Kıyaslanması

B.melitensis, B.abortus, Bakteriyemi, Tanı / B.melitensis, B.abortus, Bacteremias, Diagnosis

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Özet

Amaç: Bruselloz, Brucella melitensis ve Brucella abortus türlerinin sıklıkla etken olduğu bir enfeksiyon hastalığıdır. Bu çalışmada B. melitensis ve B. abortus'un etken olduğu bakteriyemilerin, rutinde sıklıkla yapılan tanı testlerine dayanarak (serolojik test ve kan kültürü pozitifliği), birbirinden ayırt edilebilmesi amaçlandı. Gereç ve Yöntem: Bu çalışmada, Ocak 2010 ve Nisan 2014 tarih aralığında kan kültürlerinden Brucella sp. izole edilen 42 hasta çalışma kapsamına alındı. Bruselloz şüphesi olan hastalardan 8-10 ml kan kültürü için örnek alındı ve BACTEC plus/Aerobic F kültür şişelerine aktarıldı. Alınan kan kültürü örnekleri BACTEC 9240 cihazında (BD Diagnostic, Maryland, USA) 21 gün süre ile inkübe edildi. 42 hastanın her birinin, kan kültürü ile eş zamanlı alınan kan örneğinden ayrılan serumlarda, Rose Bengal ve Standart Tüp Aglütinasyon (STA) (Spinreact, Spain) testleri çalışıldı. Bulgular: Akut bruselloz tanısı konulan hastalara ait en az 2 adet alınan kan kültürü örneklerinin, cihazda pozitif sinyal verme süreleri B. melitensis ve B. abortus türleri için karşılaştırıldığında, anlamlı bir fark olmadığı görüldü (saat için p=0.850; gün için p=0.696). Cihazda pozitif sinyalin en erken 2. günde, 44. saatte; en uzun 6.günde 123.saatte olduğu, cihazda ortalama pozitif sinyal verme süreleri açısından iki tür arasında anlamlı fark olmadığı saptandı. Tartışma: Bu çalışmada B. melitensis (n:22) ve B. abortus'un (n:20) etken olduğu bakteriyemiler arasında yaş, cinsiyet, kan kültürü pozitiflik zamanı ve STA test titre düzeyleri açısından anlamlı bir fark olmadığı görüldü.

Anahtar Kelimeler

B.melitensis; B.abortus; Bakteriyemi; Tanı

Abstract

Aim: Brucellosis are most commonly caused by the Brucella species Brucella melitensis and Brucella abortus. This study was aimed to determine the differences in the routine diagnostic tests (serological tests and blood culture positivity) that differentiate bacteremias caused by B. melitensis and B. abortus. Material and Method: This study included a total of 42 patients from whose blood cultures Brucella sp. were isolated between January 2010 and April 2014. A 8-10 ml blood sample was put into BACTEC plus/Aerobic F culture bottles after being drawn from patients (n:42) with suspected brucellosis. The obtained samples were incubated in BACTEC 9240 device (BD Diagnostic, Maryland, USA) for 21 days. Sera of the blood samples taken simultaneously with the blood culture were studied with the Rose Bengal and Standard Tube Agglutination (STA) tests. Results: In patients with acute brucellosis, B. melitensis and B. abortus species showed no significant differences with respect to time to positive signal in blood cultures (for hours p=0.850; for days p=0.696) and the mean time to positivity. The earliest signal in the device was delivered at day 2., 44th hour and the latest at day 6., 123rd hour. No significant difference was noted between the two species with respect to the mean time to positivity. Discussion: This study did not show any significant differences between B. melitensis (n=22) and B. abortus (n=20) bacteremias with respect to age, sex, time to blood culture positivity, and STA test titer level.

Keywords

B.melitensis; B.abortus; Bacteremias; Diagnosis

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Introduction

Brucellosis, caused by the Brucella species, is one of the most significant zoonotic diseases causing both human and animal infections. Brucellosis is endemic to densely populated developing countries of Asia, Middle East, and Latin America.

Humans are usually infected by directly contacting infected animal tissues, ingesting unpasteurized animal products, or breathing bacteria proliferated in laboratory media. Research has shown that although different Brucella species have been shown to infect domestic animals (cows, sheep, goats, pigs, camels, reindeers, dogs), humans are usually infected by Brucella melitensis, Brucella abortus, Brucella suis, and rarely Brucella canis species [1].

Brucella species are able to escape body defense mechanisms and live intracellularly; thus they cause prolonged, relapsing-remitting infections with a high morbidity. They cause systemic infections that potentially involve any organ or system and are characterized by serious bacteremia. Brucellosis can be diagnosed by isolating the microorganism from blood, body fluids, or infected tissues. Additionally, seropositivity can be demonstrated by a titer of 1:160 or greater in the Standard Tube Agglutination Test (STA), a titer of 1:320 or greater in the Coombs' test, or seroconversion that is supported by clinical signs [2].

Brucella infections are most commonly caused by the Brucella species B. melitensis and B. abortus [3, 4]. B. melitensis is more common in our country [5]. Distinguishing Brucella species from each other is not only important for finding the source of infection, but also for determining clinical and epidemiological characteristics. It has been reported that the infections caused by B. melitensis and B. suis have a more virulent course than those caused by B. abortus and B. canis [5-7].

Identification of these two species clinically and epidemiologically is important. Identification of the Brucella species requires a proper isolation process and a series of biochemical or serological tests (CO2 requirement for growth, urease activity, H2S formation, sensitivity to basic fuchsin and thionin stain, and Tbilisi phage).

In the present study, acute brucellosis patients having B. melitensis and B. abortus bacteremia were compared with each other with respect to age, sex, serological test (STA) titer results, and the time to positive signal in BACTEC 9240 device. Symptoms and signs of cases of acute brucellosis were defined as less than 2 months. It was aimed to differentiate bacteremias caused by B. melitensis and B. abortus by using the differences in the routine diagnostic tests (serological tests and blood culture positivity time) caused by each of the two bacteria to be used in future in cases where the suspected species cannot be isolated or identified. If we find differences between these two types, can be distinguished by using serologic tests and blood cultures positivity time results in the laboratory.

Material and Method

Patient population: This study included a total of 42 patients from whose blood cultures Brucella sp. were isolated between January 2010 and April 2014. A total of 82 patients suspected brucellosis, 42 of them (51.2%) were found positive blood culture. All of 42 patients were diagnosed with acute brucellosis and had bacterial growth in at least two blood cultures.

Blood culture: A 8-10 ml blood sample was drawn from each patient with suspected Brucellosis and then it was put into BACTEC plus/Aerobic F culture. The obtained samples were incubated in BACTEC 9240 device (BD Diagnostic, Maryland, USA) for 21 days. From the bottles that delivered a positive signal, blood samples were drawn for gram staining and subculturing in 5% sheep blood and chocolate agar media and they were incubated under aerobic and 5 to 10% CO2 conditions.

Bacteria identification: To identify proliferating bacteria, gram staining, urease activity, H2S production, and sensitivity to basic fuchsin and thionin (20 and 40 µg/ml) stains were studied. In addition, tests were performed with polyvalent antiserum specific to Brucella species (B. abortus, B. suis, B. melitensis) and lam agglutination test with Brucella abortus and Brucella melitensis monovalent antisera (RSHM antisera, Ministry of Health, Turkish Public Health Institution, Bacterial Zoonosis Research and Reference Laboratory). The species were identified according to the scheme for identification of Brucella species [8].

Serological tests: Sera of the blood samples taken simultaneously with the blood culture samples were studied with the Rose Bengal and STA (Spinreact, Spain) tests, as recommended by the manufacturer. The sera were diluted at a range of 1:20 to 1:1280 for STA.

Statistical Analysis: SPSS 17.0 software package (Version 17.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Sex, age group, serological test results, and time to positive signal in blood culture samples (hour/day) were compared in 42 patients with acute brucellosis caused by B. melitensis and B. abortus species isolated from blood cultures. The categorical data were presented as number and percentage and the continuous variables as median and minimum-maximum. The Fisher Test was used to compare the categorical variables; the non-normally distributed continuous variables were analyzed with the Mann Whitney-U test. A p value of less than 0.05 was considered statistically significant.

Results

Of 42 samples, 22 contained B. melitensis and 20 contained B. abortus. The age range was 5 to 82 years. There was no significant difference between the species with respect to age distribution (p=0.130). The numbers of both sexes were equal in the study population (each having 21 subjects). The demographic characteristics of the patients were summarized in Table 1.

Table 1. Demographics characteristics of bacteraemic patients

Gender	Brucella spp.		Total
	B.melitensis (n)	B.abortus (n)	
Female	9	12	21
	40%	60%	50%
Male	13	8	21
	59%	40%	50%
Total	22	20	42
	100%	100%	100%

The analysis of the anti-brucella antibody levels determined by the STA test revealed that three patients were negative and the maximum titer was 1:1280. No dilution was carried out beyond a titer of 1:1280.

B. melitensis and B. abortus species had no significant differences with regard to the time to positive signal in at least two blood cultures (for hours p=0.850; for days p=0.696). The earliest signal in the device was delivered on the 2nd day, 44th hour and the latest on the 6th day, 123rd hour. The two species had no significant differences in the mean time to positivity. The analysis of the seasonal distribution of the causative species showed that B. melitensis (n:8) and B. abortus (n:8) infections were most prevalent in Summer. The two species did not differ significantly with respect to the month of bacteremia (p=0.849).

Discussion

As in the rest of the developing world, Brucellosis is still endemic to Turkey. Based on the Turkish Ministry of Health Statistics 2005 data, the morbidity rate of brucellosis is 20,32/100.000 and the number of cases was reported to be 14.644 [9].

No sex predilection has been reported among cases infected by B. melitensis or B. abortus [4, 7]. Likewise, our study did not demonstrate any significant differences between the two genders with respect to infection, although B. melitensis was isolated more commonly in men (n=13) and B. abortus was more common in women (n=12) (Table 1).

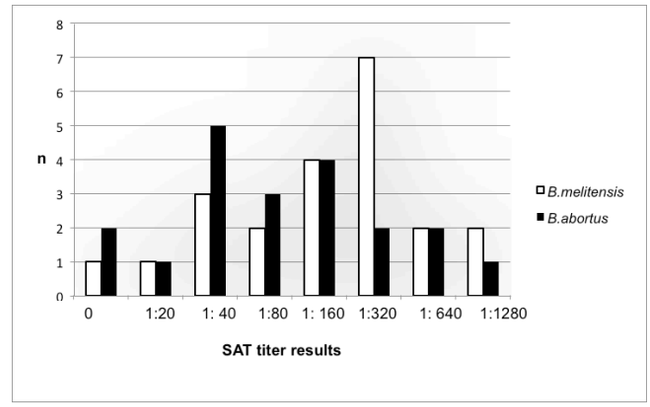
Isolation of the causative agent from blood cultures, bone marrow, and other body fluids is the gold standard for diagnosis of brucellosis [10]. However, bacterial isolation may sometimes be problematic, especially in patients with chronic brucellosis. The overall positivity rate of blood cultures ranges between 15% and 70% [2]. It has been reported that 90% of the Brucella species are isolated within 7 days of culturing with the use of the BACTEC blood culture technique [11]. Isolation rates of 82.4% (12) and 92.7% [13] have been reported after a 5-day-incubation period. In this study, approximately 93% of the acute brucellosis cases could be detected within a 5-day incubation. A positive signal for bacteria was delivered at 6th day in 3 (7%) patients. Extending the incubation period is usually required in order to diagnose all of the cases. In our study, all of 42 acute brucellosis cases could be detected with the BACTEC 9240 device within the first 7 days.

The time to blood culture positivity has been reported 2.9 days (69.87 hours) by Durmaz et al. [14] ; 3,5 days by Yakupsky et al. [15] ; and 2,8 days by Baysallar et al. [16]. There was, however, only one study that specifically studied and found no significant difference between the difference of time to a positive signal in blood cultures between B. melitensis and B. abortus species [13].

An average time to a positive signal of 65.50 hours/3.70 days for B. abortus and 66.00 hours/3.55 days for B. melitensis (p=0,696) suggested that it was not useful in distinguishing the two species from each other.

In the absence of isolation of any causative bacteria, the diagnosis of the disease is made by serological tests (STA, Coombs' test, Brucellacapt test, ELISA methods), detection of the anti-brucella antibodies, or molecular techniques [17]. We found no significant differences between the two species with respect to the titers of the STA test. As shown in Figure 1, however, blood culture proliferation most commonly occurred at a titer of 1:320 for B. melitensis (n=7) and 1:40 for the B. abortus (n=5). Despite being low in number to draw a solid conclusion, the B. melitensis cases, as compared to B. abortus cases, had higher STA titer determined simultaneously with blood culture positivity (Figure 1). This difference may be useful to differentiate the two species. It has been reported that a STA test titer of >1:160 had a sensitivity of 92% for the diagnosis of acute brucellosis [2]. In this study, 24 cases had a titer equal to or greater than 1:160. It was demonstrated that the STA test was diagnostic in 57% (n: 24) of the cases. Eleven (61%) of the 18 cases with a titer less than 1:160 had B. abortus bacteremia. This suggests that in cases with a STA titer less than 1:160 a blood culture should be sent in an attempt to hasten the diagnosis. It was noted that the majority of such cases were B. abortus bacteremia.

Figure 1. Comparison of standart tube agglutination test results with Brucella species in 42 patients



In conclusion, this study did not show any significant differences between B. melitensis (n=22) and B. abortus (n= 20) bacteremia with respect to age, sex, time to blood culture positivity, and the titer of the STA test. The available tests to distinguish species will continue to exist until novel diagnostic methods are introduced.

Competing interests

The authors declare that they have no competing interests.

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Histopathological Analysis of 422 Nononcological Hysterectomies in a University Hospital

Üniversite Hastanesinde Benign Nedenlerle Histerektomi Yapılan 422 Olgunun Histopatolojik Analizi

Histerektomilerin Histopatolojik İncelemesi / Histopathologic Analysis of Hysterectomies

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This manuscript is planned to be presented as a poster in the 13th National Congress of Obstetrics and Gynecology on May 2015.

Özet

Amaç: Bu çalışmanın amacı histerektomi endikasyonları, histerektomi yöntemleri ve histerektomi yapılan hastaların preoperatif klinik tanısı ile histerektomi piyeslerinin histopatolojik bulgularının karşılaştırılmasıdır. Gereç ve Yöntem: Üniversitemizde 2011-2014 yılları arasında histerektomi yapılan 422 hastanın kayıtları ve histerektomi piyeslerinin histopatolojik bulguları retrospektif olarak incelendi. Operasyondan önce malignite tanısı alanlar çalışma dışı bırakıldı. Preoperatif klinik tanı ve postoperatif histopatolojik bulguların korelasyonunu değerlendirmek için Cohen kappa istatistik yöntemi kullanıldı, κ 0,4 ve üzeri değerler uyumluluğu gösterdi. Bulgular: Hastaların ortalama yaşı 51,5 ± 8 idi. 378 Hastaya (%85,5) abdominal histerektomi, 55 hastaya (%12,4) vajinal histerektomi, 9 hastaya (%2) laparoskopik asiste vajinal histerektomi uygulanmıştı. En sık histerektomi endikasyonu anormal uterin kanama (%28,8) idi. Histerektomi öncesi hastaların % 75'ine endometrium örneklemesi yapılabilmişti, en sık bulgu sekretuar veya proliferatif endometriumdu. Histerektomi piyeslerinde en sık saptanan histopatolojik bulgu leiomiyom (%43,7) olup bunu leiomiyom ile adenomiyozis birlikteliği (%17,4) takip etmişti. Prolapsus ön tanısıyla opere olan hastaların %49,3'ünün piyesinde nonspesifik bulgu mevcuttu (kappa=0,407). Tartışma: Preoperatif klinik tanının histopatoloji sonuçlarıyla korelasyonu anormal uterin kanama, myom, ağrı ön tanılarıyla opere edilen hastalarda zayıf iken, adneksial kitle ön tansıyla opere edilen hastalarda güçlü idi.

Anahtar Kelimeler

Histerektomi; Histopatolojik Korelasyon; Uterin Leiomiyom

Abstract

Aim: The aim of the study was to evaluate the surgical indications, routes of surgery and the correlation between preoperative diagnosis and histopathological examination of hysterectomy specimens. Material and Method: Medical records and histopathological findings were reviewed and analyzed retrospectively, in 422 consecutive women who underwent hysterectomy over a two-year period from 2011 to 2014. Those with confirmed malignancy before operation were excluded. Cohen kappa statistics were used to measure agreement between preoperative clinical and postoperative histopathological diagnosis which was found to be fair with **κ value being 0.4. Results:** The mean age of our patients was 51.5 ± 8 years. The abdominal route was used in 378 cases (85.5%), the vaginal route in 55 patients (12.4%) and the laparoscopic-assisted vaginal hysterectomy in 9 cases (2%). Abnormal uterine bleeding (28.9 %) was the most common indication for hysterectomy. The histopathology of the endometrium prior to hysterectomy was reported in 75% of the cases and the most common finding was a secretory or proliferative endometrium. Leiomyomatous uterus was the most frequently encountered pathology (43.7%) followed by coexistence of leiomyoma and adenomyosis (17.4%) in hysterectomy specimens. Hysterectomy specimens may be unremarkable histopathologically, most of which are vaginal hysterectomies done for uterine prolapsed (kappa=0,407). Discussion: The correlation between the preoperative clinical and the pathological diagnosis were poor in cases with abdominal pain, abnormal uterine bleeding and fibroids. But there was a high correlation in cases with adnexial mass.

Keywords

Hysterectomy; Histopathological Correlation; Uterine Leiomyoma

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Introduction

Hysterectomy is widely performed all over the world to manage benign gynecological disorders including fibroids, adenomyosis, benign endometrial hyperplasia, ovarian cysts, uterine prolapsus, pelvic inflammatory disease or malignancy of reproductive organs [1]. The main purpose of hysterectomy is to relieve symptoms and improve quality of life deteriorated by symptoms such as abnormal menstrual bleeding, dysmenorrhea, chronic pelvic pain, bowel and urinary symptoms or uterine prolapsed [2]. Nowadays, the world focuses on successful, effective, safe and cost-effective, minimally invasive treatment options for benign gynecological disorders alternative to hysterectomy such as uterine artery embolization, levonorgestrel releasing intrauterine system or thermal ablation [3]. They can be offered especially as an option to women wishing to conserve their reproductive function. Despite the development of minimally invasive procedures especially for uterine fibroids, hysterectomy is still regarded as the definitive treatment for most pelvic pathologies because of their restricted availability, poor knowledge and high cost [4-7].

Fibroids and adenomyosis are the two most common indications for hysterectomy [8]. The final histopathology results of the hysterectomy specimens of women with leiomyomas revealed the coexistence with adenomyosis ranging from 15 to 57% [9,10].

All hysterectomy specimens should be carefully examined postoperatively even if the histopathological evaluation of endometrium is done preoperatively. Because preoperative histopathological evaluation of endometrium obtained by dilation and curettage (D&C) reduces the risk of unexpected malignancy but does not completely rule out the absence of malignancy in final histopathological evaluation of the hysterectomy specimens [11].

The purposes of our present study are to evaluate the indications of hysterectomy for benign gynecological disorders performed in a university hospital and to compare the correlation between preoperative clinical diagnosis and the final histopathology results of the hysterectomy specimens.

Material and Method

This retrospective study was based on the analysis of the medical records of all patients that underwent hysterectomy due to a history of fibroids, abnormal uterine bleeding, benign endometrial hyperplasia, chronic pelvic pain, ovarian cysts, postmenopausal bleeding, and uterine prolapsus. It was conducted at Bezmialem Vakif University, Istanbul, Turkey between November 2011 and December 2014. 486 women were included in the present study. Hysterectomies performed due to gynecologic malignancy were excluded. After exclusion of 44 patients with malignancies, a total of 442 cases were included in the current study for analysis during the 3- year study period.

The demographic data including age at surgery (years), parity, a history of previous miscarriage, a history of previous Cesarean section, smoking, menopausal status, the preoperative clinical diagnosis, indications for hysterectomy, the histopathology of the endometrium obtained by D&C when available and the final histopathology results of the hysterectomy specimens were all retrieved from the medical records and/or the centralized computer system by the authors. Patients with more than 1 year since the last menstrual period were considered to be menopausal.

Analyses were done using the statistical package for the Social Sciences, version 21 (SPSS, Chicago, IL). Data were reported as mean ± SD, range and percentage. Cohen kappa statistics were used for measurement of agreement between preoperative clinical diagnosis and postoperative histopathological diagnosis of the hysterectomy specimens which was found to be fair with value being 0.4.

Results

Of 422 women, 378 (85.5%) hysterectomies were abdominally performed, 55 (12.4%) hysterectomies were vaginally performed and 9 (2%) were performed via the laparoscopic-assisted vaginal hysterectomy. Hysterectomies were performed alone in 116 women and with salpingooophorectomy in 326 women. Of all women, the demographic and gynecologic characteristics of the patients including age at surgery (years), parity, a history of previous miscarriage, a history of previous Cesarean section, smoking and menopausal status were shown in Table 1. The

Table 1. Demographic and gynecologic characteristics of the cases

Age at surgery (years)	Number of cases	Percentage (%)
<39	6	1.4
40–49	207	46.8
50–59	152	34.4
>60	77	17.4
Parity		
0	18	4.1
1 or more	424	95.9
History spontaneous miscarriage		
0	314	71
1 or more	128	29
History Cesarean section		
0	358	81
1 or more	84	19
Smoking	58	13.1
Menopausal status		
Premenopausal	283	64
Postmenopausal	159	36

mean age at hysterectomy was 51.5 ± 8.2 years and the majority of women who underwent hysterectomy were in their fourth and fifth decades (81.2%). Most women were multiparous (n=424, 95.9%) and premenopausal (n=283, 64%). The indications of hysterectomy consisted of abnormal uterine bleeding, fibroids, uterine prolapse, abdominal pain, postmenopausal bleeding, and others (cervical pathologies, endometrial hyperplasia, e.g.). Abnormal uterine bleeding was the most common indication for hysterectomy accounting for 28.9% of the cases.

Of 335 cases (75%) preoperatively underwent D&C for endometrial sampling, the results of preoperative histopathological evaluation of the endometrium obtained by D&C were presented in Table 2. According to the results of preoperative histopathological evaluation of the endometrium, secretory and proliferative endometrium reported in 116 cases (34.6%) was

Table 2. Histopathology of the endometrium (335 cases)

Parameter	Number of cases	Percentage (%)
Secretory or proliferative endometrium	116	34.6
Endometrial polyp	62	18.5
Simple endometrial hyperplasia	45	13.4
Complex endometrial hyperplasia	5	1.4
Atypical endometrial hyperplasia (simple and complex)	12	3.5
Nonspecific pathology	44	13.1
Disordered proliferative endometrium	19	5.6
Insufficient tissue	17	5
Hormone imbalance effect	11	3.2
Others	4	1.1

the most common finding. The endometrial hyperplasia was found in 62 cases (18.5%). 5 of these patients, 3 of which had complex atypical hyperplasia, 1 complex non-atypical hyperplasia and 1 simple hyperplasia in the preoperative assessments had malignant disease in the final histopathological analysis of hysterectomy specimens.

According to the final histopathological results of the hysterectomy specimens, fibroids (47.5%) were the most common postoperative diagnosis and fibroids coexisting with adenomyosis (17.4%) were reported to be the second most common finding. The results of final histopathological evaluation of hysterectomy specimens including fibroids (n=210, 47.5%; 15 cases with a combination of fibroids and endometrial hyperplasia and 14 cases of fibroids and endometrial polyp), fibroids coexisting with adenomyosis (n=77, 17.4%; 4 cases with a combination of fibroids, adenomyosis and endometrial hyperplasia and 6 cases mixed of fibroids, adenomyosis and endometrial polyp), adenomyosis (n=45, 10.1%), endometrial hyperplasia (n=14, 3.2%), no specific pathology (n=65, 14.7%), endometrial polyp (n=9, 2%) and malignancy (n=9, 2%) were shown in Table 3. Of 9 cases with malignancy reported at final histopathological evaluation of hysterectomy specimens, 5 cases were found to have endometrial cancer, 1 case was found to have stromal sarcoma and 3 cases were found to have ovarian cancer.

Table 3. Final histopathology after surgery

Parameter	Number of cases	Percentage (%)
Fibroids *	210	47.5
Fibroids + adenomyosis**	77	17.4
Adenomyosis	45	10.1
Endometrial hyperplasia	14	3.2
No specific pathology	65	14.7
Endometrial polyp	9	2
Malignancy	9	2
Others	13	2.9

*15 cases with a combination of fibroids and endometrial hyperplasia and 14 cases of fibroids and endometrial polyp

**4 cases with a combination of fibroids, adenomyosis and endometrial hyperplasia and 6 cases mixed of fibroids, adenomyosis and endometrial polyp

Of all cases with malignancy in final histopathological evaluation of the hysterectomy specimens, the results of preoperative histopathological evaluation of the endometrium were reported as benign and all of them had an early stage cancer with well- differentiated. 3 cases of ovarian cancer underwent hysterectomy because of heavy menstrual loss and adnexal mass and the final histopathological evaluation of those hysterectomy specimens were found to have early stage of teratocarcinoma (moderately-differentiated squamous cell carcinoma arising in a mature cystic teratoma) and granulose cell tumor and Sertoli Leydig cell tumor. Of 442 women, 44 (9.9%) had ovarian tumors concomitantly including endometrioma (31.8%), serous cystadenoma (20.4%), teratoma (15.9%), mucinous cystadenoma (11.3%), fibrotechoma (11.3%) and Brenner's tumor (2.3%) (Table 4).

Table 4. The distribution of ovarian tumor detected in cases underwent hysterectomy

Total ovarian neoplasms (44)	
Benign ovarian tumors (41) %	
Endometrioma	14 (31.8)
Serous cystadenoma	9 (20.4)
Unilateral	8
Bilateral	1
Teratoma	7 (15.9)
Mucinous cystadenoma	5 (11.3)
Unilateral	3
Bilateral	2
Fibrothecoma	5 (11.3)
Brenner tumor	1 (2.3)
Malignant ovarian tumors (3) %	
Sertoli leydig cell tumor	1 (2.3)
Granulosa cell tumor	1 (2.3)
Teratocarcinoma	1 (2.3)

The most common indication for surgery was abnormal uterine bleeding (AUB) (n = 128). In 95.9% of women with the preoperative clinical diagnosis of abnormal uterine bleeding, a definite organic pathology was demonstrated in the final histopathology results of the hysterectomy specimens.

When the correlation between the preoperative clinical diagnosis and the final histopathological evaluation of hysterectomy specimens was evaluate: The final histopathology report confirmed the diagnosis with a positive correlation of 63% (Kappa=0.28) in 57 cases who underwent hysterectomy because of fibroids. 69% of cases with adnexal mass in preoperative clinical diagnosis had ovarian pathology in the final postoperative histopathological evaluation (Kappa=0.497). Hysterectomy was performed in 73 cases because of uterine prolapse. A pathology was found in 37 cases (50.6%) and fibroids (n=20, 27.3%) were the most common finding. Nonspecific pathology was reported in 49.3% of all cases (Kappa=0.407). After exclusion of cases with endometrial cancer by D&C in patients with a history of postmenopausal bleeding, 13 (30.9%) cases were found to have fibroids, 7 cases (16.6%) had no pathology and one case (2.3%) had endometrial cancer despite no pathological finding in the preoperative histopathological evaluation of the endometrium.

The Kappa analysis for our data demonstrated that there was no agreement between the preoperative clinical diagnosis and final histopathological evaluation of hysterectomy specimens (Kappa = 0.074). Furthermore, if analysis was stratified by preoperative diagnosis, there was only a good compliance in case

of adnexial mass (Kappa=0.497). In cases underwent hysterectomy because of uterine prolapse in the preoperative clinical diagnosis, no specific pathology was highly reported in the final histopathological evaluation of hysterectomy specimens (Kappa=0.407).

Discussion

Hysterectomy is widely performed in gynecological surgery and provides definitive cure to many benign and malign gynecological diseases although Broder et al. suggested that indications for non-oncological and nonemergency hysterectomy were found to be inappropriate [12,13]. This study focused on the correlation between preoperative clinical diagnosis and the final histopathology results of the hysterectomy specimens. The evaluation of correlation between preoperative clinical diagnosis and the final histopathology results of the hysterectomy specimens provide a contribution for determination of the appropriateness of surgery, preference of conservative therapy, avoiding unnecessary procedures and careful evaluation of indications because as other surgical procedure, hysterectomy is associated with risk factors. Furthermore, there is still a debate about sexual, physical, economical, emotional and medical results of hysterectomy.

There are few studies in the literature to compare the correlation between preoperative clinical diagnosis and the final histopathology results of the hysterectomy specimens. Moreover, their results are not concordant with each other and there is no agreement in the literature in terms of the correlation between both of them. In the light of our results, the Kappa analysis for our data revealed that there was no agreement between the preoperative clinical diagnosis and the final histopathological evaluation. However, in our study, 95.4% of cases who underwent hysterectomy because of abnormal uterine bleeding (the most common symptom of hysterectomy in preoperative clinical diagnosis) had a definite organic pathology in the final results of the hysterectomy specimens. Similarly, Gupta et al. [14] demonstrated that 100% of cases that underwent hysterectomy due to dysfunctional uterine bleeding had an abnormality in the final histopathology results of the hysterectomy specimens.

According to the literature, leiomyoma was reported as the most common indication for hysterectomy [15-17]. In our study, on the other hand, leiomyoma was the second most common indication for hysterectomy, but was the most common result of hysterectomy specimens postoperatively. The preoperative clinical diagnosis of leiomyoma was confirmed with the postoperative histopathological specimens in 63% of the cases. In spite of that, adenomyosis which is the third most common finding followed by fibroids and fibroids coexisting with adenomyosis was totally missed out. This can be explained by the fact that the diagnosis of adenomyosis could not be made preoperatively and it was generally based on the histopathological examination of uterus. Similarly Atılgan et al. [18] reported that the most common finding in the postoperative histopathological specimens was fibroids (40.1%) following by endometrial hyperplasia (38.2%) and adenomyosis (25.4%) in 358 hysterectomy cases.

Most of the hysterectomies were performed through an abdominal route in concordance with a Canadian study (abdominal 78%, vaginal 14%, and laparoscopic 5.9%) [15]. In a study from Turkey including 1484 patients underwent hysterectomy, Yılmaz et al. [19] reported that of all cases, 1072 (72,2%) hysterectomies were abdominally performed, 319 (21.4%) hysterectomies were vaginally performed and 93 (6.2%) were performed via the laparoscopic-assisted vaginal hysterectomy. However, another retrospective analysed hysterectomy cases for two years study from Turkey reported to 93,6% the ratio of abdominal hysterectomies and 6,4% the ratio of vaginal hysterectomies [20]. Despite the presence of minimally invasive surgical options for hysterectomy such as laparoscopic hysterectomy and robotic surgery abdominal route is commonly performed because of limitations of these techniques including the lack of experience, high cost and limited availability [3].

A retrospective study found that the correlation between clinical diagnosis and the pathological diagnosis were poor in cases with abdominal pain or dysfunctional uterine bleeding while there was a high positive correlation of 88% (Kappa=0.37) in cases with fibroid regarding the evaluation of 137 cases [21]. In a study including 1283 cases, Lee et al. [22] showed that 80% of the preoperative clinical diagnoses were confirmed, while Miller et al. [16] indicated that only 50% of the preoperative clinical diagnosis were confirmed in the evaluation of 246 hysterectomy specimens. Another study including 373 cases with non-oncological hysterectomies showed that leiomyoma was the most common finding followed by adenomyosis. Preoperative diagnosis of leiomyoma cases was confirmed with histopathology in almost 50% of hysterectomies whereas the preoperative diagnosis of adenomyosis was completely missed out similar to the results of our study [17].

The final histopathological evaluation of hysterectomy specimens of 5 cases were reported as malignancy of endometrium while the results of preoperative histopathological evaluation of the endometrium were reported as benign. 5 cases of early stage endometrial cancer have a history of hyperplasia in preoperative histopathological evaluation of the endometrium. Only one case with postmenopausal bleeding with preoperative benign histopathology of the endometrium was reported as malignant. A study also found that 5% of cases with preoperative benign histopathology of the endometrium had a malignancy in the final histopathological evaluation of hysterectomy specimens and endometrial hyperplasia was the most common finding in cases with postmenopausal bleeding [21]. Therefore, due to ethical, legal, diagnostic and therapeutic significance, all hysterectomy specimens should be histopathologically evaluated, especially in cases with hyperplasia in preoperative evaluation of the endometrium.

In cases with the preoperative clinical diagnosis of uterine prolapse, there is no specific pathology in final histopathological evaluation of hysterectomy specimens. In literature, the incidentally detection rate of malignancy was found as 0.22% in pre or postmenopausal patients who underwent hysterectomy because of uterine prolapsed [23]. Although a study reported that fibroids coexisting with endometriosis were 10% [24], this rate was 4.5% in our results. This may be the caused by the early age of marriage and childbearing in the present study. There was a good agreement between adnexial mass in the

preoperative clinical diagnosis and the ovarian cyst in the final histopathological evaluation.

In conclusion, although abnormal uterine bleeding was the most common symptom of hysterectomy and fibroids were the most common finding of hysterectomy specimens, the correlation between the preoperative clinical and the pathological diagnosis was poor in cases with abdominal pain, abnormal uterine bleeding and fibroids. But there was a high correlation in cases with adnexial mass. Therefore, the final histopathological evaluation of hysterectomy specimens should be done in all hysterectomy cases. The results of our study may help to reduce inappropriate indications for hysterectomy and increase the tendency towards a conservative approach.

Conflict of interest

The authors declare no conflict of interest related to this work.

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Distal Metatarsal Osteotomy in Hallux Valgus Surgery: Chevron Osteotomy

Halluks Valgus Cerrahisinde Distal Metatarsal Osteotomi: Chevron Osteotomisi

Chevron Osteotomisi / Chevron Osteotomy

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Özet

Aim: Halluks valgus, birinci parmağın laterale deviasyonu ile birinci metatarsın medial deviasyonu sonucu oluşan kompleks bir ayak deformitesidir. Bu çalışmada orta derece deformiteli, semptomatik halluks valguslu hastalara uyguladığımız chevron tipi distal metatarsal osteotomi ameliyatının radyografik ve fonksiyonel sonuçları değerlendirildi. Halluks valgus tanısı ile 22 hastanın (12 kadın, 10 erkek; ort. yaş 45±16.7;dağılım 22-69) 27 ayağına (13 sol, 14 sağ ayak) chevron osteotomisi ile cerrahi tedavi uygulandı. Ortalama takip süresi 15.4 ± 4.71 ay (dağılım, 10–24). Gereç ve Yöntem: Ameliyat sonrası ortalama AOFAS akoru 39.1 ± 8.55 (dağılım, 32–57) den 87.8 ± 4.7 (dağılım, 82–97) yükseldi (p < 0.0001). Ameliyat öncesi halluks valgus açısı (HVA) 37.4 ± 5.8 (dağılım, 29 –50) iken ameliyat sonrası 14.8 ± 3.1 (dağılım, 10 –20) (p < 0.0001) ve ameliyat öncesi ortalama intermetatarsal açı (IMA) 13.1 ± 1.5 (dağılım, 11 –17) iken ameliyat sonrası 7.1 ± 1.4 (dağılım, 5 –9) olarak tespit edildi (p < 0.0001). Ortalama sasemoid pozisiyonu ameliyat öncesi 2.9 ± 0.2 (dağılım, 2-3) iken ameliyat sonrası 1.2 ± 0.4 (dağılım, 1-2) olarak tespit edildi (p < 0.0001). Komplikasyon olarak bir hastada başparmakta hipoestezi gelişti. Takip sonunda, hastaların ameliyat sonucundan memnun kalma düzeyleri 16 ayakta (%59.2) çok iyi, 11 ayakta (%40.8) iyi olarak bulundu.Bulgular: Çalışma sonucunda chevron osteotomisi ile iyi radyolojik sonuç, ameliyat sonrası yüksek hasta memnuniyeti ve minimal komplikasyon elde ettik. Chevron osteotomi yöntemi, orta dereceli halluks valgus deformitesinin tedavisinde etkin bir yöntemdir.

Anahtar Kelimeler

Halluks Valgus; Chevron Osteotomisi; Cerrahi

Abstract

Aim: Hallux valgus is a complex foot deformity resulting from medial deviation of first metatarsal and lateral deviation of toe. Radiographic and functional outcomes of chevron type distal metatarsal osteotomy applied to symptomatic hallux valgus patients with moderate deformity were assessed in the present study. Chevron osteotomy was applied to 27 feet (13 left, 14 right) of 22 patients (12 women and 10 men; mean age: 45±16.7 years). Mean follow-up was 15.4± 4.71 months (range, 10–24). Material and Method: The average preoperative AOFAS score of 39.1 ± 8.55 (range, 32–57) improved (p < 0.0001) to 87.8 ± 4.7 (range, 82–97). The average preoperative hallux valgus angle (HVA) of 37.4 ± 5.8 (range, 29–50) improved (p < 0.0001) to 14.8 ± 3.1 (range, 10–20), and the average preoperative intermetatarsal 1-2 angle (IMA) of 13.1 ± 1.5 (range, 11–17) improved (p < 0.0001) to 7.1 ± 1.4 (range, 5–9). The average sesamoid position improved from 2.9 ± 0.2 (range, 2-3) preoperatively to 1.2 ± 0.4 (range, 1-2) (p < 0.0001). Toe hypoesthesia was developed in one patient as a complication. At the end of follow-up, patient satisfaction was found to be excellent in 16 feet (59.2%) and good in 11 feet (40.8%). Results: The results of the study that chevron osteotomy yields good radiological result, high degree of postoperative patient satisfaction with minimal complications. Chevron ostoetomy is most effective method in the treatment of moderate hallux valgus.

Keywords

Hallux Valgus; Chevron Osteotomy; Surgery

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Introduction

Hallux valgus is a common disorder of the forefoot characterized by lateral deviation of the great toe and medial deviation of first metatarsal [1, 2]. Extrinsic and intrinsic factors are thought to play role in its etiology [1, 2]. Current classification is based on radiographic measurements and classifiy the disease as mild, moderate, and severe [1-3]. Mild hallux valgus deformity is characterized by a hallux valgus angle (HVA) of less than 20 degrees and intermetatarsal 1-2 angle (IMA) of 11 degrees or less. A moderate deformity is characterized by a hallux valgus angle of 20 to 40 degrees and a first intermetatarsal angle of less than 16 degrees, while a severe deformity is characterized by a hallux valgus angle of more than 40 degrees and a first intermetatarsal angle of 16 degrees or more [2, 4].

Many procedures for correcting hallux valgus have been described [3, 5, 6]. Considerations for technical choice include the hallux valgus angle, intermetatarsal angle, arthritis in the first metatarsophalangeal (MTP) joint, hypermobility of the first tarsometatarsal joint, position of sesamoids, musculo-tendinous balance, and congruity of the first metatarsophalangeal joint [1-3]. Surgical techniques are generally classified as soft tissue procedures, metatarsal and phalangeal osteotomies, and combinations thereof [4, 7]. In general, distal metatarsal osteotomies are recommended to achieve sufficient correction of deformity in patients who has hallux valgus angulation up to 30-40° and intermetatarsal angulation up to 15° but no marked arthrosis in first MTP joint [6, 8]. Advantages of Chevron osteotomy include enabling early mobilization by providing a stable osteosynthesis, minimal shortening and ease of technique [9].

Radiographic and functional outcomes of chevron type distal metatarsal osteotomy applied to symptomatic hallux valgus patients with moderate deformity and nor arthritic changes in MTP joint were assessed in the present study.

Material and Method

Chevron osteotomy as surgical treatment was performed to 27 feet (13 left, 14 right feet) of 22 patients (12 women and 10 men; mean age: 45.0±16.7 years; range: 22-69 years) with a diagnosis of moderate symptomatic hallux valgus. There was bilateral involvement in five patients. Minimum follow-up was 10 months (mean: 15.4± 4.71 months, range: 10–24 months) (Table 1). The main operative indication for the surgery was pain and deformity in the forefoot.

In preoperative and postoperative assessment, hallux valgus (HV) and intermetatarsal 1-2 angles (IMA) were measured on weight-bearing anterior and lateral foot radiographs. All radiographs were assessed by one reviewer (OF). All patients underwent clinical assessment using the American Orthopedic Foot and Ankle Society's (AOFAS) hallux-metatarso-phalangeal-interphalangeal scale [10]. It includes pain (40 points), hallux alignment (15 points), and functional assessment (45 points). For subjective evaluation, the patients were asked to rate their postoperative satisfaction level as very good, good, moderate, or poor.

Table 1. Demographic characteristics of patients

Number of patients (feet)	22 (27)
Age, mean ± SD (range)	45 ± 16.7 (22-69)
Gender, n (%)	
Female	12 (54.5%)
Male	10 (45.5%)
Follow-up, months, mean±SD (range)	15.4 ± 4.71 (10-24)
Location, n (%)	
Right	14 (51.9%)
Left	13 (48.1%)

Sesamoid station (position of the tibial sesamoid relative to the axis of the first metatarsal) was graded using a fourpoint ordinal scale [11]: Grade 0, tibial sesamoid completely medial to the mid-axial line of the first metatarsal; Grade 1, less than 50 % overlap of the mid-axial line; Grade 2, more than 50 % overlap; Grade 3, tibial sesamoid completely lateral to the mid-axial line. The study was conducted in accordance with the Declaration of Helsinki.

Surgical technique

All osteotomies were performed by one surgeon (DF). The technique was done through an approximately 5 cm longitudinal medial incision over the first MTP joint. An inverted Y-shaped capsulotomy was performed, the medial eminence was excised, and a 60° V-shaped osteotomy was then made (Figure 1). The



Figure 1. Intraoperative imaging of chevron osteotomy.

thickness of osteotomy blade used was 0.6 mm. The capital fragment was then manually translated laterally and not exceeding 50% of the width of the metatarsal head. Then compressed and stabilized with a two cannulated screw. On indication, a distal soft tissue procedure was performed by a 1-cm longitudinal incision over the dorsal aspect of the first intermetatarsal space to expose the conjoined adductor tendon. The tendon was dissected from the lateral sesamoid and the base of the proximal phalanx. A partial capsulotomy was performed to the lateral aspect of the first metatarsophalangeal joint.

In addition to hallux valgus deformity, it was found that there was hammer toe deformity in second finger in two feet and Freiberg disease in second metatarsophalangeal joint in two feet. Proximal phalanx head resection, extensor digitorum brevis tenotomy and lengthening of extensor digitorum longus were performed for hammer toe deformity. Cheilectomy of metatarsal head and synovectomy was performed for Freiberg disease.

After surgery, short leg cast was applied to patients and no weight-bearing was allowed until end of second week. Then, full weight-bearing as tolerated was allowed by removing casts. All statistical analyses were performed using SPSS version 16.0

(SPSS Inc., Chicago, USA) for Windows (Microsoft Corporation, Redmond, USA). Paired Student's t-tests was used to analyze data. P < 0.05 was considered to be statistically significant.

Results

The average preoperative AOFAS score of 39.1 ± 8.55 (range, 32–57) improved to 87.8 ± 4.7 (range, 82–97) (p < 0.0001) (Table 2). The average preoperative HVA of 37.4 ± 5.8 (range, 29 –50) improved to 14.8 ± 3.1 (range, 10 –20) (p < 0.0001), and the average preoperative IMA of 13.1 ± 1.5 (range, 11 –17) improved (p < 0.0001) to 7.1 ± 1.4 (range, 5 –9) (Figure 2). The average sesamoid position improved from 2.9 ± 0.2 (range, 2-3) preoperatively to 1.2 ± 0.4 (range, 1-2) (p < 0.0001).

Table 2. Comparison of preoperative and postoperative radiographic results.

	Pre-operative	Post-operative	p-Value
AOFAS score	39.1 ± 8.55	87.8 ± 4.7	0.0001
HVA	37.4 ± 5.8	14.8 ± 3.1	0.0001
IMA	13.1 ± 1.5	7.1 ± 1.4	0.0001

AOFAS, American Orthopaedic Foot and Ankle Society; HVA, hallux valgus angle; IMA,intermetatarsal angle

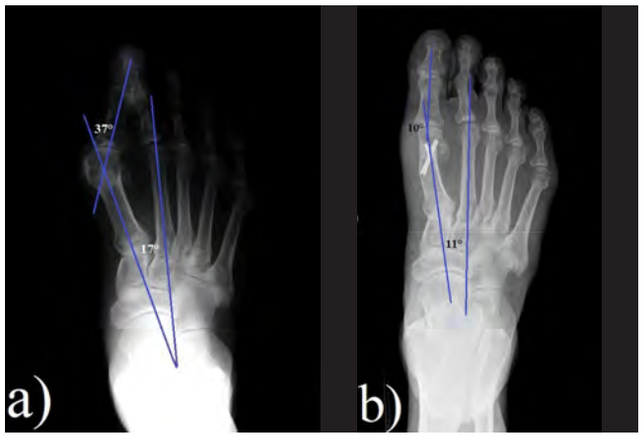


Figure 2. Preoperative and postoperative radiographs of the patient who underwent chevron osteotomy for hallux valgus deformity.

Toe hypoesthesia was developed in one patient as a complication. No patients had postoperative hallux varus deformity, osteotomy nonunion, AVN of the head of first metatarsal, dorsal malunion of the distal metatarsal osteotomy, or recurrence of the deformity after surgery. At the end of follow-up, patient satisfaction was found to be excellent in 16 feet (59.2%) and good in 11 feet (40.8%).

Discussion

Many surgical techniques have been defined for correction of hallux valgus deformity. However, there is no surgical technique that has ability to correct all constituents of deformity [3, 6, 12]. The goal of surgical intervention is provision of normal anatomy as well as normal functions. Thus, one should select most appropriate surgical intervention with lowest complication and recurrence rate by taking foot deformity, severity of deformity and patient factors [1-4, 8]. Hallux valgus deformity is classified as mild, moderate and severe based on HVA and IMA [1-3]. In our patients, mean preoperative IMA value was 13.1° (range, 11-17), whereas mean preoperative HVA was 37.4° (range: 29-50). We think that Chevron osteotomy is sufficient in our patients with moderate deformity. The results of this study that chevron osteotomy yields good radiological result, high degree of postoperative patient satisfaction with minimal complication.

The distal metatarsal osteotomy is a widely accepted method for the correction of mild to moderate hallux valgus [8, 13]. Chevron and Mitchell distal metatarsal osteotomies are frequently used in the treatment of mild to moderate hallux valgus [8, 13]. According to Heerspink et al. [13] the Mitchell ostetomy leads to further shortening of the first metatarsal compared to chevron osteotomy. This might lead to transfer metatarsalgia. Mitchell osteotomy provides better adjustment in the terms of the HV correction radiologically. It is essential for the prevention of postoperative metatarsalgia for a successful HV surgery. Therefore, chevron osteotomy may be preferred instead of Mitchell osteotomy especially in patients with a short first metatarsus [13].

Distal chevron osteotomy is one of the most commonly employed osteotomies [8, 13]. Advantages of this procedure are stability of the osteotomy, rapid healing and minimal shortening. Possible disadvantages are avascular necrosis, insufficient correction or recurrence of hallux valgus [5, 8, 12, 13]. Avascular necrosis of the metatarsal head in chevron osteotomies occurs 0-20% [3]. Excessive capsular dissection may lead to avascular necrosis of part or all of the metatarsal head since, after osteotomy, the only remaining blood supply is from the capsule [5, 8, 12]. We took care to preserve the lateral capsule and saw no signs of avascular necrosis. Only one patient developed postoperative sensory loss over the medial aspect of the great toe. It has been reported that limitations in movements were developed in first MTP joints in cases in which distal osteotomy with soft tissue releasing were performed [3, 12]. No limitation in first MTP joint was detected in our patients at the end of follow-up.

Clinical complaints as well as radiographic measures should be taken into account while making-decision of surgical indication [4]. In all patients, the complaints included pain and difficulty in wearing shoes. However, cosmetic disorder due to deformity was also striking. At the end of follow-up, patient satisfaction was found to be excellent in 16 feet (59.2%) and good in 11 feet (40.8%) when satisfaction was questioned.

For more severe hallux valgus deformities, proximal first metatarsal osteotomies have been performed [7, 9, 14]. In some studies reported that scarf method provide more correction in the amount of IMA and HVA compared to chevron [7, 15]. Given the good outcomes reported, shaft procedures did not result in a better radiographic or clinical outcome than distal corrections in hallux valgus procedures [5, 14, 16]. Deenik et al. found no differences between scarf and chevron osteotomy in correction of HVA and IMA in patients with moderate and severe hallux valgus [5, 14].

Although most authors recommend that the Chevron osteotomy should be used only for patients who are younger than 50 years of age. In our study, there were 8 (31.8%) patients aged 50 years or older. There was increase in mean AOFAS score by 52.5 points after surgery when compared to mean preoperative AOFAS score (p=0.0002). In a long-term follow up study

comparing patients younger and older than 50 years at time of surgery, Schneider et al. [8] found no differences in the clinical and radiographic outcome; thus, they concluded that chevron osteotomy need not be restricted to younger patients.

Several fixation methods are used for stabilization of distal chevron osteotomy including Kirschner wires (K-wire), mini screws, staples and bioabsorbable screws, plates [5-8, 17-20]. Each form has unique advantages and disadvantages [18, 19]. K-wires are relatively easy to insert and require limited exposure for insertion. However, they may loosen and migrate, irritate soft tissue, and provide a portal for infection if they penetrate the skin [17, 19]. To avoid the sequelae associated with metallic fixation, such as painful tissue irritation, loosening of hardware, secondary removal procedure, or pin tract infection, bioabsorbable fixation has been utilized [18]. Using plates in metacarpal and phalangeal fractures provides the most rigid, secure, and reliable fixation of implants currently available. The primary advantage is rigid fixation [21]. Potential disadvantages of using plates are foreign body reaction, allergic reaction, capsule irritation, palpable or visible fixation [19]. We used two cannulated screws for stabilization of osteotomy in our patients. The advantage of chevron osteotomy is direct weight-bearing postoperatively owing to the stable fixation. The patients were allowed for partial weight-bearing within first two months after surgery, followed by full weight-bearing. No loss of fixation, nonunion or malunion deformity was developed.

Hallux valgus is a complex deformity of the foot includes various accompanying pathologies [1, 4]. In addition to hallux valgus deformity, it was found that there was hammer toe deformity in second finger in two feet and Freiberg disease in second metatarsophalangeal joint in two feet. Proximal phalanx head resection, extensor digitorum brevis tenotomy and lengthening of extensor digitorum longus were performed for hammer toe deformity. Cheilectomy of metatarsal head and synovectomy was performed for Freiberg disease.

Secondary transfer metatarsalgia accounts for a significant proportion of failure after HV correction. The reported incidence of transfer metatarsalgia after chevron osteotomy has been 0% to 5% [12, 13]. Potential shortening of the first metatarsal can lead to transfer metatarsalgia of the head of the second metatarsal by the changed pressure distribution of the forefoot [12, 13]. In Chevron osteotomy, metatarsal shortening is generally associated to thickness of osteotomy blade used. The thickness of osteotomy blade used was 0.6 mm in this study. No transfer metatarsalgia was developed in our patients after surgery.

The present study has some limitations, including the lack of a control group for comparison and lower case numbers.

In conclusion, chevron osteotomy provides correction of deformity in patients with moderate hallux valgus deformity in complete and stable manner. It is an appropriate choice in hallux valgus surgery due to its technical ease, satisfactory functional outcomes and good patient satisfaction.

Competing interests

The authors declare that they have no competing interests.

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Relationship Between Childhood Asthma and C3435T Multidrug Resistance 1 Gene

Çocukluk Astımı ve C3435T "Multidrug Resistance 1" Geni Arasındaki İlişki

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Bu çalışma, 25-29 Ekim 2014 tarihleri arasında Bodrum'da düzenlenen, 21. Ulusal Allerji ve Klinik İmmünoloji Kongresi'nde poster olarak sunulmuştur. Çalışma tez çalışması olup, Cumhuriyet Üniversitesi Bilimsel Araştırmalar Projesi tarafından desteklenmiştir.

Özet

Amaç: Çocukluk astımı ve C3435T "multidrug resistance 1" gen polimorfizmi arasındaki ilişkiyi göstermek amaçlanmıştır. Gereç ve Yöntem: Astımlı 58 çocuk ve sağlıklı 54 çocuk çalışmaya katılmıştır. İstatistiksel analiz için kikare ve "Fisher's exact" testleri kullanılmıştır. Bulgular: "Multidrug resistance-1" geni için normal, heterozigot ve homozigot polimorfizm, astımlı çocukların sırasıyla 12 (%20,7), 31 (%53,4) ve 15 (%25,9)'inde bulunmuştur. Sağlıklı çocuklarda normal, heterozigot ve homozigot polimorfizm, sırasıyla 18 (%33,3), 28 (%51,9) ve 8 (%14,8)'inde bulunmuştur. "Multidrug resistance 1" geni açısından astımlı ve sağlıklı çocuklar arasında fark görülmemiştir. Homozigot polimorfizm ağır persistan grupta, orta ve hafif persistan gruba göre (p=0,001) ve kızlarda, erkeklere göre daha yüksek bulunmuştur (p=0,001). Tartışma: Farklılığın ağır persistan astımlı hastalardan kaynaklandığı söylenebilir. Bu bilgi, hastalar astım tanısı aldığında "multidrug resistance 1" genine bakarak klinisyenlerin hastaları sınıflandırmasına yardımcı olabilir. Böylece, özellikle kritik derecedeki hastaların tedavisi erken başlanabilir ve uzun dönemli takibi yapılabilir. Ayrıca özellikle kadın hastalar için cinsiyete özel tedavi planlanabilir.

Anahtar Kelimeler

Astım; Çocuklar; "Multidrug Resistance-1" Geni

Abstract

Aim: It was aimed to show the relationship between childhood asthma and C3435T multidrug resistance 1 gene polymorphism. Material and Method: Fifty eight children with asthma and 54 healthy children participated to the study. Chi-square and Fisher exact tests were used for statistical analysis. Results: Wild, heterozygous and homozygous polymorphism for multidrug resistance -1 gene were found respectively in 12 (20.7%), 31 (53.4%), and 15 (25.9%) of children with asthma. In healthy children, wild, heterozygous, and homozygous polymorphisms were found respectively in 18 (33.3%), 28 (51.9%), and 8 (14.8%) participants. There was no statistical difference between asthmatic and healthy children in terms of multidrug resistance 1 gene polymorphism. Homozygous polymorphism was found higher in severe persistent group than moderate and mild persistent groups (p=0.001) and in girls than boys (p=0.001). Discussion: It may be said that the difference was resulted from severe persistent asthmatic patients. And this information helps clinicians to rank the patients in terms of asthma by looking multidrug resistance 1 gene when the patient was diagnosed as asthma. Hence, treatment of patients, especially with crucial degree may begin earlier and its long-term pursuance can be made. In addition, gender-specific treatment can be planned especially for female patients.

Keywords

Asthma; Children; Multidrug Resistance-1 Gene

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Introduction

Asthma is a type of disease that cause inflammation chronically on the airway. It is the most common chronic disease that seen at children. There are some signs and symptoms such as cough, breathlessness, chest tightness and wheezing that seen in asthma [1]. It is not easy to know who will develop asthma in the future, but it is already known that environmental tobacco smoke and some factors on surrounding as well as genetic predisposition result in the development of asthma [2]. Asthma is a complex disease that shows genetic heterogeneity due to the interaction of several genes [2].

The prevalence of asthma is increasing worldwide and has been becoming a vital problem for public health. For this reason, the prevention of asthma is important [3]. Environmental factors can be arranged, however, genetic predisposition cannot be modified. So, having information about genetic factors may be important in order to provide early detection and prevention on the diseases. Out of this, it is suggested that few genetic factors have protective role for the lung. For example, multidrug resistance (MDR) 1 gene proteins may provide resistance against oxidative injury in the pulmonary tissue [4].

The multidrug resistance 1 (MDR1) gene is located on chromosome 7 at q21. It encodes a plasma membrane P-glycoprotein (P-gp) which consists of 1280 amino acids. P-glycoprotein functions as a pump molecule and reduces intensity of drugs by excreting them from the intracellular space [5]. It is a member of a large transport family which is known as the ATP-binding cassette (ABC) superfamily [6]. ATP-binding cassette transporters are basically found in all cells and play key roles in physiology. They transport drugs, lipids and steroids across membrane systems. ATP-binding cassette transporters also play important roles in the immunologic events and may lead to hereditary diseases [7]. P-glycoprotein is found in the apical surface of many cells with excretory functions include the liver, kidney, small intestine, stomach, and the blood–brain barrier [8]. Similar to many other tissues such as adrenal gland, liver, prostate, placenta, uterus; pulmonary tissue and trachea also show considerable amount of transcriptional activity for various ABC transporters [7]. In the pulmonary tissue, P-gp expression has been well studied for lung cancer [9]. It is suggested that these transporters are assigned to protect the pulmonary tissue against harmful substances [4].

Multidrug resistance gene 1 polymorphism was firstly defined by Hoffmeyer et al [10]. There are many single nucleotide polymorphism on MDR1 gene. The effect of this polymorphism on pulmonary disease is still controversial [11]. There is conclusive evidence showing that energy-dependent transporters have important functions in the pulmonary tissue. For example, it was suggested that, the main reason for the pathology of cystic fibrosis disease was the mutation on "Cystic fibrosis transmembrane conductance regulator" gene due to MDR1 polymorphism [12]. The best known single nucleotide polymorphisms on MDR1 gene are C3435T, C1236T, and G2677T/A [13]. Although there are a few studies about SNP C1236T and G2677T/A, many studies have been found related to C3435T polymorphism [14-16]. But, we did not find any study associated with C3435T SNP and childhood asthma. Single nucleotide polymorphism C3435T, located in exon 26 of the MDR-1 gene, results in decreased expression of P-gp [17]. Because asthma is an inflammatory disease, in current study evaluation of the relationship between childhood asthma and C3435T MDR1 gene polymorphism which plays a role in the inflammatory process was aimed. In addition, correlation of this gene polymorphism with the severity of asthma was also investigated.

Material and Method

One hundred and twelve children between the ages of 6 to 17 years were included in the study. The study group consists of 58 children with asthma and 54 healthy volunteers as control. The children with asthma not currently under treatment were included in the study. According to Global Initiative for Asthma (GINA) protocol, classification of asthma was made as mild persistent, moderate persistent and severe persistent asthma [18]. Participants with comorbid diseases such as chronic pulmonary disease, congenital heart disease, chronic renal failure, and growth retardation were excluded from the study. The study was conducted at the Cumhuriyet University hospital in between 2011-2012 years.

Polymorphism analysis: Three ml venous blood samples were taken into EDTA tubes from all participants. These blood samples were stored at -20°C until ready to work. Genomic DNA was extracted from 100 µl of whole blood using the Invitek kit (Invitek, Invisorb spin blood, Germany). Amplification of the multidrug resistance 1 gene was performed in a biotin labeled single multiplex amplification reaction and then 3435 CT polymorphism was evaluated. Polymerase chain reaction (PCR) was carried out in a Perkin Elmer Gene amp 9600 Thermal Cycler. The study protocol was performed as follows: 1) an initial melting step of 2 minutes at 94°C, 2) 35 cycles of 15 seconds at 94°C, 3) 30 seconds at 58°C 4) 30 seconds at 72°C, and 5) a last elongation step of 3 minutes at 72°C. The Strip Assay technique (Vienna Lab, PGX-HIV Strip Assay GmbH, Austria), based on the reverse-hybridization method, was used for polymorphism analysis.

Statistical analysis: The SPSS software package version 14 for Windows (SPSS, Chicago, IL, USA) was used for all statistical analyses. Data from the children with asthma and from the healthy children were analyzed by chi-square (x2). Comparison of study groups among each other analyzed by Fisher's exact test. $P < 0.05$ was considered as significant.

Ethical disclosures: The current study was approved by the ethics committee of Cumhuriyet University (Date: 13 December 2011 and decision number: 2011/028).

Right to privacy and informed consent: The children or their families signed an informed consent form in order to be able to participate to the study.

Results

The study group was composed of 31 boys (53.4 %) and 27 girls (46.6 %) while the control group was composed of 23 boys (42.6 %) and 31 girls (57.4 %). There was no statistical difference according to age, height and weight of patients and control groups.

Multidrug resistance 1 gene polymorphism

The comparison of multidrug resistance 1 CC (wild type), CT (heterozygous) and TT (homozygous) gene polymorphisms was

carried out between the children with asthma and healthy children. The results of the current study are shown in table I. According to these results, there was no significant statistical difference between the children with asthma and healthy children in terms of MDR-1 polymorphisms.

Table I. Distribution of MDR-1 genotype in patients with asthma and control group

Polymorphism type	Patients with asthma n (%)	Control group n (%)
Heterozygous (C/T) MDR1 polymorphism	31 (53.4)	28 (51.9)
Homozygous (T/T) MDR1 polymorphism	15 (25.9)	8 (14.8)
Wild type (C/C) MDR1 polymorphism	12 (20.7)	18 (33.3)
Total	58 (100)	54 (100)

p>0.05 MDR: multidrug resistance

Children with asthma were divided into three groups as mild persistent, moderate persistent and severe persistent asthma. This classification was made according to GINA protocol [18]. Mild persistent, moderate persistent and severe persistent asthmatic groups were composed of 24, 17 and 17 patients respectively. MDR1 CC (wild type), CT (heterozygous) and TT (homozygous) gene polymorphisms were compared among children with asthma, and homozygous TT polymorphism was found significantly higher in severe persistent asthmatic group than that of moderate and mild persistent groups (p=0.001). In moderate persistent group, heterozygous CT polymorphism was found significantly higher than that of mild persistent group (p=0.001). The results are shown in table II.

Table II. Distribution of MDR-1 genotype in patients with asthma

Polymorphism type	Mild persistent asthman (%)	Moderate persistent asthma n (%)	Severe persistent asthma n (%)
Heterozygous (C/T) MDR1 polymorphism	14 (58.4)	12 (70.6)†	5 (29.4)
Homozygous (T/T) MDR1 polymorphism	2 (8.3)	2 (11.8)	11 (64.7)¶
Wild type (C/C) MDR1 polymorphism	8 (33.3)	3 (17.6)	1 (5.9)
Total	24 (100)	17 (100)	17 (100)

†Heterozygous polymorphism was seen more in moderate persistent asthma than mild persistent asthma
¶Homozygous polymorphism was seen more in severe persistent asthma than mild and moderate persistent asthma
MDR: multidrug resistance

When the comparison at the study group was based on gender, homozygous TT polymorphism was found significantly higher than heterozygous CT and wild type CC polymorphism in girls, while in boys heterozygous CT polymorphism was found significantly higher than homozygous TT and wild type CC polymorphism (p=0.001). The results about gender and polymorphism type were shown in table III. However, in the control group there was no statistical difference between boys and girls in terms of genotype (p>0.05).

Allelic frequency

In healthy control; C and T allele frequencies were found as 59.3% and 40.7 % respectively; while in children with asthma; C and T allele frequencies were found as 47.4% and 52.6% respectively.

Table III. Distribution of MDR-1 genotype according to gender

Polymorphism type	Girls	Boys	p
Heterozygous (C/T) MDR-1 gene n (%)	11 (40.7)	20 (64.5)*	P=0.001
Homozygous (T/T) MDR-1 gene n (%)	13 (48.1) α	2 (6.5)	P=0.001
Wild type (C/C) MDR-1 gene n (%)	3 (11.1)	9 (29.0)	
Total n (%)	27 (100)	31 (100)	

*p= 0.001: heterozygous polymorphism was higher than homozygous and wild type polymorphism in boys
αp=0.001: homozygous polymorphism was higher than heterozygous and wild type polymorphism in girls
MDR: multidrug resistance

Discussion

Asthma is the most common chronic illness among children in many parts of the world. It is characterized by airway inflammation and narrowing of airway resulting in cough, wheezing, shortness of breath, fatigue. Asthmatic patients generally have impairment of their daily activities due to the lack of the disease control [18].

Early treatment is important for asthma, because a condition called remodeling occurs as the disease progresses. Risk of developing remodeling increases as the inflammation in asthma becomes chronic. Remodeling occurs both in large and in small airways. It is a heterogeneous event that cause structural changes in the airway, airway cells, and connective tissue as a result of migration, maturation and redifferentiation. Structural changes in the airway include epithelial damage, fibrosis in subepithelial area, prolonged repair process, excessive production of profibrotic growth factors, revascularization, and increase in smooth muscle mass [19]. As a result, remodeling leads to thickening and narrowing in the airways. These changes are irreversible and do not improve even with appropriate treatment [19]. Chronic damage due to remodeling can be avoided by early diagnosis and early treatment of asthma [19]. There is no cure for the disease completely, but in order to recover the symptoms, good treatment is available [1,2,19]. The aim of asthma treatment is to provide symptom control for a long period of time, prevent asthma attacks, decrease and control airway inflammation, and maintain good pulmonary function.

MDR1 gene polymorphism and asthma severity

ABC transporter family has been divided into seven subgroups extends from ABCA to ABCG. P glycoprotein is located in the subgroup of ABCB1. So far, in the human body, 48 ABC transporters have been identified in the seven subgroups. These transporter proteins are find almost in every cell and in all species and it is known that they all have basic physiological role in the cells [6]. In the pulmonary tissue, MDR1 gene and release of P-glycoprotein have been well studied especially in the lung cancer [9]. It is thought that, the existence of these transport proteins in the pulmonary tissue is important for the protection of this tissue from endogenous and exogenous toxigenic substances [9]. In addition, the efficiency of inhaled aerosol medications and of many drugs that are metabolized in the pulmonary tissue may be dependent on the presence of various energy transporters and on their activities [11]. Also many ABC transporter is required for the drugs to reach the activation site in the lung [11]. P glycoprotein is involved in cellular defense against environmental factors and they are released from the apical surface of liver and intestinal tissues. In the lung, P glyco-

protein is released from apical surface of ciliated epithelial cells or from apical and lateral surfaces of ciliated collecting ducts and from bronchial glands [20].

To our knowledge, the importance of multidrug resistance-1 gene polymorphisms had not been studied in children with asthma. This was the first study that demonstrated the association between C3435T MDR1 gene polymorphism and asthma in children. In current study, there was no significant difference in MDR1 gene polymorphism between children with asthma and healthy control group. However MDR1 TT homozygous mutation was significantly higher in children with severe persistent asthma than in children with moderate persistent and mild persistent asthma. Although it was observed that heterozygous mutation was diagnosed more in patients with moderate persistent asthmatic patients as compare to mild persistent asthmatic patients, homozygous mutation was diagnosed more in the severe persistent asthmatic patients. The situation which is important here is identifying especially severe persistent asthmatic patients and taking them into close follow-up. Severe persistent asthmatic patients are generally less than other asthmatic patients in number and covers 4.5% of childhood asthma [21]. But morbidity and mortality is seen more in these patients. It also causes absenteeism in schools among children more than other asthma groups. In addition severe asthma in childhood may be an indication of persistence of asthma later in adulthood. Decreased lung function occurs early in childhood and does not change at a later time with aging [1,2]. Observing homozygous mutation more in such patients as compare to other patients further increases the importance of this situation. Patients with whom homozygous mutation is diagnosed may be informed about heavy disease, importance of disease and necessity of regular treatment in addition to regular control. By doing so, having an attack or a possible attack in addition to chronic complications may be prevented by efficient treatment. Based on haplotype analysis, the C-C and C-T shift could be protective from severe asthma in children.

There have been variable studies about MDR1 gene polymorphism in different diseases. Taheri et al [14] studied a possible association be¬tween MDR1 gene C3435T polymorphism and its expression in 54 breast cancer patients. They did not see any difference in the frequency of C3435T polymorphism between patients and healthy controls. But, they found significant association between MDR1 expression levels and C3435T polymorphism in the patients. They reported that individuals who were homozygous for the T allele had a significantly decreased P glycoprotein expression level compared to those homozygous for the C allele [14]. They reported that, C3435T polymorphism may play a role in inducing drug resistance by altering the expression level of the MDR1 gene.

Akın et al [15] studied 31 childhood acute idiopathic thrombocytopenic purpura patients and they found no association in genotype and allele distribution between the patients and the control group. In addition, there was no difference in the treatment response between MDR1 gene genotypes.

In another study conducted on 41 adult patients, the T allele polymorphism of the MDR1 gene was shown to be associated with chronic obstructive pulmonary disease [4]. In one study, nephrotic syndrome children with mutations in MDR1 gene were found to be susceptible to steroid-resistant nephrotic syndrome [16]. In the study of Ozen et al [22] it was indicated that C3435T polymorphism MDR1 gene was associated with colchicine resistance in nonresponder familial Mediterranean fever patients. In addition, T allele frequency was found higher in these patients. Similar to these results, in current study, TT homozygous mutation was associated with severe asthma.

MDR1 gene polymorphism and genotype distribution

C3435T polymorphism decreases the expression of P-glycoprotein and this expression is highly variable between individuals and between different ethnic groups [23]. In the studies made with Turkish population, similar results were found. In the study of Bebek et al [23] made with 174 healthy adults, C and T allele frequencies were found as 51% and 49% respectively. And genotype distribution was found as %28.2 CC, 46% CT and 25.8% TT. They did not find any linkage between sex and genotype. In current study, wild (CC), heterozygous (CT) and homozygous (TT) polymorphisms were found respectively as 36.2%, 50% and 13.8% at healthy controls. Similar to previous study, C and T allele frequencies were found as 59.3% and 40.7 % respectively. In addition, in current study, there was no difference in healthy control group in terms of sex.

MDR1 gene polymorphism and gender

In children and early adolescents, asthma is more common in boys [2]. In adolescence, the pattern changes and asthma is reported more in girls. After childhood, asthma is more severe in females than in males, and is underdiagnosed and less treated in female adolescents. Females with asthma have more symptoms and worse quality of life than men [24]. However, of these differences about gender have not been fully explained. It may result from differences in sensation of airflow obstruction, increased bronchial hyper reactivity in females [25]. In addition hormonal changes and gender-specific differences in environmental exposures such as tobacco smoke have all been considered as potential causes [2,24,25]. Similar to literatures, however severe asthma was diagnosed more in the girls in current study. In addition homozygous mutation was seen more in the girls again. Medical staff has to be careful on this point. It may be suggested that specific asthma treatment should be planned according to gender especially for female patients.

Limitation of study: When we searched the literature, we could not find a study like this in asthmatic children previously. Therefore, the number of cases may be less in current study, while it is thought that this study may form an idea for further large scale studies. In addition, expression of MDR1 gene polymorphism may differ among various ethnic groups. In order to understand the disease more, there is a need to work with different ethnic groups in a larger sample size.

Conclusions: There was no statistical difference between asthmatic child patients and controls in MDR1 gene polymorphism. However, homozygous polymorphism was found more in severe asthmatic group than mild and moderate persistent groups. This difference was not different at moderate and mild persistent groups as compare to control group. So, it may be said that the difference resulted from severe asthmatic patients. And this information helps us to rank the patients in terms of

asthma by looking MDR1 gene when the patient was diagnosed as asthma. Hence, it can be concluded that treatment of patients, especially with crucial degree may begin earlier and its long-term pursuance can be made. As a result, protection of the patient against chronic complications of asthma may be provided. By doing this, attacks of the patient may be diminished and overcome easily.

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Competing interests

The authors declare that they have no competing interests.

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Effect of Body Mass Index on Endometrial Thickness in Asymptomatic Postmenopausal Women

Asemptomatik Postmenopozal Kadınlarda Vücut Kitle İndeksinin Endometrium Kalınlığına Etkisi

Vücut Kitle İndeksi-Menopozda Endometrial Patoloji / Body Mass Index-Endometrial Pathology in Menopause

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Özet

Amaç: Asemptomatik postmenopozal kadınlarda vücut kitle indeksi ile endometrial kalınlık arasındaki ilişkiyi saptamak. Gereç ve Yöntem: Bakırköy Kadın ve Çocuk Hastalıkları Eğitim Araştırma Hastanesi menopoz polikliniğine başvuran asemptomatik 114 kadın prospektif çalışmaya dahil edildi. Transvaginal ultrasonografi ile yapılan ölçümde endometrial kalınlığı ≥ 5mm olan 30 kadın çalışma grubu, <5 mm olan 84 kadın kontrol grubu olarak alınıp vücut kitle indeksinin endometrial kalınlığa etkisi araştırıldı. Çalışma grubundan Pipelle ile endometrial biopsi alındı. İstatistiksel analizde Student-t test ve Pearson korelasyon analizi kullanıldı. Bulgular: Çalışma grubunda vücut kitle indeksi ve östrojen seviyesi kontrol grubuna göre istatistiksel olarak anlamlı olarak yüksekti (p<0.05, p<0.05). Çalışma grubunda ortalama endometrium kalınlığı 6.76±1.14 mm iken kontrol grubunda 2.83±0.99 mm olarak bulundu (p<0.05). Vücut kitle indeksi ile endometrial kalınlık arasında pozitif korelasyon saptandı (p< 0.001). Her iki grup arasında yaş, menopoz süresi ve progesteron düzeyleri arasında istatistiksel olarak anlamlı fark bulunamadı (p>0.05). Tartışma: Asemptomatik obez postmenopozal kadınlar endometrial patolojiler açısından risk taşımaktadırlar. Postmenopozal dönemde endometrial patolojiler için genel tarama önerilmese de özellikle obez postmenopozal kadınların ultrasonografi ile endometrial kalınlığının takibi önemlidir.

Anahtar Kelimeler

Postmenopozal Dönem; Vücut Kitle İndeksi; Endometrial Kalınlık; Endometrial Patoloji

Abstract

Aim: To investigate the correlation between body mass index and endometrial thickness in asymptomatic postmenopausal women. Material and Method: This prospective cohort study was conducted on 114 postmenopausal women who followed at Bakirkoy Woman and Child Disease Research and Educational Hospital. The study group composed of 30 postmenopausal women endometrial thickness ≥ 5mm and control group composed of 84 postmenopausal women with endometrial thickness < 5mm. The groups were analyzed according to body mass index. The endometrial biopsy was performed from the study group by Pipelle endometrial sampler. The results were compared by using Student-t test and Pearson correlation analysis. Results: In the study group body mass index and estrodiol levels were significantly higher than the control group (p<0.05, p<0.05). The mean thickness of the endometrium was 6.76 ± 1.14 mm in the study group and 2.83±0.99 mm in the control group (p<0.05). There was a positive correlation between body mass index and endometrial thickness (p<0.001). There was no significant difference between two groups as to age, menopause time, estrodiol and progesteron levels. Discussion: Asymptomatic obese postmenopausal women have a high risk of developing endometrial pathologies. Although screening for endometrial pathology is not recommended for the general population, for high-risk populations like obese postmenopausal women, it may be important.

Keywords

Postmenopausal Period; Body Mass Index; Endometrial Thickness; Endometrial Pathology

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Introduction

Clinically, menopause is defined as the absence of menstrual period for at least 12 months [1]. In this period especially some complications observed more frequently than normal: osteoporosis, cardiovascular disease, endometrial hyperplasia (EH) and endometrial cancer (EC). The prevention of all these complications may provide a high quality of life.

Obesity is an increasing problem in the world. In Turkey nearly half of the women (44.2%) are determined as obese. It was informed that the prevalence in women older than 50 years were significantly increased (50.2%) [2]. In postmenopausal women, adipose tissue is the dominant source of estrogen; increased adipose tissue in obese postmenopausal women leads to increased estrogen [3]. It is clear that progesteron levels decrease in menopausal status. Decrease in progesteron is caused high levels of unopposed estrogen which is a risk factor for EH and EC [4].

Obesity is a risk factor for EH. The main problem about EH is progression risk of EC. The risk of progression depends on the histological diagnosis of EH. The risk is lower for women with complex EH (3%) compared with cytological atypia (8–29%) [5]. There is currently no routine screening test for EH or EC. Transvaginal sonography (TVUS) is routinely performed in postmenopausal women. Thickness of the endometrium that is measured by TVUS in postmenopausal woman may be an indicator of pathology. But in postmenopausal women without vaginal bleeding, the threshold separating normal from abnormally thickened endometrium is not known [6]. Currently in the United Kingdom (UK) an endometrial thickness (ET) over 5 mm requires further investigation by hysteroscopy and endometrial biopsy due to the risk of EC. It is thought that by using a cut-off of 5 mm, the majority of cases of both EH and EC can be further diagnosed and investigated [7].

In this study we aimed to investigate the correlation between BMI and ET and definition of the cut-off value of ET in asymptomatic postmenapousal women.

Material and Method

This prospective cohort study was conducted on 114 women who followed at Bakirkoy Woman and Child Disease Research and Educational Hospital between 1stMarch- 31st November 2001. The women subject to this study were asymptomatic, had no menstruel bleeding at least for one year and had no pathology on cervical smear. The exclusion criteria were having any malignancy or endometriosis, using hormone replacement therapy, having chemotherapy or radiotherapy before.

The demographic and clinical data were noted: gravidity, parity, weight, height, hypertension, diabetes mellitus, time of menopause, smoking and alcohol use, family history of cancer. Estrodiol (E2), progesteron, follicle stimulating hormone (FSH) and luteinizing hormone (LH) were evaluated from the venous blood sample at 8-10 a.m. by radioimmunassay technique. Body mass index (BMI) was calculated using the weight (in kg) divided by the square of the height (in meters) (BMI = weight (kg) / height^2 (m^2)). The World Health Organization (WHO) classification was used for BMI. WHO defines normal body weight as a BMI of 18 to 25, overweight as a BMI of 25 to 30, obesity as a BMI of ≥ 30, and morbid obesity as a BMI of ≥ 40 [8].

Ultrasonographic examination of all women were evaluated by the same doctor. TVUS was performed for the evaluation of ET. The ET was measured on the longitudinal axis of uterus. The measurement was performed between the echogenic part of endometrial-myometrial conjuction.

The women were divided in two groups according to ET: study group that ET was ≥ 5mm (number = 30) and control group that ET was < 5mm (number=84). The endometrial biopsy was performed on the study group by Pipelle endometrial sampler.

According to the objectives of the study, the collected data was analyzed by using appropriate statistical tests. Continuous variables with normal distribution were presented as mean ± SD. Student-t test was performed for the comparison of groups for ET and $p<0.05$ was performed for statistically significance. For all cases Pearson correlation analysis was performed.

Results

There were 114 asymptomatic postmenopausal women in our study. No patients departed from the study and there was no vaginal bleeding or malignancy during the study.

Table 1 shows the characteristics of women in our study. There was no significant difference between the groups with regard to age, parity, menapouse time. We performed Pipelle biopsy from all the patients in group 1. The results of histopathology are shown on Table 2. There was no malignancy on the histopathologic reports.

Table 1. Characteristics of women in study group (n=30) and control group (n=84)

	Study group (N=30)	Control group (N=84)	
	Mean±Std. Dev.	Mean±Std. Dev.	p value
Age (year)	51± 3.7	51± 4.7	>0.05
Menopause time (year)	3.43± 2.66	3.93± 3.36	>0.05
BMI [1] (kg/m2)	33.84±5.12	30.65±5.35	<0.05
Parity	3.53± 1.81	3.06±1.83	>0.05
Endometrial thickness (mm)	6.76± 1.14	2.83±0.99	<0.05
Estrodiol (pg/ml)	61.89±96.01	27.06±54.76	<0.05
Progesteron(ng/ml)	0.34± 0.22	0.31±0.21	>0.05
FSH [2] (U/L)	50.46±19.06	63.91±26.44	<0.05
LH [3] (U/L)	22.75±5.8	29.94±11.41	<0.05

[1]Body Mass Index; [2] Follicle stimulating hormone; [3] Luteinizing hormone

Table 2. Endometrial thickness and biopsy results

Histopathology	Number (%)	Mean endometrial thickness (mm)	Mean BMI (kg/m2)
Insufficient material	2 (6.7)	5.6	26.47
Proliferative endometrium	8 (26.7)	6.3	36.58
Secretuar endometrium	6 (20)	7.03	31,56
Simple cystic hyperplasia	6 (20)	7.3	35.01
Polypoid formation	3 (10)	7.8	35.68
Mucinous material	3 (10)	6.1	30.47
Atypic glandular hyperplasia	2 (6.7)	7.4	33.22

In study group, BMI and E2 levels were significantly higher than control group ($p<0.001$, $p<0.05$) (Table 3). There was no dif-

ference between two groups according to progesteron levels. FSH and LH levels were significantly higher in control group (p<0.05, p<0.05) but there was no correlation between these hormons and ET (p = 0.15 for study group and p = 0.22 for control group). The mean thickness of the endometrium was 6.76±1.14 mm in the study group and 2.83±0.99 mm in the control group (p<0.05). There was a positive correlation between BMI and ET (p<0.001) (Table 4).

Table 3. Body mass index in groups

BMI [1] (kg/m2)	≥ 30 (N / %)	<30 (N / %)	p value
Group 1	24 (80)	6 (20)	<0.001
Group 2	47 (55.95)	37 (44.05)	
[1]Body Mass Index			

Table 4. Endometrial histopathology and BMI in study group

Number of patients (%)	11(36.7)	19 (63.3)	p value
BMI [1] (kg/m2)	35.12	29.5	<0.001
Endometrial histopathology	Positive	Negative	
[1]Body Mass Index			

Discussion

The rate of obesity is increasing worldwide. Obesity causes not only cardiovascular problems but also multiple problems in every part of the body. Furthermore it is a major risk factor for EH. The overall peak incidence of EH in women between 50-54 years has been estimated at 386/100.000. Cumulative 20-year progression risk among women who remain at risk for at least one year is less than 5% for nonatypical EH but is 28% for atypical EH [9].

Although the relationship between obesity and EH is robust, underlying mechanisms are not well defined. Obesity adversely affects insulin homeostasis [10]. Hyperinsulinemia has several different adverse effects: It is associated with EH, it might be a key factor that triggers and promotes endometrial hyperplastic lesions. Insulin also induces androgen synthesis by ovaries and adrenals, providing substrate for adipose tissue conversion to estrogen. Especially aromatase activity in increased adipose tissue will cause the secretion of excess estrone which is not opposed by progesteron [11]. Arikan et al. reported a decrease in sex hormone binding globulin (SHBG) as the BMI increases [12]. Insulin and decrease in SHBG associated with obesity cause to increase bioavailability of systemic steroid hormones [13].

Adipose tissue is responsible for the synthesis and secretion of several polypeptide growth factors and cytokines, known as adipokines. Two of these adipokines, leptin and adiponectin, are taken roles in energy homeostasis, and are implicated as mediators of the effects of obesity on cancer development. Leptin levels are positively correlated with white adipose tissue mass and are therefore increased in obesity. Leptin plays role in hormone-dependent neoplasms by activating aromatase [14]. Leptin appears to participate in proliferative processes of the endometrium [15]. Balbi et al. reported that increased leptin levels participated the proliferative processes of the endometrium depending on BMI. In this study they showed that mean leptin concentration in serum was higher in patients who had EH than in controls (p<0.005) and the leptin levels depended on BMI [16]. Adiponectin levels are negatively correlated with body fat and BMI. Adiponectin functions as an insulin sensitizer, and low serum adiponectin reversely correlates with insulin resistance [17]. Moreover, adiponectin can inhibit cell proliferation, invasiveness and angiogenesis in vitro by suppression of estrogen receptor α and vascular endothelium growth factor [18].

Linkov et al. demonstrated decreased EH and decreased B-cell infiltration with surgically induced weight loss [19]. These data showed the relationship between obesity and EH, and implicated tissue inflammation in obesity-related EH. Furthermore, these data suggest that surgically induced weight loss reverses EH.

There are several studies about the relationship betwen obesity and ET in the literature. Epplein et al. compared nonobese women to obese women (BMI > 30 kg/m²) and showed nearly quadruple increase in the incidence of EH with atypia. They also showed women with BMI >40 kg/m² were at 13 times more risk of EH with atypia and 23 times more risk of EH without atypia [20]. Although age, weight and BMI showed a significant positive correlation with ET. Barboza et al. and Warming et al. showed a positive and significant correlation between increase in ET and BMI, demonstrating the influence of obesity on ET [21, 22]. On the other hand, Nakamura et al. concluded that BMI was not a risk factor for endometrial thickning in Japanese women. In this study ET in obese (BMI >25 kg/m²) and nonobese women (BMI <25 kg/m²) were 2.2 mm and 1.5 mm, respectively and there was no significant difference (p=0.27) [23]. Our results showed that BMI was significantly higher than control group (p<0.05) and there was a positive correlation between BMI and ET (p<0.001). After the histopathological evaluation two atypic glanduler hyperplasia were reported in our study. The mean ET of these women were 7.4 mm and their BMI were significantly higher than in control group (p<0.05). Total abdominal hysterectomy and bilateral oophorectomy with frozen section were performed for these patients. There was no malignancy on the final pathology. The other endometrial pathologies assosiated with obesity and ET in our study group were polypoid formation, simple cystic hyperplasia and atypic glandular hyperplasia including 11 (36.7%) women.

In our study we found that asymptomatic, obese postmenopausal women had a higher risk of developing endometrial pathology including hyperplasia, polipoid formation. In this current study also the pathology of proliferative endometrium was found 26.7%. In asymptomatic postmenopausal women the cut-off values of ET for EH are unclear [6, 24]. According to our results we suggest screening for endometrial pathologies in obese postmenopausal women that ET is measured ≥ 5 mm. One of the strong characteristics of this study is its prospective design, which allowed standardization of the type of measurement or evaluation. Furthermore design of study according to ET and the analysis of BMI effects on ET were makes the study stronger. The number of the patients and the absence of endometrial biopsy from control group were the limitation of our study. But the cut-off value of ET ≥ 5mm was our strict criteria for endometrial biopsy. If we would compose the groups according to intra-uterine pathologies at the first phase of the study, perhaps, the affects of BMI would be much more reliable.

Competing interests

The authors declare that they have no competing interests.

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Association Between Vitamin D Levels and Semen Parameters in Infertile Males

İnfertil Erkeklerde D Vitamin ve Semen Parametreleri Arasındaki İlişki

D Vitamin ve Semen Parametreleri / Vitamin D and Semen Parameters

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Özet

Amaç: Bu çalışmanın amacı, yıkama sonrası ileri hareketli sperm sayısına göre infertil erkeklerin klinik ve laboratuvar özelliklerini karşılaştırmak ve serum D vitamini (VD) düzeyleri ve semen parametreleri arasında bir ilişki olup olmadığını değerlendirmektir. Gereç ve Yöntem: Toplam 198 infertil erkek bu kesitsel çalışmaya dahil edildi. Çalışma popülasyonu temel olarak yıkama sonrası toplam ileri hareketli sperm sayısına (TİHSS) göre 5 milyon / ml'den az (çalışma grubu) ve 5 milyon / ml veya daha fazla (kontrol grubu) olarak iki gruba ayrıldı. Her bir hasta için kaydedilen ana parametreler; yaş, VKİ (vücut kitle indeksi), infertilite tipi, infertilite süresi, önceki ameliyat, hastalık, sigara, ilaç kullanımı ve serum 25OHVD3, toplam kalsiyum (Ka) ve testosteron (TT) düzeyleri, gonadotropinler, ve semen parametreleriydi. Bulgular: Gruplar arasında yaş, VKİ, infertilite tipi, infertilite süresi, önceki operasyon, hastalık, sigara, ilaç kullanımı, TT ve 25OHVD3 açısından istatistiksel olarak anlamlı farklılık yoktu. Serum gonadotropin düzeyleri çalışma grubunda anlamlı olarak düşük bulundu (p <0.001). Tüm grupta ortalama 25OHVD3 düzeyi 21,0 ± 7,2 ng / ml idi ve çalışma grubunda VD ile yıkama öncesi / sonrası toplam sperm sayısı arasında pozitif bir korelasyon vardı (sırasıyla, p = 0,036, p = 0,034). Serum Ka seviyesi yine bu grupta anlamlı olarak daha düşüktü (p = 0,012). Tartışma: D vitamini yetersizliği infertil erkeklerde yaygındı. VD ve Ka desteği yıkama sonrası TİHSS 5 milyondan / ml'den az, VD ve Ka eksikliği gösterilmiş infertil erkekler için uygun tedavi olabilir. Bu konuda iyi tasarlanmış ve büyük serili ileri prospektif kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler

Kalsiyum; Erkek İnfertilitesi; Semen Parametreleri; D Vitamini

Abstract

Aim: The purpose of this study was to compare clinical and laboratory characteristics of infertile males according to their postwash progressively motile sperm count and to evaluate whether there was a relationship between serum vitamin D (VD) levels and semen parameters. Material and Method: A total of 198 infertile men were included in this cross-sectional study. Study population was mainly divided into two groups according to post wash total progressively motile sperm count (TPMSC) as less than 5 million/ml (study group) and equal or greater than 5 million/ml (control group). The main parameters recorded for each patient were; age, BMI (body mass index), infertility type, infertility duration, previous operation, history of disease, smoking, drug usage and serum levels of 25OHVD3, total calcium (Ca) and testosterone (TT), gonadotropins, and semen parameters. Results: There were no statistically significant differences between groups in terms of age, BMI, infertility type, infertility duration, and previous operation, history of disease, smoking, drug usage, TT, and 25OHVD3 levels. Serum levels of gonadotropins were significantly lower in the study group (p<0.001). The mean 25OHVD3 level was 21.0±7.2 ng/ml in the total group and there was a positive correlation between VD and pre/post wash sperm count in the study group (p=0.036, p=0.034, respectively). Serum Ca level was also significantly lower in this group (p=0.012). Discussion: Vitamin D insufficiency was common among the infertile men. VD and Ca supplementation may be appropriate treatment for infertile males with documented VD and Ca deficiency, whose post wash TPMSC lesser than 5 million/mL. Further well designed and large series prospective controlled studies are needed on this issue.

Keywords

Calcium; Male Infertility; Semen Parameters; Vitamin D

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Introduction

Infertility is defined as the failure to conceive after one year of unprotected intercourse with the same partner [1]. Male factor is one of the most frequent causes of infertility (40-50%) [2]. Many infertile men are experiencing low total sperm count or different semen abnormalities such as low sperm motility and impaired sperm function, thus resulting in inability to fertilize an oocyte in the absence of a specific underlying etiologic factor [3]. Different cellular abnormalities were defined which reduce semen parameters at molecular and biochemical levels [4]. VD is primarily involved in metabolism of calcium-phosphorus and regulates bone mineralization. It is a fat soluble vitamin and provides intestinal absorption of these minerals, and also is regarded as a steroid hormone. The main source is sunlight induced synthesis in the skin. Cholesterol is converted into cholecalciferol (inactive VD3) by ultraviolet-B rays in this processes and it is hyroxylated by hepatic 25-hydroxylase subsequently and renal 1alpha-hydroxylase to form 1,25(OH)2VD3 (active VD3-calcitriol). A small amount of circulating VD is supplied by diet or food supplements.

Recent human and animal studies have shown that VD is important for both male and female reproductive functions, and VD receptor and metabolizing enzymes are expressed in male genital tract and germ cells [4, 5]. Expression of a VD inactivating enzyme in spermatozoa distinguishes normal and infertile men with a high specificity and suggested as a marker for both semen quality and VD responsiveness [6].

There is no consensus on definitive reference value for an optimal serum VD levels, yet. However, VD deficiency is considered as a 25OHVitD3 below 20 ng/ml and VD insufficiency as a 25OHVitD3 of 21–29 ng/ml. When the serum levels of VD is higher than 30 ng/mL generally accepted as sufficient [7]. In this study we aimed to evaluate serum VD levels of infertile males and to determine whether there is an association with semen parameters.

Material and Method

This cross-sectional observational study was conducted at the Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey, which is a referral medical center located in the middle region of Turkey. A total of 198 infertile men were recruited from infertility and andrology outpatient clinics between September 2013 and November 2013, after receiving approval of the hospital's local ethics committee. Informed consent was obtained from the each participant. The study was carried out during autumn time in Ankara (Longitude: 40° 4' N, Latitude: 32° 34' E, Altitude: 891 m, the average temperature is 7-18.7 °C). The weather was rainy about 6 days of each month during the study period. Also 6 hours per day was sunny during the study period.

Semen sample and blood sample were taken on the same day. The exclusion criteria are anabolic steroid intake, some supplementation of VD, obstructive azoospermia and other causes of infertility except for male factor and unexplained infertility. Whenever the semen parameters were compatible with azoospermia or oligozoospermia, it was accepted as male factor infertility. Unexplained infertility was defined after excluding common causes of infertility using standard fertility investigations, which include semen analysis, assessment of ovulation, and tubal patency test. Men whose wives had previously no pregnancy were regarded as primary infertile; if pregnancy occurs at least once it was considered as secondary infertility. The data obtained from patients were age, BMI (body mass index), infertility type, and duration of infertility, previous operation, history of disease, smoking, drug usage and obstetrical history of their partners. The cohort was mainly divided into study and control groups according to postwash total progressively motile sperm count (TPMSC) that a value of less than 5 million/ml (n: 93) constituted the study group and a value of greater than 5 million/ml (n: 105) constituted the control group.

All of the patients were asked to respect a period of sexual abstinence for 3-5 days. Semen samples were obtained from the patients by masturbation in a private room nearby the laboratory. After liquefaction for 30 minutes at room temperature, the collected semen specimens (pre-washed) were assessed for conventional semen parameters including sperm concentration and sperm motility by the computer-assisted semen analyzer. The rest of the semen was processed using standard swim up method with a sperm preparation media (Ferticult Flushing mediumTM, FertiProNV, Beernem, Belgium). Post wash analysis was again performed by the computer-assisted semen analyzer. Sperm analysis was performed by the same andrology laboratory technician according to a quality control program.

Blood samples were taken after a minimum of 8 hours fasting. Ten mL of venous blood was drawn from each participant and they were evaluated for some hormonal and biochemical parameters including total testosterone (TT), luteinizing hormone (LH), follicle stimulating hormone (FSH), calcium (Ca) and 25OHVitD3. Serum levels of 25OHVitD3 were measured by using an ELISA Kit; Immunodiagnostic AG, Germany. All blood samples were analyzed at laboratory of hormone and biochemistry of our hospital. The intra-assay and inter-assay coefficients of variation were 8.9% and 10.6% for serum 25OHVitD3.

Statistical analysis

Statistical Package for the Social Sciences version 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Statistical significance was set at $p<0.05$. Means and standard deviations for quantitative data and numbers and percents for qualitative data were computed. Independent-samples t test was used to compare unadjusted means of VD between groups. Non parametric variables between groups were compared through Mann-Whitney U test. Pearson correlation test was used for assessing the associations between VD and other parameters.

Results

The mean age of patients was 30.8±5.4 years, mean 25OHVitD3 level was 21.0±7.2 ng/mL and mean BMI was 25.8±3.6 kg/m2 in this study. The men in this sample was mainly divided into two groups, the study (n:93) and the control (n:105) group, according to postwash TPMSC as<5 million/ml and ≥5 million/ml. There was no statistically significant difference between two groups in terms of age, BMI, VD, TT and infertility duration ($p>0.05$). However, there was a statistically significant difference according to FSH, LH and semen parameters ($p<0.001$). And Ca levels were statistically significantly lower in the study group ($p<0.05$). The clinical characteristics and laboratory pa-

Table 1. The clinical characteristics and laboratory parameters of the infertile males and comparison of study and control groups.

	Total group (n:198)	Study Group (<5 m/mL) (n: 93)	Control Group (≥5m/mL) (n: 105)	P value
Age (years)	30.8±5.4	30.8±5.3	30.8±5.5	0.935
Infertility duration (years)	4.4±4.0	4.7±3.8	4.1±4.1	0.298
Semen volume (cc)	2.5±1.4	2.2±1.5	2.8±1.2	0.002
Total sperm count (million)	101.3±126.1	20.5±25.1	172.8±136.2	<0.001
Sperm concentration (million/mL)	36.1±38.8	7.4±8.7	61.6±37.4	<0.001
Progressively motility (%)	22.5±18.4	5.0±7.3	38.0±8.9	<0.001
Non-progressive motile (%)	10.2±7.3	8.2±8.8	11.9±5.3	<0.001
Kruger (%)	4.4±3.5	1.5±1.4	6.9±2.7	<0.001
FSH (IU/mL)	6.8±8.7	10.2±11.5	3.7±2.2	<0.001
LH (IU/mL)	5.5±5.2	7.3±6.9	3.8±1.9	<0.001
TT (ng/dL)	444.2±170.5	446.1±194.9	442.6±146.3	0.884
Total Ca (mg/mL)	9.7±0.5	9.6±0.5	9.8±0.4	0.012
BMI (kg/m2)	25.8±3.6	26.3±4.0	25.4±3.2	0.096
Vitamin D (ng/mL)	21.0±7.2	21.4±7.5	20.7±6.9	0.464

FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TT: Total testosterone, BMI: Body mass index, Ca: calcium. Data are presented as mean±standard deviation. P<0.05 is considered statistically significant.

rameters of study population have been summarized in Table1. The half of the patients was current smokers. Primary infertility (89.9%) is more common among the patients. The mean 25OHVitD3 level was significantly lower in secondary infertile

Table 2. Comparison of Vitamin D levels according to different variables in the total group.

	n (%)	Vitamin D levels (Mean±SD)	p
Infertility type			
Primary	178 (89.9)	21.4±7.2	0.022
Secondary	20 (10.1)	17.5±6.1	
Liquefaction			
Normal	178 (89.9)	20.8±7.1	0.283
Abnormal	20 (10.1)	22.7±7.6	
Leucospemia			
(+)	28 (14.1)	21.7±6.5	0.587
(-)	170 (85.9)	20.9±7.3	
Smoker	99 (50)	21.0±6.7	0.901
Non smoker	99 (50)	21.1±7.7	

SD:standard deviation. P<0.05 is considered statistically significant.

males (p:0.022) (Table2). Correlation analysis showed that there was a negative correlation between VD levels and BMI (r:-0.172; p:0.016), a significant negative correlation between TT levels and BMI (r:-0.332;p<0.001) and a positive correlation between VD and TT (r:164, p:0.021) in the total group. There was no statistically significant correlation between VD and serum Ca levels (p>0.05). There was a negative correlation between VD and age (p:0.002), and there was a positive correlation between VD and pre and postwash sperm concentration in the study group (p<0.05) (Table 3).

Table 3. Correlation analysis between Vitamin D levels and other clinical and laboratory parameters.

	Total group (n:198)		Study Group (<5 m/mL) (n: 93)		Control Group (≥5m/mL) (n: 105)	
	Vitamin D					
	r	p	r	p	r	p
Age	-0.137	0.054	-0.321	0.002	0.0297	0.764
Spouse age	-0.128	0.072	-0.304	0.003	0.0134	0.892
Infertility duration	-0.165	0.020	-0.231	0.026	-0.116	0.239
Infertility type	-0.163	0.022	-0.195	0.061	-0.135	0.169
Testosterone	0.164	0.021	0.167	0.110	0.162	0.099
Calcium	-0.041	0.564	-0.116	0.269	0.062	0.532
Semen volume	0.011	0.877	0.0342	0.745	0.010	0.919
Total sperm count	-0.061	0.392	0.217	0.036	-0.099	0.316
Postwash sperm count	-0.074	0.299	0.221	0.034	-0.117	0.236
TPMSC	-0.086	0.226	0.136	0.194	-0.118	0.232
BMI	-0.172	0.016	-0.204	0.050	-0.151	0.124

r: correlation coefficient, P<0.05 is considered statistically significant.

Discussion

The main finding of this cross sectional study was that VD positively correlated with pre and postwash sperm concentration in infertile men whose postwash TPMSC lesser than 5 million/mL. And also serum Ca levels were statistically significantly lower in this group of men than those whose postwash TPMSC equal to or greater than 5 million/mL. In the present study we divided the cohort into two groups according to the postwash progressively motile sperm count as<5 million/ml and ≥5 million/ml. Because, Van Weert et al. [8] designed a meta-analysis to assess the performance and clinical value of the postwash total motile sperm count to predict intrauterine insemination outcome. According to this study, a cut off value of 5 million/mL of the postwash motile sperm count achieved the highest sensitivity and specificity for pregnancy rate.

In a population based observational study mean 25OHVitD3 level was found 37.4±14.0 ng/mL in white men who were selected from general population [9]. Studies in western countries have shown that blood VD levels vary by season and that the prevalence of VD deficiency was higher during winter [10]. Nanri et al. [11] observed a high prevalence of VD deficiency in a Japanese working population in late autumn. There are only few studies conducted on the VD status of adults in Turkey. In a study carried out in the noncoastal areas of the Aegean region during winter time, it was reported that the mean 25OHVitD3 was 20.70±15.50 ng/mL in male participants [12]. Our study season was consistent with mid autumn season; the second season was seen as the lowest levels of VD.

VD levels were significantly lower in secondary infertile males than primary infertile males in our study. There is no data about infertility type and VD relationship in the literature. However, VD level was significantly negatively correlated with age in the study group. This relationship between infertility type and VD may be due to this correlation. Because, the mean age of men with primary infertile was lower than those with secondary infertile. Smoking has a negative impact on semen parameters [13]. Although there was no relationship between smoking and

VD, smoking was very common (%50) in this cohort. Leukospermia is physiologic and improves semen quality in lesser than 10^6 cells/mL, but above 10^6 cells/mL commonly indicates a prostatic infection. Rodin et al. found that leukospermia did not correlate with semen parameters and it was a poor marker for impaired semen quality [14]. In this study, we did not find an association between vitamin D levels and leukocytospermia. It was suggested that there might be a significant relationship between VD and human fertility [15]. In different animal and human studies, VD receptor and VD metabolizing enzymes were shown in male genital tract and germ cells at different stage of spermatogenesis [6, 16]. These studies make us think that VD has an important role in spermatogenesis. In addition, a group of researchers revealed that VD deficiency reduced fertility rates of male rats [17] and this effect could be compensated by Ca replacement lonely [18]. We found that serum total Ca levels were statistically significantly lower in the study group than the control group. The mean VD levels were also lower than the defined reference levels. This result is compatible with the literature when we looked from the perspective of VD's role in reproductive functions.

Bloomberg and colleagues showed that there was a positive correlation between VD levels and sperm morphology and motility [19]. They suggested that VD receptor activation via VD increased intracellular calcium by releasing Ca from intracellular Ca storage in the neck of spermatozoa and induced sperm motility and acrosome reaction in an in vitro study. In another study found out that there was an association between higher VD levels and lower median total sperm count and percentage of normal sperm morphology [20]. But this tendency got lost in the multivariate model adjusting for confounding factors. And they concluded that low VD is not a risk factor for poor semen quality in young healthy men. In our research the total study group consisted of only infertile males and they frequently had poor semen parameters due to male factor. We found that this group of men had VD insufficiency. Although we stratified them according to different semen parameters, statistically significant results were not found between these groups. We only detected a positive correlation between VD and sperm concentration in the total group.

Hammoud et al. [21] showed that serum 25OHVitD3 levels at high (>50ng/mL) and low (<20ng/mL) levels can be negatively associated with semen parameters. In addition they found a negative association between serum VD levels and BMI in their study. We also found a negative correlation between VD and BMI. Their study population was selected from general population and there is no data about their history of fertility. But we can conclude that VD levels are low and sperm parameters are poor in all infertile males according to our study.

In a population based study of middle aged and older men VD was found positively correlated with total and free T [22]. As in their study, we also found that VD was positively correlated with TT. Svartberg et al. [23] reported a bimodal seasonal variation in TT levels and a significant peak between October and November and a rare in June. In different studies considering regulatory role of VD on calcium metabolism, frequently bone mineral densitometry was also studied with sperm parameters. Yang et al. [24] suggested that infertile men have lower testosterone and bone mineral densitometry (BMD) than fertile men. VD and testosterone were both associated with low BMD and low sperm quality in infertile men. VD has been studied in different patient groups and different communities' until now. Therefore different levels of VD were found in those studies. In this study, we found that VD insufficiency was common among the infertile males.

This study focuses on the relationship between vitamin D and sperm parameters is one of the first studies. The strengths of our study are the number of patients and high quality standards of the andrology laboratory. The limitations are its cross-sectional design, the lack of control group consisting of fertile men, and the lack of knowledge of the ethnicity and socioeconomic status of the patients. Another limitation of the current study is that kits for 25OHVitD3 have large variation.

In conclusion, although we cannot rule out whether VD insufficiency is highly prevalent in the general Turkish population, VD insufficiency was common among the infertile males. VD and Ca supplementation may be appropriate treatment for azoospermic and severe oligoastenoteratospermic infertile males with documented VD and Ca deficiency. Further well designed and large series prospective controlled studies are needed on this issue.

Competing interests

The authors declare that they have no competing interests.

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Is Anxiety an Effective Factor on the Success of Ovulation Induction/Intrauterine Insemination Cycle?

Kaygı Ovulasyon İndüksiyonu/İntrauterin İnseminasyon Siklus Başarısında Etkili Bir Faktör Müdür?

Kaygı ve Intrauterin Inseminasyon / Anxiety and Intrauterine Insemination

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Özet

Amaç: Ovulasyon indüksiyonu/intrauterin inseminasyon (OI/IUI) siklus başarısında kaygının etkisini araştırmayı amaçladık. Gereç ve Yöntem: Açıklanamayan infertilite nedeniyle rekombinant folikül stimule edici hormon ile birinci OI/IUI tedavisi uygulanan 150 infertil çift bu prospektif çalışmaya dahil edildi. Tedavi sonucuna göre katılımcılar gebelik var ya da gebelik yok diye iki gruba ayrıldılar. İki farklı durumdaki kaygı derecelerini ölçmek için tüm kadınlara Durumluluk ve Sürekli Kaygı Ölçeği Anketi (State-Trait Anxiety Inventory Scale) uygulandı: 1) menstruel siklusun üçüncü gününde ovulasyon indüksiyonuna başlamadan hemen önce sürekli kaygı dereceleri ölçüldü. 2) İnseminasyon günü işlemden önce durumluluk kaygı dereceleri ülçüldü. Çoklu regeresyon analizi ile değişik faktörlerin OI/IUI sonuçları üzerine etkileri değerlendirildi. Bulgular: İnseminasyon siklusları sonrasında 22 (14.7%) kadın gebe kaldı. Durumluluk kaygı, OI/IUI sonrası klinik gebelik oranlarını olumsuz etkilerken, sürekli kaygı inseminasyon sonuçlarını etkilemedi. Çoklu regeresyon analizinde kadın yaşı, menstruel siklusun 3. günündeki antral folikül sayısı, hCG uygulamasından önceki ≥16 mm folikül sayısı ve durumluluk kaygı derecesi, OI/IUI sonrası klinik gebelik sonuçları için etkili faktörler olarak bulundu. Tartışma: Bu çalışma durumluluk kaygının OI/IUI siklus başarısına etki edebileceğini göstermiştir. Bu yüzden bu tür tedavi protokolleri ile birlikte gerekli danışmanlık hastalara verilmelidir.

Anahtar Kelimeler

Kaygı; İnfertilite; İntrauterin İnseminasyon; Ovulasyon İndüksiyonu

Abstract

Aim: To evaluate the effect of anxiety on the success of ovulation induction/intrauterine insemination (OI/IUI) cycle. Material and Method: 150 unexplained infertile couples underwent first OI/IUI cycle with recombinant follicle stimulating hormone were enrolled in this prospective study. They were cathegorized, based on their intrauterine insemination results to positive and negative pregnancy groups. All of the women were asked to fill out State-Trait Anxiety Inventory Scale to measure the different type of anxiety levels at two times: 1) On the third day of menstruel cycle, before starting the OI, trait anxiety scores were calculated 2) On the insemination day, state anxiety scores were calculated prior to procedure. The effect of various contributing factors on OI/IUI outcomes were evaluated with multivariate logistic regression analysis. Results: After IUI cycles, 22 women (14.7%) became pregnant. State anxiety levels were inversely effective on clinical pregnancy rates of OI/IUI cycles. However, trait anxiety did not influenced the IUI success. In logistic regression model including covariates, it was found that woman's age, antral follicle count on the third day of menstruel cycle, number of ≥16 mm follicle before hCG administration and state anxiety scores were effective factors of clinical pregnancy rate in OI/IUI cycles. Discussion: This study suggests that state anxiety may have an effect on success of the OI/IUI cycle. Thus, OI with IUI treatment protocols should consider offering counselling interventions.

Keywords

Anxiety; Infertility; Intrauterine Insemination; Ovulation Induction

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Introduction

A combination of controlled ovulation induction (OI) with intrauterine insemination (IUI) remains an important therapeutic step in infertility, and is especially appropriate for cases with mild male factor infertility, anovulation, endometriosis with at least one patent tube, and unexplained infertility. OI/IUI is a widely used treatment modality of infertility due to its simplicity, easy management, low cost, and absence of potentially serious complications [1].

Infertility is a mental stress-inducing condition. This mental stress, particularly anxiety and depression, may be due to various factors, including uncertainty of the cause of infertility, financial stress, and pressure from others who know the couple [2]. And also women receiving medical treatment for infertility may have some psychiatric disorders with high prevalence. Chen et al. reported that in women who visited an assisted reproduction clinic for a new course of the treatment, 40.2% had a psychiatric disorder, with generalized anxiety disorder being the most frequent diagnosis (23.2%), followed by major depression (17.0%) [3]. But, it is unclear, whether the psychological stress and anxiety effect on treatment success and whether interventions to decrease stress and anxiety are beneficial.

The aim of this study is to describe anxiety levels during OI/IUI treatment at two time points and to assess if they are effective on treatment success.

Material and Method

This study was an observational prospective cohort study determining anxiety levels of infertile women undergoing OI with IUI treatment at Zekai Tahir Burak Woman's Health Research And Education Hospital between January-May 2014. A total of 150 women were recruited for this study who agreed to participate and signed a written informed consent form. This study was approved by Ethical Committe of hospital. Study procedures conformed to the Decleration of Helsinki for Medical Research involving Human Subjects. All women participated in the sudy met the following criteria: age <30 years; normal findings on hysterosalpingography; regular menstrual cycles with normal basal serum follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and thyroid stimulating hormone; and normal sperm parameters of husbands. Women with any kind of psychiatric disorder and antipsychotic drug use were exculeded.

The Turkish version of the self-administered Spielberger State-Trait Anxiety Inventory (STAI) questionnaire form was used to measure anxiety levels. Its use to assess anxiety status has been validated [4,5]. The STAI consists of two subscales. State Anxiety (STAI-S) is a measure of situational anxiety with subjects being asked to respond based on "how you feel right now". Trait Anxiety (STAI-T) is a measure of a general tendency to be anxious with subjects being asked to respond based on "how you generally feel". Each subscale consists of 20 items scored on a four- point Likert-type scale; thus the range of possible scores on each subscale is 20 (low anxiety) to 80 (high anxiety). The reliability coefficient (Cronbach's a), referring to a normative sample of men and women, is 0.91 for STAI-S and 0.90 for STAI-T. The test-retest reliability ranges from 0.92 (after 90 min) to 0.75 (after 118 days) for the STAI-T. The participants filled out STAI-T subscale on the third day of menstrual cycle, before the start of OI and STAI-S subscale on the insemination day immediately before the IUI.

All women in the study were treated by same senior physician with the same OI/IUI procedures. All IUI cycles were started on the third day of menstrual cycle, after basal ultrasound examination and hormonal assay. And all OI cycles were continued until ovulation. Recombinant FSH was used for OI. The starting dose of FSH was 75-150 IU according to the status of the patient, including age and hormonal status. All the IUI cycles were the first attempt using FSH after three times of unsuccessful IUI treatment with clomiphene citrate. Follicular development was monitored by vaginal ultrasound and serum estradiol levels, and the dose of FSH was adjusted accordingly every 1-3 days. When at least one follicle with diameter ≥18mm was observed, 10,000 IU of human chorionic gonadotropin (hCG) was given to induce ovulation. A single IUI was performed 36 hours after administration of hCG.

Semen was collected 2 hours prior to the insemination and after 72 hours of abstinence. Swim up method was used for sperm preparation. Biochemical pregnancy was initially detected 15-20 days after insemination. Ultrasound was performed at 6 weeks of gestation to confirm fetal viability. Clinical pregnancy was defined as the presence of a gestational sac confirmed by ultrasound scanning. Spontaneous abortion was defined as the loss of a pregnancy before the 12th week.

SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) for Windows software was used for statistical analysis of the study data. Numeric variables were stated as mean±standard deviation (SD), and categorical variables were expressed as number and percentage. After descriptive tests, Kolmogorov-Smirnov test was used to determine the data distributions. Categorical variables were compared using a x2 test, and continuous variables were analyzed using Students' t-test.. The effects of factors correlated with clinical pregnancy rate after OI/IUI treatment were assessed using a multivariate logistic regression model. The p values less than 0.05 were considered statistically significant.

Results

Data were collected from 150 primary infertile couples. After OI/IUI cycles, 22 women (14.7%) became pregnant. Two of them resulted with first trimester abortions. Demographic and baseline characteristics of the couples were shown in Table 1. The mean age of women and their husbands in clinically positive pregnancy group were significantly smaller than in negative pregnancy group ($p<0.001$ and $p=0.001$ respectively). No significant differences were observed between groups with regard to educational levels, employement status, current smoking ratios, duration of infertility, body mass index (BMI), third day FSH and estradiol levels, semen characteristics, endometrial thickness on hCG day, duration of stimulation and total used gonadotropin dose. Pregnant women, had significantly higher number of antral follicle count on the third day of menstruel cycle and higher number of ≥16 mm-diameter follicle before hCG administration, compared to non-pregnant ones ($p<0.05$).

The results demonstrated that pregnant women were not significantly different from non-pregnant ones regarding their mean score for trait anxiety (38.82±3.78 and 37.58±4.25, respectively; $p=0.215$) . However, mean state anxiety score of

Table 1. Demographic and baseline characteristics of the couples

	Positive pregnancy (N=22)	Negative pregnancy (N=128)	p*
Woman's age (years)	22.86±1.49	26.76±4.13	<0.001
Infertility duration(years)	2.34±0.70	2.13±0.64	0.178
BMI(kg/m2)	24.90±2.02	24.05±2.50	0.148
Educational Level			
Elementary school	6 (27.3)	21 (16.4)	
Middle school	6 (27.3)	43 (33.6)	
High school	7 (31.3)	54 (42.2)	
University	3 (13.6)	10 (7.8)	0.442
Employed woman	8 (36.4)	57 (44.5)	0.475
Current smooking	4 (18.2)	19 (14.8)	0.688
FSH level (IU/L)	6.06±1.35	6.78±2.11	0.129
Estradiol level (pg/ml)	55.50±26.23	52.04±19.62	0.279
Number of antral follicle count	7.28±2.98	5.15±1.86	<0.001
Husband's age (year)	27.68±2.75	29.66±2.41	0.001
Semen volume (ml)	3.31±0.56	3.17±0.56	0.300
Sperm concentration (x 109/L)	63.05±8.69	64.08±6.25	0.523
Sperm motility (%)	55.50±5.17	53.96±5.30	0.221
No. of follicle (≥16 mm)	2.64±0.73	1.91±0.69	<0.001
Estradiol level on hCG day (pg/ml)	505.19±45.80	480.56±60.96	0.079
Endometrial thickness on hCG day (mm)	9.00±1.31	8.73±1.18	0.341
Duration of stimulation (day)	8.91±0.68	8.92±0.54	0.929
Gonadotropin dose (U/ml)	682.05±43.36	701.37±52.22	0.111
STAI-T score	38.82±3.78	37.58±4.25	0.215
STAI-S score	41.19±3.47	44.84±4.18	<0.001

Values are given as mean±standard deviation and number(percentage)
STAI-T: State Trait Anxiety Inventory-Trait; STAI-S: State Trait Anxiety Inventory-State; BMI:Body Mass Index, FSH: Follicle Stimulating Hormone
*p<0.05 is considered statistically significant

pregnant women were significantly lower than of non-pregnant women (41.19±3.47 and 44.84±4.18, respectively; p<0.001) (Table 1).

Analysis by logistic regression model showed that woman's age, total number of antral follicule count on the third day of menstruel cycle, ≥16mm in diameter follicule number and state anxiety level were the independent factors which affect the clinical pregnancy rate of OI/IUI treatment, significantly (Table 2).

Table 2. Multivariate logistic regression model to compare odds ratio of possible effective factors on success of OI/IUI treatment

	Wald	OR	95% CI for OR	p*
Woman's age	4.449	1.473	1.028-2.110	0.035
Infertility duration	0.897	2.332	0.404-13.460	0.344
BMI	2.632	0.625	0.354-1.103	0.105
FSH level	0.339	0.831	0.445-1.552	0.561
Antral follicle count	5.348	0.460	0.238-0.888	0.021
≥16mm follicle number	3.967	0.163	0.027-0.972	0.046
Husband's age	0.111	1.086	0.669-1.761	0.739
STAI-T score	2.014	0.680	0.399-1.158	0.156
STAI-S score	4.166	1.871	1,025-3.416	0.041

OR: Odds Ratio; CI: Confidence Interval; STAI-T: State Trait Anxiety Inventory-Trait; STAI-S: State Trait Anxiety Inventory-State; BMI:Body Mass Index, FSH: Follicle Stimulating Hormone
*p<0.05 is considered statistically significant

Discussion

IUI is often suggested as a first option treatment for infertile couples with unexplained infertility [1]. In literature, it is well established that using gonadotropins has the best treatment outcomes in controlled OI with IUI [6,7]. In our study, the pregnancy rate in OI/IUI cycles with gonadotropins was 14.6%, which was similar to two meta-analysis results reported by Hughes and Guzyck et al. [8,9].

We assessed the anxiety levels, as measured by STAI questionnaire at two time points in IUI cycle. We found STAI-Trait levels of women as 37.64±4.02 on the third day of menstruel cycle and STAI-State levels as 44.12±4.29 on the IUI day. In published reports, average STAI scores in women undergoing fertility treatment range from 33 to 50, reflecting in part the variation in mean scores among different countries as well as differences in population norms [10].

Results obtained from the logistic regression analysis showed that state anxiety was effective on pregnancy rate after IUI treatment. In other words, women who achieved pregnancy after an IUI cycle had lower anxiety score as measured by STAI-S. These findings are consistent with the findings of many previous studies [11-14], including invitro fertilization and intracytoplasmatic sperm injection treatment outcome. However, some other studies have reported no association between anxiety and reproductive outcomes [15,16].

The effects of stress and anxiety on infertility development are explained well by hypothalamic-pituitary-adrenal (HPA) axis related mechanism. Psychological factors activates the HPA axis, which is involved in the excretions of corticotrophic-releasing hormone, adrenocorticotrophic hormone and cortisol, respectively [17]. The literature suggests the mediation of the HPA axis on the down-regulation of the hypothalamic-pituitary-ovarian axis at all levels. The HPA activation in untreated women inhibits the GnRH pulse generator and consequently inhibits the secretion of gonadotropins (LH, FSH) and sex steroids [18]. However, in gonadotropin stimulated IUI and IVF, psychological effect is unlikely to occur through this pathway because of administration of gonadotropins exogenously. Thus, the state anxiety is probably effective in the implantation phase of the stimulated cycles [19].

In addition, we have also found three more factors that are statistically effective on pregnancy rate after OI/IUI cycle in our study. The woman's age is one of them, that seems to influence the outcome inversely. It is generally accepted that the woman's age is the most important factor influencing the likelihood of pregnancy and female fecundity following to IUI procedure, namely treatment success decreases as the woman becomes older [20,21]. Another factor found to be effective total antral follicle count on the third day of menstruel cycle. Similarly, Erdem et al. noted that lower antral follicle count on basal transvaginal ultrasonography was associated with lower clinical pregnancy and live birth rates in unexplained subfertile couples who were treated with controlled OI and IUI [22]. The number of ≥16 mm in diameter follicle before hCG administration was the last one that influenced the OI/IUI success, significantly. Mer-

viel et al. analyzed 1038 IUI cycles and reported that pregnancy rates were significantly influenced by the number of follicles >16mm and the estradiol levels on the day of hCG administration and also they found a string link between these two parameters and the rate of multiple pregnancies [23]. However, Noujua-Huttunen et al. did not find any link between the number of follicles and the multiple pregnancy rate, even though they also noted lower pregnancy rates with a single >16mm follicle than with three follicles [24].

This study has some limitations. Firstly, the sample size of the present study is relatively small and the sample of infertile women is drawn only from one public infertility clinic and not from many clinics, which may have introduced selection bias and may not provide to generalize the results to other populations from reproductive treatment clinics. Although we considered the effects of many possible confounding variables on the success of treatment, we did not controll lifestyle factors, such as caffeine, and alcohol intake and psychosocial factors, such as partner's stress and women's perception of stigma. Additionally, we did not evaluate anxiety levels at any time points subsequent to IUI procedure. Anxiety status following to procedure may also be effective on the success of treatment. Morover, we did not assess biochemical markers such as adrenalin, cortisol. Therefore, future studies investigating the association between anxiety and treatment outcomes should include all known aspects of anxiety, such as psychosocial aspects, lifestyle aspects, the autonomic nervous system and the endocrine system.

In conclusion, we demonstrated that state anxiety levels inversely influenced OI/IUI success. Therefore, women with fertility problems enrolling for IUI treatment should be evaluated for levels of anxiety and should be offered appropriate psychological counseling interventions, because reducing anxiety levels may be beneficial for IUI treatment outcomes. And also, younger woman age, greater number of antral follicle count on the third day of menstruel cycle and greater number of ≥16mm follicle before hCG administration was predictive factors for OI/IUI cycle success. Clinicians providing IUI for infertile couples should pay close attention to these factors.

Competing interests

The authors declare that they have no competing interests.

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Surgical Treatment Results of Benign Mediastinal Tumors; The Largest Single Institution Experience

Benign Mediastinal Tümörlerin Cerrahi Tedavi Sonuçları, Tek Merkezli En Geniş Seri

Benign Mediastinal Tümörlerin Cerrahi Tedavi Sonuçları / Surgical Treatment Results of Benign Mediastinal Tumors

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Özet

Amaç: Benign mediastinal tümörler klinikte karşılaşılan nadir tümörlerdendir ve diğer lezyonlara kıyasla bu konuda çalışmalar daha az yapılmıştır. Bu çalışmada, benign mediastinal kitlelerin klinik özellikleri ve cerrahi tedavi sonuçları değerlendirilip, literatür bilgileri ile karşılaştırılmıştır. Gereç ve Yöntem: Ocak 1999 ile Aralık 2009 tarihleri arasında, tek bir göğüs cerrahisi kliniğinde rezeksiyon yapılan 184 benign mediastinal kitlesi olan olgular retrospektif olarak incelendi. Bulgular: En sık görülen benign mediastinal lezyonlar mediastinal kistler (%29,3), timik lezyonlar (%20,1) ve nörojenik tümörler (%19) idi. Çocuk hastalar olguların %10,9'unu oluşturuyordu. Lezyonların çoğu anterior mediastinal yerleşimliydi. En sık şikayetler nefes darlığı, göğüs ağrısı ve öksürük iken, hastaların %26,1'i asemptomatikti. Olguların %61,9'una torakotomi uygulandı. Kullanılan diğer insizyonlar median sternotomi, collar kesi, mediastinoskopi, collar + median sternotomi ve collar + sağ torakotomi idi. Postoperatif komplikasyonlar olguların %12,5'inde gelişti ve bunlar atelektazi, kanama, yara yeri enfeksiyonu, efüzyon, uzamış hava kaçağı ve myastenia gravis nedeniyle solunum yetmezliğiydi. Tartışma: Benign mediastinal kitlesi olan olguların çoğunun başvuru anında klinik şikayetleri vardır ve çoğu biyopsideki zorluklar ve inflamasyon nedeniyle kesin teşhis edilememektedir. Bu çalışma, benign mediastinal tümör rezeksiyonunun düşük morbidite ve mortalite sonuçları ile başarılı bir tanı ve tedavi seçeneği olduğunu göstermektedir.

Anahtar Kelimeler

Benign; Mediastinal Kitle; Mediastinal Kist; Mediastinal Tümör; Cerrahi

Abstract

Aim: Benign mediastinal tumors are uncommon lesions encountered in clinical practice, and they have been studied less extensively than other masses. In this study, the clinical features and surgical treatment results of benign mediastinal masses are discussed and compared with a literature review. Material and Method: Between January 1999 and December 2009, 184 patients with benign mediastinal masses who underwent surgical resection in a single thoracic surgery department were analyzed retrospectively. Results: The most common benign mediastinal lesions were mediastinal cysts (29.3%), thymic lesions (20.1%), and neurogenic tumors (19%). Children made up 10.9% of the patients. Most of the lesions were located in the anterior mediastinum. While 26.1% of the patients were asymptomatic, the most frequent complaints were dyspnea, chest pain, and cough. Thoracotomy was performed in 61.9% of cases. The other incisions used were median sternotomy, collar incision, mediastinoscopy, collar + median sternotomy, and collar + right thoracotomy. Postoperative complications occurred in 12.5% of the cases and included atelectasis, hemorrhage, wound infection, effusion, extended air leakage, and respiratory failure due to myasthenia gravis. Discussion: Most of the patients with benign mediastinal lesions had clinical complaints, and most could not be diagnosed definitively, due to difficulties with the biopsies and inflammation. This study shows that the resection of benign mediastinal tumor is a successful diagnosis and treatment choice that results in low morbidity and mortality rates.

Keywords

Benign; Mediastinal Mass; Mediastinal Cyst; Mediastinal Tumor; Surgery

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Introduction

Mediastinal tumors and cysts are derived from structures that normally reside in the mediastinum or migration of embryonic tissues. They include various types of tumors and can occur at all ages. The mediastinum is divided into three regions: anterior, middle, and posterior. The most common lesions in children are neurogenic tumors, mostly seen in the posterior mediastinum. However, thymomas are the most common lesions in adults, and most are located in the anterior mediastinum.

Presenting symptoms are seen in 60% of patients with all benign and malignant mediastinal masses [1]. The symptoms are due to compression, invasion, inflammation, rupture of the cyst, or paraneoplastic syndromes.

While studies regarding mediastinal tumors have included both malignant and benign lesions, benign mediastinal masses have been studied less extensively. Some subtypes of benign lesions, such as retrosternal goiter and pericardial cysts, have been recommended for followup or medical treatment. Benign mediastinal masses should be diagnosed and treated promptly, due to potential for serious complications and malignant transformation. In this study, we present the clinical features, preoperative evaluations, and treatment results of patients with benign mediastinal tumors and cysts who underwent resection in our clinic.

Material and Method

Between January 1999 and December 2009, 234 patients who underwent surgical resection of a benign mediastinal mass in our Thoracic Surgery Department were analyzed retrospectively. Of the initial group, 184 patients were included in the study and 50 patients were excluded due to lack of available followup data. The patients were followed up for a median of 7.2 months (range, 1–26 months) after surgery. Age, symptoms, diagnostic procedures, surgical and pathological features, and survival rate were analyzed, and the results were expressed as percentages and proportions.

Results

A total of 184 cases operated on in our clinic were included in this study. The mean age was 40.4 (range, 1–80) years. The study included 20 children (under 18 years of age) and 164 adult patients. One hundred seven (58.2%) patients were female and 77 (41.8%) were male, with a female-to-male ratio of 1.4:1. The percentage of patients who were asymptomatic was 26.1%. The most common complaints were dyspnea (24%), chest pain (21.7%), cough (11.9%), swelling of the neck (4.3%), fever (2.1%), back pain (2.1%), dysphagia (1.7%), hemoptysis (1.7%), myasthenia gravis (1.7%), sweating (1.7%), nausea (0.5%), and restlessness (0.5%).

Most of the lesions (55.4%) were located in the anterior mediastinum, 28.8% were located in posterior mediastinum, and 15.8% were located in the middle mediastinum. The most common benign mediastinal lesions were mediastinal cysts (29.3%), thymic lesions (20.1%), and neurogenic tumors (19%) (Table 1). The other lesions were intrathoracic thyroid (13.5%), germ cell tumors (8.1%), mesenchymal tumors (7%), Castleman disease (2.1%), and parathyroid lesions (0.5%).

Table 1. Frequency of locations of benign mediastinal masses

	Anterior	Middle	Posterior	TOTAL
Mediastinal cysts	24	15	15	54 (29.3%)
Thymic lesions	33	4	-	37 (20.1%)
Neurogenic tumors	1	6	28	35 (19%)
Intrathoracic thyroid	23	1	1	25 (13.5%)
Benign Germ Cell Tumors	15	-	-	15 (8.1%)
Mesenchymal Tumors	4	3	6	13 (7%)
Castleman's disease	1	-	3	4 (2.1%)
Parathyroid Lesions	1	-	-	1 (0.5%)
TOTAL	102 (55.4%)	29 (15.8%)	53 (28.8%)	184

Most of the benign mediastinal masses were located in the anterior mediastinum (44.5%); 26.1% were asymptomatic. The most common masses were thymic lesions in the anterior mediastinum, mediastinal cysts in the middle mediastinum, and neurogenic tumors in the posterior mediastinum. General features of the benign mediastinal masses are shown in Table 2.

Table 2. General features, surgical approaches, and treatment results of benign mediastinal masses

	Freq	Mean age	Size (cm)	Asymp	Incision	Compl	H.S.
Mediastinal Cysts	29.3%	40.6	5.7	31.4%	Thoracotomy (83.3%)	9.2%	6.4
Thymic lesions	20.1%	40.4	7.4	32.4%	Median sternotomy (86.4%)	8.1%	7.5
Neurogenic tumors	19%	34.0	6.5	28.6%	Thoracotomy (97.1%)	22.9%	7.3
Substernal Goiter	13.5%	53.4	9.0	4%	Collar incision (72%)	12%	7
Benign Germ cell Tumor	8.1%	28.5	8.8	20%	Thoracotomy (86.6%)	20%	7
Mesenchymal tumor	7%	44.6	6.8	15.4%	Thoracotomy (69.2%)	7.7%	7.1
Castleman's Disease	2.1%	39.5	6.4	100%	Thoracotomy (100%)	25%	8
Parathyroid lesions	0.5%	55	4	-	Thoracotomy (100%)	-	7

Freq: Frequency, Asymp: Asymptomatic, Compl: Complication, H.S.: Hospital stay

A 35-year-old male patient with a 6cm bronchogenic cyst in the middle mediastinum, a 48-year-old male patient with a 7cm pericardial cyst in the anterior mediastinum, and a 69-year-old male patient with an 18cm mature cystic teratoma in the anterior mediastinum were admitted with hemoptysis due to bronchial rupture. A postoperative prolonged air leak occurred in the mature cystic teratoma case.

Myasthenia gravis was observed in three cases: a 33-year-old female patient with a 4cm thymic hyperplasia, a 49-year-old female patient with a 9cm thymic hyperplasia, and a 52-year-old female patient with a 1.5cm thymolipoma. No postoperative complications occurred in any of these patients. However, a 15-year-old female patient with a 14cm thymic hyperplasia

with accompanying autoimmune aplastic anemia required mechanical ventilation for 24 hours postoperatively.

The most commonly preferred incision was thoracotomy, used in 61.9% of the cases in this study. The other incisions were median sternotomy (25%), collar incision (9.8%), mediastinoscopy (1.6%), collar + median sternotomy (1.1%), and collar incision + right thoracotomy (0.6%).

Median sternotomy was the most common incision used for resecting anterior mediastinal masses; thoracotomy was performed most commonly to remove middle mediastinal tumors; and most posterior mediastinal tumors were removed via thoracotomy. In only one case, a collar incision and right thoracotomy was performed to resect a retrosternal goiter with ectopic thyroid in the posterior mediastinum (Table 3).

Table 3. Choice of incision and tumor location

	Anterior	Middle	Posterior	Total	Percentage
Thoracotomy	42	20	52	114	61.9%
Median sternotomy	44	2	-	46	25%
Collar incision	17	1	-	18	9.8%
Mediastinoscopy	2	1	-	3	1.6%
Collar+M.Sternotomy	1	1	-	2	1.1%
Collar+Thoracotomy	-	-	1	1	0.6%

Mediastinoscopy was used for two pericardial cysts and a bronchogenic cyst; the median size was 3.3 cm. There were no complications or recurrences after resection during the median followup period of 6.7 months (range, 2–12 months).

A 62-year-old female patient who underwent myoplasty to remove a 10cm schwannoma in the posterior mediastinum experienced postoperative hemorrhagic drainage.

Collar incision and median sternotomy was performed in two cases: a 13cm retrosternal goiter and an 8cm schwannoma that extended from the neck to the middle mediastinum. After resection, the patient with the 13cm retrosternal goiter experienced hematoma, which was treated with lavage.

A 67-year-old male patient with an 8cm retrosternal goiter had vena cava superior syndrome, and respiratory failure occurred due to compression, for which he underwent mechanical ventilation for 50 days preoperatively. After resection, a hematoma that occurred in the collar incision needed to be drained with a catheter.

Collar incision and right thoracotomy was performed in a substernal goiter with posterior mediastinal ectopic thyroid case; no complications occurred.

A patient with thymic hyperplasia and myasthenia gravis had respiratory failure postoperatively and required mechanical ventilation for 24 hours. In addition, a 65-year-old female patient with a 4.2cm pericardial cyst underwent right thoracotomy for total resection. In the second year of followup, a lung hernia developed through the thoracotomy incision, and the chest wall defect was repaired with mesh.

Early postoperative complications (postoperative 1–30 days) occurred in 12.5% of the cases in this study (Table 4); the most common complication was atelectasis. Other complications, in order of frequency, were hemorrhage, wound infection, hematoma, effusion, prolonged air leak, and respiratory failure. The complications occurred in 14% of thoracotomies, 10.9% of median sternotomies, 5.6% of collar incisions, and one of the two collar incision and median sternotomy cases. When the cases were evaluated in terms of histopathologic types, the complication rates were 25% for Castleman disease, 22.9% for neurogenic tumors, 20% for germ cell tumors, 9.3% for cystic lesions, 8.1% for thymic lesions, 8% for substernal thyroids, and 7.7% for mesenchymal tumors. There was no recurrence or death in any of the 184 cases during the followup period.

Table 4. Evaluation of incisions and complication frequency

	Thoracotomy	M. Sternotomy	Collar	Coll+M.Sternotomy
Atelectasis	8	3	-	-
Hemorragia	2	1	-	-
Openning of İncision	3	-	-	-
Effusion	2	-	-	-
Hematoma	-	-	1	1
Prolonged Air Leak	1	-	-	-
Respiratory Failure	-	1	-	-

Discussion

While mediastinal tumors are rare, malignant tumor rates have been increasing in recent years [1, 2]. Many studies have evaluated benign and malignant tumors together, and according to their results, the mediastinal masses are located, in order of frequency, in the anterior, posterior, and middle mediastinum [3]. The most common lesions are thymoma in the anterior mediastinum, congenital cysts in the middle mediastinum, and neurogenic tumors in the posterior mediastinum [4]. While neurogenic tumors are the most common mediastinal tumors found in children, the most common mediastinal tumor in adults is thymoma [5].

We observed in our study that most of the benign mediastinal masses were located in the anterior mediastinum. The most common benign mediastinal masses were thymic lesions in the anterior mediastinum, cystic lesions in the middle mediastinum, and neurogenic tumors in the posterior mediastinum. In many studies, thymoma is the most common mass found in the mediastinum. However, in our study, mediastinal cystic lesions were more common than thymomas. Neurogenic tumors were the most common benign lesions found in children, and the most common masses in adults were cystic lesions.

Complaints associated with mediastinal masses and lesions vary according to the location of the mass, complications, and secretion of hormones and cytokines. Symptomatic patients are more likely to have malignant masses. A previous study reported that only 46% of patients with benign tumors were symptomatic, compared to 85% of patients with malignancies [4]. In our study, 73.9% of the patients were symptomatic. In order of frequency, the most common symptoms were dyspnea, chest pain, cough, swelling in the neck, fever, back pain, dysphagia, hemoptysis, myasthenia gravis, sweating, nausea, and restlessness.

Thoracic computed tomography (CT) is used to identify mediastinal masses and their relationship to the surrounding structures, as well as to determine cystic, solid, vascular, and soft-

tissue structures. CT was used for preoperative evaluations in all of the cases in our series. In addition, magnetic resonance, positron emission tomography CT, echocardiography, CT angiography, neck CT, thyroid ultrasonography, thyroid and parathyroid scintigraphy, and esophagoscopy were used in 26.1% of the patients in this study.

If investigation results show that a mediastinal mass is likely to be benign, it can be removed surgically without biopsy [4]. Otherwise, transthoracic or transbronchial needle biopsy, mediastinoscopy, anterior mediastinotomy, or video-assisted thoracic surgery can be used for diagnosis, depending on the anatomic location and radiographic appearance of the lesion. The sensitivity of transthoracic needle biopsy is 42–91% and the specificity is 96–100% for anterior mediastinal masses [6]. Surgical resection is required for patients that cannot be diagnosed with noninvasive methods. Pulmonary atelectasis, compression of adjacent structures, adhesions, and malignant transformation do not preclude the surgery [7].

Surgical resection is recommended for bronchogenic cyst cases, due to risk of malignant transformation, definitive diagnosis, and perforation prevention, even if the patients are asymptomatic [8]. Recurrence can occur because of incomplete resection. In this study, a bronchogenic cyst case presented with hemoptysis due to rupture of the cyst, and no complications occurred after surgery. We performed a subtotal resection with mediastinoscopy for a 3cm bronchogenic cyst, and no complications or recurrence occurred. We found no malignant transformation in any of our bronchogenic cyst cases.

Myasthenia gravis is an autoimmune disease, and 15.6% of those patients have thymic hyperplasia [9]. In our series, myasthenia gravis was observed in three patients: two thymic hyperplasia cases and one thymolipoma. Diaz's review showed that myasthenia gravis patients undergoing thymectomy were likely to achieve improvement and medication-free remission and to become asymptomatic, compared to patients who did not undergo thymectomy [10]. Thymic cysts represent 1% of mediastinal masses [11], and while some authors have pointed out that surgery is not required if the definitive diagnosis is thymic cyst, most publications suggest resection due to the potential of malignancy [12-15].

Most pericardial cysts are asymptomatic and are detected incidentally. The 2004 European Society of Cardiology guidelines suggest that the treatment for congenital and inflammatory cysts is percutaneous aspiration and ethanol sclerosis [16]. In our study, 57.9% of the cases were symptomatic, and one patient had hemoptysis due to cyst perforation. Aspiration and subtotal cyst wall excision with mediastinoscopy were performed in two cases, and total resection with thoracotomy was performed in the other cases. Hemorrhagic drainage and wound infection occurred in the patients who underwent thoracotomy; however, none of the patients experienced recurrence.

When more than 50% of the thyroid parenchyma is located below the sternal notch, it is called retrosternal goiter. The standard treatment for substernal goiter with compression symptoms is surgery. If surgery is not feasible, radioiodine can be an alternative treatment choice, especially for patients with high risks of complications [17].

Rupture of mature cystic teratoma into the bronchus, pleura, pericardium, or mediastinum occurs rarely, but it can lead to serious complications [18]. We observed in our study a mature cystic teratoma case with rupture into the bronchus and occurrence of hemoptysis. The mass size was 17.8 cm, and a thoracotomy was performed for resection, after which a postoperative prolonged air leak occurred. However, the patient was discharged on the tenth postoperative day.

Mediastinoscopy can be used for histological diagnosis and treatment of anterosuperior-located mediastinal masses, with very low morbidity and mortality rates [19]. A previous review determined that morbidity, recovery times, and discharge times were all higher with more invasive procedures compared to mediastinoscopy. The researchers also mentioned that although total excision of the cyst wall is difficult via mediastinoscopy, removal of more than 90% of the cyst wall is necessary for absorption of fluid secreted by the remnant tissue through the surrounding structures. It is important to follow up carefully with these patients to monitor them for recurrence. We performed mediastinoscopies for three mediastinal cystic lesions (two pericardial cysts and one bronchogenic cyst), with no complications or recurrence.

Video-assisted thoracoscopic excision of mediastinal masses is a safe and feasible approach that might offer significant postoperative advantages over open procedures. In a previous study, the border of indication for thoracoscopic resection in cystic mediastinal tumors was described as smaller than 7 cm [20]. The researchers also suggested that mediastinal cysts with wall thicknesses less than 5 mm and no FDG accumulation might be observed without resection, due to the very unlikely chance of being a neoplasm. During the study development period, we did not have enough experience in VATS resection therefore the results were not evaluated in this study.

The incision of choice for diagnosis and treatment depends on the lesion location, its characteristics, and the patient's clinical manifestations. We used median sternotomy more frequently for anterior mediastinal masses. Median sternotomy is more suitable for lesions located in the anterior side of the middle mediastinum, and thoracotomy is a better choice for the posterior region of the middle mediastinum. Thoracotomy is best for exploration of posterior mediastinal masses.

Median sternotomy complications occur in less than 3% of patients. Infections often develop due to unsuccessful bleeding control, and 0.2–3% of patients develop mediastinitis [21-22]. The most common complication of thoracotomy is hemorrhagic drainage. In our series atelectasis was the most common complication, and thoracotomy complications were more frequent than with other incisions.

Surgery is the management of choice for patients with benign mediastinal lesions [23]. With minimal operative risk, we can achieve a definite histological diagnosis and total excision of the lesion.

Conclusion

Histopathologic features, tumor size, and location are the factors involved in deciding on a treatment choice for benign mediastinal masses. Some studies have suggested, conservatively, nonsurgical treatment modalities such as percutaneous aspiration or followup for a few histopathologic types of benign medi-

astinal tumors. However, surgery provides diagnosis and treatment of mediastinal lesions. In this study, we evaluated a large series of benign mediastinal lesions that underwent resection, and we compared our results with others in the literature.

Competing interests

The authors declare that they have no competing interests.

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Facial Canal Dehiscence in Patients with Chronic Otitis Surgery

Kronik Otiti Cerrahisi olan Hastalarda Fasiyal Kanal Dehissansı

Fasiyal Kanal Dehissansı / Facial Canal Dehiscence

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Özet

Amaç: Kronik otitis media (KOM) cerrahisi geçiren hastalardaki fasiyal kanal durumunu incelemek ve orta kulak patolojisiyle ilişkisini saptamaktır. Gereç ve Yöntem: Ocak 2006 ile Aralık 2012 arasında KOM nedeniyle mastoidektomili veya mastoidektomisiz timpanoplasti ve radikal mastoidektomi yapılan hastaların cerrahi bilgileri retrospektif olarak analiz edildi. Hastaların demostratif verilerinin yanı sıra fasiyal kanalın durumu ile hastaların preoperatif tanıları, yapılan ameliyatın tipi, orta kulağın durumu, cerrahinin sayısı, kolesteatom varlığı, kemikçik defektin varlığı, lateral kanal defektinin varlığı ve dura defektinin varlığı değerlendirilerek fasiyal kanal dehissansı (FKD) ile aralarındaki ilişki istatistiksel olarak araştırıldı. Bulgular: Yediyüzdoksanaltı hasta çalışmaya dahil edildi. Hastaların %10.05'inde FKD saptandı. FKD en sık timpanik segmentte görüldü. Orta kulağın patolojisi, kolesteatom, revizyon cerrahi, lateral semisirküler kanal defekti ve kemikçik defekti ile FKD arasında istatistiksel olarak anlamlı ilişki görüldü($p<0.05$). Tartışma: KOM cerrahisi uygulanacak hastaların preoperatif tanılarına, orta kulak patolojilerine, ameliyat sayısına ve kemikçik zincir defektlerine göre fasiyal kanalda defekt olabileceği öngörülmeli ve gerekli önlemler alınarak fasiyal sinir yaralanma riski en aza indirilmelidir.

Anahtar Kelimeler

Fasiyal Kanal Dehissansı; Kronik Otitis Media; Otolojik Cerrahi Prosedürler

Abstract

Aim: To examine facial canal status in patients with chronic otitis media (COM) surgery and to detect the relation between facial canals dehiscence (FCD) with middle ear pathology in these patients. Material and Method: The surgery data of patients who were subjected to tympanoplasty with or without mastoidectomy and radical mastoidectomy due to COM were analyzed retrospectively from January 2006 to December 2012. In addition to demonstrative data of the patients, status of facial canal and preoperative diagnoses of patients, type of the operation performed, status of middle ear, number of surgeries, existence of cholesteatoma, existence of ossicular chain defect, lateral canal defect and dura defect were assessed and the relation thereof with facial canal dehiscence (FCD) was analyzed statistically. Results: Seven hundred ninety six patients were included in the study. FCD was detected in 10.05% of the patients. FCD was most frequently observed in the tympanic segment. It was found out that there was a statistically significant relationship of middle ear pathology, cholesteatoma, revision surgery, lateral semicircular canal and ossicular chain defect with FCD. Discussion: COM diagnosed patients may have defect in facial canal according to their preoperative diagnoses, middle ear pathologies, number of operations and ossicular chain defects. These patients should be applied a more careful surgery and closely followed up in postoperative periods.

Keywords

Facial Canal Dehiscence; Chronic Otitis Media; Otological Surgery Procedures

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Introduction

Facial canal is a significant structure that should be known and protected in otological surgeries. Existence of a defect on the bone that surrounds the canal in the temporal bone in which the facial nerve is located is called facial canal dehiscence (FCD). In such a case facial nerve is only covered with a weak fibrosis membrane and it may be herniated to the tympanum [1, 2]. And sometimes it may imitate tympanum tumors as well [3, 4]. The most frequent reason for acquired FCDs is cholesteatomas. Apart from such life-threatening complications including central nerve system injuries or meningitis, facial nerve injury is the most frightening sequel in otological and neuro-otological surgeries. Although sensorineural hearing loss and/or vestibular injuries are serious, the ability of the normal contralateral internal ear to compensate these complications decreases the effects of these injuries. However facial nerve dysfunction is a permanent and troublesome event for both the patient and the surgeon [5, 6]. For this reason to be aware of anatomical and morphological variations of facial nerve is crucial for this sort of operations [6].

Recognition of how and where the Fallopian Canal is weak during ear surgery is of critical in order to be able to preserve integrity thereof. FCD may happen as a consequence of chronic inflammatory processes or secondary to the surgery and facial canal which is injured as a consequence of the disease may cause the nerves to be injured more easily [5]. Furthermore, congenital anomalies of facial nerve compose a predisposition for those two injury mechanisms. Preoperative facial nerve injury is rare in cholesteatoma but one may not claim that cholesteatoma located close to any dehiscence in tympanic segment is rare. It may be secondary to either congenital or chronic infections. In such ears tympanic segment may be vulnerable to injury during cleaning cholesteaotoma of tympanum and epitympanum. Nevertheless the case for intraoperative injury of mastoid segment is different. FCD in most mastoid segments is created depending on circulation during FCD mastoidectomy [6]. It is known that dehiscence facilitates development of neuritis and facial palsy in acute and chronic suppurative otitis media. Failure of closing of facial nerve sulcus with ossification during embryologic development and Reichert cartilage malformation's facilitating this closing defect was accused to be the reason for congenital FCD. Additionally, FCD may develop as secondary to middle ear located tumors as well [5].

The purpose o this study is to examine facial canal status in patients who had chronic otitis media (COM) surgery and to detect the relation thereof with middle ear pathologies.

Material and Method

Data of the patients who had surgical operation for COM in the Ministry of Health, Ankara Dışkapı Yıldırım Beyazıt Education Hospital, Ear Nose and Throat and Head Neck Surgery Clinics from January 2006 to December 2012 were examined retrospectively. Different surgeons in the surgery team performed operations. The findings about the status of the facial canal during surgery were classified according to intactness of the canal and whether there was any defect in mastoid, tympanic and geniculate segment. The findings in all surgeries performed were obtained using intraoperative microscope and autoendoscope.

Preoperative diagnoses of all ears subjected to surgery were classified as benign ear, granular COM, adhesive otitis and COM with cholesteatoma. Tympanum status was classified as normal, granular, tympanosclerosis and cholesteatoma. The surgeries performed were classified as tympanoplasty without mastoidectomy, tympanomastoidectomy where the canal is not reduced (CWU), tympanomastoidectomy where the canal is reduced (CWD) and radical mastoidectomy. Furthermore patients were grouped as primary and revision according to the number of surgeries. The relation between those groups and frequency of occurrence of FCD was researched.

The data of the patients were analyzed using SPSS version 18 program (SPSS Inc., Chicago, Illinois) for Windows. The data were assessed using Person Chi-Square test.

Results

Seven hundred and ninety six patients with an average age of 32,09 ±14,69 were included in this study. Data on demonstrative characteristics of the patients, preoperative diagnosis, type of surgery, status of the facial canal and other preoperative findings are summarized in Table-1 and Table-2.

FCD was detected in 80(10,05 %) of the 796 patients. In assessment of the segments of the defect in those 80 patients with FCD, defect was present at tympanic segment in 70 patients (87,5%); at mastoid segment in 8 patients and at genicu-

Table 1. Demonstrative parameters of patients and FCD rates observed

Characteristics		n	%	n (FCD)	% (FCD)	p
Sex	Male	428	53,8	52	14,1	p<0,05
	Female	368	46,2	28	6,5	
Side	Left	392	49,2	41	10,4	p>0,05
	Right	404	50,8	39	9,7	
Preoperative Diagnosis	Benign	381	47,9	1	0,3	p<0,05
	Granular COM	137	17,2	6	4,3	
	Adhesive Otit	62	7,8	5	8,1	
	Tymphanosclerosis	31	3,9	3	9,7	
	Cholestheatoma	185	23,2	65	35,2	
Type of Surgery	Tymphanoplasty	247	31	0	0	p<0,05
	CWU	383	48,1	18	4,7	
	CWD	112	14,1	40	35,8	
	Radical	54	6,8	22	40,8	
Middle Ear Pathology	Normal	340	42,7	5	1,5	p<0,05
	Granular	198	24,9	8	4	
	Tymphanosclerosis	94	11,8	3	3,2	
	Cholestheatoma	164	20,6	64	39	
Number of Surgery	Primary	656	82,4	48	7,3	p<0,05
	Revision	140	17,6	32	22,9	
Cholestheatoma	No	592	74,4	10	1,7	p<0,05
	Yes	204	25,6	70	34,3	
Ossicular Chain Defect	No	442	55,5	4	0,9	p<0,05
	Yes	354	44,5	76	21,4	
LSC Defect	No	772	97	66	8,5	p<0,05
	Yes	24	3	14	58,3	
Dura Defect	No	790	99,2	78	9,9	p<0,05
	Yes	6	0,8	2	33,3	

Table 2. FCD rates according to segment.

Facial Canal Status	n	%
İntact	716	89,95
FCD	80	10,05
Thymphanic	70	87,5
Mastoid	8	10
Geniculate	2	2,5

FCD: Facial canal dehiscence.

late segment in 2 patients.

Mean FCD length was detected as 2,9±2,2 mm. FCD was observed at higher rates in men (14,1%) compared to women (6,5%) and the difference was found to be statistically significant (p<0,05). FCD was statistically significantly more commonly observed in revision surgeries compared to those performed as primary (p<0.05).

It was found out that FCD had a correlation with cholesteatoma status and the probability of the patients with cholesteatoma to have FCD was found to be higher at a statistically significant degree (p<0,05). Furthermore FCD was found to be in correlation with ossicular chain defect and LSC defect and the probability of the patients with these defects to have FCD was found to be higher at a statistically significant degree (p<0,05). Existence of FCD was found to be statistically significantly related to preoperative diagnosis (p<0,05).

Tympanoplasty was applied to 247 of 796 patients and while FCD was not observed in any of those patients. However FCD was observed in 18 (4,7%) of 383 patients who were applied CWU, in 40 (35.7%) of 112 patients who were applied CWD and in 22(42.3%) of 52 patients who were applied Radical mastoidectomy. The rate of occurrence of FCD in radical mastoidectomy and CWD surgeries were observed to be higher compared to tympanoplasty and CWU. A statistically significant relation was detected between middle ear pathologies and existence of FCD (p<0,05).

Looking through FCD rates according to middle ear pathologies; while FCD was observed in 5 of 340 patients with normal mucosa in middle ear, FCD was detected in 3 of 94 patients with sclerosis, in 8 of 198 patients with granular mucosa and 64 of 164 patients with cholesteatoma. The rate of occurrence of FCD in patients with cholesteatoma and granular middle ear mucosa was detected to be higher compared to the patients with normal and sclerotic middle ear mucosa.

Discussion

Facial nerve is one of the anatomical structures located in the temporal bone, which differ most frequently. For this reason patients with FCD are under higher risk during ear surgeries compared to normal patients [6]. There is no consensus in the relevant literature about acquired FCD development mechanism. Although the initial theories focus on the idea that primary mechanism is pressure necrosis, today it is considered that bone resorption is primarily due to the excessively activated osteoclasts. Disintegration of organic and inorganic components of the bone occurs by secreted acid phosphatase collagenase and acid protease enzymes in the inflammatory process. Cytokines and growth factors including interleukin-1, interleukin-6, colony stimulating factor-1, tumor necrosis factor-alpha, and epidermal growth factor transforming growth factor-beta play a role in this situation as well [7]. Those mechanisms are also responsible from the complications secondary to ossicular chain and bone erosions as well.

Intraoperative FCD is observed between the rates of 0,5% and 33% in the studies performed. Stapes surgery and tympanoplasty without mastoidectomy are also included in these ratios and in those operations all segments of facial canal cannot be visualized. By this reason, in FCD studies on cholesteatoma, dehiscence ratio is determined to be higher [8,9]. Moreover, different surgeons perform surgeries. It is a truth that the dehiscence ratios may also change depending on the surgeons' experience and the technical devices. In this study, the FCD incidence was determined as 10.05% in all cases and 87.5% of those were in tympanic segment. Although FCD was not observed in cases with tympanoplasty, it was reported in mastoidectomy cases.

It is considered that real FCD prevalence is higher than FCD rates detected intraoperative period. The temporal bone dominance in this study was also supported with anatomic and histopathological studies as well. Moreano et.al [10] encountered minimum one FCD at a proportion of 56% in the histopathological study they conducted on 1000 temporal bones without any explicit disease or inflammation evidence in order to attract the attention to anatomic variations. They detected that it was located most frequently in tympanic segment and particularly around oval window (74%), and in the second elbow (12%). Baxter [1] reported facial canal dehiscence in 55% of 535 temporal bones in a similar anatomic study he conducted [11].

Wang et.al. [7] found FCD at a rate of 29,7% in the study they performed on 155 patients with cholesteatoma. Kim et.al. [8] specified this rate as 8,6% in the study they performed on 152 patients who were diagnosed with COM without cholesteatoma. Sheehy et.al. [12] detected 15% congenital FCD, 17% disease caused FCD, and determined that 44% FCD depending on surgery was created without explaining how discrimination was made on 1024 mastoid surgery cases they performed in 10 years. Beyazıt et.al. [11] detected an 8,9% FCD rate in the study they performed on 219 patients.

Facial nerve injury may either be a direct complication of cholesteatoma or be a complication of ear surgery made because of cholesteatoma [13]. In the analysis performed by Green et.al. [14] on 22 patients with iatrogenic facial nerve injury developed as secondary to non-neurootological procedures, it was detected that it occurred during mastoidectomy in 57% of the patients, and during exocytosis excision in 14% of the patients and additionally existence of cholesteatoma caused iatrogenic injury at a proportion of 36% as a predisposing factor. They suggested that the most frequently injured segment was the tympanic segment. In our study 35.2% FCD was determined in patients with cholesteatoma and 1,7% in patients without cholesteatoma. We suppose the existing pathology particularly cholesteatoma is related to FCD and that cholesteatoma is a risk factor for FCD development and consequently for preoperative facial nerve injury.

In the study performed by Selesnick et.al. [9] 30% FCD was observed in primary cases and 35% in revision cases. Revision surgeries were defied as risk factors for FCD in the study performed by Di Martino et.al [5]. Iatrogenic facial nerve injury

incidence was reported between 0,6-3,6% in primary cases and between 4-10% in revision surgeries in the literature [8]. Nevertheless Wiet [15] defended that iatrogenic facial nerve injury incidence depends on the form of the surgery performed and detected in the study he performed that facial nerve injury rate was between 0,6 and 3,6% in all otological surgeries and this rate increased up to 4-10% in revision cases. In our study 22,9% FCD was found during revision surgeries and the difference was found to be statistically significant. We are convinced that revision surgeries are risk factors for facial nerve injury due to high FCD incidence.

Wang et.al. [16] detected positive correlation between lateral semicircular canal (LSC) defect and FCD in their study and it was expressed that most of the patients with LSC defect had FCD particularly in tympanic segment. Fourteen (17,5%) of 24 (3) patients with LSC defect had FCD in our study and the section with dehiscence was in the tympanic segment in all of them. It was supposed that this was related to close neighborhood of LSC and facial nerve in tympanic segment [11, 17].

In the study performed by Wang et.al. [7] dural defect in mastoid tegmen was detected in 26 of 155 patients having ear surgery and it was expressed that most of these were related to cholesteatoma. Although the relation between dural defect and FCD was not found to be statistically meaningful in the same study, it was defended that this risk was related to the localization of cholesteatoma. Dural defect in mastoid tegmen was detected in 6 of 796 patients having surgery in our study.

FCD was detected in surgeries made for non-cholesteatoma reasons as well. Among these, FCD was detected in 5 (1,5%) of 340 (42,7%) patients whose middle ear mucosa was normal, in 8 (4%) of 198 (24,9%) patients in whom granular mucosa was observed, in 3 (3,1%) of 94 (11,8%) cases with sclerotic mucosa. FCD was observed in mucosal diseases where no cholesteatoma was observed and it is considered that it may be a risk factor in this case in terms of facial nerve injury. Additionally, it has been reported that facial nerve monitoring and computerized tomography do not have any contribution to the detection of FCD, particularly those in the tympanic segment [5].

According to the literature and the statistical analysis of the study a significant relation was detected between FCD with cholesteatoma, revision surgery, LSC defect, ossicular defect. We consider that the existence of those parameters is significant risk factors in the development of preoperative facial nerve injury. For this reason we recommend that those pathologies should be examined carefully in preoperative assessment and measures including selection of high definition video systems and microscopes, otoendoscope, proper surgery tools and intraoperative facial nerve monitoring should be taken in order to detect dehiscence more clearly in the patients within the risk group and avoid complications.

As a consequence; it should be anticipated that COM diagnosed patients may have a defect in facial canal according to their preoperative diagnoses, middle ear pathologies, number of operations and ossicular chain defects. Taking the necessary measures should minimize facial nerve injury risk. Furthermore, patients who are considered likely to have FCD should be applied a more careful surgery and close follow-up in postoperative periods should be done.

Competing interests

The authors declare that they have no competing interests.

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Type III Supracondylar Humerus Fractures in Children: Open Reduction and Pinning

Çocuklarda Suprakondiler Humerus Tip III Kırıkları: Açık Redüksiyon ve Pinleme

Supracondylar Humerus Fracture / Suprakondiler Humerus Kırığı

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Özet

Amaç: Humerus suprakondiler kırıkları, çocuk dirsek çevresi kırıklarının en sık görülen tipidir. Açık redüksiyon, deplase olmuş suprakondiler kırıklı hastaların tedavisinde başarılı bir yöntem olarak kullanılmaktadır. Açık redüksiyon yönteminin en önemli avantajı, kırık hattının görülerek tam bir anatomik redüksiyona izin vermesi, iyatrojenik damar ve sinir yaralanma riskinin azlığıdır. Bu çalışmada Gartland ekstansiyon tip III çocuk humerus suprakondiler kırıkların cerrahi tedavisinde uyguladığımız açık redüksiyon ve çapraz pinleme tedavisinin sonuçları değerlendirildi. Gereç ve Yöntem: Gartland tip III ekstansiyon tip humerus suprakondiler kırık gelişen 18 çocuk hasta (5 kız, 13 erkek; ort. yaş 7.3 ± 2.02; dağılım 3-12) çalışmaya alındı. 11 (%61.1) hastanın sağ dirseğinde, 7 (%38.8) hastanın sol dirseğinde kırık mevcuttu. Ortalama ameliyat süresi 53.3 ± 8.5 dakika (dağılım, 45-70). Hastaların ortalama hastanede yatış süresi 1.7 ± 0.75 gün (dağılım, 1-3), ortalama takip süresi 2.2 ± 0.6 yıl (dağılım, 1.5–4) idi. Bulgular: Flynn kriterlerine göre taşıma açısı değişiklikleri altı (%33.3) hastada çok iyi, 12 (%61.7) hastada iyi sonuç alındı. Fonksiyonel değerlendirmede hastaların eklem hareket kaybı değişiklikleri açısından 14 (%77.7) hastada çok iyi, dört hastada (%22.3) hastada ise iyi sonuç elde edildi. Radyolojik değerlendirmede ortalama Baumann açı değişimi 75.6° (dağılım, 70 – 85) idi. Tartışma: Gartland ekstansiyon tip III humerus suprakondiler kırıkların cerrahi tedavisinde açık redüksiyon tekniği ile kırıklarda iyi klinik sonuçlar elde edilebilmektedir. En önemli dezavantajı ise ameliyat sonrası dirsekte oluşan insiziyon skarıdır.

Anahtar Kelimeler

Suprakondiler Humerus Kırıkları; Açık Redüksiyon; Posterior Yaklaşım; Çocuk; Triseps

Abstract

Aim: Supracondylar humerus fractures are the most common type of fractures involving the elbow region in children. Open reduction is a successful method for the management of displaced supracondylar fractures, with the most important advantages being complete anatomical reduction by visualising the fracture line and the lower level of risk for iatrogenic neurovascular injuries. In the present study, we assessed outcomes of open reduction and cross-pinning employed in the surgical management of paediatric Gartland type III supracondylar humerus fractures. Material and Method: The study included 18 children with Gartland extension type III supracondylar humerus fractures (13 boys, 5 girls; mean age: 7.3 ± 2.02 years; range, 3–12). There were fractures in the right elbows of 11 patients (61.1%) and in the left elbows of seven (38.8%). The mean operative time was 53.3 ± 8.5 minutes (range, 45–70). The mean length of hospital stay was 1.7 ± 0.75 days (range, 1–3), while the mean follow-up time was 2.2 ± 0.6 years (range, 1.5–4). Results: According to the Flynn criteria, excellent results were obtained in six patients (33.3%), and good results in 12 (61.7%) regarding changes in the carrying angle of the elbow. Functional assessment results were excellent for 14 patients (77.7%) and good for four (22.3%) regarding their loss of joint movement. Radiographic examinations revealed an average Baumann's angle of 75.6° (range, 70–85). Discussion: Good clinical outcomes can be achieved through the management of Gartland extension type III supracondylar humerus fractures using the open reduction technique. The most important disadvantage, however, is the post-surgical appearance of the elbow incision scar.

Keywords

Supracondylar Humerus Fractures; Open Reduction; Posterior Approach; Child; Triceps

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Introduction

Supracondylar humerus fractures are the second most common fractures after forearm fractures and the most common type of fractures involving the elbow in children [1]. These fractures can cause severe functional and cosmetic problems if left untreated or treated insufficiently [2]. Severe complications include Volkmann's ischemic contracture, neurovascular injuries, cubitus varus/valgus deformity, myositis ossificans and limitations in joint motion [2-5].

Supracondylar humerus fractures are classified into two groups based on the direction of the displacement: flexion and extension [2]. Extension fractures are more common than flexion fractures, and were classified into three subgroups by Gartland [6]: type I, with no displacement; type II, with moderate displacement and intact posterior cortex and type III, with complete displacement.

The primary goal of the surgical treatment of supracondylar humerus fractures is to achieve complete recovery of the motion of the elbow joint and normal cosmetic appearance [2, 3, 7, 8]. Open reduction is one type of surgical treatment that has been used successfully in the management of displaced supracondylar humerus fractures [9]. The most important advantages of this method include complete anatomical reduction by visualising the fracture line and lower risk for iatrogenic vascular and neurological injuries [2, 8, 9].

In the present study, we assessed the outcomes of open reduction and cross-pinning employed in the surgical management of paediatric Gartland extension type III supracondylar humerus fractures.

Material and Method

The study included 18 children (5 girls, 13 boys; mean age, 7.3 ± 2.02 years; range, 3–12) with Gartland extension type III supracondylar humerus fractures who underwent open reduction and fixation by Kirschner (K)-wires between 2011 and 2014 (Table 1). Exclusion criteria were as follows: age >16 years, Gartland type I-II fractures, open fractures, metabolic bone disease and ipsilateral upper extremity fracture. There were fractures in the right elbows of 11 patients (61.1%) and in the left elbows of seven patients (38.8%). All fracture operations were performed on the same day. The study was conducted in accordance with the Declaration of Helsinki.

Table 1. Demographic characteristics of patients.

Patients, n	18
Years of age, mean ± SD (range)	7.3 ± 2.02 (3–12)
Gender, n (%)	
Female	5 (27.7%)
Male	13 (72.3%)
Years of follow-up, mean ± SD (range)	2.2 ± 0.6 (1.5–4)
Fracture location, n (%)	
Right elbow	11 (61.1%)
Left elbow	7 (38.8%)

SD, standard deviation.

Surgical Technique

At the elbow region, a skin excision was made beginning from 5 cm proximal and extending to 1–2 cm distal to the olecranon via a posterior approach. The distal humerus was exposed through the medial and lateral aspects of the triceps muscle, preserving the ulnar nerve and not detaching the triceps from its insertion in the olecranon. After reduction of the fracture, fixation was achieved under fluoroscopy by a cross-pin configuration of 2–3 K-wires (1.5 mm in thickness; Figure 1). K-wires were bent over the skin and the wound was closed. After surgery, a long arm cast was applied to maintain a neutral position of the forearm and elbow joint. Weekly wound care was performed, and skin sutures were removed on post-surgical day 10. The K-wires and long arm cast were removed without anaesthesia at an outpatient clinic 3–4 weeks after surgery based on patient age and radiological findings. Active exercises were prescribed in order to improve the range of motion of the elbow.

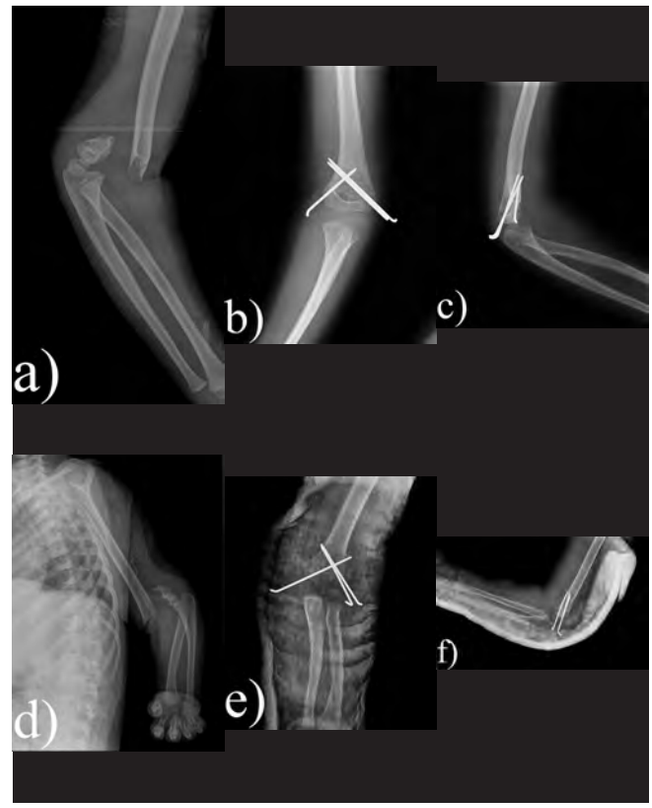


Figure 1. Pre- and post-operative radiographic images of patients with Gartland extension type III supracondylar humerus fractures. (a, b, c, d, e, f)

At the final follow-up, anteroposterior and lateral elbow radiographs were obtained. Cosmetic and functional results were evaluated based on radiographs using the Flynn criteria (Table 2) [10], and the Baumann's angle was measured in all patients (Figure 2). The neurovascular status was recorded pre- and post-operatively.

Table 2. Flynn criteria for grading supracondylar humerus fractures [10].

	Cosmetic factor: carrying angle loss (°)	Functional factor: motion loss (°)
Excellent	0–5	0–5
Good	6–10	6–10
Fair	11–15	11–15
Poor	>15	>15

Results

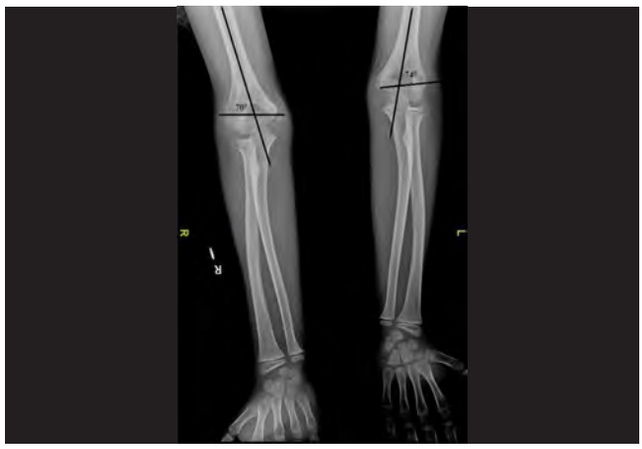


Figure 2. The change in the Baumann's angle two years after surgery in a patient with a Gartland type III supracondylar fracture of the right humerus.

The mean operation time was 53.3 ± 8.5 minutes (range, 45–70), and the mean hospitalisation time was 1.7 ± 0.75 (range, 1–3) days. The mean follow-up time was 2.2 ± 0.6 years (range, 1.5–4). In the three patients who had anterior interosseous nerve lesions before surgery, lesions completely recovered within 3–4 months after surgery; the nerve injuries were considered as neuropraxia. No wound site infections or superficial pin-tract infections developed in any patient.

According to the Flynn criteria, excellent results were obtained in six patients (33.3%), and good results in 12 (61.7%) regarding changes in the carrying angle of the elbow (Figure 3). In the functional assessment, excellent results were obtained for 14 patients (77.7%) and good results for four (22.3%) regarding their loss of joint movements (Figure 4). The radiographic examination revealed an average Baumann's angle of 75.6° (range, 70–85).



Figure 3. The change in the carrying angle of the elbow four years after surgery in a patient with a supracondylar fracture of the left humerus(a). Incision scar at the elbow(b).

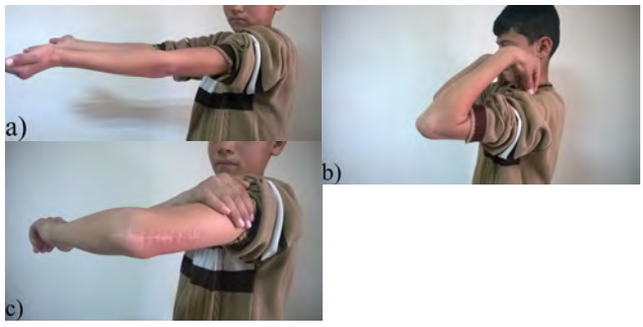


Figure 4. Pictures of a patient three years after surgery; a) Elbow extension. b) Elbow flexion. c) Incision scar.

None of the patients complained of elbow pain or developed neurological deficits, myositis ossificans or cubitus varus. The most common complaint involved the appearance of the post-surgical incision scar (Figure 5).



Figure 5. Incision scar formation two years after open surgery.

Discussion

For supracondylar humerus fractures, the primary goal is to achieve anatomical position and support it by fixation while providing maximum stability and minimum morbidity [2, 8, 11]. The treatment guidelines for type I and II fractures have been well established, and many methods have been recommended for the treatment of type III fractures [8, 12]. Type III fractures may be associated with neurovascular injuries, and treatment may be complicated by malunion, elbow stiffness, iatrogenic neurovascular injury and compartment syndrome [12]. Surgical treatment of type III fractures is complicated and entails technically difficult orthopaedic procedures.

According to many authors, the ideal treatment for type III supracondylar humerus fractures is closed reduction and percutaneous pinning [11, 13, 14]. However, the results from several studies using open reduction and pinning suggested that it is at least comparable to, or even favourable to, closed reduction and pinning [11, 13, 15]. Traditionally, open reduction had been reserved for cases in which closed reduction failed, displacement recurred or vascular complications occurred during the closed attempt [5, 16]. Additionally, certain portions of the displaced fractures cannot be reduced using the closed method. Brachialis muscle entrapment at the fracture site, for example, is the most common cause of blocked reduction, as the distal spike of the proximal fragment is driven through the substance of the muscle [17, 18]. Furthermore, open surgery preferred after one or two attempts at closed reduction may produce adverse effects on the epiphysis and also lead to myositis ossificans [12]. Considering these factors, we achieved osteosynthesis by open surgical intervention in Gartland type III fractures without attempting closed reduction. The rationale for this approach was that it afforded the opportunity to avoid complications related to manoeuvres, the possibility of achieving reduction more readily and the potential for reductions in radiation exposure doses during surgery.

Kazımoğlu et al. [12] reported that outcomes of closed reductions demonstrated no superiority over open reductions in their study, which compared closed surgery and open reduction via

the lateral approach in Gartland extension type III supracondylar fractures.

In supracondylar humerus fractures, open surgical intervention can be achieved via anterior, posterior, medial, lateral or postero-medial approaches [2, 8, 11-13, 19-21], each of which has associated advantages and disadvantages. The posterior approach can allow for effective surgical access by exposing both cortexes directly, although it is thought that the posterior approach can cause loss of joint movement abilities [13, 19, 20]. In a long-term study, Gürkan et al. suggested that the posterior approach with a V transection of the triceps muscle was a reliable surgical approach which was not associated with morbidity [20]. The results of a study conducted by Özkoç et al., in which a postero-medial incision was used for the open reduction of supracondylar humerus fractures, suggested that the postero-medial incision was an easy, safe and cosmetic incision for open reduction of supracondylar humerus fractures [8]. Proponents of the anterior approach posited that it provided for excellent exposure of the fracture site and had the advantage of not adding surgical injury to the unharmed posterior structure [17, 19]. In our study, we completed the surgical intervention with medial and lateral distinct incisions, which allowed for the exposure and reduction of fractures without detaching the triceps from its insertion in the olecranon after the posterior long incision of the skin. In this way, surgical intervention was achieved without harming the triceps muscle while exposing both columns of distal ends of humerus.

Open reduction has been associated with disadvantages including loss of motion, myositis ossificans, increased risk for infection, prolonged hospital stay and formation of marked scar tissue at the incision line [2, 5, 11, 13, 14]. However, we observed no adverse event other than incision scars in our patients. The mean length of hospital stay was 1.7 ± 0.75 days (range, 1–3) in our study. It should be noted that a study by Sibly et al. [14] found no correlation between stiffness and surgical approach.

The results of a few studies have suggested that closed reduction with two lateral pins was an effective method associated with avoidance of iatrogenic ulnar nerve injuries [22, 23]. However, biomechanical studies have definitively demonstrated that the cross-pin configuration is more stable than the two lateral pin configuration [23, 24]. The results of a study by Zionts et al. [24] indicated that the most stable K-wire composition was a cross-pin configuration with two K-wires used at medial and lateral locations. According to Sankar et al. [25], the loss of fixation is more likely to occur when Gartland type III fractures are treated with the two lateral pin fixation operation. Because we were of the opinion that more stable fixation was needed in Gartland type III fractures, the cross-pin configuration was used in our study.

Nerve injuries associated with displaced supracondylar humeral fractures may be attributable to the injury itself or to iatrogenic injury during treatment [3, 13]. The ulnar nerve is most commonly injured after percutaneous crossed K-wires treatment, with an incidence of 2–6% [3, 7, 8, 11, 13, 23]. No neurological problems occurred in our study, as we preserved the ulnar nerve during open surgery. The pin tract infection rate has been reported as 2–7% [11, 13, 20, 26]; however, no infections developed in our study.

Traditionally, acute treatment of displaced supracondylar fractures has been recommend [8, 20]. The reasons behind the recommendation were to decrease the risk of peri-operative complications, such as compartment syndrome, infection and nerve injuries, as well as reduce the probability of conversion to an open reduction [2, 5, 11, 13]. However, the results of several studies have found no significant differences between early and delayed treatment of supracondylar humeral fractures in children with regard to perioperative complications and the need for open reduction [26-28]. All patients in our study underwent surgery within one day after anaesthesia preparation, and no adverse events were observed due to early surgical intervention.

Our study has also some limitations. There is not any control group such as results of closed reduction or opened reduction with triceps muscle dissection that we could compare with our opened reduction surgical technique.

In conclusion, good reductions were obtained using the open reduction technique via a posterior approach without transection of the triceps muscle. Additionally, good clinical outcomes were also achieved in the management of Gartland extension type III supracondylar humerus fractures. However, the incision scar formation after open surgery remains problematic from a cosmetic perspective.

Competing interests

The authors declare that they have no competing interests.

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Metallic Foreign Body in the Foot

Ayakta Metalik Yabancı Cisim

Yabancı Cisim / Foreign Body

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Özet

Amaç: Ayağın yabancı cisim yaralanmaları sık karşılan bir problemdir. Penetre oldukları dokularda çeşitli komplikasyonlara yol açabilmektedirler. Yabancı cisimleri çıkarmak güç ve zaman alıcı olabilmektedir. Bu nedenle yabancı cisimlerin çıkarılması iyi bir preoperatif hazırlık gerektirir. Bu çalışmada ayakta yabancı cisim batması olarak kırık iğne tespit edilen hastalar ve cerrahi tedavi sonuçları değerlendirildi. Gereç ve Yöntem: Ayağına iğne batması nedeniyle 2011-2013 tarihleri arasında ameliyat edilen 34 hasta (11 erkek, 23 kadın; ortalama yaş 30.2) çalışmaya alındı. Hastaların değerlendirilmesinde etkilenen ekstremite, iğnenin yerleşimi, görüntüleme tekniği, yaralanmanın olduğu mevsim, yaralanma ile müdahale arasında geçen süre, anestezi tipi, cerrahi tedavi sırasında floroskopi kullanımı ve cerrahi müdahaleye bağlı komplikasyonlar incelendi. Bulgular: 20 (%58.8) hastada sağ ayak, 14 (%41.1) hastada sol ayakta iğne batması mevcuttu. Yerleşim yeri açısından; 14 (%41.1) hastada ayak parmaklarında, 12 (%35.2) hastada ayak ortasında, 8 (%23.5) hastada ise topuk bölgesinde kırık iğne tespit edildi. Yaralanma zamanı olarak 13 (%38.2) hastada yaz, yedi (%20.6) hastada kış, bir (%2.9) hastada ilkbahar, 13 (%38.2) hastada ise sonbahar mevsimi olarak belirlendi. İğne batması 28 (%82.3) hastada evde, altı (%17.6) hastada ev dışı ortamda gerçekleştiği tespit edildi. Ortalama takip süresi 8.9±2.8 ay idi. Tartışma: Ayağın yabancı cisim yaralanmalarında cisimlerin çıkarılması iyi bir preoperatif hazırlık gerektirir. Yabancı cisimler penetre oldukları dokularda çeşitli komplikasyonlara yol açabilmektedirler. Ayrıntılı fizik muayene ve radyolojik tetkikler, iyi sonuç alınması yönünden önem taşımaktadır.

Anahtar Kelimeler

Yabancı Cisim; Dikiş İğnesi; Ayak; Floroskopi; Sterotaksik

Abstract

Aim: A foreign body injury of the foot is a frequently encountered problem. These foreign bodies can lead to various complications in the affected tissues, and their removal can be difficult and time consuming. Therefore, the removal of a foreign body requires good preoperative preparations. The surgical treatment results of patients with a foreign body, identified as a sewing needle, that had penetrated their foot were evaluated. Material and Method: Thirty-four patients (11 males, 23 females; mean age, 30.2 ± 18.6 years) who were surgically treated between 2011 and 2013 were included. Data concerning the affected limb, placement of the needle, imaging techniques, season when the injury occurred, time between medical intervention and injury, anaesthesia type, fluoroscopy of use during surgery and surgical complications were analyzed. Results: A sewing needle had penetrated the right foot of 20 (58.8%) patients and the left foot of 14 (41.1%) patients. Broken needles were found in the toes of 14 (41.1%) patients, in the middle of the foot of 12 (35.2%) patients and in the heel area of 8 (23.5%) patients. The injuries occurred in summer in 13 (38.2%) patients, in winter in seven (20.6%) patients, in spring in one (2.9%) patient and in autumn in 13 (38.2%) patients. Needle penetration had occurred in 28 (82.3%) patients at home and 6 (17.6%) patients outside of the home environment. The average follow-up time was 8.9 ± 2.8 months. Discussion: Removal of foreign bodies from the foot requires good preoperative preparations. Foreign bodies can lead to various complications in the affected tissues. It is important to perform detailed physical and radiological examinations to obtain good treatment results in these patients.

Keywords

Foreign Body; Sewing Needle; Foot; Fluoroscopy; Stereotaxic

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Introduction

A foreign body injury of the foot is a frequently encountered problem. The penetrating objects are often pieces of metal or non-radiopaque objects such as pieces of wood or glass [1-3]. Such foreign bodies can cause infection with chronic drainage and pain in the affected tissues where their effect may not be immediate; however, later can cause chronic pain. Furthermore, these foreign bodies can cause damage to neurovascular structures depending on the penetration location [2-6].

Detection and removal of foreign bodies can be difficult. Therefore, removal requires good preoperative preparations [2, 7]. Sometimes foreign bodies can be very difficult to localise and may increase the operation time, also failure to remove the object may cause unnecessary tissue damage [2, 6]. Various removal techniques are used, such as blunt dissection, stereotactic techniques and percutaneous removal, and these techniques may be guided by xeroradiography, computed tomography (CT), magnetic resonance imaging (MRI), fluoroscopy or ultrasound (US) [3, 6-13]. The removal process is sometimes performed in the emergency department or in the operating room, and can be performed under local or general anaesthesia [3, 6, 7].

Sewing needles are found in almost every house in our society; therefore, may pose a risk to family members. Sewing needle penetration of the sole of the foot is seen quite often in our own community and funded mostly ordinary. We believe that a higher incidence of these injuries is a cultural phenomenon, and these injuries are probably less common in other societies. Literature descriptions of detection of broken needles in the body have mostly been presented in reports of metallic foreign body injuries.

In this study, we presented in this study the stinging needle phenomenon as a case series involving patients with foreign body injuries identified as sewing needle penetrations of the sole of the foot and evaluate and discuss the results of surgical treatment.

Material and Method

Thirty-four patients (11 males, 23 females; mean age, 30.2 ± 18.6 years; range, 5–75 years) who were surgically treated between 2011 and 2013 were included in this study (Table 1). All patients underwent preoperative plain radiography. Tetanus prophylaxis was performed for patients with acute injuries who had not had tetanus shots within the last 5 years. All patients underwent preoperative and postoperative prophylactic antibiotic treatment. Data were collected and analysed in all patients regarding the affected limb, placement of the needle, imaging techniques, season when the injury occurred, time between medical intervention and injury, anaesthesia type, scope of use during surgery and surgical complications. The study was conducted in accordance with the Declaration of Helsinki.

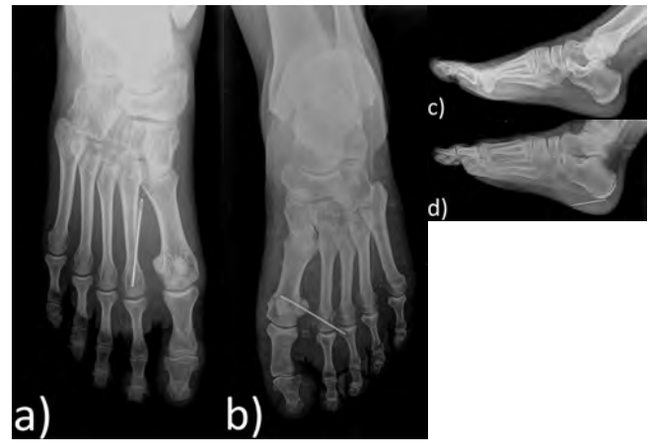
Results

A sewing needle had penetrated the right foot of 20 (58.8%) patients and the left foot of 14 (41.1%) patients (Figure 1). Broken needles were found in the toes of 14 (41.1%) patients, in the middle of the foot of 12 (35.2%) patients and in the heel area of 8 (23.5%) patients. The injuries occurred in summer in 13 (38.2%) patients, in winter in seven (20.6%), in spring in one (2.9%) and in autumn in 13 (38.2%). Needle penetration had occurred in 28 (82.3%) patients at home and outside of the home environment in six (17.6%). The average follow-up time was 8.9 ± 2.8 months.

Table 1. Patient demographic and clinical data.

Number of patients	34
Age, years, mean (range)	30.2 ± 18.6 (5–75)
Sex, n (%)	
Female	23 (67.6)
Male	11 (32.3)
Follow-up, months, mean (range)	8.9 ± 2.8 (6–14)
Location, n (%)	
Right foot	20 (58.8)
Left foot	14 (41.1)
Duration of the operation, minutes, mean (range)	26.3 ± 10.5 (15–45)
Season, n (%)	
Spring	1 (2.9)
Winter	7 (20.6)
Autumn	13 (38.2)
Summer	13 (38.2)
Anaesthesia, n (%)	
Local	19 (55.8)
Spinal	9 (26.4)
Sedation	6 (17.6)

Figure 1. Radiographic images showing broken needles in the feet of patients (a, b, c, d).



During the operation, 19 (55.8%) patients received local anaesthesia, nine (26.4%) received spinal anaesthesia and six (17.6%) were sedated. In the patients who required spinal anaesthesia, the procedure was performed by using a tourniquet. A fluoroscopic device was used to guide removal of the foreign bodies in all patients. In 19 patients with especially deep-seated broken needles in the soles of their feet, at least three 20-gauge injection needles were used to mark the foreign needle location (stereotaxic method) (Figures 2, 3). In the other patients, the foreign needle was marked by making an incision in the skin over the broken needle to allow it to be reached and removed.

The time between the injury and the removal operation was 1 day in 27 (79.4%) patients, 2 to 10 days in four (11.7%) patients, 4 months in one (2.9%) patient, 1 year in one (2.9%) patient and 8 years in one (2.9%) patient. The mean operative time was 26.3 ± 10.5 minutes (range, 15–45 minutes). Four patients were hospitalized for 2 days for postoperative wound

care and antibiotics. The average length of hospital stay was 1.1 ± 0.3 days (range, 1–2 days).

Figure 2. (a, b) A marking method used to aid removal of the broken needle.



Figure 3. Radiographic images of the marking methods used to determine the locations of broken needles (a, b, c, d).



Discussion

Foreign body-related injuries are one of the most common types of injuries seen in the foot [6]. Foreign bodies embedded in soft tissues can be toxic and cause serious allergic reactions, inflammation and infection [3, 5, 14, 15]. The severity of these complications varies. Removal of foreign bodies sometimes can be difficult and time consuming [3, 14, 15]. While attempting to remove a foreign body, larger incisions than those planned may be necessary, and in some cases, may cause more damage than that caused by the initial injury [7, 15].

Although there are no classical methods for preoperative detection of impalpable objects in soft tissue, many different methods can be used [3, 10]. Standard X-ray radiography is the most clinically practical method of screening for foreign bodies [16]. However, radiography may only detect foreign bodies in 15% of affected patients [1]. For detection of non-metallic objects, US, CT and MRI are typically used [3, 6-13]. A study published by Bernardino [4] that compared ultrasound, CT and xeroradiography found that CT was more sensitive for detection of wooden objects. Preoperative determination of the foreign body location decreases the time needed for surgical excision and minimizes unnecessary dissection [6]. Therefore, it is very important to use imaging techniques to determine the correct location. A stereotaxic method is often used for removal of superficial foreign bodies in the absence of a fluoroscopic device [7]. In our study, the use of a stereotaxic method for locating metallic objects in deep tissue decreased the removal time and resulted in less exposure to X-rays when using fluoroscopic equipment.

Sewing needle penetrations of the foot occur commonly in the home [7]. In our study, needle penetrations occurred in 28 (82.3%) patients at home and occurred outside the home environment in six (17.6%) patients. Injuries occurred in 38.2% of the patients in summer, in 38.2% of the patients in autumn, in 20.6% of the patients in winter and in 2.9% of the patients in spring.

It is evident that the most appropriate time to remove a foreign body is immediately after injury. However, a wait of a few days may be acceptable if treatment must be delayed. These injuries usually lead to development of an abscess or fibrous tissue reaction in a few weeks around the foreign body [3-5]. Our best long-term phenomenon, a patient complained of increased foot pain after sports trauma, and we subsequently identified and removed a broken sewing needle from the foot. Symptoms appeared eight years after the apparent trauma, which had been forgotten. The needle was found to be covered with fibrotic tissue.

Foreign body migration varies according to the structural features of the anatomical region where the foreign body settled [14, 15, 17]. Flat plates that are thin, long and localized in the tendon sheath and foreign bodies in the upper extremities can move more easily and over a greater distance than other types of foreign bodies [17]. In our cases, none of the foreign bodies had moved very far from their initial entry points.

Incisions required to remove a foreign body should avoid weight-bearing surfaces and should be followed by creation of a relaxed skin tension line if possible. In long dissections of the plantar, Z incisions or S-shaped incisions can be used at appropriate places if required. We mostly chose mini-incisions because of the fluoroscopic equipment we use and stereotaxic method we prefer. None of our patients experienced problems related to the surgical scar tissue formed after surgery.

The patient's age and location of the foreign body are important factors in decision making for removal of the foreign body in the operating room or emergency room, either performed under general or local anaesthesia [13]. In particular, it is recommended that foreign bodies in paediatric patients and those that are deep seated be removed in the operating room [13]. The interventions in all of our patients were performed in the operating room. During surgery, 19 (55.8%) patients received local anaesthesia, nine (26.4%) patients received spinal anaesthesia and six (17.6%) patients were sedated.

Various techniques have been developed for removal of foreign

bodies [3, 6, 16]. Sharma and Azzopardi [18] reported that radio-opaque bodies were removed by using a marking technique involving three 20-gauge needles. However, many variations can be created with needles placed at various angles for localization of foreign bodies. Mardel [19] stated that the Trendelenburg position for patients with surgical wounds reduced the blood flow to the lower extremities and, thus, enabled sharper images to be obtained that facilitated easier removal of foreign bodies. Some authors have proposed that foreign bodies be removed in the presence of ultrasound in an operating room [9, 13]. Bradley [16] reported a success rate of 88% for removal of percutaneous foreign bodies in the presence of ultrasound. Tao et al. [6] described a 3D CT guidance technique for removal of small superficial metal foreign bodies. Foreign bodies under the skin require relatively complete location information of neighbouring muscles, tendons and neurovascular structures to ensure a more controlled surgical dissection. In our study, nine patients underwent surgical procedures that were performed with a tourniquet. Fluoroscopy was used in all patients for guidance. In 19 patients with especially deep-seated broken needle in the soles of their feet, a marking technique using at least three 20-gauge injection needles (stereotaxic method) was used in different variations to localise the foreign needles. The mean operative time was 26 minutes, and no significant damage occurred to the structures by using this procedure.

Foreign bodies that appear to have been present for a long time in extremities may not require removal because of the lack of functional effects or damage to anatomical structures. Patients with these circumstances have been reported in the literature, and they were informed that there was no need to remove the foreign body [3, 5]. On the other hand, patients showing symptoms require removal of the foreign body. Foreign bodies that cannot be removed might cause serious complications such as infection, delay in healing, persistent pain, migration, cellulitis or pseudotumours [2, 5]. We did not encounter any complications resulting in osteomyelitis in our patients during the follow-up period. Postoperative inflammation at the incision site was detected in four patients. At the end of follow-up, no problems were detected.

Foreign body injuries of the foot should not be considered insignificant. These injuries can easily lead to various complications in the affected soft tissues. Detection and removal of foreign bodies can often be problematic, so good preoperative preparations are required. The structural features of the foreign body should dictate the imaging techniques to be used, if possible. Detailed physical examination and radiological examinations are extremely important for achieving successful treatment of patients.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Surgical Treatment of Mid-Shaft Clavicle Fractures: Plate Fixation and Clinical Outcomes

Klavikula Cisim Kırıklarında Cerrahi Tedavi: Plak Tespiti ve Klinik Sonuçlar

Klavikula Cisim Kırıkları / Midshaft Clavicle Fractures

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Özet

Bu çalışmada klavikula kırığı nedeniyle, açık redüksiyon ve anatomik plak ile internal tespit yöntemi uygulanan hastaların klinik, radyografik sonuçlarıyla birlikte ilişkili komplikasyonları değerlendirildi. Çalışmaya 27 (64.2%) erkek, 15 (35.7%) kadın toplam 42 hasta dahil edildi. Hastaların ortalama yaşı 31 (dağılım 19-51), ortalama takip süresi 16.2 ay (dağılım 9-26 ay) idi. Hastaların 23' ünde (54.7%) sağ klavikulada, 19' unda (45.2%) sol klavikulada kırık mevcuttu. Hastaların takip sonunda ortalama Constant skoru 85.2 (dağılım: 65-96) idi. Postop beş (%11.9) hastada implant yetmezliği, iki (%4.7) hastada implant irritasyonu saptandı. İmplant yetmezliği gelişmeyen hastaların takip sonundaki ortalama klavikular uzunluğu 164.45 mm (dağılım 124.78-188.19), sağlam taraf klavikulaların ortalama uzunluğu 165.82 mm (dağılım 124.17-189.04) olarak tespit edildi (p=0.41). İmplant yetmezliği gelişen hastaların ortalama klavikula uzunluğu 161.93 mm (dağılım 137.16- 172.54), sağlam taraf klavikulaların ortalama uzunluğu 171.05 mm (dağılım 149.49- 181.72) olarak tespit edildi (p=0.02). Kortikal temasın kaybolduğu deplase klavikular kırıkların plak ile anatomik restorasyonu klavikular uzunluğu korumakta ve fonksiyonel olarak iyi sonuçlar sağlamaktadır.

Anahtar Kelimeler

Klavikula Kırığı; Plak Tespiti; Kısalma; Tedavi; Komplikasyon

Abstract

In the present study, we assessed the clinical and radiographic results and complications in patients who underwent open reduction and internal fixation using a plate for clavicle fracture. A total of 42 patients were enrolled in the study, including 27 men (64.2%) and 15 women (35.7%). The mean age was 31 years (range, 19–51 years), and the mean follow-up time was 16.2 months (range, 9–26 months). Twenty-three patients (54.7%) had left clavicle fractures, and 19 patients (45.2%) had right clavicle fractures. The mean constant score was 85.2 (range, 65–96) at the end of follow-up. In the post-operative period, implant failure was detected in five patients (11.9%), and implant irritation was detected in two patients (4.7%). In patients without implant failure, the mean clavicular length was measured as 164.45 mm (range, 124.78–188.19 mm) on the treated side and 165.82 mm (range, 124.17–189.94 mm) on the intact side after follow-up (p = 0.41). In patients with implant failure, the mean clavicular length was measured as 161.93 mm (range, 137–172.54 mm) on the treated side and 171.05 mm (range, 149.49–181.72 mm) on the intact side (p = 0.02). We conclude that anatomical restoration using plates in displaced mid-shaft clavicle fractures with loss of cortical contact spares clavicular length and provides better functional outcomes.

Keywords

Clavicle Fracture; Plate Fixation; Shortening; Treatment; Complication

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Introduction

Clavicle fractures are frequently encountered orthopaedic injuries. Clavicle fractures comprise 5–15% of all fractures and 44% of fractures involving the shoulder region [1-6]. This injury is more common in young, active men [6]. The mechanism of injury generally involves direct impact to the shoulder, such as that occurring during falls [6, 7]. Approximately 70–80% of clavicle fractures occur as mid-shaft fractures [2, 4, 6, 8-12]. The mid-shaft is the thinnest part of the clavicle and is not stabilized by strong ligaments and muscles as in the lateral and medial aspects [12]. However, the mid-shaft has lower bone density compared with the medial and lateral aspects of the clavicle, and its anatomical structure makes it more vulnerable to external lateral forces [6, 13].

In clavicle fractures, displacement occurs due to an imbalance in muscular strength. The displacement of the medial fragment is superior and posterior due to forces applied by the sternocleidomastoid muscle, while the displacement of the lateral fragment is anterior and inferior due to forces applied by the pectoralis major and deltoid muscles [11]. In adults, limited remodelling, persistent clavicular shortening and angulation can develop after clavicle fracture.

Traditional management of clavicle fractures is conservative [1, 4, 11]. In preliminary studies, a lower incidence of non-union and better functional outcomes were reported with conservative treatment [7, 14, 15]. In particular, conservative treatment can yield good or excellent functional outcomes in clavicle fractures with preserved cortical contact in children and adolescents [16, 17]. However, good outcomes reported in conservative treatment are not universal. Recent findings suggest that the shoulder can be at high risk for residual pain, non-union and shoulder dysfunction after conservative treatment [8, 16]. Thus, it is recommended that management of clavicle fractures should be individualised on the basis of the characteristics of the fracture and the patient's expectations [8, 16].

When only conservative treatment is provided, non-union or symptomatic mal-union are highly common in clavicle fractures, including deformities such as shortening above 20 mm, displacement, angulation above 30° or fragmentation after high energy traumas [18]. This may cause a significant reduction in the patient's satisfaction due to shoulder asymmetry and poor cosmetic appearance [19].

In the present study, we assessed clinical and radiographic results as well as related complications in patient who underwent open reduction and internal fixation using a plate due to midshaft clavicle fracture.

Material and Method

Patients who underwent surgery due to clavicle fracture between October 2010 and November 2013 were retrospectively reviewed. Patients with isolated mid-shaft clavicle fracture without cortical contact between primary fracture fragments were included in the present study. Based on Orthopedic Trauma Association (OTA) classification [20], there were 20 patients (47.6%) with OTA type 15-B1 clavicle fracture, 17 patients (40.4%) with OTA type 15-B2 and five patients (11.9%) with OTA type 15-B3 fracture. There was clavicular shortening >2 cm in 31 patients (73.8%) and fragmented segmental fracture in 11 patients (26.2%). All patients underwent surgery within three days after trauma. The study was conducted in accordance with the Declaration of Helsinki.

Surgical technique

Operations were performed under general anaesthesia in a semi-standing position through a transverse incision over the fracture line. During surgery, care was taken to avoid excessive smooth tissue and periosteum injuries. The supraclavicular nerve was dissected and spared (Figure 1). After reduction of fracture, fixation was achieved superior to the clavicle using a clavicular plate. No auto-graft or allograft was used during surgery.

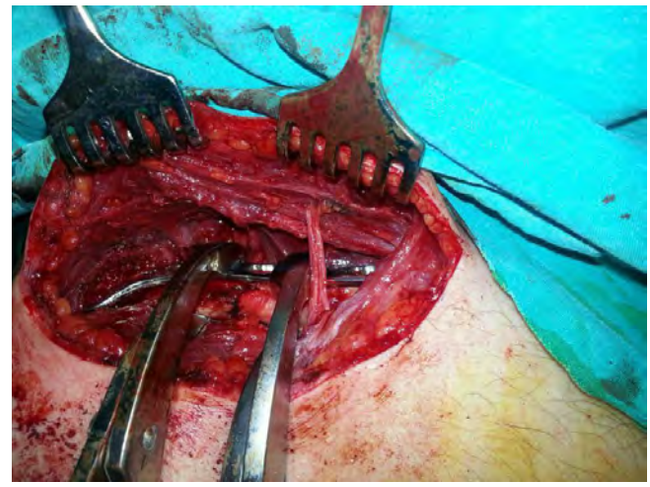


Figure 1. Reduction of fracture fragments in clavicle and appearance of the dissected supraclavicular nerve.

Post-operative care

After surgery, all patients used an arm sling pouch for three weeks. Passive shoulder exercises were initiated at the end of the first week, while active shoulder range of motion exercises were initiated after three to four weeks, depending on the patient's tolerance. After four months, all activities were allowed without any limitations.

All patients were assessed for wound site, superficial and profound infections, neurovascular complications and irritation problems related to implants in the early post-operative period. In the late post-operative period, complications such as delayed union, non-union, mal-union, implant failure and keloid formation at the incision site were assessed.

Radiological evaluation

Radiologically, callus formation beyond 24 weeks was defined as delayed union, while the presence of pain and pathological movement at fracture line without callus tissue was defined as non-union [21, 22]. Mal-union was defined as the presence of asymmetry with impaired anatomical alignment of clavicle [22]. Implant failure was defined as impaired reduction of fracture with breaking or bending of the plate or screws [22].

At the final follow-up, posteroanterior thoracic radiographs were obtained to compare length differences between the intact clavicle and fracture site [23]. At the final follow-up visit, functional assessment was performed on the basis of the Constant score [24].

Statistical analyses

All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, USA) for Windows (Microsoft Corporation, Redmond, USA). Paired Student's t-tests and Mann–Whitney U-tests were used to analyze data. $P < 0.05$ was considered to be statistically significant.

Results

A total of 42 patients were enrolled in the study, including 27 men (64.2%) and 15 women (35.7%). The mean age was 31 years (range, 19–51 years), and the mean follow-up time was 16.2 months (range, 9–26 months). Twenty-three patients (54.7%) had left clavicle fractures, and 19 patients (45.2%) had right clavicle fractures (Table 1). Clavicle fractures were caused by falls in 29 patients (69%), accidents in 11 patients (26.1%) and sports injuries in two patients (4.7%). In addition to clavicle fractures, one patient had a humerus fracture, six patients had rib fractures and one patient had compartment syndrome of the hand with phalanx fractures (Figure 2).

Table 1. Demographic characteristics of patients.

Patient, n	42
Age, mean ± SD (range)	31±8.4 (19-51)
Gender, n (%)	
Female	15 (35.7%)
Male	27 (64.2%)
Follow-up, months, mean±SD (range)	16.2±3.9 (9-26)
Location, n (%)	
Right	23 (54.7%)
Left	19 (45.2%)
Fracture class, n (%)	
15-B1	20 (47.6%)
15-B2	17 (40.4%)
15-B3	5 (11.9%)

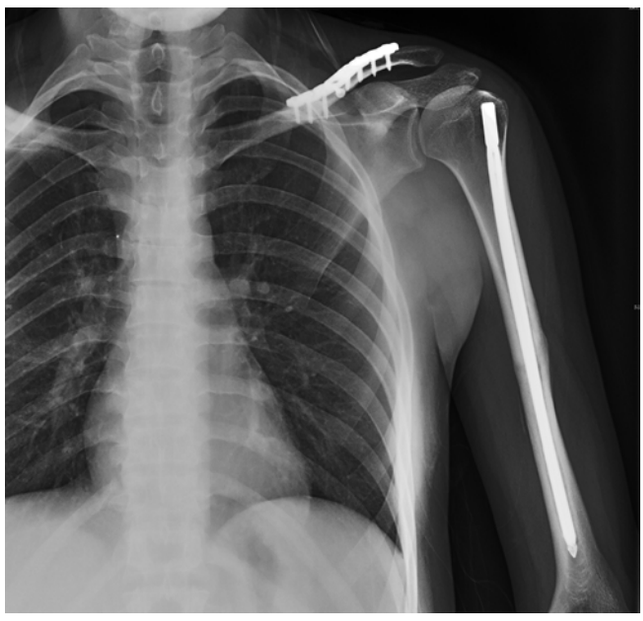


Figure 2. Radiograph at post-operative month 15 in a patient with clavicle fracture accompanied by humerus shaft fracture.

No neurovascular complications were observed after surgery. No superficial or profound infections were detected during the postoperative period. At the final follow-up visit, no keloid formation was observed at the incision sites. After three months, implant failure was detected in five patients (11.9%). Screw pull-out and reduction loss at the fracture line was observed in one patient, while implant breakage was observed in four patients (Figure 3). Autogenous grafting and plate fixation was performed in these patients following removal of implants. Implant irritation was detected in two patients (4.7%); thus, implants were removed after union.

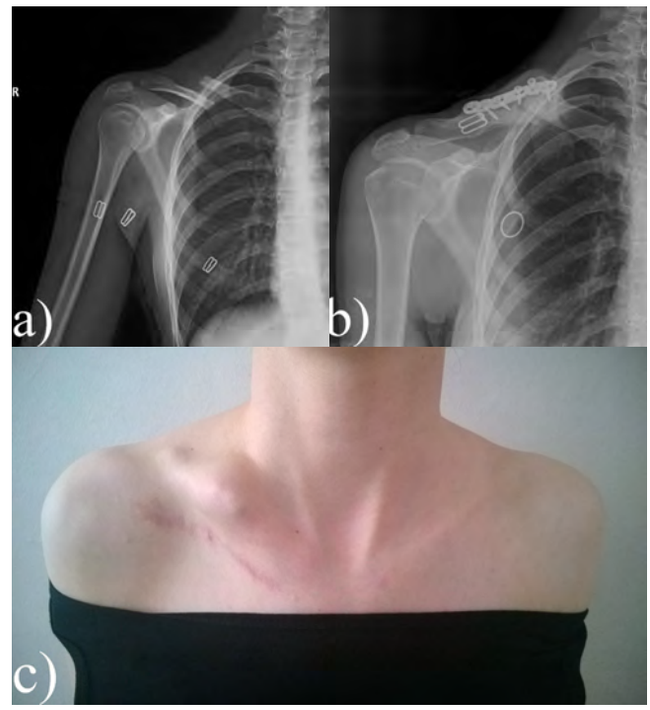


Figure 3. A patient with implant failure after surgical treatment of clavicle fracture: a) Pre-operative radiograph. b) Radiograph at post-operative month 16. c) Poor cosmetic result.

In patients without implant failure, the mean clavicular length was measured to be 164.45 mm (range, 124.78–188.19 mm) on the treated side, while it was 165.82 mm, (range, 124.17–189.94 mm) on the intact side ($p = 0.41$) (Figure 4). In the five patients (11.9%) with implant failure, the mean clavicular length was measured to be 161.93 mm (range, 137.16–172.54 mm) on the treated side, while it was 171.05 mm (range, 149.49–181.72 mm) on the intact side ($p = 0.02$).



Figure 4. Measurement of clavicular length at fractured and intact sites in a patient who underwent surgical treatment: Pre-operative radiograph (A). Clavicular length of 145.94 mm on the right and 141.71 mm on the left after completion of follow-up (B).

The mean Constant score was 85.2 (range, 65–96) in the final follow-up visit. The mean Constant score was 74.8 (range, 65–89) in seven patients (16.6%) with complications (five patients

with implant failure and two patients with implant irritation), while it was 89.2 (range, 83–96) in those without complications. The mean Constant score was found to be significantly lower in patients without complications compared with those with complications (p = 0.001).

Discussion

The aim of clavicle fracture treatment is to ensure healing with minimal dysfunction, morbidity and cosmetic deformity [16]. In the present study, we observed that clavicular length was preserved with minimal shortening. We believe that this shortening will not cause shoulder dysfunction. In addition, good functional outcomes were achieved in our study. However, complications did occur, particularly implant failure together with non-union and requirement of implant removal during the post-operative period.

Mal-union and shortening are frequently observed complications in clavicle fractures [17]. Non-union rates are 15–20% in displaced, fragmented fractures, while mal-union can be seen in up to 14–36% of patients who underwent conservative treatment [6, 25]. Hill et al. reported that the risk for adverse consequences and non-union was higher in clavicle fractures with a shortening of >2 cm initially treated with conservative treatment [3]. In that study, poor results were reported in 31% of patients, while non-union was reported in 15% of the patients. In a meta-analysis, Zlowodzki et al. reported a non-union rate of 15.1% in clavicle fractures after non-surgical therapy [26]. In an anatomical and functional study, Ledger et al. reported a mean shortening of 21.4 mm in 10 patients with clavicle fracture after conservative treatment [11]. In addition, authors also detected significant decreases in VAS scores and limitations in adduction and internal rotation of the involved shoulder. Lazarides et al. reported shortening in 120 patients at a mean follow-up of 30 months after conservative treatment among 132 patients with displaced mid-clavicular fractures [10]. The authors found that the extent of shortening was 14.4 mm in men and 11.2 mm in women. They also found impaired shoulder movements in 13.6% and decreased strength in 16% of the patients. In a study conducted by Robinson et al., the non-union rate was found to be 21% in displaced mid-shaft fractures of the clavicle [27]. In addition, Nowak et al. found permanent problems and weakness in 46% of 208 patients with clavicle fracture after conservative treatment [28].

Mal-union with a shorter clavicle leads to abnormal biomechanical stress and glenohumeral and scapulothoracic dysfunction [29]. It is believed that mal-union and clavicular shortening cause rotation in the glenoid fossa, which, in turn, results in disruption of the glenohumoral joint and scapular rotation [10, 19, 30]. It has been reported that limitations in extension and abduction develop in disordered glenohumoral joints. Some authors have suggested that clavicular shortening enhanced angulation upwards to the sternoclavicular joint and anterior scapular version; in turn, resultant static changes in anatomy can cause limited function of the shoulder [19, 29].

Smekal et al. measured clavicular length in mid-shaft fractures using different imaging modalities [22]. Based on their findings, the authors suggested the use of posteroranterior thoracic radiography to detect clavicular shortening. In our study, we compared clavicular length between intact and operated clavicles using posteroanterior thoracic radiographs. We measured the amount of shortening due to surgery at the end of follow-up. We found that the mean shortening was 1.37 mm in patients without implant failure. This shortening is markedly smaller than those reported after conservative therapy in the literature; in addition, it does not cause functional impairment in the shoulder.

Recent studies have demonstrated that surgical therapy is more effective than non-surgical management with regard to non-union, mal-union and patient satisfaction [31]. In a multicentre study, it was found that radiological union developed less than 12 weeks after surgery in clavicle fractures. The authors reported lower rates of non-union and no cases of mal-union in the surgery group and better functional outcomes one year after surgery [20].

There is a progressive increase in the number of patients undergoing surgery. However, surgical management is not free from risk, with reported complication rates of 15–27% [10, 17, 21, 25, 32]. Complications include infection, skin problems, non-union, implant failure and poor cosmetic results [25, 33-35].

Bostman et al. reported complication and re-operation rates of 43% and 14%, respectively [34]. In a study involving 20 patients, Kulshrestha et al. reported that implants were removed due to implant irritation in four patients (9%) and that mal-union was detected in four patients (4.4%) [8]. In a study comparing a conservative approach with surgical therapy, Mırzatolooei et al. detected non-union secondary to infection in one patient (3.4%) and mal-union in four patients (13.7%) among 29 patients in the surgery group. The authors also reported implant removal in two patients (6.8%). In their study, the Constant score was reported as 89.8, and there was a mean shortening of 4 mm compared with the intact clavicle [36]. In a study comparing locking intramedullar fixation and plate fixation, Ferran et al. reported a Constant score of 88.7 in the plate group and implant removal in eight patients (53%) after a mean follow-up of 12.4 months [33].

Infraclavicular hypoaesthesia secondary due to supraclavicular nerve injury with reported incidence of 10–29% is the most common complication following surgical therapy [5, 21]. However, no nerve injuries were detected after surgery in our patients. In the literature, it has been emphasized that re-operation would be required for removal of the implant in the majority of cases treated surgically [7, 16, 17, 25, 31, 34-36]. In our study, implants were removed due to implant irritation in two patients (4.7%), and five patients (11.9%) underwent re-operation due to implant failure.

In conclusion, surgical therapy allows rapid anatomic restoration with stable fixation and early mobilization, although there is no consensus on choice of treatment in mid-shaft clavicle fractures. The present study has some limitations, including the lack of a control group for comparison. Based on our results, we believe that clavicular shortening and resultant potential shoulder dysfunction can be avoided by anatomical restoration with a plate in displaced mid-shaft clavicle fractures with loss of cortical contact.

Competing interests

The authors declare that they have no competing interests.

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Association of Polymorphisms in TCF7L2 Gene with Gastric Cancer Risk: A Preliminary Study in Turkish

TCF7L2 Genindeki Polimorfizmlerin Mide Kanseri Riski ile İlişkisi: Türk Populasyonunda Bir Ön Çalışma

TCF7L2 Geni ve Mide Kanseri Riski / TCF7L2 Gene and Gastric Cancer Risk

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Dudu Erkoç Kaya, Hilal Arıkoğlu, İncilay Çelik Sümen, Ebru Avcı, Özlem Ata, Emine Arslan. Transkripsiyon Faktörü 7 Benzeri-2 gen polimorfizmleri (rs12255372 ve rs7903146) ve Mide Kanseri ile ilişkisi. XIII. Ulusal Tıbbi Biyoloj ve Genetik Kongresi, pp-S, 27-30 Ekim 2013, Kuşadası, İzmir, Türkiye.

Özet

Amaç: Kromozom 10q25.3'te lokalize transkripsiyon faktörü 7-benzeri 2 (TCF7L2) geni birçok kanser tipi ile ilişkisi gösterilmiş, yüksek hareketli grup içeren bir transkripsiyon faktörünü kodlar. Bu faktör, embriyonik gelişimin ve olgun dokularda homeostazinin düzenlenmesinde kilit rol oynayan Wnt/β-katenin sinyal yolağının önemli bir parçasıdır. Wnt/β-katenin sinyal yolağının devamlı aktivasyonunun kanser gelişimine yol açabileceği bilinmektedir. Bu çalışmada, Wnt/β-katenin sinyal yolağının kilit efektörü TCF7L2 genindeki rs7903146C>T ve rs12255372G>T tek nükleotid polimorfizmlerinin mide kanseri ile ilişkisinin ortaya konulması ve ilişkili risk allellerinin belirlenmesi amaçlanmıştır. Gereç ve Yöntem: Çalışmamızda; TCF7L2 genindeki polimorfizmler, 38 mide kanseri hastası ve 48 sağlıklı bireyde, PCR-RFLP tekniği kullanılarak genotiplendirildi. Elde edilen veriler istatistiksel olarak analiz edildi ve tüm değerlendirmelerde p<0.05 anlamlı kabul edildi. Bulgular: rs12255372G>T polimorfizmi additif model altında (OR: 0.366 [95% CI: 0.135-0.989] p= 0.047) hastalıkla ilişkili bulunurken rs7903146C>T ile mide kanseri arasında anlamlı bir ilişki tespit edilmedi (p> 0.05). Tartışma: Çalışmamız, TCF7L2 gen polimorfizmlerinin mide kanseri ile ilişkisinin belirlenmesine yönelik Türk popülasyonunda yapılan ilk araştırmadır ve rs12255372G>T polimorfizminin mide kanseri için bir risk belirteci olabileceğini göstermektedir. Diğer taraftan örnek sayısının artırıldığı daha geniş bir populasyonda yapılan ileriki çalışmalara ihtiyaç vardır.

Anahtar Kelimeler

TCF7L2 Geni; SNP; Mide Kanseri; Türk Populasyonu

Abstract

Aim: The Transcription factor 7-like 2 (TCF7L2) gene, located on chromosome 10q25.3, encodes a transcription factor, which contains a high mobility group box, demonstrated in association with many cancer types. This factor is a critical part of Wnt/β-catenin signaling pathway that plays key roles in regulation of embryonic development and homeostasis in mature tissues. It is known that the constant activation of Wnt/β-catenin signaling pathway can cause cancer development. In this study, it is aimed to reveal the association between rs7903146C>T and rs12255372G>T single nucleotide polymorphisms in TCF7L2 gene, the key effector of Wnt/β-catenin signaling pathway, and gastric cancer and to determine associated risk alleles. Material and Method: In our study, polymorphisms in TCF7L2 gene were genotyped using PCR-PFLP technique in 38 patients with gastric cancer and 48 healthy individuals. The obtained data were statistically analyzed and p<0.05 was accepted significant in all assessments. Results: No significant association was determined between rs7903146C>T and disease (p> 0.05) while 12255372G>T polymorphism was associated with the disease under additive model (OR: 0.366 [95% CI: 0.135-0.989] p=0.047). Discussion: This is the first study to examine the association between TCF7L2 gene and gastric cancer risk in Turkish population and suggests that rs12255372G>T could be a potential indicator for gastric cancer. On the other hand, further studies are required which will be carry out in more increased number of samples in a wider population.

Keywords

TCF7L2 Gene; SNP; Gastric Cancer; Turkish

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Introduction

Gastric cancer (GC) is the fourth most common malign tumor type in the world and the incidence rate between countries and even in different regions of a country shows significant differences [1]. Although numerous biological and epidemiological studies, the mechanisms revealing GC are not yet fully understood but it is known that gastric carcinoma is a very gradual and multifactorial process which genetic and environmental factors are in interaction with each other [2, 3].

Helicobacter pylori infection, smoking, inadequate fruit and vegetable, high meat and salt consumption and lack of food cooling are the major environmental factors [4]. On the other hand, positive family history means high risk for GC [5] and genetic susceptibility accounts for 35% of disease etiology [6]. In recent years, studies have focused on the effects of single nucleotide polymorphisms (SNPs) which thought to cause disease development by altering the functions of a variety of biological pathways in GC. In this context, the association of the SNPs in genes such as NFKB1, PSCA, MUC1, TGFBR1, ERCC4, TOX3 with GC was investigated in various studies conducted in order to reveal the genetic basis of GC [2, 7-9].

The transcription factor 7-like 2 (TCF7L2) gene located on 10q25.3, encodes a high mobility group (HMG) box-containing transcription factor (TCF-4) which is associated with multiple types of cancer [10].This transcription factor is an important part of Wnt/β-catenin signaling pathway that modulates cell proliferation, cell polarity and cell differentiation during embryonic development and also plays a key role on homeostasis in mature tissues [11]. It is known that any mutation which may occur in Wnt/β-catenin signaling pathway causes neonatal defects, osteoporosis, cancer, and other various diseases [11].

Bipartite transcription factor β-catenin/T cell factor (β-cat/TCF), is the major effector of Wnt signaling which is formed by the heterodimerisation of free β-cat with one of the four members of the TCF family [(TCF7 (also known as TCF-1), lymphoid enhancer binding factor (LEF-1), TCF7L1 (also known as TCF-3) and TCF7L2 (also known as TCF-4)] [12]. The active nuclear complex formed by β-catenin and one member of the TCF family; activates the transcription of the Wnt target genes involved in cellular proliferation, evasion of apoptosis, tissue invasion and metastasis [12].

Due to many of these target genes are the proto-oncogenes, the constant activation of Wnt/β-catenin signaling is associated with various cancer types such as colorectal cancer, hepatocellular carcinoma and gastric carcinoma [13-16]. The association of SNPs in various genes with GC was shown in different populations [17]. In the present study, we conducted a case-control association study to evaluate the effect of rs7903146 (C/T) and rs12255372 (G/T) variations in TCF7L2 gene, the key effector of Wnt/β-catenin signaling pathway, on the risk of GC in a Turkish population.

Material and Method

Study subjects

38 patients (12 female, 26 male) diagnosed with GC from Selcuk University, Faculty of Medicine, Department of Oncology and 48 volunteers (29 female, 19 male) with no family history of cancer were included in this study. Informed written consent was obtained from each individual before participation into the study and the Ethical Committee of the Selcuk University, Faculty of Medicine approved the study (decision no:2011/014).

Genomic DNA isolation and genotype analysis

Genomic DNA was extracted from peripheral blood leukocytes using standard proteinase K (Sigma, St Louis, America) and SDS (Sigma, St Louis, America) procedure. The nucleotide sequence of the TCF7L2 gene was obtained from the GenBank™ database. A polymerase chain reaction (PCR)-based restriction fragment length polymorphism (RFLP) method was used to genotype rs7903146 (C/T) and rs12255372 (G/T) polymorphisms. PCR amplification was carried out in a 30µl volume containing 50–100 ng genomic DNA, 1X PCR buffer (Fermentase, Vilnius, Litvania), 0.6mM deoxynucleoside triphosphates (Fermentase, Vilnius, Litvania), 0.1 units Taq polymerase (Fermentase, Vilnius, Litvania) and 0.4 µM of each primers (Biomers, Singapur) for rs7903146(C/T) (forward: 5'-GAGAGCTAAGCACTTTTTAGGTA-3' and reverse: 5'-CTGACATTGACTAAGTTACTTGC-3') and for rs12255372 (G/T) (forward: 5'-TGTTAATGGCTTGCAGGTCAG-3' and reverse: 5'-CACCCAAGGTTTGAGGCCTAA-3') polymorphisms. PCR reactions were performed as follows: an initial denaturation at 94 °C for 5 min was followed by 35 cycles of denaturation at 94 °C for 30 s, annealing at 65,5°C and 54°C for rs7903146 and rs12255372, respectively for 30 s, elongation at 72 °C for 30 s, and a final extension at 72 °C for 2 min. After amplification , 10µl PCR products were digested with RsaI (Fast Digest, Fermentase, Vilnius, Litvania) at 65˚C for 1 h and with TasI (Fast Digest, Fermentase Vilnius, Litvania) at 37˚C for 1 h for genotyping of rs7903146 (C/T) and rs12255372 (G/T) polymorphisms, respectively. After treatment with restriction enzymes, DNA fragments were visualized on 3% agarose gel electrophoresis and stained with ethidium bromide (Sigma, St Louis, America). Genotyping results were validated by direct sequencing of randomly selected samples for each genotype of all two SNPs.

Statistical analysis

Initial comparison was performed between patient and control groups using t-test. x^2 goodness of fit test was carried out to evaluate Hardy-Weinberg equilibrium (HWE) in patient and control groups. Analyses were carried out using dominant, additive, and recessive models. Dominance was defined in terms of allele 2 (minor allele) effects. In dominant allele 2 models, homozygous individuals for allele 1 were compared with carriers of allele 2. In recessive allele 2 models, homozygous individuals for allele 2 were compared with carriers of allele 1. The odds ratio (OR) and its 95% confidence interval (CI) was obtained by logistic regression method to determine the correlation between the genotypes or alleles of TCF7L2 rs7903146 (C/T) and rs12255372 (G/T) polymorphisms and GC risk by SPSS 18.0 software (SPSS Inc., Chicago, IL). In all analyses, a p value <0.05 was considered statistically significant.

Results

After the incubation with restriction enzymes; the rs7903146 C allele was cut into two fragments of 91 and 22 bp, while the rs7903146 T allele remained uncut (113 bp). For rs12255371

polymorphism; the DNA obtained from the GG homozygote individuals were digested into five fragments (162, 130, 99, 36, and 35bp); from TT homozygote individuals were digested into six fragments (145, 130, 99, 36, 35 and 17bp). When seven bands were visualized, the individuals were genotyped as being GT heterozygotes. According to result of X^2 analyze, both of the SNPs were in Hardy-Weinberg equilibrium ($p<0.05$) except deviation observed in patient group for rs12255372 ($p<0.05$). Genotype distributions of the SNPs were detailed in table 1.

There was no significant association between rs7903146C>T and disease ($p> 0.05$) while 12255372G>T polymorphism was associated with the disease under additive model [OR: 0.366 (95% CI: 0.135-0.989) p=0.047] after odds analyzing carried out under dominant, recessive and additive models.

Table 1. Genotype distributions and results for association analysis between rs7903146 and rs12255372 polymorphisms and gastric cancer

Gene Location	SNP	Genotype n (%)			Odds ratio (95% CI-P)		
					Additive	Dominant	Recessive
Intron 4	rs12255372 G>T	G/G	G/T	T/T	0,366 [0,13-0,99]	0,46 [0,19-1,12]	0,85 [0,22-3,28]
	Patient	17(44,74)	16(42,10)	5(13,15)	p= 0,047	p= 0,089	p=0,819
	Control	31(65,96)	10(21,28)	6(12,76)			
Intron 3	rs7903146 C>T	C/C	C/T	T/T	1,2 [0,31-4,651]	1,6 [0,44-5,62]	0,6 [0,23-1,34]
	Patient	14(36,84)	18(47,37)	6(15,79)	p=0,792	p=0,484	p=0,191
	Control	25(52,08)	18(37,5)	5(10,42)			

Discussion

Gastric cancer (GC), which is the third leading cause of cancer related death in men and the fifth in women worldwide, mostly occurred in countries of Far East such as China and Japan and Eastern European countries [17]. Evidence from several molecular genetics studies indicates that genetic factors of an individual are involved in his/her susceptibility to GC as well as environment and viral/bacterial infections [18]. In a Han Chinese population study, homozygote GG genotype of rs4648068 in NFKB1 gene is associated with increased GC risk [7] while an other Chinese population provided evidence that polymorphism in PSCA gene is involved in susceptibility to GC [8]. Also, rs6478974 and rs10512263 polymorphisms in TGFB1 gene were shown to be associated with GC development under dominant models by Chen et al [9]. Ferrer-Ferrer et al [19] reported an association between HSP70 genotypes and the development of GC in a population in Costa Rica. The SNP rs6983267 is another polymorphism demonstrated to be predisposing the susceptibility of GC in a case-control study whereas Zhang et al [2] showed that rs3803662 in TOX3 gene was significantly associated with survival of GC.

The TCF7L2 gene was firstly reported to be associated with type 2 diabetes (T2D) by Grant et al [20] and has been confirmed to be one of the strongest susceptibility gene of T2D with following studies further. On the other hand, it is hypothesized that TCF7L2 gene may affect cancer independently of diabetes because of its product (TCF4 protein) is involved the Wnt/B-catenin signaling pathway as a transcription factor that induces the expression of target genes such as the cyclin D1 (CCND1) and c-myc oncogenes involved in cellular proliferation, evasion of apoptosis, and also tissue invasion and metastasis [21]. The frameshift mutations in TCF7L2 gene have been found in GC with high microsatellite instability [16]. The association of some SNPs in TCF7L2 gene with various cancer types was shown in recent studies. Of these SNPs, rs7903146 (C>T) polymorphism was reported to be associated with colorectal and lung cancer [22] prostate cancer and increased breast cancer risk [23]. Neverthless, Connor et al [10] determined three polimorphisms rs3750805, rs7900150 and rs1225404 as well as rs7903146 in TCF7L2 to be associated with breast cancer. Rs12255372 (G>T) was shown to be associated with familial breast cancer risk [23] while it was shown to increase prostate cancer aggressiveness in another study [24]. Results of a meta-analysis indicated that there was a significant association between TCF7L2 rs7903146 (C>T) polymorphism and the risk of breast, prostate and colon cancer rather than colorectal, lung and ovarian cancer [21]. Although numerous studies have shown different genes and variants as genetic risk factors for gastric cancer, revealing the exact molecular mechanism of GC is still a challenge. The strong candidate TCF7L2 gene, as a transcription factor, may enhance the canceration of gastric epithelial cells by changing the expressions of a variety of genes involved in cell cycle such as c-myc oncogenes. In our country, although it is the second most common type of cancer subsequently breast cancer in women and lung cancer in men [25], there is no study on the genetic basis of GC. Up to now, the associations between polymorphisms in various genes and GC have been investigated in several studies worldwide, but the association between TCF7L2 gene polymorphisms and the GC risk was not investigated in any study to the best of our knowledge. We investigated the risk associated with rs12255372(G>T) and rs7903146(C>T) SNPs in TCF7L2 gene for the first time in a Turkish population with GC.

In our study we did not detect a significant association between rs7903146C>T and GC ($p> 0.05$) but rs12255372G>T polymorphism was significantly associated with the disease risk. Our findings suggest that rs12255372 (T) variant may increase the susceptibility of GC, thus could be a potential indicator for GC risk. Lack of association between rs7903146 and GC could be due to our relatively small sample size. The other limitations of the present study is; not determining the effect of gene-gene/gene environment interaction and of analyzing stratified of tumor size, histological type, dept of invasion, drinking status, information of tumor site, etc. However, it is the first study which investigates the association between TCF7L2 gene polymorphisms and GC which presents the initial data obtained from Turkish population about whether TCF7L2 gene polymorphisms are associated with GC.

Further studies are required to confirm our findings and the role of these variants in GC susceptibility in larger sample sizes among ethnically and geographically different populations.

Competing interests

The authors declare that they have no competing interests.

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Depression, Inflammation, and Social Support in Hemodialysis Patients

Hemodiyaliz Hastalarında Depresyon, İnflamasyon ve Sosyal Destek

Hemodiyaliz Hastalarında Depresyon ve Sosyal Destek / Depression and Social Support in Hemodialysis Patients

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Özet

Amaç: Depresyon ve inflamasyon son dönem böbrek yetmezliği (SDBY) hastalarında sıktır. Çalışmamızda depresyon, inflamasyon ve sosyal destek arasındaki ilişkiyi incelemeyi amaçladık. Gereç ve Yöntem: Çalışmaya 137 hasta alındı. Tüm hastalarda Beck Depresyon Ölçeği (BDÖ), Çok Boyutlu Algılanan Sosyal Destek Ölçeği (ÇBASDÖ) ve Malnütrisyon İnflamasyon Skoru(MİS)' nu kullandık. Bulgular: BDÖ, ÇBASDÖ ve MİS sırasıyla 15.9±9.5, 60.5±15.1, 7.8±2.9 olarak bulundu. Hastalar BDÖ puanlarına göre; depresyonu olan hastalar (BDÖ puanı≥ 17, n= 55, % 40) ve depresyonu olmayan hastalar (BDÖ puanı< 17, n = 82, % 59) olmak üzere iki gruba ayrıldı. Depresif hastaların çoğunluğu kadındı (% 58) ve yalnız yaşıyorlardı (% 97). Haftalık eritropoeitin dozu ve CRP düzeyleri depresyonu olmayan hastalara göre depresyonu olan hastalarda daha yüksekti ve bu fark istatistiksel olarak anlamlı değildi (p>0.05). MİS, depresyonu olan hastalarda (6±2.2), depresyonu olmayan hastalara (10.5±1.8) göre daha yüksekti (p<0.001). Depresyonu olan hastaların ÇBASDÖ puanları (57.3±17.9), depresyonu olmayan hastaların puanına göre (62.7±12.5) daha düşük bulundu (p<0.05). BDÖ ve ÇBASDÖ puanları arasında negatif korelasyon varken, BDÖ puanı ve MİS arasında pozitif bir korelasyon saptandı. Yapılan çok değişkenli lineer regresyon analizinde (cinsiyet, BUN, albümin, MİS ve ÇBASDÖ), depresyon bağımsız olarak MİS (β= 0.60, t=9.9 p<0.001) ve ÇBASDÖ (β= -0.37, t=-6.2 p<0.001) ile ilişkili bulundu. Tartışma: Hemodiyaliz hastalarının daha fazla sosyal ve psikolojik desteğe ihtiyacı vardır. Çalışmamızda yüksek düzeyde inflamasyon ve düşük sosyal destek, depresyonun varlığı ile ilişkili bulundu. Ancak, bu sonuçların doğrulanması için büyük ölçekli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler

Depresyon; Malnütrisyon; İnflamasyon; Sosyal Destek

Abstract

Aim: Depression and inflammation are common in patients with end-stage renal disease (ESRD). In our study, we aimed to investigate the relationship between depression, inflammation and social support. Material and Method: Accordingly, 137 patients were enrolled. We used Beck Depression Inventory (BDI) and Multidimensional Scale of Perceived Social Support (MSPSS) and Malnutrition Inflammation Score (MIS) in all patients. Results: BDI, MSPSS and MISS were 15.9±9.5, 60.5±15.1, 7.8±2.9 respectively. The patients were divided into two groups with respect to BDI scores: patients with depression (BDI score ≥ 17, n= 55, 40.2%) and patients without depression (BDI score< 17, n = 82, 59.8%). In depressive patients, the majority were female (58%) and lived alone (97%). The weekly erythropoietin dose and CRP levels were higher in patients with depression than in patients without depression and this difference did not reach statistical significance (p>0.05). MIS scores were higher in patients with depression (10.5±1.8) than in patients without depression (6±2.2) (p<0.001). Patients with depression (57.3±17.9) had lower MSPSS scores than patients without depression (62.7±12.5) (p<0.05). There was positive correlation between BDI and MIS, while negative correlation was observed between BDI and MSPSS. In the multivariate linear regression analysis (gender, BUN, albumin, MIS and MSPSS), depression was independently associated with MIS (β= 0.60, t=9.9 p<0.001) and MSPSS (β= -0.37, t=-6.2 p<0.001). Discussion: Hemodialysis patients needed more social and psychological support. They had higher inflammation and lower social support that associated with the presence of depression, although large-scale studies are needed to confirm our results.

Keywords

Depression; Malnutrition; Inflammation; Social Support

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Introduction

Depression is a common psychiatric condition in end-stage renal disease (ESRD) patients. Depression often causes a serious decline in energy level, loss of appetite and reduced interest in everyday activities. Most ESRD patients show such symptoms and they can be overwhelming [1]. Depression may also lead to malnutrition which is a common problem in the ESRD patients [2].

All the evidence points that malnutrition is an important cause of morbidity and mortality in ESRD patients. As depression is commonly associated with poor oral intake, it can aggravate malnutrition in chronic dialysis patients. In many studies, it is suggested that increased cytokines may trigger signs of depression and stimulate catabolism and cause negative protein balance. Moreover, ongoing chronic inflamation may contribute to malnutrition. A new scoring system called Malnutrition Inflammation Syndrome (MIS) is helpful for showing us the hospitalization risk in ESRD patients [2,3]. A triad of depression, malnutrition and, inflammation contributes to the high mortality in these patients [4,5]. Social affection and support is an important issue for the treatment of depression in patients with chronic ilness. For several reasons, hemodialysis patients need serious medical, social and psychological support and social support is an essential part of ESRD treatment. The patients can get social help and support from family, friends and also the medical personnels. Indeed, ESRD and its treatment with dialysis, often prove to be a huge burden on the psychology and social lives of these patients [6]. One way of measuring the level of social support is to use the MSPSS. Although how it works is not clearly known, social support seems to have a positive effect on the cardiovascular, endocrinologic and immune system in patients with normal kidney functions.

On the other hand, poor social support and unhappy marital life are related with higher blood pressure, higher circulating levels of catecholamines, and worse immune function [7,8]. Good social support has been associated with lower BDI score and higher MIS score in hemodialysis patients [9]. The objective of this study was to evaluate the relationship between depression, malnutrition inflammation and social support in hemodialysis patients.

Material and Method

The study protocol was approved by our local scientific ethics committee (The IRB approval number is 2007/179). In this study 137 hemodialysis patients (male/female, 78/59, mean age, 53.3±13.2 years, mean dialysis duration 56.1±5.4 months), who had been on hemodialysis for the last six months were included from Ondokuz Mayıs University Hemodialysis Unit and Samsun Training and Reserach Hospital Nephrology Department. If the patients had a history of malignity, acute or chronic inflammatory illness or a hospitalization period within last six months were excluded. The therapies such as corticosteroids and antidepressants could affect the results and thus these patients were eliminated.

Standard bicarbonate dialysis solution by semisynthetic membranes (dialysis filters surface area 1.1 to 1.7 m2) were used in all patients three times a week. All patients were normotensive and without edema by the exact dry weight target. The average urea Kt/V in these patients was 1.4±0.2. In all patients, age, gender, duration of ESRD, education duration, and body mass index (BMI) were recorded. Moreover, patients' medication was recorded in terms of erythropoietin dose. At the beginning of the inflammatory infectious state blood tests were performed. Serum calcium, phosphorus, C-reactive protein (CRP), albumin, hemoglobin, total iron-binding capacity, and ferritin were measured following at least an eight hour of fasting. All blood samples were obtained during the midweek hemodialysis session and serum samples were made by standard methods in the routine clinical laboratory. Social support was assessed by the MSPSS, depression was assessed by BDI and the malnutrition and inflammation status was assessed by the MIS.

The BDI is an inventory that utilizes the existent symptoms of depression. The BDI score ranges from 0 to 63. The BDI was used for the diagnosis of depression. We used the MSPSS to evaluate perceived social support. The MSPSS consisted of three support categories: social support from family, social support from friends, and from one special person. Research demonstrated that MSPSS outcomes are related with depression in renal failure patients who receive maintenance hemodialysis [6]. MIS is a new, comprehensive scoring system created using seven components of the Subjective Global Assessment, and combining them with three new parameters (body mass index, serum albumin, and total iron-binding capacity). Each component of the MIS has four levels of severity, from 0 (normal) to 3 (very severe). In malnutrition, MIS tends to rise. The MIS is an indicator of malnutrition inflammation complex syndrome and MIS score is used to estimate morbidity and mortality in hemodialysis patients [9]. SPSS software (Statistical Package for the Social Sciences version 10.0; SPSS Inc., Chicago, IL, USA) was used for the analysis of the statistics datas. Statistical significant p value was <0.05 for the results. Datas were shown as mean±standard deviation. Data were expressed as mean±standard deviation. According to BDI score, the patients were divided into two groups. BDI score ≥ 17 indicates mild-to-moderate depression. Comparisons of continuous variables were assessed by student's t test. Comparisons of the categoric variables were assessed by the pearson chi-square test. To show the correlations we used the pearson r coefficient. The situations that predicts depression in hemodialysis patients were detected by using multiple linear regression analysis. The factors affecting depression (variables included gender, BUN, albumin, MIS, and MSPSS) were evaluated with linear regression analysis.

Results

Table 1 shows the demografic, clinical and laboratory data of 137 hemodialysis patients. Table 2 shows the demografic and laboratory data of patients with and without depression. BDI, MSPSS and MIS were 15.9±9.5, 60.5±15.1, 7.8±2.9 respectively, in all patients. Most of the patients were married (67.3%), living with family, and unemployed (61.2%) in all patients. We grouped the patients into two according to their BDI scores: patients with depression (BDI score ≥ 17, n= 55) and patients without depression (BDI score< 17, n = 82). In the non-depressive group, BUN and serum albumin levels were higher than the depressive group (p<0.05). In depression group, most of the pa-

Table 1. Demographic, clinical and laboratory data of all patients

Variable	Mean ±SD (n=137)
Mean Age, y	53.2±13.2
Gender, M/F	78/59
Mean duration of dialysis, months	56.1±5.4
Mean duration of education, year	6.60±4.89
BMI (kg/m2)	26.2±5.7
Married (%)	67.3
Lives with family (%)	91.5
Unemployed (%)	61.2
MSPSS (12-84)	60.5±15.1
MIS (0-30)	7.8±2.9
BDI (0-63)	15.9±9.5
Kt/V	1.4±0.2
BUN, mg/dL	83.3±14.6
Creatinine, mg/dL	9.3±2.6
Calcium, mg/dL	9.4±0.7
Phosphorus, mg/dL	5.12±1.53
iPTH, pg/mL	382.1±97.9
Total cholesterol, mg/dL	178.1±53.2
LDL, mg/dL	94.7±33.1
Triglyceride, mg/dL	184.7±94.5
Albumin, g/dL	3.9±0.5
CRP, mg/L	14.4±9.6
Hemoglobin, g/dL	10.8±1.3
Ferritin, ng/mL	328.9±213.2

SD; standard deviation, MSPSS; Multidimensional Scale of Perceived Social Support, MIS; Malnutrition Inflammation Score BDI; Beck Depression Inventory.

Table 2. Comparison of demographic and laboratory data in patients with depression and without depression

Variable	Patients Without Depression (BDI<17) (n=82)(59.8%) Mean±SD	Patients With Depression (BDI≥ 17) (n=55)(40.2%) Mean±SD	P
Mean Age, y	53.6±14.5	53.1 ±11.3	NS
Gender, M/F	55/27	23/32	NS
Mean duration of dialysis, months	60.2±62.5	49.9 ±37.8	NS
Mean duration of education, year	7.8±4.3	5.6±3.8	p<0.05
MSPSS (12-84)	62.7±12.5	57.3±17.9	p<0.05
MIS (0-30)	6±2.2	10.5±1.8	p<0.05
BUN, mg/dL	86.3±14.6	78.3±1.3	p<0.05
Creatinine, mg/dL	9.6±2.5	8.8±2.1	NS
Calcium, mg/dL	8.7±0.8	10.5±11.6	NS
Phosphorus, mg/dL	5.8±1.6	5.6±1.3	NS
iPTH, pg/mL	318.3±57.5	477.15±41.6	NS
Total cholesterol, mg/dL	172.7±48.1	185.9±49.5	NS
LDL, mg/dL	91.7±32	99.2±34.4	NS
Triglyceride, mg/dL	186.7±97.3	182.1±91.1	NS
Albumin, g/dL	3.9±0.3	3.3±0.3	p<0.05
CRP, mg/L	12.7±11.1	16.8±7.9	NS
Hemoglobin, g/dL	10.8±1.6	10.5±1.3	NS
Ferritin, ng/mL	415.17±266.96	351.63±207.66	NS

SD; standard deviation, MSPSS; Multidimensional Scale of Perceived Social Support, MIS; Malnutrition Inflammation Score

tients were living alone (97%) and females (58%) but there was no certain statistical change between the depressive and non depressive patients groups when we compare in terms of lonely status and gender. Additionally we observed no significant difference in patients with and without depression in terms of marital status and occupational status (p>0.05). Depression score was higher for patients paying rent in comparison with patients not paying rent (p<0.01). The erythropoietin requirement was higher in patients with depression than without depression (6535.6±3713.5, 5439.7±2548.1, p>0.05 respectively). Accorging to our analysisis, MIS scores were higher in patients with depression (10.5±1.8) than in patients without depression (6±2.2) (p<0.001), and patients with depression (57.3±17.9) had lower MSPSS scores than patients without depression (62.7±12.5) (p<0.05). While BDI and MIS (r=0.62, p<0.001), showed positive correlation, BDI and MSPSS (r=-0.41, p<0.001) showed negative correlation. In the multivariate linear regression analysis, depression was independently associated with MIS (β= 0.60, t=9.9 p<0.001) and MSPSS (β= -0.37, t=-6.2 p<0.001) (variables included gender, BUN, albumin, MIS, and MSPSS) (Table 3).

Table 3. Multiple linear regression model of factors affecting depression in hemodialysis patients.

Variable	β coefficient	t	P Value
Gender	0.46	3.98	>0.05
BUN	0.51	9.17	>0.05
Albumin	0.73	8.7	>0.05
MIS	0.60	9.9	<0.001
MSPSS	-0.37	6.2	<0.001

MIS; Malnutrition Inflammation Score, MSPSS; Multidimensional Scale of Perceived Social Support

Discussion

In the present study we observed that hemodialysis has significant negative affects on the physical and psycho-social lives of ESRD patients. Depression and malnutrition-inflammation also are major problems in hemodialysis patients. Depressive patients had lower education level, MSPSS, serum albumin levels and higher MIS levels than non-depressive patients. Moreover, our results show that higher MIS and lower MSPSS values were associated with the presence of depression.

The prevalance rate for depression in patients with ESRD is high [2]. Koo et al. showed that depression is related with malnutrition in the ESRD patients [2]. However, they did not evaluate the relationship between the demographic data (such as education, marital status, work status, living with family, and social support) and depression. Some studies, reported that an association between depression and MSPSS values, and in patients with depressive mood MSPSS was significantly lower than in patients with non-depressive mood [8,9]. There are a few studies on the triad of social support, depression and, malnutrition-inflammation [9]. In our study, we also evaluated the triad of depression, social support and malnutrition-inflammation.

In hemodialysis patients nearly half of them complain from depression and 5-20% have major depression [10]. High depression score in the ESRD patients is associated with mortality [11]. In our patients, the mean depression score was 15.9±9.5

and we found that 40.2% of our patients had depression according to the BDI. In fact, diagnosis of depression is not easy in the ESRD patients. There is usually an overlap between the symptoms of uremia and depression. Symptoms and signs of renal failure, side effects of treatments (such as weight loss and low appetite) are similar to those of depression [10-12]. The main risk factors of depression in ESRD patients are female gender, living alone, low education, and low albumin levels [12]. and higher inflammation may be contributing to this quite high depression rate.

Protein-energy malnutrition and inflammation are disorders that often appear together and follows each other in hemodialysis patients [13]. It is suggested that malnutrition can lead to inflammation. Inflammatory process in ESRD is connected with the uremic environment and also elevated levels of proinflammatory cytokines are found paralelly to the process [13]. Serum levels of proinflammatory cytokines elevated in depressed patients [2]. BDI score influences MIS score, and thus, it may lead to poor oral intake, muscle loss, hypoalbuminemia, recurrent anemia and increased atherosclerosis by aggravating malnutrition and inflammation in patients with ESRD [14] and there was a significant association between depression and MIS values [9]. Morever a study showed that MIS and CRP were predictors of mortality and morbidity in the ESRD patients [15]. In our study we measured serum albumin levels, CRP levels, and MIS to evaluate the causes of inflammation. Patients with depression had higher MIS, CRP levels, and lower serum albumin levels, Accordingly, our findings suggest that the MIS score is an important factor for depression in hemodialysis patients. Anemia has been associated with increased fatigue, lethargy and weakness in individuals and also with sleep disorders in hemodialysis patients. In one study, fatigue is related to presence of depression [16]. Because depression is connected with appetite and oral intake. Bilgic et al. reported a strong correlation between depression and lower levels of hemoglobin [17]. In our study, although hemoglobin levels did not differ between the patients with and without depression, although the erythropoietin dose was higher in patients with depression than in patients without depression.

Social support is a complex relationship in which feelings affections ,help and obligations are given bilaterally [18]. Most of the times family members relatives close friends or a special person give social supports [18]. Life style modifications change of social activities restricted independence are often found in patients with ESRD. All of these changes make easy to develop depression state. Social support clearly is a good cure for depressive symptoms in the ESRD patients. The ESRD patients receive either functional or emotional support which can be given by a family member or spouse [8]. Some studies suggested a relationship between social support and low mortality, and showed that perceived social support is closely related with depression in the ESRD patients [6]. In our study, most of the patients were married, unemployed and lived with family patients with and without depression. We observed that the patients with depression was living alone, had significantly lower social support, lower educational status. Single patients were significantly more depressive than others, this showed the importance of protected family stracture. Healty family structure is considered value for hemodialysis patients as a section of social support. Also social support and marital status seems to have a positive effect on depression. This strong family structure can be protecting from depression in the developing country like Turkey.

Depression, inflammation, and absence of social support are still common problem in hemodialysis patients. Higher inflammation and lower social support were associated with the presence of depression. Hemodialysis patients needed more social and psychological support. Thus, the clinicans and the hemodialysis personnel should be aware of pschological and social signs and symptoms in hemodialysis patients. As a result, we advice to spend sufficient attention to detect the diagnosis of depression and effectual therapies and social supporting programs for hemodialysis patients.

Study limitations

This study is conducted with a somewhat small population. There was no control group in the study, and a control group was formed by dividing patients into study groups. DSM-IV R is the gold standard for diagnosis of depressive disorder. In the current study, depression was diagnosed using BDI. CRP and MIS levels were used to determine inflammation; use of IL-6 and TNF-α may further increase the value of our study.

Competing interests

The authors declare that they have no competing interests.

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Determination of the Pre-Hospital Practices Performed for Children with Burn Injuries

Çocuklarda Meydana Gelen Yanıklarda Hastaneye Başvuru Öncesi Yapılan Uygulamaların Belirlenmesi

Hastaneye Başvuru Öncesi Yapılan Uygulamalar / Pre-Hospital Practices Performed

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Özet

Amaç: Bu araştırma, yanıklarda hastaneye başvuru öncesi yapılan, ilk uygulamaların ve bunları etkileyen faktörlerin belirlenmesi amacıyla yapılmıştır. Gereç ve Yöntem: Araştırma, Erzurum'da bulunan iki hastanenin yanık ünitelerinde, Aralık 2013-Ağustos 2014 tarihleri arasında yapılmıştır. Araştırmanın evrenini, çalışmanın yapıldığı tarihlerde, ilgili hastanelerin yanık ünitelerinde yatarak tedavi gören 0-12 grubu çocuklar ve anneleri oluşturmuştur. Çalışma, araştırmaya alınma kriterlerine uygun olan toplam 121 çocuk ve onların anneleri ile yürütülmüştür. Verilerin toplanmasında anket formu kullanılmıştır. Veriler, yüzdelik dağılımlar, ortalama ve ki-kare testi kullanılarak değerlendirilmiştir. Bulgular: Araştırma sonucunda; Yanık meydana geldiğinde annelerin yaptığı ilk uygulamanın soğuk suya tutup kıyafetlerini çıkarma olduğu (%57.9), ikinci olarak (27.3%) yalnızca soğuk su uygulama, daha sonra yaptıkları uygulamanın ise, başka bir uygulama yapmadan çocuğu hastaneye götürme (%75.2), yanık yarasının üzerine zeytin yağı sürme (%10,7), yanık yarasının üzerine yoğurt sürme (%8.3) olduğu saptanmıştır. Tartışma: Yapılan araştırma sonucunda annelerin ilk yardım bilgilerinin yeterli düzeyde olmadığı ve eğitim seviyesi düşük olan, kırsal alanda yaşayan ve yaşı küçük olan annelerin daha hatalı ilk yardım uygulamaları yaptıkları saptanmıştır.

Anahtar Kelimeler

Yanık; Çocuk; Anne; İlkyardım; Hemşire

Abstract

Aim: The objective of this study was to determine the first aid practices performed and, effecting factors in burn injuries in before hospital admission. Material and Method: The study was conducted in burn centers of two hospitals in the Erzurum, between December 2013 and August 2014. The population was consisted of inpatient children aged 0-12 years who were treated in burn centers of related hospitals and their mothers at the date of the study. The study was carried out with a total of 121 children and their mothers who met the research inclusion criteria. Questionnaire data was used to collect data. In data analysis, percentage distributions, means and chi-square test were used. Results: It was found that, children' mothers applicate the cold water first when the burns ocur (57.9%), secondly only applying cold water (27.3%), then the mothers took off their children to hospital not to any application (75.2%), burn wound on the olive oil riding (10.7%), burn wound yogurt riding (8.3%). Discussion: As a result, it was determined that children' mothers don't have an adequate level of first-aid knowledge, and younger mothers with low levels of education living in rural areas perform incorrect first aid practices.

Keywords

Burns; Children; Mother; First Aid; Nurse

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Introduction

Burns in childhood represent a significant issue due to both the challenging treatment process and the physical and psychological trauma suffered by the child and his/her family [1]. In high-income level countries, the numbers of burn injuries have substantially decreased as a consequence of changes in first aid training, good socioeconomic status, and important improvements in the treatment of burns [2]. However, similar improvements have not been observed in low and middle income level countries such as Turkey [3]. In studies conducted in different cities within Turkey, the rate of burns in children was found to be 40–75% [4]. Although the mortality rate is lower in children compared to adults, burn injuries are still among the significant reasons for death in children [5].

Developmental and family characteristics combination increase, the risk of burn injuries in children. Many factors, such as movements of small children to explore their surroundings, their ability to reach hot liquids and other flammable substances, negative conditions home, overcrowded environment, child negligence and abuse, playing with matches or dangerous fire setting behavior fire-setting behavior, and unsafe movements pose a risk for burns in children [6,7].

Burns and scalds in most babies and young children are caused by boiling water. These are followed by burns from flame, hot contacts, and electrical and chemical burns [8, 9]. Despite technological progress, burns are still a serious, life-threatening problem. The most inexpensive and efficient method of dealing with this concern is through preventing burns before they occur [10]. Therefore, a number of security measures should be put in place and families' awareness of this issue should be enhanced in order to protect children from burns [11]. When burns occur, correct first aid practices are very important to reduce the width of the burn and possible complications in patients [12]. A conscious effort is required to engage in these practices, since performing them incorrectly may threaten health and cause poor cosmetic results in burns [13, 14].

Nurses have the greatest responsibility for the care of children with burns treated in hospitals. The nurse is the healthcare worker that has the most contact with patients among the burn team; moreover, the nurse has a primary role in training families on first aid practices required for burn injuries and facilitating the patient's psychological adjustment [15]. The aim of this study is to assess pre-hospital practices performed for children with burn injuries and affecting factors these practices in the age group of 0–12 years.

Material and Method

Study setting

The study was conducted as descriptive in burn centers of a university hospital and a state hospital in the Province of Erzurum, Turkey, between December 2013 and August 2014.

Sample size and sample tecnique

The study population consisted of inpatient children aged of 0–12 years who were treated in burn centers in related hospitals during the study period, along with their mothers. The study was carried out with total 121 children and their mothers who met the research inclusion criteria. Any sample selection was not performed during the study; rather, whole effort was made to reach all inpatient children and mothers during the study period. The inclusion criteria for the study were as follows:

• 0-12 aged group of children, children with second- to third-degree burns (first-degree burns were not included in the study because patients with first-degree burns are not hospitalized),

• Mothers who agreed to participate in the research and had no audiovisual or psychological problems.

Data Collection

Questionnaire

A questionnaire was developed by the researchers based on the literature data and used for data collection [16-19]. Data were collected through face-to-face interviews with mothers of inpatient children' in the burn centers of the respective hospitals. Data collection time was approximately 15-20 minutes for each participant. Immediately after data collection, the "First Aid for Burns" pamphlet, which was created by the researcher using the relevant literature to raise awareness about the correct first aid practices for burns, was distributed to mothers [6, 7, 20, 21].

Ethical considerations

Legal permission was obtained from the relevant institutions to conduct the study. The research began after approval from the Ethics Committee was received. Official permissions from the respective hospitals were obtained to collect the study data. Informed consent was obtained from mother which under 7 years age of children. For children 7 years and older consent was obtained from both the mothers and themselves.

Statistical analysis

Demographic and other individual characteristics of participants were reported using descriptive statistics. Then we conducted bivariate analyses using percentage distributions, means, and the chi-square test. Statistical significance was considered at $p<0.05$. All analyses were conducted using the Statistical Package for Social Science (PASW) software version 18.

Results

It was found that 68.6% of children participating in the study were aged 0–6 years age group, 55.4% were male, and 62.8% lived in a rural area. Looking at the characteristics of the children' families, 57.8% had an intermediate level of income; 62.8% lived in rural areas; 67.8% lived within a nuclear family; 95.9% of the mothers was housewives, of which 45.5% were illiterate; and 82.6% of the fathers was self-employed (farmers, builder's laborers, cleaners, etc.), and 48.8% was primary school graduates (Table 1).

It was found that the first practices in the burns area were "applying cold water and removing clothes." Following these practices, 75.2% of the participants took their child to hospital without performing any other intervention, 10.7% applied olive oil burn wounds, 8.3% applied yogurt burn wounds, and 5.8% applied toothpaste or grated potatoes burn wounds. Of the people who performed first aid on the burn wounds, 70.2% were found to be the mother of the child with burn injuries. It was determined that 82.6% of children were taken to the hospital on the day of the accident; moreover, hospitals were the first

Table 1. Distribution of descriptive characteristics of children, their mothers and burn.

Descriptive characteristics	N	%
Age of children		
0-12 month	16	13.2
1-6 age	83	68.6
7-12 age	22	18.2
Gender of children		
Famale	54	44.6
Male	67	55.4
The income level of the family		
High	12	9.9
Middle	69	57.0
Low	40	33.1
Place of residence		
City	45	37.2
Town	76	62.8
Type of family		
Nucleus	82	67.8
Extended	39	32.2
The age of the mother	30.59±6.08	
Age of mother		
19-34 age	88	72.7
35 age and ↑	33	27.3
The occupation of mother		
Homemaker	116	95.9
Working	5	4.1
The education of mother		
Illiterate	55	45.5
Literate/primary school	49	40.5
Junior high school/high school grad	17	14.0
Type of burn		
Scald burns	93	76.9
Flame burns	22	18.1
Electrical burns	6	5.0
Place of being burn		
Kitchen	33	27.2
Living room	67	55.4
Other	21	17.4
Total	121	100.00

Table 2. Distribution of first aid applications applied to burn area

First aid applications	N	%
The first aid application when burn occur	70	57.9
Applying cold water and removing clothes	33	27.3
Only applying cold water	18	14.9
Take away without doing nothing		
The application was later	91	75.2
Took to hospital without performing any other intervention		
Applied yogurt to the burn wounds	10	8.3
Applied olive oil to the burn wounds	13	10.7
Other*	7	5.8
The person who performing first aid		
Mother	85	70.2
Father	8	6.6
Grandma	17	14.0
Other**	11	9.1
The time to contact to the hospital		
On the same day	100	82.6
After 1-2 days	21	17.4
First referenced health institutions		
Emergency room	36	29.8
Cottage hospital	28	23.1
Hospital	57	47.1

* Applied toothpaste or grated potatoes to the burn wounds, ** Neighbors, relatives

medical institutions to which children were admitted (Table 2). If we look at the burn characteristics of the children, statistically significant difference was found between the children' age group, gender, type of burn, and place of the burn accident; between children' place of residence and place of the burn accident; and between the burn practices and the first health institution to which the children were admitted. In relation with the burn characteristics of children, the mother's age was found to be related to the type of burn, place of burn accident, and first practices performed on the burn injury. Moreover, the mother's educational level was determined to be correlated only with the first interventions performed on burn injuries (Table 3).

Discussion

In the past 5 years, 120,000 children have been admitted to hospitals as a result of home accidents in Turkey [22]; approximately one-third of these accidents were burn cases [23, 24]. As a result of this study, burns were found to be more prevalent in preschool children aged 0–6 years. In the literature, by far the most burn cases were reported to have occurred in the preschool period [25, 26]. Different behavioral and physical characteristics from adults, lack of awareness of the dangers, curiosity, their highly mobile nature, and living areas not suitable for children are among the reasons for high prevalence of burn cases in preschool children [27].

Looking at the first practices in burn injuries, it was found that more than half of the people performing first aid applied cold water and removed clothing from the area, 27.3% applied cold water only, and 14.9% took the child to the hospital without any intervention. Looking at the following these practices, 75.2% took the child to the hospital without performing any intervention other than applying cold water and/or removing clothing from the area, 10.7% applied olive oil to the burn wound, 8.3% was applied yogurt to the burn wound, and 5.8% was applied toothpaste or grated potatoes to the burn wound. In a study previously conducted in Turkey, it was found that 67.6% of mothers applied cold water to their children's burn wounds, 11% applied ice, 5.5% applied tomato paste, 5.5% applied toothpaste, and 3.7% applied butter on the burn area [28]. In their study, Battaloğlu-İnanç et al. was found that 44.5% of mothers applied cold water to burn wounds, 14.8% applied ice and took the child to the hospital, and 3.7% applied tomato paste, toothpaste, yogurt, or another home remedy [1].

In this study, it was reported that mothers, grandparents, and fathers were the persons applying the first aid respectively. Similarly, another study reported that most first aid practices were applied by mothers [23]. Knowledge and application of the

Table 3. Comparison of descriptive characteristics of children and mothers according to burn features

Distribution of burn features	Age of children 0-12 month/ 1-6 age/7-12 age	Gender Female/ Male	Place of residence City/Town	Mother age 19-34/35 and ↑	Mother education Illiterate/ Literate-primary school /high school
Type of burn					
Scald burns	16/67/10**	47/46*		75/18**	
Flame burns	0/15/7	7/15		13/9	
Electrical burns	0/1/5	0/6		0/6	
Place of being burn					
Kitchen	4/23/6	14/19	19/14	25/8	
Living room	12/51/4**	36/31*	20/47*	55/12**	
Other	0/9/12	4/17	6/15	8/13	
The first aid application when burn occur					
Applying cold water and removing clothes			24/46*	48/22*	47/36/7*
Only applying cold water			18/15	30/3	19/6/8
Take away without doing nothing			3/15	10/8	9/7/2
The application was later					
Took to hospital without performing any other intervention			38/53*		
Applied yogurt to the burn wounds			1/9		
Applied olive oil to the burn wounds			6/7		
Other*			0/7		
First referenced health institutions					
Emergency room			20/16		
Cottage hospital			5/23		
Hospital			20/37*		

proper first aid practices on the part of the parents, who are the closest to the child and responsible for their supervision, may save the child's life; in contrast, incorrect practices may lead to injury and death [11, 23]

In the study, scald burns were found to be most prevalent in all age groups. Aytac et al. was also found that scald burns are more frequent in all age groups than other types of burns [16]. In the comparison of the age groups of the children and place of the burn accidents, it was determined that most burns occurred in children aged 0–12 months and 1–6 years, and most often in sitting rooms. This can be explained by referring to the cold winter months in the Province of Erzurum; severe hard winter conditions caused children to spend most of their time indoor areas such as the home, and particularly the sitting room, rather than open playgrounds.

Comparison of the genders of children, types of burns, and locations of the burn accidents, it was found that most burn incidents occurred in sitting rooms and scald-type burns were more common in female children. In the study results, the majority of burn accidents experienced by people living in rural areas also occurred in sitting rooms ($p<0.05$). In previous studies in the literature, it was reported that burn incidents were more frequent in rural areas than urban ones [29, 30]. Factors such as the frequent use of stoves in sitting rooms for heating in rural areas in Erzurum, as well as meeting, cooking and hot water needs by using stoves result in burn accidents in sitting rooms [31]. The frequent scald burns in female children can be explained by the fact that daughters spend more time with their mothers in Turkish culture, prefer playing in the house more, and see their mothers as their role models; therefore, they try to emulate their mothers' tasks around the home.

In this study, it was found that the first practice in burns injuries in rural areas was to apply cold water and remove children's clothes from the area ($p<0.05$). The first aid to be performed immediately is very important when it comes to reducing possible complications in patients with burns, even if the size of the burn is small [32]. Application of cold water to the burn area is a useful first aid practice that reduces the risk of deep burns, edema, and fibrosis [33, 34]. However, attempting to remove adherent clothes may cause larger skin tissue losses; therefore, clothing must be cut and then removed carefully [27].

Looking at the practices following the first intervention, incorrect practices such as applying yogurt, olive oil, tomato paste, and toothpaste to the burn wounds of the children were found to be more frequent in rural areas. Applying foreign substances such as yogurt, oil, soap, toothpaste, liniments, and so on an incorrect first aid practice that may cause wound infections, delay the healing process, and lead to poor cosmetic results [35]. In the literature, interventions of families such as applying yogurt, toothpaste, and so on, when they were unaware of the correct first aid methods, were reported as significant factors bringing about morbidity and mortality [36].

In the study results, the comparison of the healthcare institutions to which patients were admitted based on the places of settlement revealed that children living in urban areas were taken to emergency services, whereas children living in rural areas were taken to the outpatient clinics of hospitals ($p<0.05$). Treatment in the first hours after a burn is vital. Therefore, it is necessary to know which primary healthcare provider a patient should be taken to. Any healthcare provider can treat patients with minor burns; however, children with more severe burn injuries should be taken to burn centers for treatment [37]. The higher rate of hospital admissions in the study indicates that families know that they need to consult healthcare providers

in burn cases.

The study results revealed that burn incidents were less common in children of mothers aged 35 years and over ($p<0.05$). In the literature, it was reported that the frequency of household accidents and health risks of children decrease as the maternal age increases, because younger mothers tend to be inexperienced [30].

Looking at the comparison of educational levels of mothers and first aid practices performed, it was found that illiterate mothers applied incorrect first aid practices more frequently ($p<0.05$). Moreover, in previous studies, burn incidents were found to be more prevalent in families with lower parental education levels [23]. In a study by Coksun et al. on the first aid knowledge of mothers of children aged 0–14 years, mothers' first aid knowledge was found to increase as their level of education increased [37].

Conclusion

In general, the study determined the following: the rate of incorrect first aid practices was higher; scald burns were more prevalent in all age groups; incorrect practices such as applying yogurt, olive oil, tomato paste, and toothpaste to the burn wounds were more frequent in rural areas; burn injuries were less common in children of mother aged 35 years or over; correct first aid practices were more frequent in older mothers (above 35 years); and incorrect first aid practices increased with lower levels of education among the mothers.

Based on these results, training should be given by nurses to parents of children aged 0–12 years on the first aid practices to be applied for burn injuries, as well as recommendations on furniture arrangement that suit the developmental characteristics of children in order to reduce the risk of burn injuries in the childhood period. Another recommendation is that comprehensive research should be conducted on this topic with larger samples. The study findings are limited to data on children aged 0–12 years with second- and third-degree burns and their mothers. Therefore, the study results can only be generalized to this group.

Competing interests

The authors declare that they have no competing interests.

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Effect of Coenzyme Q10 on Acute Pulmonary Damage Following the Experimental Thoracic Trauma

Deneysel Toraks Travması Sonrası Oluşan Akciğer Hasarı Üzerine Koenzim Q10 Etkinliği

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Özet

Amaç: Deneysel künt toraks travması sonrası oluşan pulmoner kontüzyondaki birincil ve ikincil hasar üzerine Koenzim Q10'un etkisinin biyokimyasal ve histopatolojik parametreler ile değerlendirilmesi amaçlanmıştır. Gereç ve Yöntem: Bu çalışmada Wistar Albino cinsi 16 haftalık, 205±45 gr. ağırlığında 56 adet dişi rat kullanıldı. Her gurupta sekiz rat olacak şekilde rastgele yedi guruba ayrıldı. Travma modeli için sabit bir platform ve alimünyum tüpten oluşan bir travma düzeneği hazırlandı. Pulmoner kontüzyonu oluşturmak için 2.45 joule'lük bir travma şiddeti oluşturuldu. Kontrol ve Çalışma gurupları sakrifiye edilme zamanlarına göre isimlendirildi. Şam grubuna travma ve/veya ilaç uygulanmazken Kontrol gruplarına sadece travma oluşturuldu. Çalışma gruplarına ise travma uygulandıktan sonra 0. - 24.- 48. saatlerde Koenzim Q10 intraperitoneal uygulandı. Şam gurubu hemen, Kontrol ve Çalışma gurupları travmadan 24, 48, 72 saat sonra sakrifiye edilerek kan ve akciğer doku örnekleri alınarak incelendi. Bulgular: Şam grubu ile Çalışma 72 arasında Yüksek Duyarlıklı C-Reaktif Protein değeri açısından anlamlı fark yoktu. Histopatolojik olarak incelendiğinde; Çalışma grupları ile Kontrol grupları arasında fark gözlenmedi. Şam grubu ile Çalışma grupları arasında fark gözlenmez iken, Şam grubu ile Kontrol grupları arasında fark gözlendi. Tartışma:Künt toraks travmasında sekonder hasarı azaltamak için Koenzim Q10 antioksidan bir ajan olarak kullanılabilir.

Anahtar Kelimeler

Pulmoner Kontüzyon; Koenzim Q10; Deneysel Çalışma

Abstract

Aim: Pulmonary contusion negatively affects prognosis in the case of damages following a trauma. Objective of this experimental study performed in Turkey was to evaluate effects of coenzyme Q10 on primary and secondary damages of pulmonary contusion following experimental thoracic blunt trauma using biochemical and histopathological parameters. Material and Method: A total of 56 Wistar Albino female rats with a mean weight of 205±45 g were included in this study. Rats were randomly divided into seven groups with each group having eight rats. A trauma device which consisted of a fixed platform, and an aluminium tube was prepared. Rats were administered 2.45 J of chest impact energy in order to generate pulmonary contusion. Control and Study groups were named according to the sacrificed time. No process (trauma and/or medication) was performed in the sham group, while only trauma was induced in the controls. On the other hand, after induced trauma, intraperitoneal Q10 (0. - 24. - 48. hours) was administered to study group. Rats were sacrificed at the end of the after trauma 24, 48 and 72 hours, and their blood and lung tissue samples were analyzed. Results: No significant difference was found between sham and Study-72 groups in terms of high-sensitivity C-reactive protein. On the histopathological examination, no significant difference was found between study and control groups. While no significant difference was found between the sham and study groups, significant difference was observed between sham and control groups. Discussion: Coenzyme Q10, an antioxidant agent, can be used as an antioxidant agent in order to reduce the secondary damage in blunt thoracic trauma.

Keywords

Thoracic Injuries; Coenzyme Q10; Animal Experimentation

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Introduction

Traumas are one of the most important public health problems in the world. Severe thoracic trauma cases are accounted for about one-third of the patients hospitalized due to trauma. Increasing number of thoracic injuries, mainly due to traffic accidents is encountered in our country [1, 2].

Pulmonary contusion (PC) negatively affects prognosis in the case of damages following a trauma. Blunt thoracic trauma is often accompanied by moderate blunt trauma and severe PC. Thus, resuscitation efforts and supportive interventions have a positive effect on the prognosis if performed early. Although the exact mechanism is not fully understood, PC may cause various pathophysiological changes in a wide spectrum [3, 4]. Currently, there is not any widely accepted and standardized pharmacologic treatment approach for PC. Available treatment methods are limited to the options which are originated from the empirical observations and clinical judgments. Supportive care therapies are applied such as oxygen, cardiopulmonary monitoring, analgesia and preventive care for infection [4].

Pulmonary contusion has been demonstrated to be concomitant with a progressive inflammatory response mediated by the local and systemic immunological changes [4, 5]. Therefore, efficiency of antioxidant agents for treatment of PC is investigated.

The aim of the present study was to evaluate the effects of coenzyme Q10 on primary and secondary damages of pulmonary contusion following experimental thoracic blunt trauma using biochemical and histopathological parameters.

Material and Method

This experimental study was conducted with the permission of Erciyes University Experimental Animals Ethics Committee. Fifty-six 16-week Wistar Albino female rats with a mean weight of 205±45g were used. The standards recommended by the Council of Europe (European Convention For the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposed: ETS 123) were followed in this experimental study. The rats were accommodated in cages meeting the requirements of cleanliness and nutrition with a room temperature of 20 to 26 °C before and during the study as to be four rats per cage with circadian rhythms as 12-hour day/night in Erciyes University Experimental Animals Research and Breeding Laboratory. The rats were fasted 12 hours before the experiment. The rats were randomly divided into seven groups with each group having 8 rats:

• Group 1 (Sham group): Lung tissue and blood samples were collected without creating trauma.

• Group 2 (Control-24): Blunt thoracic trauma was created. Lung tissue and blood samples were collected by thoracotomy performed at 24th hour of trauma.

• Group 3 (Control-48): Blunt thoracic trauma was created. Lung tissue and blood samples were collected by thoracotomy performed at 48th hour of trauma.

• Group 4 (Control-72): Blunt thoracic trauma was created. Lung tissue and blood samples were collected by thoracotomy performed at 72nd hour of trauma.

• Group 5 (Study-24): Blunt thoracic trauma was created. CoQ10 was administered intraperitoneally at the hour zero. Lung tissue and blood samples were collected by thoracotomy performed at 24th hour of trauma.

• Group 6 (Study-48): Blunt thoracic trauma was created. CoQ10 was administered intraperitoneally at the hour zero and 24. Lung tissue and blood samples were collected by thoracotomy performed at 48th hour of trauma.

• Group 7 (Study-72): Blunt thoracic trauma was created. CoQ10 was administered intraperitoneally at the hour zero, 24 and 48. Lung tissue and blood samples were collected by thoracotomy performed at 72nd hour of trauma.

A trauma device which consisted of a fixed platform, and an aluminum tube was prepared. Our model to create blunt thoracic trauma was prepared by examining the similar studies in the literature, considering features such as variability of the trauma impact, easily ensured standardization (weight and height of the weight dropping may be changed), reproducibility, ease of implementation and portability [3, 4, 6].

Previous studies have shown that a trauma of approximately 2.45 j is required in order to create a life compatible PC in rats [3, 4, 6]. Cylinder height and weight to be dropped are calculated with the formula of E=mgh, in which, E stands for energy to be applied (joule), m stands for weight to be dropped (kg), g stands for gravitational acceleration (9.8 m/s2) and h shows height of the weight to be dropped (m). The proper height was found as 50 cm, and the weight 500 g. by this way, the trauma to be created was standardized.

Using this mechanism, rats were administered anesthesia and analgesia, and laid on the foam surface platform in a supine position as to be 45 degrees toward the left side in order to decrease the risk for the heart contusion. Except for Sham group in this position, a metal weight of 500 g was dropped from height of 50 cm with free fall at a constant speed through a cylindrical aluminum tube on the right hemithorax. Rats were followed after trauma.

All the rats were administered xylazine at a dose of 10 mg/kg and ketamine hydrochloride of 75 mg/kg through intraperitoneal route before the surgical processes. The doses not exceeding 20% of the initial doses were intermittently repeated when it was deemed necessary. Analgesia was provided with intraperitoneal morphine sulfate administration of 0.05 mg/kg before and after the trauma and surgical processes.

Coenzyme Q10 was dissolved in soybean oil. Soybean oil was sterilized at 135 °C in a gravity autoclave for 5 minutes. It was intraperitoneally administered at a dose of 30 mg/kg/day for anti-inflammatory efficiency of CoQ10 once a day. Then thoracotomy was performed using midsternotomy technique following the analgesia and anesthesia, and 5 ml of blood was drawn from the heart.

Blood samples sent for biochemical analysis were centrifuged at 3000 rpm for 10 minutes and separated to their serums. High - sensitivity C - reactive protein (Hs - CRP) was studied blindly with ELISA method. The results were evaluated as µg/mL.

Following the blood collecting, right and left main bronchi were clamped and euthanasia was applied. Lung tissues were rapidly removed. The samples collected for histopathological examination were put into 10% formaldehyde and fixed.

Sections of 5 mm thickness were obtained from the paraffin

blocks prepared from the lung tissues removed from the rats. These sections were stained with Hematoxylin and eosin (H & E) and studied blindly by a single pathologist under a light microscope at 40 and 100 magnification (Table 1) [3, 4, 6, 7].

Table 1. Evaluation of the histopathologic examination

		Grade 0	Grade 1	Grade 2	Grade 3
Atelectasis, congestion and intraalveolar hemoorhage		No	Focal	Patched (small, but multifocal foci from 5 magnification areas)	Diffused (along 5 magnification areas)
Parenchymal inflammation	According to cell density	No inflammation	Mild inflammation/ Individual cells	Moderate inflammation/ Aggregations forming groups of 2-4 cells	Severe inflammation/ aggregations > 5 cells
	According to cell type	No inflammation	Neutrophil weighed	Neutrophil and mononuclear cells weighed	Mononuclear cells weighed
Perivascular mononuclear inflammation		No	Mild (individual cells)	Moderate (cell groups)	Severe (aggregation forming cuff around the vessel)
Bronchial damage		No	Damage to focal epithelium	Destruction of focal wall	Intense damage in bronchiole with abscessing

Statistical analysis: Statistical analysis was performed with SPSS 15.0 (Statistical Package for Social Sciences, SPSS Inc, Chicago, USA) software. Evaluation of the differences between the groups was carried out with "Chi-Square" test. Mean levels of Hs-CRP were compared with "One-Way Analysis of Variance (ANOVA)" and histopathological evaluations were compared with Kruskal Wallis test. Holm-Sidak Test from the "Post - Hoc" test was applied. Compliance of the data with normal distribution was evaluated with "Shapiro-Wilk" and the data were found to comply with normal distribution. Values of P<0.05 were considered statistically significant.

Results

Hs-CRP: Mean level of Hs-CRP was found at the lowest level in the sham group, while this value was observed to be high in the control and study groups that were exposed to trauma. ANOVA results showed that groups were statistically different in terms of Hs-CRP (P=0,000). Holm-Sidak test to see statistically different groups indicated sham and Study-72 groups did not differ significantly (P>0.05), while other control and study groups had significantly higher Hs-CRP levels than the sham group (P<0.05). No statistically significant difference was found between control and study groups at 24, 48, and 72 hours (P>0.05) (Table 2) (Figure 1).

Histopathological Evaluation: Kruskal Wallis Test results showed that groups were statistically different in terms of histopathological evaluation terms (P=0.002 for atelectasis, congestion and intraalveolar hemorrhage, P=0.001 for cell density of parenchymal inflammation, P=0.000 for parenchymal inflammation according to cell type, P=0.000 for perivascular mononuclear inflammation and P=0.045 for bronchial damage) (Table 3).

Atelectasis, congestion and intraalveolar hemorrhage: Significant differences were observed between sham and control groups at 24, 48, and 72 hours in terms of atelectasis, congestion and intraalveolar hemorrhage (P<0.05), while no significant difference was observed between sham and study groups at 24, 48, and 72 hours (P>0.05). No statistically significant difference was found between control and study groups at 24, 48, and 72 hours (P>0.05) (Figure 2).

Cell density of parenchymal inflammation: Significant differences were observed between sham and Study-48 groups in terms of cell density of parenchymal inflammation (P<0.05), while no significant difference was observed among sham, Study-24 and Study-72 groups (P>0.05). No statistically significant difference was found between control and study groups at 24, 48, and 72 hours (P>0.05) (Figure 2).

Parenchymal inflammation according to cell type: Significant differences were observed among sham, control and Study-48 groups in terms of the cell type (P<0.05), while no significant difference was found between sham and Study-72 groups (P>0.05). No statistically significant difference was found between control and study groups at 24, 48, and 72 hours (P>0.05) (Figure 2).

Table 2. ANOVA results for Hs-CRP.

Groups	n	Mean	Std. Dev.	F	p	Homogenous Subsets
Sham	8	28.80	13.99	6.110	0.000	a
Control-24	8	52.80	9.44			b
Control-48	8	61.75	16.32			b
Control-72	8	56.24	14.21			b
Study-24	8	69.29	15.26			b
Study-48	8	52.75	8.12			b
Study-72	8	50.08	19.84			ab

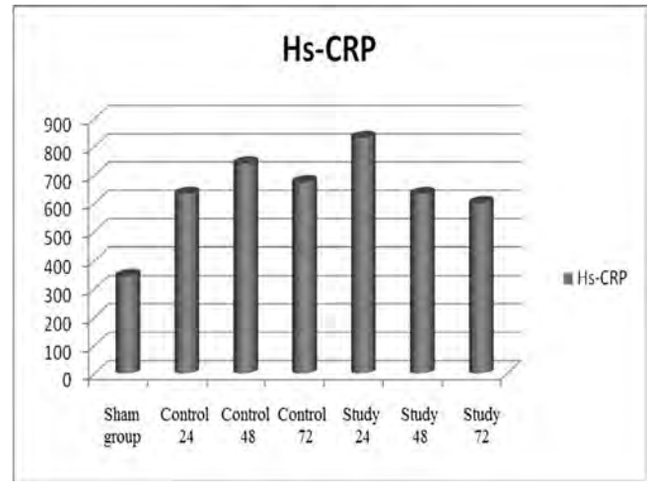


Figure 1. Mean value of Hs-CRP variations of the groups.

Table 3. Kruskal Wallis test results for histopathological evaluation

Histopathological Evaluation	Groups	n	Median	IQR	p	Homogenous Subsets
Atelectasis, congestion and intraalveolar hemorrhage	Sham	8	0.00	1.00	0.002	a
	Control-24	8	1.00	1.00		b
	Control-48	8	2.00	1.75		b
	Control-72	8	1.00	0.75		b
	Study-24	8	1.00	1.00		ab
	Study-48	8	1.00	0.75		ab
	Study-72	8	1.00	0.00		ab
Parenchymal inflammation	Sham	8	0.00	0.75	0.001	a
	Control-24	8	1.00	0.00		ab
	Control-48	8	2.00	1.00		ab
	Control-72	8	1.00	0.00		ab
	Study-24	8	1.00	1.00		ab
	Study-48	8	1.00	0.00		b
	Study-72	8	0.50	1.00		ab
Cell type	Sham	8	0.00	0.75	0.000	a
	Control-24	8	1.00	0.75		b
	Control-48	8	2.00	0.00		b
	Control-72	8	3.00	0.00		b
	Study-24	8	1.00	1.00		b
	Study-48	8	1.00	0.00		b
	Study-72	8	0.50	1.00		ab
Perivascular mononuclear inflammation	Sham	8	0.00	0.00	0.000	a
	Control-24	8	1.00	1.50		b
	Control-48	8	2.50	1.75		b
	Control-72	8	1.00	0.00		b
	Study-24	8	0.00	0.75		ab
	Study-48	8	0.00	0.75		ab
	Study-72	8	0.00	1.00		ab
Bronchial damage	Sham	8	0.00	0.00	0.045	a
	Control-24	8	-	-		-
	Control-48	8	0.50	1.00		b
	Control-72	8	0.00	0.75		ab
	Study-24	8	-	-		-
	Study-48	8	0.00	0.00		ab
	Study-72	8	0.00	0.00		ab

Perivascular mononuclear inflammation: Significant differences were observed between sham and control groups in terms of perivascular mononuclear grades (P<0.05), while no significant difference was found between sham and study groups (P>0.05). No statistically significant difference was found between control and study groups at 24, 48, and 72 hours (P>0.05) (Figure 2).

Bronchial damage: Because there was not any branchial damage observed on histopathologic examination of all the subjects in the sham, Control-24 and Study-24 groups, the differences between them could not be calculated. Significant differences were found between sham and Control-48 groups (P<0.05), while no significant difference was found among sham, Control-72, Study-48 and Study-72 groups (P>0.05). No statistically significant difference was found between control and study groups at 24, 48, and 72 hours (P>0.05) (Figure 2).

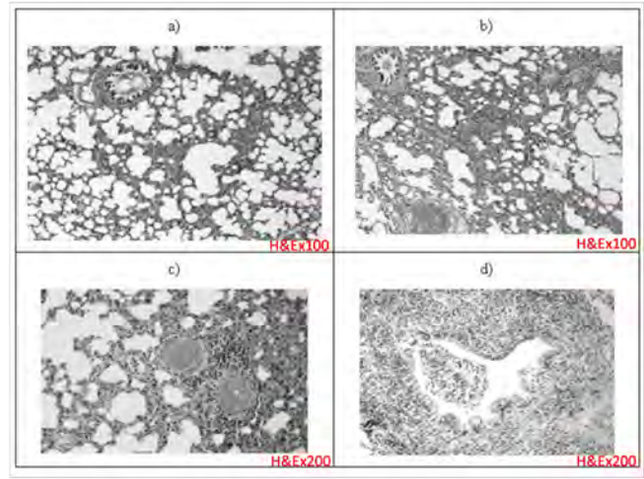


Figure 2. Appearances of histopathologic examination with Hematoxylin and Eosin (H&E) staining. a) Histopathological appearance of hemorrhage area in the parenchyma in the lung tissue of the rat at examination with H&E x 100. b) Histopathological appearance of inflammation area in the parenchyma in the lung tissue of rat at examination with H&E x 100. c) Histopathological appearance of lymphoplasmacytic cell infiltration around vessel in the lung tissue of the rat at examination with H&E x 200. d) Histopathological appearance of inflammation and damage in bronchial epithelium in the lung tissue of the rat at examination with H&E x 200.

Discussion

Blunt thoracic trauma may cause to PC in lung parenchyma. PC radiologically begins to be seen about six hours after trauma. Edema and interstitial hemorrhage begin to develop in the lung one or two hours after the injury. Blood and proteins begin to fill into intrapulmonary airways about 24 hours after the trauma. Contusion reaches to a maximum within 48 hours. Radiologically abnormal increase of opacity in a patch form and air bubbles develop. Lesions may be single or diffused. Lesions may be located in the perihilar region and areas adjacent to vertebra, sternum and ribs [8]. It is clear that understanding of the pathophysiology of blunt thoracic injury and demonstrating of the correlation between this pathophysiology and duration will elucidate the diagnosis and treatment processes, reducing morbidity and mortality [9].

Alpha-fetoproteins are known to elevate in traumas. Hs-CRP is an alpha-fetoprotein group. It is highly sensitive and can be detected even in the low levels, providing an advantage. It is more valuable than CRP in detection of slight elevations [10]. In their study, Is et al. stated that Hs-CRP elevates to very high levels in serum and cerebrospinal fluid samples of the patients with severe head traumas, thus might be used as an inflammatory index in traumas [11]. In a study by Turkyilmaz et al., level of PO2/FiO2 in arterial blood gas was the most sensitive parameter in determination of the grade of lung injury due to thoracotomy, which was followed by CRP, white blood cell, erythrocyte sedimentation rate, D - Dimer and fibrinogen [12]. In this study, mean values of Hs-CRP were found significantly higher in the groups exposed to trauma, consistently with the above-mentioned studies. In our study, no significant difference was found between the control and study groups in terms of Hs-CRP values (P>0.05). However, there was not a significant difference between the sham group and study 72 groups, which received more CoQ10 (three times; at the 0, 24 and 48th hours)

than the other study groups in terms of Hs-CRP values (P>0.05). We believed that this might increase the antiinflammatory efficacy of CoQ10.

In a study by Raghavendran et al., PC was studied by creating an experimental blunt thoracic trauma [13]. They found hemorrhagic damage beginning at 8th minute of the trauma, being observed at 4th and 8th minutes, involving perihilar areas and extending to the surface of the visceral pleura and concomitant impairment in alveoli with areas of diffuse intra-alveolar hemorrhage. They observed atelectasis to become prominent at 24th hour of the trauma and leukocyte count to increase with neutrophil predominant in alveolar cavity and interstitial area. They found at 48th hour of the trauma neutrophilic infiltration to maintenance to be predominant and intraalveolar edema to be observed. In their study, Turut et al. found intraalveolar hemorrhage, congestion and alveolar edema to be predominant with fragmented alveoli in the post-traumatic early period and leucocytic infiltration and atelectasis to be obvious at 24th hour of the trauma [3]. In this study, atelectasis, congestion and intraalveolar hemorrhage in a focal appearance, neutrophil weighed mild parenchymal inflammation and perivascular inflammation in the form of individual cells were observed, while no bronchial damage was found at the 24th hour. Atelectasis, congestion and intraalveolar hemorrhage were found to be increased; diffused and mononuclear cell weighed severe inflammation, perivascular mononuclear inflammation forming a cuff around the vessels and mild bronchial damage were observed at 48th hour. Atelectasis, congestion and intraalveolar hemorrhage in a focal appearance, mononuclear cell weighed mild parenchymal inflammation, and mild perivascular mononuclear cell inflammation were observed and bronchial damage was found to quite decrease at 72nd hour of the trauma. These results were similar to those of Raghavendran et al. and Turut et al. [3, 13].

Relative ischemia emerging with injury is followed by reperfusion. However, injury becomes more serious due to formation of free oxygen radicals during reperfusion [14]. In a healthy organism, there is a balance between formation and environmental accumulation rates of free radicals and removal or deactivation of these by antioxidants [15]. This is known as oxidative balance. Organism is not influenced by free radicals as long as the oxidative balance is maintained. Cells encounter with attack of the oxidant agents after a trauma. If the systems fail to neutralize this attack, irreversible destruction emerges [16].

Today, generally fluid restriction, high-dose steroids, antibiotics, diuretics, oxygen and mucolytic are used for treatment of PC due to blunt thoracic trauma. In addition, increasingly more understanding of the role of oxidant in development of PC and ARDS leads to increase in the number of the studies on the treatment to be managed through antioxidants. Aribogan et al. administered pentoxifylline as an antioxidant agent in adult patients with PC in the early periods following the injury; while Maxwell et al. used albumin in the pigs in which they created blunt thoracic injury and demonstrated it was effective as an antioxidant [17, 18]. In their study on rats with experimentally produced PC, Turut et al. used dexamethasone (DXM), N - acetylcysteine (NAC) and aprotinin (APR), and observed histopathological and biochemical improvement in lung damage [3]. In our study, CoQ10 was used as an antioxidant agent.

CoQ10 is a strong antioxidant which is a part of the mitochondrial electron transport chain, playing a role in membrane stabilization [19]. Decrease of CoQ10 indicates the occurrence of a secondary damage [20]. In their study, Kaikkonen et al. [21] demonstrated CoQ10 to decrease oxidative stress and to increase antioxidant capacity at in vivo settings. Furthermore, CoQ10 supplementation was seen to reduce lipid peroxidation and increase antioxidant capacity of plasma. In their study on rats with experimentally produced spinal trauma, Kerimoglu et al. demonstrated that methylprednisolone administered with CoQ10 is effective in spinal cord damage [7]. These studies indicate that CoQ10 can be used as an antioxidant. Numerous studies are conducted about many antioxidant agents in lung injuries [3, 17-20]. However, no study was found conducted using CoQ10.

In their study on rats with experimentally produced PC, Turut et al. used DXM, NAC and APR, and found a slight improvement both in PaO2 and PaCO2 values [3]. In addition, they demonstrated in the patients that level of MDA in lung tissue were decreased. Examining bronchoalveolar lavage fluid, they found neutrophil count of DXM to decrease. They demonstrated significant improvement on histopathologic examination of rat lungs received APR and DXM. Consequently, they observed that administration of DXM, NAC and APR in the early period results in desired improvement in lung tissue, which is affected from PC implementation.

Aribogan et al. found that pentoxifylline administration in early period following the injury, might be effective in acute inflammatory response and controlling of lung damage in the patients with PC identified [17]. In their study with pigs in which they created blunt thoracic trauma, Maxwell et al. used albumin as an anti-inflammatory agent [18]. They found albumin to decrease the damage mediated by oxidants that occurred in pulmonary alveolar capillary membrane, which plays a role in secondary damage.

In our study, on histopathologic examination significant difference was found between the Sham and control groups in terms of atelectasis, congestion and intraalveolar hemorrhage, while no significant difference was found between the sham and study groups. This indicates that CoQ10 decreases atelectasis, congestion and intraalveolar hemorrhage which occurred in PC. On evaluation in terms of parenchymal inflammation, a significant difference was found between sham and control groups, while no significant difference was found between Study-24 and Study-72 groups. This is consistent with other studies in the literature [3, 7, 17, 18, 20] and indicates CoQ10 to decrease inflammation and to have anti-inflammatory efficiency. However, in our study, no significant difference was found between Sham and Study-48 groups in terms of parenchymal inflammation. CoQ10 is seen not to have an impact on parenchymal inflammation at 48th hour. However, efficiency of CoQ10 compared to the other parameters is seen clearly. No difference was found between sham and Study-48 groups, suggesting it may be resulted from the inflammation to be maximal at 48th hour. When the environment of blood vessels was examined in terms of the grade of mononucleate inflammation, a significant difference was found between Sham group and Control groups,

while no difference was found between the study groups. This result is consistent with the other studies in the literature [3, 7, 17, 18, 20] and CoQ10 decreases the inflammation which occurred in PC.

This is caused by damaged areas and could not be clearly detected on histopathologic sections. Surface of weigh used in trauma mechanism covered all the surface of the rat lung. Thus, PC did not occur diffusely in all areas of rat lung tissue. A new trauma mechanism is needed to produce equally or proportionally distributed contusion in all areas of rat lung tissue.

In conclusion, although no significant difference was observed between the control and study groups; also no significant difference was found between the sham and study groups, suggesting CoQ10 that is an antioxidant agent may be used in order to reduce effects of oxidants, which are responsible for the secondary damage in blunt thoracic trauma. It is believed that increasing the frequency and dose of CoQ10 may increase anti-inflammatory efficiency. Further studies with a greater number of subjects, longer follow-up duration and increased frequency of implementation are needed in order to demonstrate that CoQ10 can be useful in PC treatment and increasing of its frequency and dosage to increase its efficiency.

Limitations: Trauma device is not completely involved the chest wall of a rat. In this case; same contusion is not developed in both sides of the lung. On the histopathological examination; encountering the affected cells due to trauma is completely depended to the macroscopic examination. Probability of the lung tissue being to be less or more affected from the trauma might negatively affect the study. A device would create an equal trauma severity on all the lung tissue is needed in order to prevent this condition.

Competing interests

The authors declare that they have no competing interests.

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Retrospective Analysis of Human Serum Albumin use From Gynecologic and Obstetric Point of View

Jinekoloji ve Obstetri Bakış Açısı ile İnsan Serum Albumin Kullanımının Retrospektif Analizi

İnsan Serum Albumin Kullanımı / Human Serum Albumin Use

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Özet

Amaç: İnsan serum albumini (İSA] dolaşım sisteminde bulunan en belirgin proteindir. İSA, koloid solüsyon olarak özellikle yoğun bakım ünitelerinde birçok endikasyonla yaygın olarak kullanılmaktadır. Birçok endikasyonu olmasına rağmen günlük kullanımda uygunsuz endikasyonlara sıklıkla rastlenmaktadır. Jinekoloji ve obsterti de çeşitli endikasyonlarla İSA kullanımının sık olduğu bir branştır. Uygunsuz kullanımının yanında, yüksek maliyeti, teorik hastalık bulaş riski, daha az maliyetli alternatiflerinin de bulunduğu göz önüne alındığında, bu çalışmamızda Sağlık bakanlığının İSA kullanım yönergesi ışığında üçüncğ basamak dal hastanesi olan hastanemizin verilerini kullanarak, jinekoloji pratiğinde İSA kullanımı ve kullanım endikasyonlarındakideğişiklikleri değerlendirmeyi amaçladık. Gereç ve Yöntem: Çalışma için hastanemiz bilgi işlem sisteminden perinatoloji, jinekolojik onkoloji ve reprodüktif endokrinoloji kliniklerindeki HSA kullanım oranları ve kullanım endikasyonları incelendi. 2012 yılı sonunda Sağlık Bakanlığı tarafından yayınlanan İSA kullanımı ile ilgili yönerge öncesi İSA kullanım sıklığı ve kullanım endikasyonlarındaki değişiklikler istatistiksel olarak karşılaştırıldı. Bulgular: Perinatoloji kliniğinde 2012 yılında Albumin kullanımı doğum başına 0,0027 iken bu oran 2013 yılında 0,018'e gerilemiştir. Yönerge sonrası İSA kullanımı artan tek kliniğin jinekolojik onkoloji olduğu gözlenmiştir. Tartışma: Jinekolojik onkoloji hariç diğer kliniklede HSA kullanım oranında bir azalma göze çarpmakla birlikte, endikasyon dışı kullanım oranı halen yüksek düzeylerdedir. Uygun endikasyonların özümsenmesi ve günlük pratikte uygulamaya geçirilebilmesi jinekologlar arasında kliniklerinde uygun tedavi verilebilmesi için önem taşımaktadır.

Anahtar Kelimeler

İnsan Serum aLbumini; Jinekoloji ve Obstetri; Hipoalbuminemi; İSA

Abstract

Aim: Human serum albumin (HSA) is the most abundant circulating protein in the body. HSA, as a colloid solution, used for several conditions in daily clinical practice especially in intensive care units. HSA is commonly used for several indications but its administration could often be considered as inappropriate. Gynecology and obstetrics is an important specialty that HAS administration is necessary for several different conditions. Beside the proportion of inappropriate use, the elevated cost, the theoretical risk of disease transmission and the existence of more economical alternatives of rationalize, we would like to emphasize the appropriate use of HSA in obstetrics and gynecology practice by the help of hospital's data, which is a tertiary care center in Turkey for Obsterics and gynecology practice. Material and Method: Retrospectively we investigate the percentage of human albumin use in term of sub departments such as perinatology, gynecological oncology and reproductive endocrinology. At the end of 2012 Ministry of health published a guideline for hospital to regulate the use of Human Albumin in medical practice. They mentioned the appropriate indications and alternative treatment methods for human Albumin use for the clinicians. The change in the HSA use indications and rate of HSA use per cases was statistically compared. Results: In 2012 Albumin use per birth in perinatology clinic is 0, 0027/birth, in 2013 it is dropped to 0, 0018/ birth. The only department that HSA use increases after implementation of guideline is gynecologic oncology Discussion: There is a significant decrease in HSA use in clinics except gynecologic oncology in daily practice. Besides this decrease inappropriate use is still common. We believe that understanding the appropriate indications and common mistakes in daily practice could be useful for gynecologists to determine the definitive treatment of options in their services.

Keywords

Human Serum Albumin; Obstetrics and Gynecology; Hypoalbuminemia; HSA

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Introduction

Human serum albumin [HSA] is the most abundant circulating protein in the body a nd show typical blood concentration of 3,5-5.0 gr/dl (35-50gr/l) [1]. It is a soluble and monomeric protein produced in the liver with a production rate of 0.2 gr/kg per day [2]. HSA synthesis is governed by a single copy gene lying on the long arm of chromosome 4, near the centromere at position q11–22 [3]. Under physiological conditions, a steady state exists between synthesis and metabolism. The amount of albumin metabolized daily is approximately 10% of total plasma albumin [4]. There is a distribution pattern of albumin that is fitted to a two-compartment model, which about 40% of albumin is stored in intravascular and 60% in the extravascular space [5]. The escape rate of albumin from intravascular space to extravascular space is increased in a variety of diseases as hypertension, major surgery and trauma, sepsis, burns etc [2].

The well-known function of HSA is providing oncotic pressure in the circulation. HSA is the main modulator of fluid distribution in the various compartments of the body as it accounts for about 70–80% of the plasma oncotic pressure [6]. Besides oncotic properties another function of albumin in the circulation is to act as a transporter for several endogenous (steroids, thyroxine, fatty acids, bile salts, metals) and exogenous (drugs; warfarin, antibiotics, furasemide) molecules. HSA also act as sweeper for oxygen radicals in the circulation with the help of free sulphydril group in its structure. The capacity to bind nitrous oxide (NO) prevents rapid inactivation of NO and causes prolongation of its anti-aggregant effect.

Clinical Use:

HSA as a colloid solution that is used for several conditions in daily clinical practice is prepared from pooled human plasma by alcoholic precipitation. For pathogen inactivation, albumin is pasteurize for at least 10 h at -60 degree Celcius [2].

HSA is largely used in clinical practice with several indications, but its administration is often inappropriate. Lots of guidelines for regulation of HSA use are published by several institutes and committees. Most widely used indication for HAS supplementation is correction of hypovolemia. Hypovolemia due to various reasons such as burns, trauma, and surgery can be indications for albumin usage. HSA usage in hypovolemia always controversial in the literature. First Cochrane meta-analysis was published in 1998 claims that infusion of HSA solutions in hypovolemia due to injury or surgery, burns and hypoproteinemia increased the risk of death by 6% [7]. However, in the following meta- analysis published in 2001 and 2004 claims that there is no increase in mortality whether HSA is used to treat hypovolemia, supporting the safety use of HSA in critically ill patients [8, 9]. Moreover, the Saline versus Albumin Fluid Evaluation (SAFE study) was also published in 2004 compared saline vs. 4% HSA solution for fluid resuscitation demonstrated that the 28-day mortality was similar [9]. Finally in 2011 the most recent meta-analysis was published by Cochrane Database showed no evidence of survival benefit of HSA compared to the other cheaper alternatives [10].

Prevention from post-paracentesis circulatory dysfunction (PPCD) which is defined as reduction of effective blood volume, rapid re-accumulation of ascites, dilutional hyponatremia, and increased mortality after large volume paracentesis is another indication for HSA administration [11]. Cirrhosis itself can be a cause for hypo-albuminemia because of decrease in production but also dilution of the extracellular fluid protein content, due to the plasma volume expansion consequent to renal sodium and water retention, and from the increased trans-capillary escape rate towards the extravascular space, at least in the most advanced stage of cirrhosis [12].

Spontaneous bacterial peritonitis, hepato-renal syndrome can be counted for other important indications for HSA use. HSA is defined as the first line treatment for these disorders [13]. The way of administration and indications for these life-threatening disorders are defined in several guidelines that are discussed earlier.

Clinical Use in Obstetrics and Gynecology:

Gynecology and obstetrics are an important specialty that Human Serum Albumin use is necessary for several different conditions. In assisted reproductive practice Ovarian Hyperstimulation Syndrome (OHSS) is one of the important conditions that characterized with hypoalbuminemia and intravascular fluid loss. Decreased intravascular oncotic pressure results accumulation of fluids in the extra-vascular areas such as pleura and peritoneum. In 2011 a Cochrane Review was published about HSA administration in OHSS. In the result section they concluded that there was borderline evidence of benefit with the routine use of human albumin in the prevention of OHSS but also they claimed that there was good evidence to support the use of hydroxyethyl starch in the prevention of OHSS in high risk patients [14]. The most common contraindication to the use of crystalloids was fluid restriction in daily practice about HSA usage [15]. By this point of view HSA use in OHSS is the most appropriate indication in gynecologic practice.

In perinatology unit HSA is also commonly used for correction of hypovolemia after surgical interventions and in special circumstances like preeclampsia. There are no controlled studies on volume substitution to correct hypovolemia in preeclampsia. In gynecologic oncology practice hypovolemia due to accumulation of ascites like in ovarian cancer or severe hypovolemia due to extensive surgery are the indications of HSA use.

For preventing the overuse of HSA in daily practice Turkish Government Ministry of Health implemented a guideline about indications for HSA use at the end of 2012. According to this guideline the indications for Albumin use is indicated for gynecology and obstetrics as follows:

1- In preeclampsia and eclampsia, the patients with serum albumin level >2g/dl

2-In OHSS, the patients with serum albumin level >2g/dl and ascites, pleural effusion or pulmonary edema

3- As additional therapy for patients with spontaneous bacterial peritonitis and ascites

In this study we try to investigate whether the implementation of Ministry of Health has made any change for the indications of HSA use in gynecology and obstetrics practice by using the data of the biggest Women Health Hospital in Turkey.

Material and Method

At the end of 2012 Ministry of health published a guideline for

hospital to regulate the use of Human Albumin in medical practice. They mentioned the appropriate indications and alternative treatment methods for human Albumin use for the clinicians. For determining the use of human albumin in gynecology and obstetrics practice and define whether any differences in clinical use after rational drug use policy for human albumin began to be implemented by Turkish Government Ministry of Health we investigate the record of our hospital which is the biggest tertiary care center for women's health in Turkey. Retrospectively we investigate the percentage of human albumin use in term of sub departments such as perinatology, gynecological oncology and reproductive endocrinology. By using the hospital's online patient database and patient charts the data about the indications for HSA use, total amount of HSA for a patient, total patients who had undergone any treatment in each subdivision in 2012 and 2013 was obtained. The indications for HSA use were investigated case by case to determine the use with correct indication according to guideline of Turkish Ministry of health for HSA use. The difference between HSA use before and after publication of guideline is statistically analyzed. SPSS 19.0 was used for statistical analysis. The demographic features of the study are demonstrated as total numbers, difference between two years was investigating by using student t test. A p-value of <0.05 was considered statistically significant.

Results

In perinatology practice, to determine the effect of Human albumin use policy Human Albumin used per birth is used. In 2012 Albumin use per birth in perinatology clinic is 0, 0027/birth, in 2013 it is dropped to 0, 0018/ birth. (Table 1) The difference between two consecutive years is statistically significant. The specific indications for Human albumin, is also changed after the active implementation of this guideline. (Table 2) Preeclamptic patients, who have volume deficit in the intravascular space, were used to be treated more often with Human albumin in 2012.

Table 1. Albumin use in perinatology department before and after drug use policy

		2012	2013
Perinatology	Total birth	17690 birhs (7996 C/S vs. 9694 Vaginal delivery)	17917 births (8412C/S vs. 9505 Vaginal delivery)
	Albumin use	48 patients	33 patients
	Albumin use per birth	0,0027	0,0018

p<0,05

In reproductive endocrinology department, most common use of albumin is for the treatment of Ovarian Hyperstimulation Syndrome. Taking into account the nature of the disease, strict volume restriction is mandatory for the treatment. If so, human albumin use is seemed to be the first choice for replacing the intravascular oncotic pressure and fluid loss. (Table 3)

Table 2. Indications for albumin use in perinatology department

Indıcatıons for Human Albumin	2012	2013
Preeclamsia	27	11
Placenta previa	7	9
Hypertension	3	2
Ablatio Placenta	2	4
DIC	2	4
Cholestasis	0	2
Not-specified	7	0

Table 3. Albumin use in reproductive endocrinology department before and after drug use policy

		2012	2013
Reproductive Endocrinology	Total Embryo transfers	362	412
	OHSS	18	9
	Albumin Use	12 patients	5 patients
	Albumin use per OHSS	0,66	0,55

p>0,05

The only department that HSA use increases after implementation of guideline is gynecologic oncology. When the indications of HSA use was investigated in more than %90 percent cases hypoalbuminemia is the cause of administration. (Table 4) In 34 out of 36 patients in 2013 was administered due to serum albumin levels below 2 g/dl. Other two patients HSA were used for supportive treatment in bacterial peritonitis and ascites.

Table 4. Albumin use in gynecologic oncology department before and after drug use policy

		2012	2013
Oncology	Total Malignant Cases	272	324
	Albumin Use	22 patients	36 patients
	Albumin use per malignant cases	0.08	0,11

Discussion

Beside the high proportion of inappropriate use, the elevated cost, the theoretical risk of disease transmission and the existence of more economical alternatives of rationalize and render more appropriate the use of HSA [16]. HSA can be prescribed as the first choice to expand effective intravascular volume in patients with advanced cirrhosis and should be used to prevent renal failure after spontaneous bacterial peritonitis and the post-paracentesis circulatory dysfunction after large volume paracentesis or to diagnose and treat hepato-renal syndrome. HSA is also the second-line treatment for fluid resuscitation in critically ill patients when crystalloids and non-proteic colloids are not effective or contra-indicated. Most common contraindication for crystalloids can be defined as fluid restriction and electrolyte imbalance. Among the heterogeneous population of ICU patients, accumulating data indicate that those with sepsis, severe sepsis, and septic shock benefit more from HSA administration.

For gynecologist OHSS is seemed to be the one of the most common condition that albumin use can be evaluated as the first line choice to replace the intravascular oncotic pressure. Ovaian carcinoma with massive ascites can be defined as other appropriate indication for HSA use. Paracentesis or surgical removal of massive ascites can cause PPCD. HSA can prevent development of PPCD. In other circumstances like preeclampsia and treatment of hypoalbuminemia after surgical interventions can be defined as inappropriate use of HSA.

Practioner tends to treat the intravascular volume deficit in pre-

eclamsia by non-coloid solutions just as crystalloids etc. after the implementation of the guideline.

The albumin use percentage in reproductive endocrinology is seemed to be remaining stable after the implementation of drug policy regimen. This can be because of the nature of hyperstimulation of ovaries, which can be defined as the only indication for albumin use in reproductive endocrinology practice, which is explained above.

The implementation of human albumin use policy does not seem to be effective for gynecologic oncology department. On contrary, the use of albumin increases between consecutive years. However, when the indications for use are investigated, this increase cannot be explained by inappropriate use. It can be explained by severity of disease and increase in total number of patients that needs HSA treatment because of their conditions and co-morbid diseases.

HSA is a lifesaving human serum protein analog whether in appropriate indications. It can be easily observed that it is inappropriately prescribed for both adult and pediatric patients. Gynecology and obstetrics should also define specific indications and guidelines for HSA use to prevent the excessive and inappropriate use of such a valuable weapon for specific conditions. The data collected from our hospital record have revealed that there is an alteration in the human albumin use after the use of human albumin policy. These alterations are in positive or negative manner in different clinics. These findings indicate that the enactment of the policy cannot be sufficient enough to ensure the decrease in inappropriate use of human albumin. There should be more organized, department based policies should be developed. Moreover the use of human albumin indications should be documented better in order to review more efficiently in the following years.

Competing interests

The authors declare that they have no competing interests.

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Species Distribution and Antifungal Susceptibility of Candida Species Isolated From Blood Cultures (2012-2015)

Kan Kültürlerinden İzole Edilen Candida Türlerinin Dağılımı ve Antifungal Duyarlılığı (2012-2015)

Kandidemi / Candidemia

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Özet

Kandidemi önemli bir kan kaynaklı enfeksiyondur ve yüksek oranda mortalite ve morbidite ile ilişkilidir. Uygulanan kompleks medikal ve cerrahi prosedürlere paralel olarak insidansı artmaktadır. Bu çalışmada, Şubat 2012 ile Mart 2015 tarihleri arasında saptanan kandidemilerin tür dağılımı ve antifungal duyarlılıkları retrospektif olarak incelenmiştir. Hastanemizde, Şubat 2012 ile Mart 2015 tarihleri arasında 157 kandidemi olgusu saptanmıştır. Kandideminin toplam insidansı, 0.09/1,000 başvuru olarak bulunmuştur ve 3 yıllık analizde değişiklik saptanmamıştır (P=0,238). Candida albicans en sık izole edilen enfeksiyon ajanıdır (%39.5). C. albicans' ı, C. parapsilosis (%22.9), C. tropicalis (%14,1), C. famata (%7.6) ve C. glabrata (%5.7) izlemektedir. En sık kandidemi olgusu yoğun bakım ünitesinde (%50,3) saptanmış, bunu pediatri ve hematoloji onkoloji servisleri izlemektedir. Test edilen 157 izolatın %14.6 'sı flukonazole dirençli olarak saptanmıştır. CLSI ve EUCAST sınır değerleri kullanılarak, izolatların sırasıyla %12.7 ve %7.6' si varikonazole dirençli veya doza bağlı duyarlı olarak bulunmuştur. En yüksek MIK değerleri C. tropicalis suşlarında saptanmıştır (MIK90, 128 µg/ml). En düşük MIK değerleri Amfoterisin B için bulunmuştur.

Anahtar Kelimeler

Candida; Antifungal Duyarlılık

Abstract

Candidemia has become an important bloodstream infection that is frequently associated with high rates of mortality and morbidity, and its growing incidence is related to complex medical and surgical procedures. We conducted a retrospective study and evaluated the species distribution and antifungal susceptibility of candidemia episodes. In the period of January 2012 to May 2015, 157 episodes of candidemia were identified in the hospital. The overall incidence of candidemia was 0,09 cases per 1,000 admissions and remained stable during the 3- year analysis (P=0,238). Candida albicans was the leading agent of infection (39.5%), followed by C. parapsilosis (22.9%), C. tropicalis (14,1%), C. famata (7.6%) and C. glabrata (5.7%). The majority of the candidemia episodes were found in the intensive care units (50,3%), followed by the pediatric, and the hemato-oncology ward. Overall, 14.6% af the isolates tested were resistant to fluconazole and 12.7% and 7.6% of the 157 isolates tested were resistant or susceptible dose dependent (SDD) to voriconazole based on CLSI and EUCAST breakpoints respectively. Higher MICs for fluconazole were found, especially with C. tropicalis (MIC90, 128 µg/ml). Amphotericin B had the lowest MICs.

Keywords

Candida; Antifungal Susceptibility

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Introduction

Candida spp are an important cause of bloodstream infections (BSIs), leading to significant mortality and morbidity rates and with increased costs of patient care and duration of hospitalization. Despite the availability of effective antifungal therapy, mortality has remained high, ranging from 36% to 63% [1]. The incidence of Candidaemia is growing with the increasing complexity of surgical procedures, the existence of patient populations who are at higher risk of infection and increased use of broad-spectrum antimicrobial agents, advanced life-support and aggressive chemotherapy. Candida spp are currently the fourth [2] and sixth most common blood stream isolates found in studies done in the United States and Europe. Candidemia rates vary geographically. It seems that differences do exist in the epidemiology of candidemia between different countries as well as region to region, underscoring the need for continuous surveillance to monitor trends in the incidence, species distribution, and antifungal drug susceptibility profiles and thus are providing the information necessary for appropriate empirical antifungal therapy [3-7]

Although Candida albicans remains the most prevelant yeast isolated from blood cultures, a shift toward greater isolation of non-C. albicans Candida species has been reported, especially in hematological, transplanted, and intensive care units (ICU) patients [2,3,8].

A reduced antifungal susceptibility in non-C. albicans Candida species and a correlation with routine fluconazole prophylactic use has been suggested. Intrinsic and emerging resistance to azoles represents a major challenge for empirical therapeutic and prophylactic strategies [3].

This study was performed to evaluate the species distribution and antifungal susceptibilities of Candida spp growing in the blood cultures retrospectively in Baskent University Adana Practice and Researche Center between January 2012 and May 2015 from laboratory-based surveillance.

Material and Method

All consecutive patients who developed candidemia at Baskent University Adana Practice and Researche Center, a 576 beds tertiary care hospital with about 519,488 admissions per year were enrolled in the study during the period January 2012-May 2015. Patients with at least one positive blood culture for Candida spp. were identified through the microbiological laboratory database and all informations was recorded in an electronic database. For each patient, only the first episode of candidemia was recorded. The information with regard to candidemia episodes were analyzed, including the fungal species and resistance to antifungals. Patients whose cultures grew > 1 species of Candida were excluded from the analysis.

During the study period there were no changes in microbiological laboratory techniques. Candida species were isolated from blood using BACTEC 9240 system (Becton Dickinson) following the manufacturer' s instructions. Yeast isolates identification was based on germ tube production and sugar assimilation profiles by using the API-20C AUX system (bioMérieux, France). Antifungal susceptibility testing isolates of Candida spp. was performed using ATMTM FUNGUS 3 (bioMérieux, France). Yeast identification and antifungal susceptibility testing were repeated for azole resistant C. albicans species. The interpretive breakpoints used for tests were based on values recommended by the Clinical Laboratory Standards Institute (CLSI) [9] and European Committee on Antimicrobial Susceptibility Testing (EUCAST) [10]. The following antifungal drugs were tested: Amphotericin B, fluconazole, itraconazole and voriconazole.

The chi-square test was used to compare categorical variables. Differences between the groups were considered to be significant for variables yielding a P value of <0.05.

Results

A total of 157 episodes of candidaemia were identified during the study period (January 2012-May 2015) with an overall incidence of 0,09 episodes/1000 admissions and remained stable during the 3-year analysis (Table 1). The age-specific incidence rate was highest in infants (0.1 episodes/1,000 admissions). Children (≤ 18 years, 57.5 % younger than 1 year) comprised 86 (54,8%) of the patients, and adults comprised 71 (45.2%) of the patients. The median patient age of pediatric patients was 2.2 years (0-18 years) and the median patient age of adult patients was 58.7 years (19-92 years). In our study, males (54.8%) were more prevelant than females (44%). There were not important differences in the incidence of candidemia from 2012 to 2015 (P=0.238) (Table 1). The demographic and clinical chracteristics of the patients are summarized in table 1.

The distribution of isolated Candida species is shown in figure 1 and figure 3. C. albicans was the leading cause of infec-

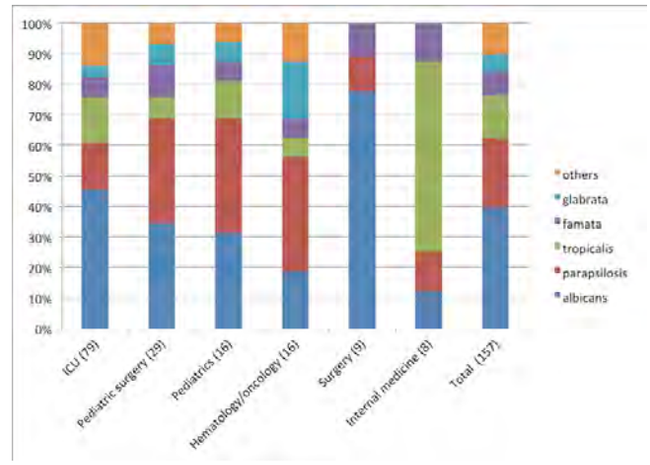


Figure 1. Distribution of the Candida species according to underlying pathology/ medical care (n)

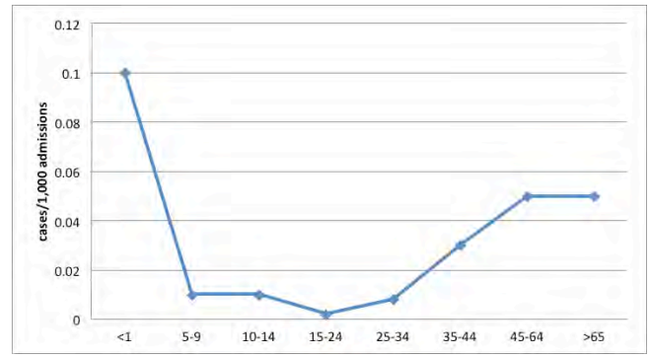


Figure 2. Age specific incidence of candidemia at Baskent University Adana Practice and Researche Center between January 2012 and May 2015. The incidence was low in people aged 5-40 years but started tor ise among people aged 41 to 50 years. Incidence subsequently increased with advancing age, peaking among patients aged 61 to 92 years (0.06 cases/1,000 admissions). With a high incidence occuring in the youngest age group (<1 year, 0.1 cases/1,000 admissions).

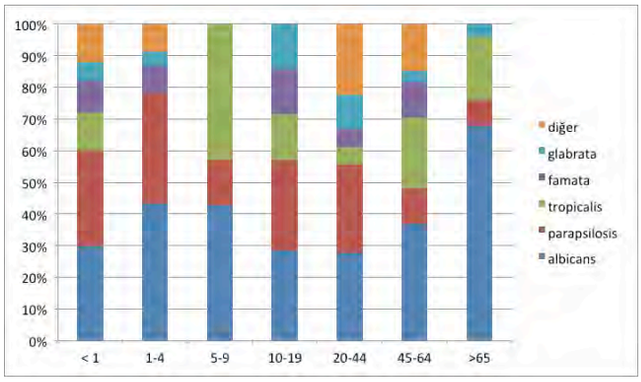


Figure 3. Age specific distribution of Candida spp at Baskent University Adana Practice and Researche Center between January 2012 and May 2015.

ity was seen with C. tropicalis (54,5%) and C. famata (75%). As, our MIC breakpoints did not contain 4 µg/ml, we did not evaluate SDD to fluconazole. Overall, 14.6% of the 157 isolates tested were resistant to fluconazole based on CLSI and EUCAST breakpoints. The rates of susceptibility to voriconazole were 100% for C. parapsilosis, 95.2% for C. albicans. Decreased susceptibility was seen with C. tropicalis (54.5% [CLSI] and 59.1% [EUCAST]). The six strains (1 C albicans, 4 C. krusei, and 1 C. tropicalis) were susceptible dose dependent (SDD) to voriconazole. Overall, 12.7 % and 7.6% of the 157 isolates tested were resistant or susceptible dose dependent (SDD) to voriconazole based on CLSI and EUCAST breakpoints respectively. Amphotericin B had lowest MIC values.

Table 1. Patient characteristics and incidence (episodes/1000 admissions)

	Candida species C. albicans (n=62)	C. parapsilosis (n=36)	C. tropicalis (n= 22)	C. famata (n= 12)	C. glabrata (n=9)	Other* (n=16)	Total (n=157)
	39.5%	22.9%	14.1%	7.6%	5.7%	10.2%	100.0%
Patients characteristic							
Female sex, n (%)	30 (42.3)	15 (21,1)	9 (12.7)	4 (5.6)	3 (4.2)	10 (14.1)	71 (45.2)
Male sex, n (%)	32 (37.2)	21 (24.4)	13 (15.1)	8 (9.3)	6 (7)	6 (7)	86 (54.8)
Underline diseases, n (%)							
Surgery	26 (41.3)	17 (26.9)	7 (11.1)	5 (7,9)	4 (6.4)	4 (6.4)	63 (40.1)
Hematologic malignancy	5 (22.7)	8 (36.4)	2 (9.1)	0 (0)	2 (9.1)	5 (22.7)	22 (14)
Solid tumour	18 (47.3)	6 (15.8)	2 (5.3)	5 (13.2)	3 (7.9)	4 (10.5)	38 (24.2)
Cardiovascular diseases	10 (55.6)	0 (0)	6 (33.3)	0 (0)	0 (0)	2 (11.1)	18 (11.4)
Diabetes mellitus	0 (0)	0 (0)	2 (66.7)	0 (0)	0 (0)	1 (33.3)	3 (1.9)
Congenital anomalies	1 (2.5)	3 (37.5)	3 (37.5)	1 (2.5)	0 (0)	0 (0)	8 (5.1)
Prematurity	2 (50)	1 (25)	0 (0)	1 (25)	0 (0)	0 (0)	4 (2.5)
Immunodefficiency	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)
Incidence (episodes/1000 admissions)							
2012	0,04	0,02	0,02	0,01	0,01	0,01	0,11
2013	0,02	0,02	0,01	0,01	0,01	0,01	0.07
2014	0,05	0,02	0,02	0,01	0	0,02	0.10
2015	0,04	0,01	0,01	0,001	0	0,01	0,07

*Candida krusei (6), Candida kefyr (3), Candida lusitaniae (2), Candida magnoliae (1), Candida norvegensis (1), Candida pelliculosa (3).

tion (39,5%). Globally, non-C. albicans Candida species caused around 60,5% of the cases each. Non-C. albicans Candida species included Candida parapsilosis (22.9%), Candida tropicalis (14.1%), Candida famata (7.6%) and Candida glabrata (5.7%). The distribution of albicans and non-C. albicans Candida strains differed according to the type of population, risk factors and age, as shown in Figure 1. In hemato-oncology patients, C. parapsilosis was isolated in 37,5% (6/16) of the cases, C. albicans in 19% (3/16), and C. glabrata in 19%(3/16); in the overall pediatric wards, C. parapsilosis accounted for 34.8% (16/45) and C. albicans accounted for 33.3% (15/45); in the ICU and the surgery ward, C. albicans was isolated 45,6%(36/79) and 77,8% (7/9) respectively. In the internal medicine wards, C. tropicalis was the leading cause of infection (62,5%) (5/8).

Table 2 shows the results of the in vitro activity of 4 systemically active antifungal agents tested against 157 BSI isolates of Candida spp. By appliying species-specific new clinical breakpoints (CBPs) of CLSI and EUCAST breakpoints. The rates of susceptibility to fluconazole were 100% for C. parapsilosis and C. glabrata and 93,5 % for C. albicans. Decreased susceptibil-

Discussion

Several studies have shown a substantial increase in the incidence of candidemia in the past two decades. Our data show that in our hospital the incidence of candidemia was stable in the past 3 years. Our rates (0,09 episodes/1000 admissions) are not higher than those reported for centers, including the United States (0.28 to 0.96 case per 1,000 admissions), Europe (0.20 to 0.53/1,000 admissions) [11,12], Latin America (1.18 cases per 1,000 admissins) [13] and Iceland (0. 55 case per 1,000 admissions) [14]. The differences in candidemia rates between countries may reflect differences in representativeness and age distributions of the study populations, variations in health care practices, patterns using blood cultures, and antibiotic usage as well as the resistance situation.

Over the past 10 years, some studies have reported a shift in the etiology of candidemia. While C. albicans still considered the most common species causing candidemia, increasing rate of candidemia caused by C. tropicalis, C. parapsilosis, C. glabrata, and C. krusei have been reported worldwide. The species

Table 2. Antifungal susceptibility test results for selected species of Candida isolated during the study period

Species (n)	Antifungal agent	MIC range (µg/ml)	MIC 50a (µg/ml)	MIC 90b (µg/ml)	No. (%) of resistant or susceptible dose dependent c	
					CLSI	EUCAST
C. albicans (62)	Amfotericin B	0,5-16	0,5	0,5	NA	0
	Fluconazole	1-128	1	1	4 (6.5)	4 (6.5)
	Itraconazole	0,125-4	0,125	0,125	NA	NA
	Voriconazole	0,06-8	0,06	0,06	3 (4.8)	3 (4.8)
C. parapsilosis (36)	Amfotericin B	0,5-16	0,5	0,5	NA	0 (0)
	Fluconazole	1-128	1	1	0 (0)	0 (0)
	Itraconazole	0,125-4	0,125	0,125	NA	NA
	Voriconazole	0,06-8	0,06	0,06	0 (0)	0 (0)
C. tropicalis (22)	Amfotericin B	0,5-16	0,5	0,5	NA	0 (0)
	Fluconazole	1-128	1	128	10 (45.5)	10 (45.5)
	Itraconazole	0,125-4	0,5	4	NA	NA
	Voriconazole	0,06-8	0,06	8	10 (45.5)	9 (40.9)
C. famata (12)	Amfotericin B	0,5-16	0,5	0,5	NA	0 (0)
	Fluconazole	1-128	1	1	3 (25)	3 (25)
	Itraconazole	0,125-4	0,125	0,25	NA	NA
	Voriconazole	0,06-8	0,06	0,06	3 (25)	NA
C. glabrata (9)	Amfotericin B	0,5-16	0,5	0,5	NA	0 (0)
	Fluconazole	1-128	1	8	0 (0)	0 (0)
	Itraconazole	0,125-4	0,25	0,5	NA	NA
	Voriconazole	0,06-8	0,06	0,25	NA	NA
All Candida spp (157)	Amfotericin B	0,5-16	0,5	0,5	NA	0
	Fluconazole	1-128	1	16	23 (14.6)	23 (14.6)
	Itraconazole	0,125-4	0,125	4	NA	NA
	Voriconazole	0,06-8	0,06	0,5	20 (12.7)	12 (7.6)

NA: breakpoint not available.
aMIC at which 50% of the isolates tested are inhibited.
bMIC at which 50% of the isolates tested are inhibited
c As, our MIC breakpoints did not contain 4 µg/ml, we did not evaluate SDD to fluconazole.

distribution in the our study is characterized by a predominance of C. albicans, C. parapsilosis and C. tropicalis consistent with other studies from Turkey [15-17]. We observed a predominance of non-C. albicans Candida species (60,5%), however C. albicans was the most frequently isolated species (39.5%). Traditionally, C. tropicalis has been the second and C. glabrata the third or fourth most common Candida species from blood [1,6]. In our study, C. parapsilosis (22.9%) surpassed the other non-C. albicans Candida species to become the most common species isolated after C. albicans. The high incidence of C. parapsilosis candidemia has been previously reported some studies from Turkey [15-17], France [18], Spain, Italy and Latin America [13]. The relative contribution of different Candida species varies between countries in Europe. C. albicans was identified in 56% of cases. C. glabrata, causing 12% of the episodes, was the second most common species recovered in all the countries, except in Italy and Spain where it ranked 3 and 4, respectively. C. topicalis occured in 7% of the cases, ranging from 2% to 10%. C. parapsilosis was the second most common species in Spain and Italy [11].

Several investigators postulated that the widespread use of fluconazole would have selected yeast species intrinsically resistant or less sensitive to fluconazole, such as C. krusei, C. glabrata or C. tropicalis. Some published reports confirmed this hypothesis, while others did not [8]. However, it be recognised that other events might have played a role in the selection of different species [1]. For example, in our study, the increased proportion of candidemias due to C. parapsilosis, a yeast species almost always susceptible to fluconazole, is not readily explained by increased fluconazole use. It is likely that changes in the proportion of fungemias due to C. parapsilosis reflect nosocomial acquisition of this species.

We identified that 50,3% of episode of fungemia occured in patients in ICU. Our findings was similar that some studies from Turkey identified that 45,7%-70,1% of episodes of nosocomial fungemia occured in patients in ICU [15,16,19]. C. albicans dominated in our study in surgery wards with 77,8% and ICU with 45,6% of the species isolated. Non-C. albicans Candida species occurs frequently among pediatric, haemato-oncological and internal medicine patients. In hemato-oncology patients, C. parapsilosis was isolated in 37,5%, C. albicans was isolated in 19% (3/16), and C. glabrata was isolated in 19%(3/16) of the cases; in the overall pediatric wards, C. parapsilosis accounted for 34.8% and C. albicans accounted for 33.3% (15/45); in the internal medicine wards, C. tropicalis was the leading cause of infection (62,5%)

Our findings of overall fluconazole-resistant (14.6 %) was higher than the rates observed in studies from Turkey (21.81-7.48%), European (6,3%), North American (6.6%) and Latin America (7.1%) [13, 15-17, 19-21]. Our proportion of voriconazole resistant (12.7 [CLSI] and 7.6 [EUCAST]) was higher than that studies from Turkey (0%-4.4%) [15-17, 19, 21]. Azole-resistant C. albicans strains and antifungal susceptibility testing were confirmed by repeating the reference method. CLSI recently developed new Candida species-specific clinical breakpoints (CBPs) for fluconazole and voriconazole as the EUCAST for three common Candida species. A recent report has shown that resistance to azoles of Candida species was increased using the new CLSI CBPs [8]. In our study when the old breakpoints applied for C. albicans strains, only two strains were found as resistant to fluconazole and voriconazole (2/62, 3.2%). We didn' t compare the results of new and old breakpoints. We hypothesed that using these species-specific CBPs may increase the resistance to fluconazole and voricoazole in this study. None of our Candida bloodstream isolates had MIC of >1 µg/ml for amphotericin B, some studies from Turkey and Europe reported the low level of amphotericin B resistance [15-17, 19].

In our study, the proportion of children in this study was very high (54,8%). C. albicans was the most prevelant yeast isolated from blood cultures in all age groups. The dominant causes of Candida BSI in the pediatric and adolescent age groups (0-19) were C. albicans (34.5%) and C. parapsilosis (29.9%) similar with previous studies [6]. The high incidence of Candida BSI among infants observed here is consistent with previous studies (Figure 2) [2]. We observed the most common species that recovered from neonates are C. albicans (15 of the 50 cases, 30%) and C. parapsilosis (15 of the 50 cases, 30%), consistent with previous studies [2,11], with increasing age, a reduction in the percentage of C. parapsilosis was seen (from 14,3-34.8% to

8%). A similar trend has been noted both in population-based and in sentinel surveilance studies conducted in the USA [11]. In contrast to other studies that reported the proportion of C. glabrata inreased with patient age [6,11,13], we found that the proportion of C. glabrata BSI did not increase with patient age and the lowest proportion (4%) was seen in the > 65 year age group. In our study, the proportion of C. albicans increased with patient age and the highest proportion (68%) was seen in the > 65 year age group.

Our study was subject to limitations. The major one is that this is a single center study, regional conditions such as features of the patient population and antimicrobial/infection control practices of this specific tertiary care centre may influence the results. As, the data we have reported are based on records from the microbiology laboratory, the lack of clinical data, severity of illness measures, risk factors and antifungal drug exposure data limit the clinical utility of the study.

It is well known that positive blood culture for Candida spp is a life threatening situation, requiring an empirical antifungal treatment which should started with the appropriate agents as soon as possible. Therefore, the knowledge of the local epidemiological trends in Candida species isolated in blood cultures is important to guide therapeutic choices.

Competing interests

The authors declare that they have no competing interests.

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Comparison of Pneumatic and Laser Lithotripsy in the Endoscopic Treatment of Upper Ureteral Stones

Üst Üreter Taşlarının Tedavisinde Pnömatik ve Lazer Litotriptör Kullanımının Karşılaştırılması

Üst Üreter Taşı Tedavisi / Upper Ureteral Stone Treatment

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Özet

Amaç: Üst üreter taşlarının semirijit üreterorenoskop ile endoskopik tedavisinde, pnömatik ve holmiyum lazer litotriptör kullanımının karşılaştırmayı amaçladık. Gereç ve Yöntem: Çalışmaya toplam 74 hasta dahil edildi. Balistik lithotriptör kullanılan 33 hasta Grup 1 ve lazer litotriptör kullanılan 41 hasta Grup 2 olmak üzere hastalar 2 gruba ayrıldı. Her iki grup taş boyutu, operasyon süresi, postoperatif hastanede kalış süresi, taşsızlık oranı ve komplikasyon oranları açısından karşılaştırıldı. Bulgular: Tüm hastaların yaş ortalaması 47.6 yıl idi. Ortalama taş boyutları Grup 1 ve 2'de sırası ile 16.4mm ve 11.0mm idi (p=0.043). Bir aylık takipler sonrasında Grup 1 ve 2'deki taşsızlık oranları sirası ile %78.7 ve %80.5 idi (p=0.391). Grup 1'de 1 ve Grup 2'de 2 hastada minör komplikasyon (Clavien I-II) saptandı. Grup 1'de 3 hastada üreteral perforasyon nedeni ile majör komplikasyon gelişir iken (Clavien 3a ve 3b), Grup 2'de majör komplikasyon saptanmadı. Tartışma: Bulgularımıza göre lazer litotripsi daha güvenli olarak kabul edilebilir. Merkezlerinde lazer litotriptör bulunan kliniklerin üst üreter taşlarında bu yöntemi ilk tercih olarak kabul etmeleri gerektiğini düşünüyoruz.

Anahtar Kelimeler

Üst üreter taşı, endoskopik tedavi, litotripsi, lazer

Abstract

Aim: We aimed to compare the success rate of the use of a pneumatic and a holmium laser lithotripter for endoscopic treatment of upper ureteral calculi with semirigid uretero-renoscopy (URS). Material and Method: A total of 74 patients were included in this study. The patients were divided into two groups; a ballistic lithotripter was used for group 1 containing 33 and a Holmium-YAG laser lithotripter for the remaining 41 patients in group 2. Both groups were compared in terms of stone size the duration of the operation, postoperative hospitalization time, stone-free rate and complications. Results: The mean age of the patients was 47.6. The mean stone size in groups 1 and 2 were 16.4mm and 11.0mm, respectively (p=0.043). The mean stone-free rate groups 1 and 2 were 78.7% and 80.5% respectively at the approximately 1 month follow-up (p=0.391). In group 1 two patients and in group 2 two patients had a minor complication (ClavienI-II). In group 1 three patients had major complications due to ureteral perforation (Clavien 3a and 3b). No major complications (Clavien III-V) occurred in Group 2. Discussion: Based on these findings laser lithotripsy can be regarded as safer. If laser lithotripter is available in medical centers, we argue that it should be the first choice for the treatment of upper ureteral stones.

Keywords

Upper ureteral stone, endoscopic treatment, lithotripsy, laser

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Introduction

In the endoscopic treatment of ureteral stones the gold standard method is semirigid uretero-renoscopy (URS) accompanied by a stone crushing process. The highest success rate is obtained in the treatment of lower ureteral stones [1]. For lower ureteral stones the success rate was approximately 95-100% and 90-95% for stones mid-ureter. Recently, for upper ureteral stones, in the literature there have been reports of success rates varying between 70-100% [2,3].

The endoscopic treatment of upper ureteral calculi can be challenging either due to difficulty in reaching the stone or more likely as a result of push-back. For stone fragmentation, various energy sources are used, such as; electrohydrolic, pneumatic and Holmium-YAG laser. Parallel to technological developments, the most preferred energy sources are pneumatic and laser lithotripters [4,5].

The present study reports on the success of the pneumatic and holmium laser lithotripter methods for the endoscopic treatment of upper ureteral calculi using a semirigid URS in our clinic.

Material and Method

A total of 74 patients who had undergone semirigid URS due to the existence of upper ureteral stones in our clinic between January 2009 and August 2013 were included in this study. The energy source for the 33 patients in group 1 was the Ballistic lithotripter (Vibrolith™, Elmed Medical Company, Turkey) and for the 41 patients in group 2 the energy source was a Holmium-YAG laser lithotripter (SphinxX™, Lisa, Germany).

All the patients were preoperatively evaluated with X-ray KUB (Kidney, ureter, and bladder), urinary ultrasonography, and non-contrast computed tomography or intravenous urography (IVU), or both. In stone size measurement, the dimension of the largest stone in the IVP or X-ray KUB was used for the radiopaque stones and in the abdomen ultrasonography or computerized tomography for the radiolucent stones.

All the patients were evaluated with urinalysis and culture. Patients with an infection were treated with appropriate antibiotics in accordance with the preoperative urine culture based on the antibiotic susceptibility. Other patients underwent an operation following the appropriate antibiotic prophylaxis under general anesthesia. For the stone fragmentation, a pneumatic lithotripter (Vibrolith, Elmed, Ankara, Turkey) was used until May 2012 and the holmium-yttrium-aluminum-garnet (Ho: YAG) has been used since that date.

Operations were performed with a 9.5 F semirigid ureteroscope (Karl Storz, Germany) under the guidance of a 3-5F ureteral catheter. The fragmentation process was continued until all the stone particles were reduced to a size of 3 mm or less. A ureteral or JJ (4.8-6F) stent was placed in patients determined as necessary by the surgeon (such as edema, mucosal damage or prolongation of operation). The stents were removed after a 3 or 4 week postoperative period. One month after treatment all the patients were evaluated using an X-ray KUB or IVU. Patients who had stone fragments at the size of 3 mm or less were considered to be stone-free. Both groups were evaluated and compared in terms of age, gender, stone size, duration of the operation, the postoperative hospitalization time, stone-free rate and complications.

Statistical analysis

Statistical Package for the Social Science for Windows (SPSS, Chicago, IL) version 13.0 software was used for statistical evaluation of the results. Descriptive statistics were given as mean± Standard deviation. Chi-square, Fisher's Exact and Mann-Whitney tests were used to compare the group parameters. A p value of less than 0.05 was considered significant.

Results

The mean age of all the patients was 47.6±14.9 (range:16 to 80) years. The mean age of the groups 1 and 2 were 48.1±15.6 (range: 22 to 88), and 47.2±14.5 (range:16 to 77) years, respectively. Twenty-three patients were female and 51 were male. In groups 1 and 2, the F/M ratio was 9/29 and 14/27 respectively and there was no statistically significant difference between groups. The mean stone size in groups 1 and 2 were 16.4±7,7 mm (range: 5 to 30) and 11±2.9mm (range:5 to 17), respectively (p=0.043). The mean duration of operation in groups 1 and 2 were 58.9±35.8 minutes (range:20-160) and 38.7±12.8 (range: 20 to 70) minutes, respectively (p=0.035). The mean postoperative hospitalization days in groups 1 and 2 were 1.8±1.8(1-9) and 1.20±0.5(1-3), respectively (p=0.483). These results are summarized in Table 1.The average residual stone size in group 1 was 12.5±2.1 mm (10-15) and 6.5±1.7 mm (5-10), in group 2 (p=0.004). The mean stone-free rates for group 1 and 2 were 78.7% and 80.5% respectively approximately at the 1 month follow-up with no statistically significant difference (p=0.391) (Table 2). In group 1, ureteral perforation, requiring open surgery, occurred in 2 patients during URS. In group 1 only one patient with ureteral perforation was treated with a JJ stent. In group 2 there was no ureteral perforation or other procedure that required open surgery. In four patients in group 1 and 1 patient in group 2 a stone push-back was observed. These two patients with push-back were directed to Extracorpore-

Table 1. Demographic data of the groups.

	Group 1 (n=33)	Group 2 (n=41)	Total	p value
Mean age±SD(year)	48.1±15.6	47.2±14.5	47.6±14.9	0.461+
Sex (Female/Male)	9/24	14/27	23/51	0.630#
Mean stone size (mm)	16.4±7.7	11.0±2.9	13.4±6.1	0.043+
Duration of operation (min)	58.9 ±35.8	38.7±12.8	47.7±27.5	0.035+
Postoperative hospitalization (day)	1.8±1.8	1.20±0.5	1.4±1.3	0.483+

+Mann-Whitney test, #Chi Square

Table 2. Stone free rate and residual stone size of the groups.

	Group 1 (n=33)	Group 2 (n=41)	Total	P value
Stone free rate (%)	78.7	80.5	79.6	0.391#
Mean residual stone size±SD (mm)	12.5±2.1	6.5±1.7	8.5±3.4	0.004+
Major peroperative complications	3/33	0/41	3/74	0.006*
Push-back	4/33	1/41	5/74	0.165*

+Mann-Whitney test, #Chi Square, *Fisher-Exact test

al Shock Wave Lithotripsy (ESWL) and in 3 patients, retrograde intrarenal surgery (RIRS) was performed.

In group 1, two patients had a fever of over 38°C and one patient who had undergone open surgery developed a wound infection (Clavien I-II). Two patients switched to open surgery and 1 patient placed JJ stent due to ureteral perforation was considered Clavien 3b and Clavien 3a complications, respectively. In group two, 2 patients had a fever (over 38°C) (Clavien I-II). There were no major complications (Clavien III-V) in Group 2. There was no bleeding which required a blood transfusion in either of the groups. In the first month after the operation, one of the two patients who had ureteral stricture in group 1 underwent open surgery and the other had ureteral perforation. In group 2 there was only one patient who had a ureteral stricture. No perioperative complications were observed. (Table 3)

Table 3. Per-operative and postoperative complications.

	Group1 (n=33)	Group2 (n=41)
Fever	2	2
Hematuria	0	0
Need for open surgery	2	0
Transfusion	0	0
Ureteral stricture	2	1

Discussion

Today, in upper ureteral stones, the first choice is ESWL for stones with a size below 10 mm stones and ESWL or ureterorenoscopy for stones over 10 mm. The stone free rate is 70-89% for ESWL and 81-84% for rigid-semirigid URS [2,3].Youssef et al., compared ESWL and semirigid URS in a total of 427 patients with upper ureteral stones. They found the stone free rate to be 83.7% in the ESWL group and 88.4% in the semirigid URS group. The need for retreatment was 65% in the ESWL group and 2.3% in the URS group (p<0,001). The complication rates were 4.7% and 14% respectively in the ESWL and URS groups. The authors commented that ESWL is safer and less -invasive whilst URS is more effective and has a lower requirement rate for re-treatment [6].

In the endoscopic treatment of ureteral stones, pneumatic lithotripter has long been used during semirigid URS in many medical centers [7,8]. The success rate of pneumatic lithotripters for ureteral stones has been reported to be approximately 95-100%. This success rate is reduced as the localization becomes closer to the upper ureter [9,10]. In a study by Sozen et al, a total of 500 patients who had undergone semirigid URS with a pneumatic lithotripter. This was administered as a primary procedure in 124 patients (24.8%) and as a secondary procedure in the remaining 376 patients after ESWL. The overall stone free rate was 94.6%, however it was found to be 83.3% for upper ureteral stones. The authors reported that either after unsuccessful ESWL treatment or as a first line of treatment, semirigid URS with pneumatic lithotripter provided safe and effective treatment for ureteral stones [11]. Gunlusoy et al., reported that in a study consisting of 1296 patients, the success rates of pneumatic lithotripsy for upper, middle, and lower ureteral stones were 90.5%, 93.1%, and 98.1%, respectively (P < 0.05) [12]. In another recent study by Razzaghi et al., 112 patients were divided into a Ho-YAG laser (n=56) and a pneumatic group (n=56) and the mean stone size was found to be 11.7 and 10.0 mm respectively. In addition, the average stone fragmentation time was 13.7 minutes and 7.9 minutes (p<0,001) (4) with stone free rate of 100% and 42.9% in the Ho-Yag and pneumatic groups respectively. In a study by Jeon et al., data from patients who had undergone URS with pneumatic lithotripter (n=26) and laser lithotripter (n=25) were evaluated. In the early postoperative period the stone free rate was found to be 73.1% and 96.0%, respectively (p<0,049). After 3 months, this rate was 84.6% and 96.0% respectively (p=0,350). The mean operating time was found to be 76.9 minutes and 49.8 min respectively thus being significantly lower in the laser group (p=0.003) [13]. We did not examine the stone free rate in the early postoperative period. However, after 1 month after the operation, our stone free rate of 78.7% in pneumatic group and 80.5% in laser group (p=0.391) was similar to the findings in the literature. Similar to the current literature, our operating time was significantly lower for the laser group (58.9 min in group 1 vs 38.7 min in group 2, respectively, p=0.03).

One of the major disadvantages of semirigid URS is high possibility of stone push-back [14,15]. In a study by Razzaghi et al., while stone push-back was not detected in the laser lithotripter group, it was detected in 10 patients (17.9%) in the pneumatic lithotripter group. The authors reported that, particularly in upper ureteral stones, laser lithotripsy was established to be safer and more effective than the pneumatic lithotripter [4]. Similarly, Garg et al., found that the stone push back rate was 16% in the pneumatic lithotripter group and there was no such case [16]. In the present study, stone push back was found in 4 patients (12,1%) who had undergone pneumatic lithotripsy and in only one patient (3,2%) who had received laser lithotripsy. In recent years, in view of the aforementioned findings, particularly in upper ureteral stones, there is a tendency, in upper ureteral stones, to use laser lithotripsy.

There are many studies reporting a negative correlation between stone size and the success of treatment. However, there are also studies which report no association between stone size and success of treatment [17]. In our study, the groups were not analyzed separately according to their stone size. We think that the residual stone size was higher in the pneumatic group and this was associated with the larger preoperatively stone size. In our study, although there was no significant difference between the stone-free rates in the two groups, the most important difference was seen in the complication rates, and switch to open surgery was determined to be higher in patients in the pneumatic lithotripsy group. In pneumatic lithotripsy, the stone must be compressed between probe and mucosa. This is the most common cause of ureteral perforation [18,19]. However, this problem hardly occurs in laser lithotripsy procedure due to the semi-contact fragmentation [20,21]. Mucosal tissue lesions can be ignored because the tissue depth is very low during fragmentation with laser probe [22,23]. Razzaghi et al., found no difference was found between the pneumatic and laser lithotripsy groups in terms of complication rates [4]. However, Jeon reported that the complication rate was 7.7% in his study in relation to the pneumatic lithotripsy group, and there were no complications in the laser lithotripsy group [13]. In our clinics,

the arrival of the laser lithotripter in May 2012 has marked a major shift the choice of treatment by the surgeons.

To date, Open surgery was needed in two patients using pneumatic lithotripter. The larger average size of the stone in this group may also have affected the results. None of the patients in the laser lithotripsy group needed open surgery. Consistent with the current findings, according to our results the laser is safer. Degirmenci reported that in the proximal ureteral placement and impaction of the stones, the complication rate increases by 2.4 times and 4.3 times, respectively [24]. A study published by Binbay et al., compared the use of pneumatic and laser lithotripsy in impacted ureteral stones. A stone free rate was reported to be 80% and 97.5% respectively (p=0.03). The mean operating time was 48 and 30 minutes, respectively, which was significantly lower in the laser lithotripsy group (p<0.001) [25]. In this study, it was emphasized that the use of Ho:YAG as an intracorporeal lithotripter during the ureteroscopic management of impacted ureteral stones is highly efficient with high success rates, regardless of the location of the stone . In the present study, ureteral stones have not been evaluated separately according to whether or not they are impacted. However, the stone-free rate and the average duration of operation are consistent with these findings.

In conclusion, the overall success rate is high for the treatment of upper ureteral stones with semirigid URS. In terms of the success of the treatment, pneumatic and laser lithotripsy are effective methods. However, considering the duration of the operation, possibility of push-back and complication rates, laser lithotripsy can be regarded as safer. If the laser lithotripter is available in medical centers, we propose that it should be the first choice in the endoscopic treatment of the upper ureteral stones.

Competing interests

The authors declare that they have no competing interests.

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Variations of Sulcus Arteria Vertebralis and Correlation with Clinical Symptoms

Sulkus Arteria Vertebralis Varyasyonları ve Klinik Bulgular ile Korelasyonu

Sulkus Arteria Vertebralis Varyasyonları / Variations of Sulcus Arteria Vertebralis

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Özet

Amaç: Pontikulus postikus olarak da bilinen Kimmerle anomalisi birinci servikal vertebranın(atlas) yaygın bir varyasyonudur. Vertebral arter ve C-1 spinal sinirin arka dalını içeren sulkus arteriovertebralis üzerinden geçen posterior atlanto-oksipital membranın kısmi veya tam kemikleşme ürünüdür. Çalışmamızda sulkus veretbralis ile ilgili varyasyonların Türk toplumunda sıklığının araştırılmasını amaçladık. Gereç ve Yöntem: Hastanemize baş ve boyun ağrısı, böş dönmesi, çınlama şikayetleri ile başvuran, 18- 99 yaş aralığında, 719 hastanın MDBT görüntüleri retrospektif olarak incelendi. Arkuat foramen varlığı ve tipi açısından görüntüler değerlendirildi. Bulgular: 106 vakada total foramen tespit edildi. Total foramen varlığı oranı % 14,74 olarak hesaplandı. Vakaların 48'inde(%6,67) bilateral total foramen tespit edildi. 21 vakada(%2,92) sağda tek taraflı, 37 vakada(%5,14) solda tek taraflı total foramen varlığı görüldü. Bilateral total forameni olan 30 hasta, tek taraflı total forameni olan 30 hasta ve total foramen görülmeyen 30 hastadan oluşan üç grup oluşturuldu. Gruplar arasında baş ağrısı, baş dönmesi, boyun ağrısı, kulak çınlaması gibi semptomlar açısından karşılaştırma yapıldı. Gruplar arasında semptomlar açısından istatistiki olarak anlamlı farklılık saptanmadı. Tartışma: Türk toplumunda arkuat foramen bulunma olasılığı yüksek bulunmuştur ve posterior yaklaşımlarda akılda tutulması gerekmektedir.

Anahtar Kelimeler

Sulkus Arteria Vertebralis; Arkuat Foramen; Pontikulus Postikus

Abstract

Aim: Kimmerle's anomaly (ponticulus posticus) is a common anatomical variation of the atlas, is the product of the complete or incomplete ossification of the posterior atlanto-occipital membrane over the vertebral groove, resulting in the formation of a foramen (arcuate foramen) containing vertebral artery and C1 nerve. We aimed to search the variations related to the sulcus arteriae vertebralis which is on the first cervical vertebrae in Turkish population. Material and Method: We retrospectively reviewed 719 3-D CT scanning digital images of consecutive patients between 18-99 years of age with complaints of headache, neck pain, vertigo, tinnitus, hearing loss in relation to the presence of complete or incomplete arcuate foramen. Results: Ponticulus posticus was found unilateral or bilateral in 106(14,7%) patients, bilateral in 48(6,6%), right side alone in 21(2,9%) patients and left side alone in 37(5,1%) patients. We found no statistical significiant difference in symptoms like headache, servical pain, vertigo, tinnitus between the patients with bilateral, unilateral and without arcuate foramen. Discussion: The probability of the presence of arcuate foramen in Turkish population is very high which has to be known in posterior approach.

Keywords

Sulcus Arteriae Vertebralis; Arcuate Foramen; Ponticulus Posticus

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Introduction

Sulcus Arteria Vertebralis is the name given to the groove which is found on C1 vertebra and where vertebral artery passes. As a result of the ossification of posterior atlanto-occipital membrane on the sulcus, arcuate foramen develops in which vertebral artery and the back branch of C1 spinal nerve passes through(Figure 1-2). Arcuate foramen can be one or two sides,

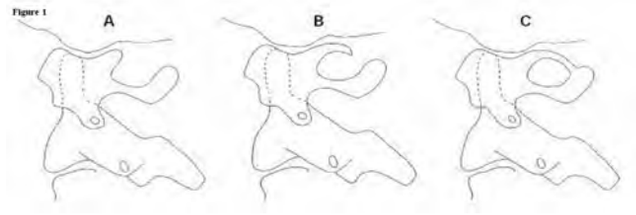


Figure 1. The forms of vertebral sulcus A: Normal sulcus vertebralis B: Partial arcuate foramen C: Total arcuate foramen



Figure 2. A)Total arcuate foramen, B: Partial arcuate foramen on lateral cervical radiograph

partial or complete. The presence of foramen can lead to external mechanic pressure to artery in the extension and rotation movements of the head. These variations of vertebrobasilar disorder symptoms are associated with several types of headaches and acute hearing loss [6].

The purpose of this study is to determine the frequency of these variations in normal population, compare the rates of the symptoms such as headache, dizziness, neck pain, hearing loss and tinnitus in variation and normal cases and determine the potential connection between variation and clinic symptoms.

Material and Method

719 patients who were examined and applied with preliminary diagnoses to Suleyman Demirel University Faculty of Medicine Department of Radiology between May 2010 and October 2013 were taken to the study. The examinations of the patients were examined retrospectively. 54 of the examinations were carotid CT angioradiography, 246 of them were cervical vertebra CT, 154 of them were neck CT, 265 of them were paranasal sinus CT. All examinations fully contained C1 vertebra. Carotid CTA and neck CT analyses were made by non- ionic IV contrast substances, cervical and paranasal sinus CT was made without contrast substance. CT analyses were made by 128-section CT device (Definition AS, Siemens Medical Solutions, Forchheim, Germany). The images were taken by 1 mm section thickness. All of the images were re-evaluated in PACS (picture archiving and communication system). Axial images were analyzed in bone window. In each case, multiplanar (MPR) and volume rendering (VRT) reconstructions were made. The images were carefully analyzed in terms of the presence of arcuate foramen in both sides if there was a foramen, either partial or total (Figure 3).



Figure 3. Three-dimension VRT images of sulcus vertebralis A: Normal sulcus vertebralis on the both sides, B:total arcuate foramen on the left.

18 of the 48 cases with bilateral complete foramen were excluded from the study due to chronic diseases (such as malignity, diabetes), chronic sinusitis diagnosis or hypertension disease which can lead to headache, injury on the head and neck as a result of trauma and common degenerative osteophyte changes on the neck. The remainder 30 patients constituted our first group. The second group of patients was selected from those with one side complete foramen. 20 of total 61 patients with one side foramen were excluded from the study due to the above mentioned reasons. Among 41 patients, 30 patients were selected from the group with the age and sex similar to those in the first group. The third group was constituted randomly from the patients similar in terms of age and sex to the first group among the patients without arcuate foramen. The groups were queried in terms of symptoms such as headache, neck pain, dizziness, tinnitus, syncope attacks, hearing loss, and epilepsy. The patients who had headache complaints were queried and were classified as migraine and other headaches. The differences in terms of clinical findings were assessed between the groups. Statistical assessment was made in the computer environment by Mann-Whitney U test by using SPSS for Windows (version 15.0). When p value is less than 0.05, the difference was accepted as statistically significant. The distribution of the cases according to the gender and foramen type was drown as a graph (Figure 5).

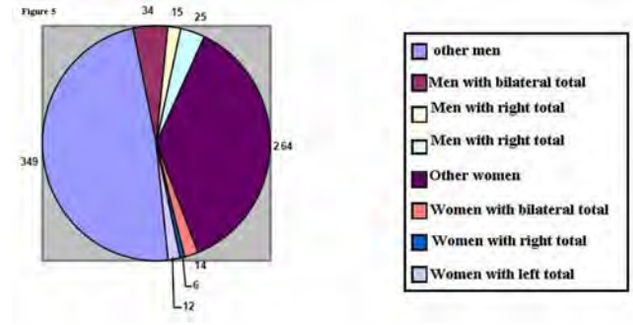


Figure 5. The distribution of the cases according to the gender and foramen type

Results

From total 719 cases, 296 were women (41.2%), 423 were men (58.8%). The age average of the cases was 46.5 (18-99). Bilateral complete foramen was diagnosed in 48 of the cases. 21 cases had one side complete foramen on the right, 37 cases had one side complete foramen on the left. Complete foramen was seen on the right in total 69 cases, and on the left in 85 cases. Complete foramen on the right was determined 1.2 times more. Complete foramen was found in total 106 cases. The presence of complete foramen was calculated as 14.7%.

Among 106 patients with bilateral and one side total arcuate foramen, 74 of them were men (69.8%), 32 of them were women (30.1%). Complete foramen was determined at the rate of 17.4% in men, and 10.8% in women(Table 1). Complete foramen in men was statistically found significantly higher (p<0,02). 68.9% of the patients with one side total arcuate foramen and 70.8% of the patients with bilateral arcuate foramen were men. No statistically significant difference was found in terms of sex in the patients with one side and two side complete foramen (p<0,05).

Table 1. The distribution of total arcuate foramen according to the gender

	Bilateral	Right	Left	Sum
Women	14	6	12	32
Men	34	15	25	74
Sum	48	21	37	106

The presence of bilateral complete foramen corresponded 6.67% of all cases, 2.92% of the cases with one side foramen on the right, and 5.14% of the cases with one side complete foramen on the left. Higher arcuate foramen on the left was statistically found significant (p<0,05). Among 296 women, 14 had bilateral complete foramen, 6 had one side complete foramen on the right, and 12 had one side complete foramen on the left. Among all women, the presence of bilateral complete foramen was found as 4.7%, the presence of one side foramen on the left was found as 2,1%, and the presence of one side foramen on the left was found as 4.1%. Among 423 men, 34 had bilateral, 15 had one side on the right, and 25 had one side complete foramen on the left. Among all men, the presence of bilateral complete foramen was found as 8.1%, the presence one side foramen on the right was found 3.5%, the presence of one side foramen on the left was found as 5.9% .

The average age of all patients was 46.5, the average age of 106 patients with complete foramen on the right and on the left was 46.9, and the average age of the patients with bilateral foramen was 46.9. It was accepted that the prevalence of total arcuate foramen did not show significant difference with the age.

The number of cases with partial foramen on both sides was found as 39 (25 men, 14 women). These numbers corresponded 5.9% of men and 4.7% of women. 88 patients had partial foramen on the right while 91 patients had partial foramen on the left (Figure 4).

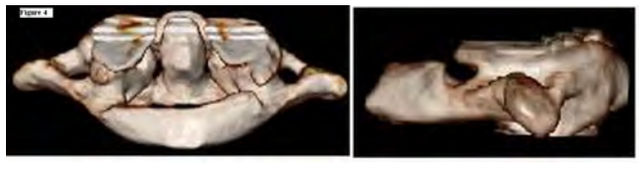


Figure 4. Three-dimension VRT images of partial arcuate foramen. A: Normal sulcus vertebralis on the right, partial arcuate foramen on the left. B: Lateral VRT image of partial arcuate foramen.

19 of the patients with partial foramen on the right (11 men, 8 women), also had complete foramen on the left; 12 of the patients with partial foramen on the left (8 men, 4 women) had complete foramen on the right. 30 (15 men, 15 women) cases, only had partial foramen on the right, 40 (25 men, 15 women) cases only had partial foramen on the left. Total 140 patients had partial foramen (19.5%). 18.9% of women, 19.8% of men had partial foramen. The prevalence of partial foramen did not show any difference with sex. There was no significant difference between the right and the left, either (Table 2).

Table 2. The distribution of partial arcuate foramen according to the gender

	Bilateral	Only right partial	Right partial and left total	Only left partial	Left partial and right total	Sum
Women	14	15	8	15	4	56
Men	25	15	11	25	8	84
Sum	39	30	19	40	12	140

There was no difference in terms of age and sex among the three groups which were created to be analyzed in terms of clinical symptoms. The age average of the first group was calculated as 34.1, the age average of the second group was calculated as 34.1 and the age average of the third group was calculated as 34.4. Each of the three groups involved 10 women, 20 men patients. The age average of these groups was quite lower when compared to the age average of 719 patients. This was because the cases which were excluded from the study due to chronic diseases were older.

Headache complaint was determined in 12 patients (6 women, 6 men) in the first group; 7 patients (4 women, 3 men) in the second group, 8 patients (4 women, 4 men) in the third group. No statistically significant difference was found among the groups although headache complaint was higher in number in the first group (p=0,329).

Among the patients with headache complaint, migraine was diagnosed in 4 patients (2 women, 2 men) patients in the first group, 2 patients (2 women) in the second group, 3 patients (2 women, 1 men) in the third group. The number of patients in whom migraine was diagnosed was also higher when compared to the others in the first group but it was not statistically found significant (p>0,69).

Neck pain was found in 3 men patients in the first group, 1 women patient in the second group, 3 men patients in the third group. No statistically significant difference was found among the groups (p>0,538). The number of the patients with dizziness complaint was 5 (3 men, 2 women) in the first group, 2 (2 men) in the second group, 2 (2 women) in the third group. Dizziness complaint in the group with bilateral foramen was numerically higher when compared to the two groups. However, no statistically significant difference was found (p>0,329). There were 2 (1 women, 1 men) in the first group, 2 (2 men) in the second group, 1 women patient in the third group who occasionally had syncope attacks. There was no significant difference in this group, either (p>0,809).

There was 1 women patient with hearing loss in the first group, and 2 men patients in the second group. None of the patients complained hearing loss in the third group. 2 men patients in the first group, and only one men patient in the third group had tinnitus. No statistically significant difference was found in terms of these symptoms. None of the patients described epileptic attack in three groups.

Discussion

Arcuate foramen is a variation which is randomly found in radiologic examinations made for several clinic conditions, which is not so rare. Patients are usually asymptomatic. The clinic importance of this anatomic variation has not been clearly determined yet and there are a few studies in literature which state that the presence of arcuate foramen can be connected with clinical symptoms such as headaches and neck aches, vertigo, nausea, vomiting, loss of balance, sight, swallowing, and hearing problems.

In literature, there are many different results in relation to arcuate foramen incidence and prevalence in women and men from different countries (Table 3).

Table 3. The incidence of total arcuate foramen on various materials and studies

Study	Materials	Incidence
Pyo, 1959[10]	Radyografi	12.6
Romanus, 1964	Radyografi	14.3
Lamberty, 1973[7]	Kemik spesmenler	15
Lamberty, 1973[7]	Radyografi	7.5
Başoğlu, 1983	Kemik spesmenler	9.5
David M. 1991	Radyografi	13.5
Mitchell, 1998	Kemik spesmenler	9.8
Malas, 1998[8]	Radyografi	2.6
Hasan, 2001	Kemik spesmenler	3.4
Kavaklı,2004[5]	Kemik spesmenler	12.8
Krishnamurthy, 2007	Kemik spesmenler	8.33
Yong Jae Cho, 2009[2]	3D BT	15.5

In our study, we determined complete foramen (right, left and bilateral) at the rate of 14.7%. This result was higher when compared to many studies as in the study by M.A. Malas et al. that the complete foramen was found at the rate of 2.6% while 1000 lateral cervical radiographs were evaluated. According to this study, complete foramen was significantly higher in men, partial foramen was significantly higher in women [8]. Likewise, it was determined in another study which was done in our country by E. Unur et al., complete foramen rate was found as 5.1% in cervical radiographs [13].

The reason why the incidence was lower in these studies when compared to our study was because the studies were done by cervical radiographs. In an autopsy study which was performed in Kenya, this rate was calculated as 14.7%. According to this study, the prevalence of foramen was higher on the right when compared to the left and in women when compared to men [4]. In the study by Kavaklı et al. with bone specimens, total arcuate foramen incidence was found as 12% [5]. Likewise, this rate was 15% in a study in England which was again done with bone specimens. This rate was found only 7.58% in the part of the same study which was done with lateral cervical radiographies [7]. In another study which was done in Greece, the rate of incidence of arcuate foramen was reported as 10.2% in bone specimens [9]. The rate of incidence of arcuate foramen was higher in our study when compared to some studies because it was primarily done with CT. Monitoring the atlanto-occipital region in lateral cervical radiographs can be superimposed by the mastoid bone or malpositioning. Stronger incidence of arcuate foramen in the studies which are done by cervical radiographs can lead to such low results. And, the similar results in the studies which were done by autopsy and bone specimens with our studies show that CT is a more effective method in the assessment of this variation. Hence, in a study which was done by analysing 3-D CT images of 200 patients in Korea, arcuate foramen incidence was found as 15.5% as similar to our study [15].

The presence of complete foramen in our study was statistically found significantly higher in men. The presence of complete foramen was found higher in men in many studies [8, 11, 12]. In another study, it was reported higher in women [4]. And no significant difference was found in terms of age in some studies [13,10, 8].

The association of the presence of partial foramen with gender was not found statistically significant in our study. However, the presence of partial foramen was reported as significantly higher in women in a study in literature [12].

The prevalence of partial foramen is in a quite wide interval in literature. In our study, we found this rate as 19.5%. In a study in Chile which was performed with cervical radiographies which contained asymptomatic cases, partial foramen incidence was reported as 10.1% [11]. And, in the study with cervical lateral radiographs by Çakmak et al.., partial foramen was observed at the rate of 6.2% [6].

In the study by Kavaklı et al. which was done with bone specimens, this rate was 9.3% [5]. In the study by Lamberty and Zivanovic which was also done with bone specimens, partial foramen rate was found as 21.6% [7]. In a study in Greece which was done with bone specimens, this rate was reported as 24.4% [9]. Wright et al. reported an important correlation between arcuate foramen and non-aura migraine. The purpose of this study is to research the prevalence of arcuate foramen in persons with migraine and cervicogenic headache and compare it with the group without headache. The study involved the patients who applied to the chiropractic clinic for the first time and whose cervical radiographs; the patients were divided into categories which are namely those with aura migraine, non-aura migraine, cervicogenic headache and only headache complaint. As a result, although arcuate foramen incidence was found numerically higher in patients with aura migraine and non-aura migraine and patients with cervicogenic headache, this difference was statistically found higher only in patients with non-aura migraine [13].

In our study, most of the symptoms (headache, syncope, vertigo) were particularly found numerically higher in patients with bilateral complete foramen, this difference was not statistically found significant. This result may have been because our study group involved a few patients. This difference can be statistically found significant in the studies which will be done with more patients within a long time.

Total arcuate foramen was found in 5 of the 8 epileptic patients which were randomly included in the study by Wright et al. which were done with the patients who applied to chiropractic clinic. This incidental result was interpreted as there might be a connection between arcuate foramen and epilepsy. However, there were no patients who described epilepsy in our study groups.

The age average of our patient group decreased because the

patients who were excluded due to chronic diseases were elder. Having younger patients might also have led to significant difference in the complaints of the patients with and without arcuate foramen. Degenerative skeleton changes and atherosclerosis which emerge upon ageing might increase the symptoms which are caused by arcuate foramen.

In the study by Wright et al. in which arcuate foramen incidence was reported as significantly higher in non-aura migraine patients, the age average of the patient group was found as 46 [14]. In this study, the higher age average of the patients when compared to our study might have increased the incidence of clinical symptoms.

A similar study by Çakmak et al. scrutinized the association between the presence of arcuate foramen and clinical symptoms such as headache, dizziness, lacrimation, shoulder, arm and neck pain. In this study, the patients with complete foramen were compared to the patients with partial foramen. All symptoms excluding lacrimation were found significantly higher in patients with complete foramen [6]. This study involved patients between 29 and 79 years old and the age average was reported as 49.5. The higher age average of the patients in this study when compared to our study might also have increased the incidence of clinical symptoms.

Neither study by Wright et al. nor the study by Çakmak et al. included any information indicating that the patients with degenerative – osteophyte changes in the cervical area were excluded from the study. The exclusion of these patients from our study group can also explain the reason why the symptoms were lower when compared to these studies. In a study which was done in Chile and researched arcuate foramen incidence in asymptomatic patients, the age average was reported as 18.4 [11]. Total arcuate foramen incidence was found as 9.2%, partial arcuate foramen incidence was found as 10.1% in these patients. That this patient group consists of younger patients can also support the fact that the incidence of arcuate foramen related symptoms increased along with the changes that emerge upon ageing.

Moreover, retrospective study and the impossibility of face-to-face interview with the patients also limited our study. As a result, arcuate foramen is a variation whose incidence is reported at varying rates in literature, which is associated with many different symptoms and is not rare.

Conclusions

The association of this variation with clinical symptoms has not been clearly set before. The possible association between the clinical symptoms and the variation should be researched more comprehensively. Even though its association with the symptoms has not been proven indeed, it is obvious that the presence of this variation should be known at the phase of planning the operations concerning craniovertebral junction.

In the posterior approach for craniovertebral junction, knowing the presence of foramen in advance during lateral dissection and C1 laminectomy or other stabilization procedures such as screwing of the lateral mass of the atlas will reduce the risk of vertebral artery injury.

Competing interests

The authors declare that they have no competing interests.

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The Effect of Working Conditions to the Health Status in Taxi and Bus Drivers in Çanakkale, Turkey; Community Based Study

Taksi ve Otobüs Şoförlerinin Çalışma Koşullarının Sağlık Durumlarına Etkisi, Çanakkale; Toplum Tabanlı Çalışma

Şoförlerin Çalışma Koşullarının Sağlık Durumlarına Etkisi / Working Conditions to the Health Status in Drivers

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Özet

Amaç: Taksi ve otobüs şoförlerinin artan iş yükü kötü sağlık durumuna, obezite, hipertansiyon, metabolik sendrom ile birlikte artan kardiyovasküler hastalık riskine neden olmaktadır. Bu çalışmada taksi ve otobüs şoförlerinde çalışma koşulları ile sağlık durumlarının arasındaki ilişkinin belirlenmesi amaçlanmıştır. Gereç ve Yöntem: Bu çalışma tanımlayıcı bir çalışmadır. Çalışmanın evrenini Çanakkale il merkezindeki taksi ve otobüs şoförleri oluşturdu. Çanakkale Şoförler ve Otomobilciler Esnaf Odasına bağlı toplam 250 taksi ve otobüs şoförü bulunmaktaydı. Çalışmada 70 taksi şoförü ve 93 otobüs şoförüne ulaşıldı. Katılımcılar çalıştıkları yerde ziyaret edildi. Sosyo-demografik özellikleri, alışkanlıkları ve çalışma koşullarını sorgulayan anket uygulandı. Kan basıncı, bel-kalça ölçümleri ve herhangi bir zamanda kapiller kan şekerlerine bakıldı. Bulgular: Toplam 163 erkek çalışmaya alındı. Dokuz (%12,9) taksi şoförü ve 6 (%6,5) otobüs şoförü hipertansifti ve 1 taksi şoförü ve 2 otobüs şoförünün random kapiller glukoz seviyesi 200 mg/dl. den yüksekti. Hipertansiyonun prevalansı %9,2, diabetes mellitusun %1,8 ve obezitenin %49,4'dü. Tartışma: Şoförler stres ve immobil olmak gibi birçok KVH riskine sahiptirler. Çalışmamızda Çanakkale'de şoförlerin sosyo-demografik ve çalışma koşulları hipertansiyon, diabetes mellitus ve obezite oluşumundaki risk faktörlerini açıklamakta sınırlı kalmıştır. Çalışma büyükşehirlerde yapılmalıdır. Bu açıdan şoförler kendi yerleşim yerleri ve çalışma koşullarında değerlendirilmelidir.

Anahtar Kelimeler

Şoförler; Çalışma Koşulları; Sağlık Durumları

Abstract

Aim: The growing taxi and bus driver workforce is at risk for poor health status, obesity, hypertension, metabolic syndrome and with increased risk for cardiovascular disease. We aimed to determine the relationship between working conditions and health status in taxi and bus drivers. Material and Method: This study is a descriptive study. The population of the study was taxi and bus drivers in central of Çanakkale. There were total 250 taxi and bus drivers who registered in The Chamber of Çanakkale Drivers and Vehicle. We reached the 70 taxi drivers and 93 bus drivers. The participants were visited at their workplace. We performed the questionnaire that include the socio-demografic features, habits, the working conditions. We evaluated the blood pressure, waist-hip measurements and capillary blood glucose at any time. Results: Total of the 163 men drivers were enrolled the study. Nine (12.9%) taxi drivers and 6 (6.5%) bus drivers were hipertensive, and 1 taxi driver and 2 bus drivers with random capillary blood glucose levels higher than 200 mg. The prevalence of hypertension was 9.2%, diabetes mellitus was 1.8, obesity was 49.4%. Discussion: Drivers have many risk factors for CVD like stress and immobility. In our study, the socio-demografic and working conditions are limited for explaining the risk for hipertension, diabetes mellitus and obesity in drivers in Çanakkale. These study have to be done in metropolitan cities. In this aspect, the drivers can be evaluated in their own living spaces and working conditions.

Keywords

Drivers; Working Conditions; Health Status

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Introduction

Recently, death from cardiovascular disease is in the first place in the world. The policy makers maintained the reduction of cardiovasculary risk in the population as a strategy of the health management. The American Heart Academi (AHA) as set an ambitious national goal to achieve by the year 2020: to improve the cardiovascular health of all Americans by 20%, while reducing deaths from CVD and stroke by 20% [1]. This goal is aimed both primary and secondary prevention from the cardiovasculary death. Hyperlipidemia, increasing blood pressure, smoking, unhealthy diet and sedantary lifestyle are the changeable of cardiovasculary disease.

Taxi and bus drivers labor burden is increasing with growing population in the world. Working condition are different and defined as increased risk for CVDs. The drivers have irregular working conditions. The severity of work is so different even during the day. Their job is stressfull and working time is usually unclear. Hours of sleep, varying meal times due to working shifts and with constantly living and traffic related obligations are some of the reasons for the CVDs. On the other hand, these conditions are also the risk factors of hipertension, diabetes mellitus and metabolic syndrome and also CVDs [2,3]. Drivers are considered to be involved risk for myocardial infarction in Europe last 60 years. Bigert et al. [4] found the myocaridal infarction risk increased 1.66 in truck drivers, among taxi drivers 1.88 and in bus drivers was 2.14. This risk was related with the duration of work and social factors. The environment factors were defined as the other related factors for myocardial infarction.

We aimed to determine the effect of working conditions to health status in taxi and bus drivers.

Material and Methods: This study is a descriptive study. The population of the study was taxi and bus drivers in central of Çanakkale. There were total of the 250 drivers who registered in The Chamber of Çanakkale Drivers and Vehicle in March 2015. We calculate the sample size 152 drivers with confidence level 95% and confidence interval 5%. We reached the 70 taxi drivers and 93 bus drivers in the study.

The drivers were visited at their workplace. We performed the questionnaire that includes the socio-demografic features, habits, the working conditions. We evaluated the blood pressure in both arms, waist-hip measurements and capillary blood glucose at any time.

Measurements

Questionnaire: The questionnaire form was included, the socio-demographic (age, gender, marital status, education, income level, having any chronic disease), habits (smoking, alcohol), working conditions variables (data about driven car, duration time as driver, hour of driving, kilometers, sleeping time).

Anthropometric Measurements: The anthropometric measurement of driver's weight was measured standing with shoes off using a Standing Height Meter. Weight measurements used a calibrated digital scale. The digital scale with sensitivity 0.01 kg was placed on the floor during measurements and drivers removed shoes and any other weight, and stood with weight equally distributed on both feet. Waist and hip circumference measurements were taken with a non-elastic measuring tape. Waist circumference measurement was taken with a measuring tape midway between the lower rib and the iliac bone on the right with stomach free. Hip measurement was taken with standing straight at the highest point of the hip with a measuring tape. Measurements were completed with sensitivity of 0.01 cm.

Blood Pressure: Blood pressure of the drivers was measured both arms according to the guideline of Turkish Society of Cardiology. The mean of the blood pressure was taken for evaluation.

Capillary Blood Glucose Level: We used the capillary blood glucose strip.

Permissions and Consent: This study received permission from the Çanakkale Onsekiz Mart University Ethics Committee. The researchers get both orally and written permission from the drivers.

Statistics: We used the descriptive tests for the socio-demografic variables. Kolmogorov–Smirnov test revealed that not all variables were normally distributed. We used the Mann Whitney-u Test for non-parametric variables. We therefore used Kendall tau_b correlation coefficients (rho) for assessing the correlation between the health conditions parameters and working conditions. We examined the relation between the socio-demografic, working condition variables with the measurements in Multivariable Linear Regression Backward Model. $p<0.05$ is statistically significant.

Results

There were 70 taxi drivers and 93 bus drivers. The mean age of the taxi drivers was 41.2±11.7 [24-68] and bus drivers 42.4±9.6 [24-61] years. The mean of the working year as bus driver was 17.8± 8.9 year [2-42] and 16.5±10.4 [2-43] year as taxi driver. Socio-demographic features and working conditions of drivers are given in Table 1.

Of the 70 taxi drivers 55.6% and 27.5% of bus drivers had 2 days off. Of the 70 taxi drivers 54.3% work only during day, 10.0% work only nights, 25.7% work day and night. Of the 93 bus drivers 39.9% work during day, 5.4% work only nights, 54.7% work day and night.

Nine (12.9%) taxi drivers and 6 (6.5%) bus drivers were hipertensive. There was no statistical significant between them (chi-square2 =1.961;p=0.161). There were 1 taxi driver and 2 bus driver with random capillary blood glucose levels higher than 200 mg. In this study, based on the ATP III criteria, the prevalence of Metabolic Syndrom was found 9.6%. Of the 8 (11.4%) taxi drivers and 8 (8.6%) bus drivers were met the criteria of ATP III (chi-square2 =0.360;p=0.548). Fifty one drivers were (31.5%) overweight and 80 (49.4%) drivers were obese. There was only statistical significant relationship between smoking and DM (chi-square2 =10.762;p=0.005). Diabetics were much current smoker. There was no significant relation between alcohol consumption and the other factors.

Metabolic Syndrome and working hours was statistical significant (u=750; p=0.015). MetS patients had 11,0±1.3 hours/day with higher working hours. There was statistical significant between obesity and age (u=2720;p=0.028). Mean age of the obese drivers was 43.6±10.6 years with higher than non-obese. In study, there was no statistical relation with blood pressure, socio-demografic and working condition variables. Capillary blood glucose levels and weight were relation with kilometers

Table 1. Socio-Demografic Features and Working Conditions of Drivers

	Taxi Drivers mean±SD	Bus Drivers mean±SD	Statistical test	p
Age	41.2±11.7 [24-68]	42.4±9.6 [24-61]	chi-square2= 64.284	<0.05
Education				
Primary school	23(32.9%)	65(69.9%)	chi-square2= 23,762	<0.05
High school	34 (48.6%)	24 (25.8%)		
University	13(18.6%)	4(4.3%)		
Marital status				
Single	19 (27.2%)	20 (21.5%)	u=3139.5	>0.05
Married	51 (72.8%)	73 (78.5%)		
Smoking				
smoking	30 (42.9%)	63 (67.7%)	chi-square2= 10,170	<0.05
Non-smoking	40 (47.1%)	30 (33.3%)		
Alcohol				
Yes	47(67.1%)	64(68.8%)	chi-square2= 2.247	<0.05
No	23(32.9%)	29(31.2%)		
Driver year	16.5±10.4 [2-43]	17.8±8.9 [2-42]	chi-square2= 34.266	>0.05
History of Chronic Disease	32 (45.7%)	35 (37.6%)	chi-square2= 1.077	>0.05
Hour of working as driver (hour/day)	10.5±2.5 [3-15]	9.1±2.5 [2-15]	chi-square2= 27,547	<0.05
Hour of driving	5.8 ±2.9 [1-12]	6.8±2.8 [1-14]	chi-square2= 107,162	<0.05
Kilometers (km/day)	64.7±33.3 [10-200]	186.0 ±117,5 [10-1000]	chi-square2= 24,197	<0.05
Sleeping hours/day	6.7±1.6 [4-12]	7.5±1.5 [4-12]	t=-3.022	<0.05
Sistolic Blood Pressure (mmHg.)	135.3±14.5 [100-182]	128.8±11.7 [101-159]	t=3.176	<0.05
Diastolic Blood Pressure (mmHg.)	80.2±10.9 [55-110]	78.9±8.7 [53-100]	t=0.836	>0.05
Waist circumference (cm)	102.5±11.6 [76-143]	104.4±12.8 [75-142]	t=-0.964	>0.05
Capillary Blood Glucose (mg/dl)	117.7±27.8 [75-205]	123.1±38.8[70-409]	t=-0.993	>0.05

chi-square2 ; chi-square test, t; independent t test, u; Mann Whitney u test

driven in day. The relation with variables are shown in Table 2. In the multivariable Linear Regression Backward Model, we examined the relation between the socio-demografic, working condition variables with the measurements. According to this model; the sistolic, diastolic blood pressure, weight, waist circumference were not significant relation with the variables written above. But the capillary blood glucose level was relation with the the age, being married and driven old car. The relation of them were shown in Table 3.

Table 2. The relationship with socio-demographic and measuring variables

Blood glucose level	r*	p
Waist circumference	0.151	0.005
Weight	0.137	0.011
Waist circumference (cm)		
Blood glucose level	0.151	0.005
Weight	0.444	0.000
Kilometers (km/day)	0.122	0.029

*Kendall tau-b correlation p<0,05

Discussion

In this study, we determined the effect of working conditions to health status in taxi and bus drivers. The prevelance of DM, MetS and HT in drivers was lower than population, overweight and obesity prevalence was higher, 31.5% and 49.4% respectively. MetS patients had 11.0±1.3 hours/day with higher working hours. Increased capillary blood glucose levels depended to age, being maried and driven old car. In our study, the socio-demografic and working conditions are limited for explaining the risk for hipertension, diabetes mellitus, MetS and also the cardiovascular disease risk in drivers.

Hypertension is one of the most important risk factors for stroke, coronary heart disease, and renal disease and be considered that will effect the 29.2% of whole population in the world [5-7]. The prevalence rates of hypertension and diabetes mellitus in drivers was 18.2% and 8.8% in China; and 42.9% and 7.7% in Iran [8,9], respectively. The mostly age of drivers was 30-50 in China and 36.6 ± 10.7 (21-73) years in Iran. In Turkey, 11% in men and 16% in women is hypertensive between the 20-61 years old [10]. In our study, the mean age of the drivers was 41.2±11.7 [24-68], the prevalance of hypertension was 9.2% and diabetes mellitus was 1.8%. In Çanakkale, the prevelance of hipertension and DM is lower in drivers than the other countries. The drivers experience may decrease physical activity, hard work, job stress, and a disruption in normal sleep and waking patterns, which might explain the higher prevalence of hypertension and DM. These factors are varying in each country and cities. Working conditions are affected by the population of the city. In Çanakkale the population of the center of study is 120.000. In our detailed analyzing, none of the variables that specified did not effect the hypertension and DM in study.

Table 3. The relation between the capillary blood glucose level in the Multivariable Linear Regression Backward Model

	Blood Glucose Level			
	β	p*	Lower Bound	Upper Bound
Constant	-89,032	.129	-206,283	28.220
Age	2,899	.008	0,892	4.966
Marital status	24,624	.011	-6.197	43,051
1=single				
2=married				
Duration as driver (year)	0,014	.080	-0.002	0.029
Driven old car	19,364	.035	-1.548	37,180
1=yes				
2=no				
Driver	-15,413	.213	-40.399	9.593
1=Taxi driver				
2=Bus driver				

adjusted r2=0.443
*p<0.05 is significant

The drivers have sedantary life style all day. The physical activity is limited. In Italy, 61% of the truck drivers were obese and overweight. The researchers declared that the traveling more than 40,000 miles per year and hours spent behind the wheel per day increase the risk of obesity [11]. In Poland; 45.3% had overweight and 17.4% were diagnosed with obesity and in Saudi Arabia 73.2% of the drivers were obese [12,13]. In Turkey; obesity prevelance is 20.6% and overweight was 41.5% in males [14]. Obesity is increased the cardiovasculary risk. In our study, the prevelance of obesity and overweight were 31.5% and 49.4% respectively. They did not related with any social or work related factors in our study. The working conditions, sedantary lifestyle and diet features effect the obesity and overweight.

Metabolic Syndrome have a risk factor for about 25% of the new cases of cardiovascular diseases [14]. Cavagioni et al. [15] declared that the MetS prevelance in drivers was 24% and it correlates with the Framingam Risk Score in Portugal. In Turkey, the MetS prevalence is 10.7% in 20-29 years old, 23.9% in 30-39 years old, 36.7% in 40-49 years old, 41.1% in 50-59 years old and in total prevelance is 33.9% in males [16]. In our study, the prevelance of MetS was 9.6% with lower than the general population. In this study, we can not evaluate the driver according the all ATP III criterias. We could examine only the waist circumference, blood pressure and random blood glucose levels. The other criterias including trigliserid and HDL-C levels could not able to evaluate for diagnosing MetS. One of the diagnostic criteria of the MetS is capillary blood glucose levels. Capillary blood glucose was increasing with age, being married and driven old car. So many older drivers were married in this study. Older drivers had increasing blood glucose. Usage old car is stressfull event because of crashing.

In Sweden, job strain, smoking, overweight and low phsical activity was higher in drivers than the general population [4]. There had been developed many instruments for measuring the drivers stress. One of them is occupational stress. Occupational stress is defined as ongoing stress that is related to the work and workplace. In Serbia, total elevated occupational stress risk was related with hipertension, and dislipidemia [17,18].

There had been done many studies for increasing the awareness about cardiyovasculary disease. Giving education to the drivers about cardiyovasculary disease had been found effectively [19,20].

Conclusion

Drivers have many risk factors for CVD like stress and immobility. In our study, the socio-demografic and working conditions are limited for explaining the risk for hipertension, diabetes mellitus and obesity in drivers in Çanakkale. These study have to be done in metropolitan cities. In this aspect, the drivers can be evaluated in their own living spaces and working conditions.

Limitations

Limitations of the study;

-This study is descriptive study and data collected in the area. So we could not able to get the laboratuary test including lipids and we could not able to evaluate all of the cardiovasculary risk, eg. measurements of LDL, HDL, Trigliserid, fasting blood glucose.

-There are many tools for evaluating the cardiovasculary risk like Framingam risk score. But in our study we could not use these assesment tools for not providing financial support.

-In Çanakkale all of the drivers were male so we could not able to enroll the female drivers in study.

Competing interests

The authors declare that they have no competing interests.

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Do Different Stimulation Protocols Effect Oocyte Quality and IVF Outcomes in IVF–ET?

Farklı Stimülasyon Protokolleri IVF-ET'de Oosit Kalitesi ve IVF Sonuçlarını Etkiler mi?

Stimülasyon Protokollerinin IVF Sonuçlarına Etkisi / The Effect of Stimulation Protocols on IVF

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Özet

Amaç: Bu çalışma IVF-ET' de hMG ve uFSH protokollerinin oosit maturasyonu ve IVF sonuçlarına etkisini araştırmak amacıyla planlanmıştır. Gereç ve Yöntem: Ankara Üniversitesi Kadın Hastalıkları ve Doğum Kliniğinde IVF bölümüne başvuran 82 hasta çalışmaya alındı. Bütün hastalara uzun protokol GnRHa uygulandı. Ovulasyon indüksiyonu için 59 hasta hMG (grup:1), 23 hasta uFSH (grup:2) kullandı. Maksimum follikül çapı, dominant follikül sayısı, hCG günü endometrium kalınlığı, tedavi süresi, kullanılan gonadotropin miktarı, aspire edilen oosit sayısı ve kalitesi, fertilizasyon oranı, elde edilen embriyo sayı ve kalitesi, transfer edilen embriyo ve siklus başına ve transfer başına gebelik oranlan kaydedildi. Bulgular: Maksimum follikül çapı, dominant follikül sayısı, immature oocyte sayısı hMG alan grupta uFSH grubundan anlamlı olarak fazla bulundu(p<0.05). Diğer parametreler açısından iki grup arasında istatistiksel anlamlı farklılık saptanmadı. Siklus başına gebelik oranı grup 1 ve 2 de sırasıyla % 27.1, % 34.8 idi (p>0.05). Tartışma: Çalışmamızda klinik gebelik oranları açısından hMG veya uFSH kullanan gruplar arasında anlamlı farklılık saptanmamıştır. Gelişmekte olan ülkelerde ovulasyon stimülasyon preparatları hasta özellikleri ve maliyet dikkate alınarak seçilmelidir.

Anahtar Kelimeler

İn Vitro Fertilizasyon; İnsan Menopozal Gonadotropin; İdrar Kökenli Folikül Stimulan Hormon

Abstract

Aim: This study was planned to compare the effect of different stimulation protocols (hMG and uFSH) on oocyte maturation and in vitro fertilization outcomes. Material and Method: Eighty-two patients admitted Ankara University Obstetrics and Gynecology Clinic- IVF Department were included in this retrospective study. All patients used long GnRH agonist protocol. Fifty-nine patients used human menopausal gonadotropin (hMG) (Group 1) and 23 patients used urine derived follicle-stimulating hormone (uFSH) (Group 2) for ovulation induction. Maximum follicle diameter, dominant follicle number, endometrial thickness at human chorionic gonadotropin day, duration of induction, dose of gonadotropin, oocyte number and quality, fertilization rate, embryo number and quality, pregnancy rate per cycles and transfer were reported. Results: Maximum follicle diameter, dominant follicle number, immature oocyte number were significantly higher in hMG group vs. uFSH group (p<0.05). For the other parameters, there were no significant differences between the groups. Pregnancy rate per cycles were 27.1%, 34.8% in Group 1 vs. 2 respectively (p>0.05). Discussion: Clinical pregnancy rate was not significantly different in hMG vs. uFSH group. In developing countries, ovarian stimulation agents should be chosen based on patient characteristics and cost.

Keywords

In Vitro Fertilization; Human Menopausal Gonadotropin; Urine Derived Follicle-Stimulating Hormone

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Introduction

The first in vitro fertilization (IVF) cycles were put into practice in natural cycles [1]. The quality of oocytes and developing preembryos is one of the most important factors determining the success of an IVF treatment. In order to improve the efficacy of the treatment, either more embryos at a time will be transferred or a well-established stimulation protocol and embryo-selection procedure with lower number of transferred embryos is practiced. As ovarian stimulation protocol is one of the eligible factors during an IVF treatment, its embryo quality influencing effects are necessary to know. Controlled ovarian hyperstimulation (COH) has been used to generate multiple follicular growth to obtain an increased quantity of oocytes and a higher pregnancy rates. Different drug protocols have been used, such as clomiphene citrate, human menopausal gonadotropins (hMG), urine derived follicle-stimulating hormone (uFSH), recombinant FSH (rFSH) and LH (Luteinizing hormone). During ovarian stimulation gonadotrophin-releasing hormone (GnRH) analogues are co-administered in order to prevent premature LH surges. Although GnRH antagonist protocols are in common use, standard long protocol GnRH agonist regimen is a well-established strategy for COH. In such a protocol, GnRH agonist administration is primarily followed by 'gonadotropin' with FSH or hMG.

Because of the detrimental effects of high LH activity present in hMG on follicle and oocyte maturation, purified, highly purified and recombinant FSH are in use.

Assisted reproductive techniques are expensive. The costs of medication are especially important for developing countries. Hormonal stimulation covered the main part of the costs per cycle due to the relatively high cost of recombinant technology. Our aim is to test the clinical efficiency of cheaper medications in terms of hMG and FSH.

Material and Method

This study was conducted at Ankara University Obstetrics and Gynecology Clinic- IVF Department with 82 patients. The study protocol was approved by the institutional review board. We included all our first IVF cycles. Control and study groups were similar with regard to infertility etiology (Tubal factor, endometriosis, male infertility and unexplained infertility). Exclusion criteria were advanced age and repeated implantation failure.

Patients received long term down-regulation with GnRH agonist and controlled ovarian hyperstimulation with 150-300IU/day hMG (n=59) or 150-300IU/day uFSH (n=23).

Oocyte retrieval was performed 35–36 h after the hCG injection by transvaginal ultrasound-guided double lumen needle aspiration. ICSI was performed only in cases with severe male factor or previous fertilization failure. Ultrasound guidance was used for all embryo transfers, which were performed 2 or 3 days post-oocyte retrieval, Day 2 and Day 3 embryo transfers were equally distributed in the two groups. Luteal phase support with intravaginal progesterone and intramuscular hCG was initiated after oocyte retrieval.

The primary outcome measure was oocyte maturity and clinical pregnancy. Clinical pregnancy was defined as the presence of gestational sac with fetal heart beat detection at 6–7 weeks of gestation. Secondary outcome measures were duration of stimulation, total dose of ampules, endometrial thickness on day of hCG administration, maximum diameter of dominant follicles, number of dominant follicles, oocyte retrieved and embryos, and fertilization rates.

Student-t test, chi-square test, Mann Whitney U test were used for statistical analysis. Statistical significance was accepted when $p < 0.05$.

Results

Baseline characteristics and clinical and laboratory outcomes of the patients analyzed are shown in Table 1, Table 2 shows oocyte maturation characteristics. No significant differences were observed between the two groups regarding baseline characteristics (age, infertility duration). Control and study groups were similar with regard to infertility etiology (Tubal factor, endometriosis, male infertility and unexplained infertility).

Table 1. Clinical and laboratory parameters

	Group 1 (hMG)	Group 2 (FSH)	p
	n: 59	n:23	
Age	33.1 ± 5.3	34.3 ± 4.6	> 0.05
Infertility duration (years)	8.1 ± 5.5	8.5 ±4.6	> 0.05
Stimulation day	10.7 ± 2.3	10.3 ± 2.4	> 0.05
Number of ampoules	36.9 ± 13.3	38.0± 16.7	> 0.05
Endometrial thickness (mm)	9.7± 1.9	9.3 ± 2.2	> 0.05
Max. follicle diameter	20.0 ± 2.9	17.9 ± 2.6	< 0.05
Number of dominant follicle	5.1 ± 2.6	3.3 ± 2.4	< 0.05
Number of retrieved oocyte	8.6 ± 5.8	10.2 ± 7.1	> 0.05
Fertilization rate (%)	49.2	43.1	> 0.05
Abnormal fertilization	2.68	1.96	> 0.05
Number of embryos	4.1±3.7	4.1 ± 4.8	> 0.05
Number of transferred embryos	2.7± 1.6	2.5±1.7	> 0.05
Pregnancy rate (%)	27.1	34.8	> 0.05

Table 2. Oocyte maturity in two groups

	Immature	Intermediate	Mature	Post-mature
Group 1	% 4.34	% 33.75	% 53.02	% 8.87
Group 2	% 0.56	% 32.85	% 59.56	% 6.46
p	< 0.05	>0.05	>0.05	>0.05

No significant differences were found between the two groups in stimulation duration, total dose of ampoules, endometrial thickness on day of hCG administration, number of retrieved oocytes, fertilization rate, number of embryos and number of transferred embryos ($p>0.05$). Maximum follicle diameter was 20.0 ± 2.9 mm in group 1, and 17.9 ± 2.6 mm in group 2. Maximum follicle diameter, dominant follicle number, immature oocyte number were significantly higher in hMG group vs. uFSH group ($p<0.05$). Immature oocyte ratio was 4.34% and 0.56%, in both groups, respectively ($p<0.05$). Table 3 and 4 summarizes the grading of embryos. We found no difference between the groups. Pregnancy rate per cycles were 27.1%, 34.8% in Group 1 vs. 2, respectively ($p>0.05$).

Discussion

The clinical impact of different stimulation protocols, analysis of ovarian stimulation on quality of oocytes and developing

Table 3. Embryo quality in two groups

	2 pn	gr 1	gr 2	gr3	gr 4
Group 1 (%)	9.56	49.62	27.16	6.89	6.74
Group 2 (%)	7.91	33.82	39.57	10.14	
p	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

pn:Pronucleus;
gr: grade

Table 4. Transferred embryo quality in two groups

	2 pn	gr 1	gr 2	gr 3	gr 4
Group 1(%)	8.84	55.93	24	5.15	6.06
Group 2(%)	5	43.33	40	6.66	5
p	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

embryos has been studied.

A number of studies have shown that increased concentrations of LH during the follicular phase of the menstrual cycle may be associated with reduced rates of fertilization and implantation and increased miscarriage rates [2]. Especially for the patients with PCOS with high levels of LH, there are studies comparing FSH and hMG [3, 4] Westergaard et al. [5] found no detrimental effect of the LH activity of HMG on the clinical outcome of FVF in GnRHa down-regulated normogonadotrophic women.

In the present study, we compared the effect of different stimulation protocols (hMG and FSH) on oocyte maturation and in vitro fertilization outcomes. We found significantly higher maximum follicle diameter, dominant follicle number, immature oocyte number in hMG group compared with FSH group.

Placido et al [6] revealed a significant increase in the number of oocytes in patients with ovarian steady response who received rLH in the course of ovarian stimulation, when compared with those undergoing an increase in rFSH dose. Bjercke et al [7] tested the clinical efficiency of recombinant FSH and highly purified human menotrophin in terms of pregnancy and live birth rates during the first treatment cycle of IVF or ICSI. In the study of Bjercke et al [7] similar pregnancy and live birth rates were observed with hMG and rFSH. Compared to hMG, treatment cycles with rFSH were characterized by significantly shorter stimulation, lower gonadotrophin consumption, and increased number of oocytes and embryos. Andersen et al [8] revealed that superiority of highly purified-hMG over recombinant FSH in ongoing pregnancy rate could not be concluded.

We also found no significant differences between the two groups in stimulation duration, total dose of ampoules. Our results are in agreement with the other studies [9].

Van Wely et al [10] made a review of studies comparing recombinant gonadotrophin with urinary gonadotrophins (hMG, purified FSH, highly purified FSH) for ovarian hyperstimulation in IVF and ICSI cycles and revealed that live births are similar irrespective of the gonadotrophin used.

Kumbak et al[11] found recombinant LH supplementation in agonist long ART cycles to have a detrimental effect on the oocyte quality, without a beneficial or adverse effect on the embryo quality in normoresponder women <40 years. They also stated that inclusion of rLH during stimulation in antagonist ART cycles, on the other hand, is neither favourable nor deleterious for the oocyte or the embryo quality in normoresponder women <40 years.

As a conclusion, although we had a limited number of patients, clinical pregnancy rate was not significantly different in hMG vs. FSH group. Parallel with Cochrane review [10], based on our results any type of gonadotrophin can be chosen depending on the situations eg. cost, patient characteristics. Larger studies are needed to clarify our results.

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Competing interests

The authors declare that they have no competing interests.

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Relationship Between Second to Fourth Digit Ratios and Obesity, Muscle Mass

2.ve 4. Parmak Oranının Obezite ve Kas Kitlesi ile İlişkisi

2D:4D Obezite ve Kas Kitlesi ile İlişkisi / 2D:4D Relationship Obesity, Muscle Mass

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Özet

Amaç: Genetik geçişle aktarılan ve sonra değişmeyen 2.ve 4.parmak oranı (2D:4D), oranı testesterone hormonu ile alakadardır. Bizde bu oranın kas kitlesi ve obesite olan ilişkisini incelemeyi amaçladık. Gereç ve Yöntem: Diyet polikliniğine gelen yetişkin hastalar hastaların vücut tipi analizi, yaşı ve cinsiyeti kategorize edildi. Boy, kilo, BMI(Body mass Index) hesaplanarak Tanita (TANITA BC-418 MA III) cihazıyla vücut analizleri yapıldı. Ayrıca bu hastaların dijital kumpas aracılığıyla her iki elinin işaret ve yüzük parmakları ayrı ayrı ölçülerek kayıt edildi. Ölçülen değerlerin birbirine oranları belirlenerek Tanita cihazıyla elde edilen değerlerle karşılaştırma yapıldı. Bulgular: Diyet polikliniğine gelen 216 hastanın 168'i kadın 48 ise erkek idi. Her iki el 2d/4d oranı 1 ve üzeri olan kişilerle 1 'in altında olan kişilerin yapılan ölçümleri karşılaştırıldı. TF(Total Fat), FFM(Fat Free Mass), FM(Fat Mass)ler açısında olarak fark gözlendi. Her iki elin 2d/4d oranlarının ölçümü ile BMI, FM, ve TF ile pozitif yönde korelasyon olduğu görülürken, FFM ile negatif yönde korelasyon gözlenmiştir. Tartışma: 2D:4D parmak oranın obezite ile doğru orantılı vucut kas kitlesi ters orantılı olabileceğini düşünmekteyiz

Anahtar Kelimeler

2.Parmak; 4.Parmak; Oran; Obezite; Kas

Abstract

Aim: Transmitted through genetic inheritance and later unchanging, the ratio of 2nd and 4th fingers (2D:4D) is related to the hormone testosterone. We aimed to investigate the correlation of this ratio to muscle mass and obesity. Material and Method: Adult patients attending the diet clinic were categorized by body type analysis, age and gender. Body mass index (BMI) was calculated from height and weight, and body analysis was completed with a Tanita (TANITA BC-418 MA III) device. Additionally patients had the index and ring fingers of both hands separately measured with the aid of digital calipers and recorded. The ratio of the values was determined and compared with the values obtained by the Tanita device. Result: Of 216 patients at the diet clinic, 168 were female and 48 were male. The measurements of individuals with 2D:4D of both hands above 1 were compared with those of individuals with 2D:4D of both hands below 1. Differences were observed in terms of total fat (TF), fat free mass (FFM) and fat mass (FM). While there was a positive correlation of the 2D:4D of both hands with BMI, FM and TF; there was a negative correlation observed with FFM. Discussion: We believe the 2D:4D may be directly related to obesity and inversely related to body muscle mass.

Keywords

2D; 4D; Oran; Obesity; Muscle

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Introduction

Obesity results from the body's intake of energy from nutrients being greater than the energy expended and is a chronic disease characterized by fat mass of the body increasing in proportion to the fat-free body mass [1]. Obesity has become a global public health problem. Worldwide, the proportion of adults with a body mass index (BMI) of 25 kg/m2 or greater increased from 28.8% to 36.9% in men, and from 29.8% to 38.0% in women between 1980 and 2013 [2]. In parallel with the world in general, obesity is a significant public health problem in our country. As a result there is a need for governments to create emergency action plans to reduce this epidemic and for the food industry [3]. Studies on the genetics of obesity have generally been performed on twins, as it was considered that the body mass index (BMI) may be transmitted through genetic inheritance [4]. Another thing transmitted by genetic inheritance is finger length ratio. Research has found that from the moment these are determined in the mother's womb, this does not change either in the adolescent period or in adulthood [5]. There are many studies reporting that the ratio of 2nd and 4th fingers (2D:4D) on the hand is related to the level of gender hormones in the body. Accordingly, there is a relationship between index finger length and the level of the hormone estrogen in the female gender and a relationship between ring finger length and the level of the hormone testosterone in the male gender [6]. Another supporting study found a negative relationship between the ratio of index finger to ring finger on the hand and testosterone in blood [5]. Testosterone increases protein formation and muscle development and is one of the important male-specific hormones that is known to contribute to development of muscle after puberty [7].

In this study based on the association of testosterone levels in patients attending the diet clinic with greater fat mass and lower muscle mass measured by Tanita device, we aimed to investigate the link with 2D:4D length on the hand.

Material and Method

The study included patients attending the Dietary clinic at Çanakkale Onsekiz Mart University Education and Research Hospital from February to June in 2015. The study obtained local ethics committee approval. Patients in the study were categorized according to body type analysis, age and gender.BMI was calculated and recorded along with height and weight. Body types were categorized in three groups. Patients had body analysis completed with a Tanita device (TANITA BC-418 MA III). Basal metabolism rate (BMR), total fat (TF), fat free mass (FFM), total body water (TBW), right leg muscle mass (RLMM), left leg muscle mass (LLMM), right arm muscle mass (RAMM), left arm muscle mass (LAMM), trunk muscle mass (TMM) and fat mass (FM) were calculated. The patients with Tanita measurements had the index and ring fingers of both hands measured individually with digital calipers. Measurements were from the proximal curve on the volar face of the metacarpophalangeal joint to the tip of the finger with digital calipers, (BMI 770150) sensitive to 0.01 mm. The ratios of the measured values were later determined. All measurements were completed by the same person. 2D: 4D1 and is greater than 1, testosterone were considered dominant. Patients were asked about additional diseases. The study excluded patients with osteoarthritis, birth deformities, hand injuries, burns, trauma and fracture history and those who attended the diet clinic for reasons such as anorexia nervosa.

Statistical analysis; All analyses were performed using SPSS 15.0 (SPSS Inc. Chicago, IL, USA). Continuous variables were expressed as mean±SD and categorical variables were expressed as percentages. The comparison of variables between the two groups was performed using the x2 test and Student's t-test. Pearson's correlation analysis was conducted to determine the relationship between relevant parameters. In all analyses, $p<0.05$ was taken to indicate statistical significance.

Results

It was observed that the majority of patients attending the diet clinic were female; of the total of 216 patients, 168 were female and 48 were male.

According to the data obtained in our study the 2D:4D of females was 0.9962±0.325 for the right hand and 0.994±0.403 for the left hand. For males the 2D:4D was 0.999±0.297 for the right hand and 0.996±0.279 for the left hand. While there was no statistically significant difference observed between the finger ratios of both hands, significant differences were observed for the separate measurements. Both fingers and hands were longer in the male gender. This is a clinically expected situation. There was a statistically significant difference between height, weight and BMR ratios between the genders; however this is an expected situation. Additionally of patients included in our study, 72.2% (109 people) of patients with BMI 30 and above were female and 27.8% (42 people) were male. Of patients with BMI below 30 90.8% (59 people) were female and 9.2% (6 people) were male. There were statistically significant differences observed between the genders in terms of TF, FFM, TBW, trunk and extremity muscle mass (MM) ($p<0.001$) (Table 1).

According to statistics obtained as a result of correlating values with 2D:4D, the measurements of people with 2D:4D of 1 and above on both hands were compared with those whose 2D:4D was below 1. 2D: 4D1 and is greater than 1, testosterone were considered dominant. While there was a statistical difference observed in terms of total fat, FFM, and fat mass, there was no difference in terms of the other measurements. As can be seen, the individuals with 2D:4D of 1 and above had high total fat and fat mass, while FFM values were low (Table 2). As a result it may be considered that this ratio is related to body muscle mass.

While there was a positive correlation between 2D:4D measurements of both hands with BMI, fat mass and total fat, a negative correlation was observed with FFM (Table 3). In other words; as 2D:4D increases fat mass increases, and as the ratio decreases muscle mass is observed to decrease. This leads to the consideration that 2D:4D may be related to obesity.

Discussion

Obesity is a widespread health problem observed in nearly all societies and is becoming a global epidemic. The TURDEP-II study found that the incidence of obesity was 44% for women, 27% for males and 35% in the general population. We observed that 77.7% of patients attending our diet clinic were female [8].

Table 1. Comparison by gender

	Female (n=168)	Male (n=48)	P value
Ages (year)	39.1±13.9	41.1±13.3	0.377
Height(cm)	160.2±5.5	173.5±7.9	<0.001
Weight(kg)	86.9±18.3	106.5±20.0	<0.001
BMI(Body mass index)			
30≥	109(72.2%)	42(27.8%)	
30<	59(90.8%)	6(9.2%)	0.002
Body type			
Ectomorph	23(56.1%)	1(0.9%)	<0.001
Mezomorph	32(52.5%)	18(43.9%)	<0.001
Endomorph	113(99.1%)	29(47.5%)	0.116
Right hand 2D	67.0±4.0	72.5±4.6	<0.001
Right hand 4D	67.3±4.3	72.6±4.8	<0.001
Left hand 2D	67.2±4.0	72.0±4.7	<0.001
Left hand 4D	67.7±4.8	72.3±4.9	<0.001
Right hand 2D:4D	0.9962±.0325	0.999±.0297	0.503
Left hand 2D:4D	0.994±.0403	0.996±.0279	0.685
BMR	1587.6±202.5	2242.2±357.1	<0.001
TTF	39.9±6.4	30.1±6.0	<0.001
FFM	51.0±5.9	73.9±10.6	<0.001
TBW	37.2±4.3	54.1±7.7	<0.001
RLMM	8.6±1.3	13.0±2.2	<0.001
LLMM	8.5±1.2	12.9±2.2	<0.001
RAMM	2.5±0.3	4.4±0.8	<0.001
LAMM	2.6±0.4	4.4±0.8	<0.001
TMM	28.2±2.9	38.8±4.8	<0.001
FM	36.2±15.0	32.6±11.5	0.133

Table 2. The right 2D:4D, a comparison with are smaller than 1 to 1 and above ones.

	Right 2D:4D 1≥	Right 2D:4D 1<	P value	Left 2D:4D 1≥	Left 2D:4D 1<	P value
BMR	1778.9±371.6	1700.5±360.9	0.122	1772.9±375.5	1706.1±359.2	0.189
TF	37,9±13,7	33,5±10,8	*0.010	37,9±13,6	33,6±11,0	*0.015
FFM	56,2±12,8	60,0±11,7	*0.026	56,3±13	59,9±11,6	*0.038
TBW	41.9±8.9	40.3±8.6	0.201	41.9±9.0	40.4±8.5	0.227
RLMM	9.9±2.3	9.4±2.4	0.107	9.9±2.3	9.4±2.4	0.141
LLMM	9.8±2.3	9.3±2.4	0.123	9.3±2.3	9.8±2.3	0.162
RAMM	3.0±0.9	2.9±0.9	0.363	3.0±0.9	2.9±0.9	0.362
LAMM	3.1±0.9	3.0±0.8	0.222	3.1±0.9	3.0±0.8	0.190
TMM	31.1±5.8	30.2±5.4	0.295	31.1±5.9	30.3±5.4	0.310
FM	37,9±14,1	33,4±10,8	*0.013	37,8±14,0	33,6±11,0	*0.020

The left 2D:4D a comparison with are smaller than 1 to 1 and above ones.

Tables 3. Right hand and left 2D:4D ratio of BMI, Fat Mass, Total Fat while there is a correlation with a positive value, a negative correlation is observed by the FFM.

		BMI	Fat Mass	Total Fat	FFM
Right 2D:4D	Pearson Correlation	r: 0,166*	r: 0,175	r:0,177**	r:-0,152
	Sig. (2-tailed)	p: 0,015	p:0,010	p:0,009	p:0,026
Left 2D:4D	Pearson Correlation	r:0,172*	r:0,171	r:0,164*	r:-0,142
	Sig. (2-tailed)	p:0,011	p:0,012	p:0,016	p:0,038

The 2D:4D is a popular measurement transmitted by genetic inheritance, with many studies on this ratio published in the literature in recent years. Studies have shown that the 2D:4D is related to the hormone testosterone [9-12]. Other studies have shown that a low 2D:4D on both hands is inversely correlated with sports ability, performance and success level [13-16]. The sport of athletics is related to prenatal testosterone and finger length and there is said to be strong evidence of this ratio being a marker of predisposition [17]. We considered that 2D:4D may be linked to the muscle mass of the body and may affect sports ability and performance. However, there are studies stating that this ratio has no place in the determination of athletic skills and physical fitness of adolescent girls [18]. Testosterone increases muscle mass, reduces adiposity and has a relationship with the 2D: 4D ratio, thus we thought it might be a risk factor for obesity.

In our study body type analysis of both genders indicated that the majority were endomorph body type. A somatotype study of university students observed that in both genders endomorph body type was dominant and in spite of similar waist circumference values to the national mean, increased cardiometabolic risk was found [19].

The relationship between 2D:4D and severe knee and hip osteoarthritis risk requiring total joint replacement has been investigated. The study found that low 2D:4D was related to severe knee osteoarthritis, though this relationship was not found for hip osteoarthritis. This cohort study with high numbers of patients concluded that knee and hip osteoarthritis diseases may have different mechanisms [20]. We believe that as 2D:4D increases, there is a tendency toward obesity and osteoarthritis.

The most important limitation of our study is that hormonal laboratory results, such as testosterone, were not studied. As finger ratio is determined in the womb and it is considered that it does not change in adolescence and adulthood, the lack of this measurement may not have affected the study. Another limitation is that there was no control group of normal individuals and the low numbers of patients.

In conclusion, in this study we observed that 2D:4D may be directly correlated to obesity and inversely correlated to body muscle mass. Maybe this rate in the future be considered as a risk factor.However, there is a need for more comprehensive studies about it.

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Competing interests

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Analysis of 175 Cases Underwent Surgical Treatment in Our Hospital After Having Abdominal Wounding by Firearm in the War at Syria

Suriye'deki Savaşta Ateşli Silahla Abdominal Yaralanma Geçirdikten Sonra Hastanemizde Cerrahi Tedavi Gören 175 Olgunun Analizi

Ateşli Silah ile Karın Yaralanması / Abdominal Injury by Firearms

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Özet

Amaç: Suriye'deki savaşta ateşli silah nedeniyle abdomen yaralanması geçirerek hastanemizde cerrahi tedavi görmüş olan hastaları retrospektif olarak analiz etmeyi amaçladık. Gereç ve Yöntem: 2011 ile 2014 yılları arasında Harran Üniversitesi Tıp Fakültesi Acil Servisine ateşli silah yaralanması ile başvuran ve abdominal yaralanma nedeniyle Genel Cerrahi kliniğine yatırılarak ameliyat edilen Suriyeli hastaların dosyaları retrospektif olarak incelendi. Bulgular: Ateşli silah nedeniyle abdominal yaralanma geçiren 175 Suriyeli hasta genel cerrahi kliniğimizde ameliyat edildi. Hastaların % 99.4 (n=174)'ü erkek, % 0.6 (n=1)'i kadındı. Tüm olguların travma-hastane kabul süresi 6 saat ≥ idi. Hastaların % 62.8'i (n= 110) izole abdominal yaralanma, % 37.1 (n= 65)'si iki ve daha fazla sistem yaralanmalı hasta idi. En sık yaralanan intraabdominal organlar kolon, ince barsak ve karaciğerdi. Abdominal yaralanmalarda birden fazla organ yaralanması görülme sıklığı % 44.5 (n=78) ve en sık görülen komplikasyon yara enfeksiyonu idi (%10). Negatif laparoskopi % 2.8 (n= 5), yoğun bakım desteği % 38.2 (n= 67), ortalama yoğun bakım kalış süresi 5.57 gün, mortalite % 9.7 (n= 17) idi. Tartışma: Çalışmamızda ateşli silahla abdominal yaralanma nedeniyle hastanemize başvuran hastaların, özellikle gastrointestinal sistem perforasyonu olanlar, travma-hastane kabul süresi 6 saat ≥ ise enfeksiyon kaynaklı morbiditesi ve mortalitesi artmaktadır. Bu da bize gastrointestinal traktı perfore eden yaralanmalara erken müdahalenin morbidite ve mortaliteyi azaltmada önemli bir faktör olduğunu göstermektedir.

Anahtar Kelimeler

Ateşli Silah Yaralanması; Abdominal Yaralanma; Mortalite

Abstract

Aim: We aimed at analysing the patients, who underwent surgical treatment in our hospital after having abdominal wounding by firearm in the war at Syria, retrospectively. Material and Method: The files of Syrian patients, who applied to Emergency Service of Harran University Medical Faculty because of gunshot wounds and had operation after being hospitalized in General Surgery Clinic due to abdominal injuries between the years of 2011 and 2014, were analysed retrospectively. Results: 175 Syrian patients, who had abdominal injuries by firearms, underwent operation in our general surgery clinic. 99.4% (n=174) of the patients were male, and 0.6% (n=1) were female. Trauma-admission to hospital times of all cases were ≥ 6 hours. 62.8% (n=110) of the patients had isolated abdominal injuries, and 37.1% (n=65) had two or more system injuries. The frequency of more than one organ injuries in abdominal region was 44.5% (n=78) and the most frequent complication was wound infection (10%). Negative laparoscopy was 2.8% (n=5), support for intensive care was 38.2% (n=67), average duration of intensive care unit stay was 5.57 days and mortality was 9.7% (n=17). Discussion: In our study, it was seen that infectious morbidity and mortality increased for the patients, who applied to our hospital because of abdominal injuries by firearm, particularly the ones with gastrointestinal perforation, if trauma-admission to hospital times were ≥ 6 hours. And this shows us that the early intervention to injuries that perforate gastrointestinal tract was an important factor for decreasing morbidity and mortality.

Keywords

Gunshot Wound; Abdominal Injury; Mortality; Morbidity

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Introduction

Syria is a country neighbouring on Lebanon, Israel, Jordan, Iraq and Turkey in the Middle East, with an approximate population of 22 million (2009). The civil war in Syria caused to deaths and injuries of a great number of people since the year 2011. The Syrian patients, injured by firearms, receive treatment in our hospital, because it is close to the war territory geographically. Abdominal injuries are one of the most important surgical emergencies at war and in non-combatant times. Firearm, stab and blunt traumatic injuries increase at war times. The newly developed high energy weapons increase wounding severity and personal and collective injuries. Multiple system and multiple organ injuries occur usually with gunshot wounds. Because of their ballistic efficiencies and deflexion features, bullets not only devastate the organ they hit, but also cause damage in adjacent organs beside the tissues they entered. For this reason, it may be deceptive making diagnosis and planning treatment only by considering bullet holes [1, 2].

Gunshot wounds are the injuries with high morbidity and mortality in our country and the world. They comprise 25% of traumatic deaths in the USA. Mortality in abdominal injuries by firearms is between 3-35 % (15% on average). Deaths based on gunshot wounds are generally between the ages of 1-45. We are in a period, when wars and regional conflicts continue in tens of regions of the world, particularly in the Middle East, and the number of physical injuries increases gradually. Early and right diagnosis of such injuries enables appropriate intervention and planning treatments by estimating possible complications, and decreases mortality [1-3].

In this study, our aim is sharing the data of Syrian patients, who were injured in their abdomens by firearms since the beginning of the civil war in Syria and treated in our hospital, and contributing to the experience in this respect.

Material and Method

175 patients with gunshot injuries applied to the emergency service of our hospital in the civil war in Syria between the years of 2011-2014, were hospitalized and treated in our General Surgery Clinic because of abdominal injury. Injured patients taking first-aid support in border regions was brought to the hospital. The files of these patients were analysed retrospectively. It was received local ethics committee permission from our University before the study. After the evaluation of the general situations and vital signs of the patients through multi-disciplinary approach, their laboratory analyses were carried out. Digital rectal examinations were carried out and urethral foley catheters were placed to all patients. In addition, patients were monitorized after being given prophylactic tetanus vaccine, antibiotic (1st Generation cephalosporin and/or metronidazole) and intravenous isotonic solution. Emergency laparotomy was implemented to patients with unstable hemodynamically (systolic blood pressure of <90 mmHg), evisceration and peritonitis. After the completion of emergency examinations of stable patients, elective laparotomy was implemented. Ages and genders of patients, firearm type causing to injury, time elapsed between wounding and admission to hospital, abdominal organs injured and their number, number of extra abdominal organs injured, surgical procedures implemented, lengths of intensive care unit, need of blood transfusion, developing complications and mortalities were recorded. Patients with isolated abdominal injuries and the ones with extra-abdominal injuries, who underwent laparotomy, were included in our study.

Patients without abdominal injuries, patients brought to hospital arrested and patients to the records of who could not be accessed were excluded from the study.

All statistical analyses were performed by using SPSS for Windows version 17.0 (SPSS, Chicago, IL, USA). Descriptive statistics were performed and the data were expressed as mean ± Standard deviations, minimum, maximum, and percentiles.

Results

99.4% (n=174) of the patients included in the study were male and 0.6% (n=1) were female and the age average was 30.6 (16-65). 12% (n=21) of 175 patients had shrapnel and 88% (n=154) had gunshot wounds. Trauma-admission to hospital times of all cases were ≥ 6 hours. 62.8% of the patients had isolated abdominal, 20.5% had abdominal-extremity, 9.7% had abdominal-thorax, 0.6% had abdominal-head and 6.4% had multiple system (more than two systems) injuries (Table 1). 52.6% of abdominal injuries had intra-abdominal single organ injury, 27.4% had two organ injuries, 14.9% had three organ injuries, 2.3% had intra-abdominal ≥4 organ injuries. And any intra-abdominal organ injury was not determined at 2.8% of the patients (Table 2). 28(16.0%) of the patients were hemodynamically unstable.

Table 1. Clinical features of the patients

Injured region	Patient N (%)	NIC N (%)	LAIC Day	Mortality N (%)
Isolated Abdomen	110(62.8)	29(26.3)	4.53	8(7.2)
Abdomen-Extremity	36(20.5)	14(38.8)	4.30	5(13.8)
Abdomen-Thorax	17(9.7)	13(76.5)	4.85	2(11.8)
Abdomen-Head	1(0.6)	1(100)	5.00	0(0)
More than two systems	11(6.4)	10(91)	9.20	2(18.2)
Total	175(100)	67(38.2)	5.57	17(9.7)

NIC = Need of intensive care LAIC = Length average of intensive care unit

Table 2. Number of injured organs, need of intensive care and blood transfusion, mortality.

Number of Injured Organs	PATIENT N (%)	NIC N (%)	ALIC Day	BTA Unit	CMP N (%)	MRT N (%)
0	5(2.8)	0(0)	0	0	0(0)	0(0)
1	92(52.6)	23(25)	3.60	3.6	15(16.3)	3(3.26)
2	48(27.4)	24(50)	4.17	4.17	11(22.9)	7(14.6)
3	26(14.9)	16(61.5)	6.68	6.7	12(46.1)	6(23)
4≥	4(2.3)	4(100)	7.6	7.3	4(100)	1(25)

NIC: Need of intensive care, ALIC: Average length of intensive care unit, CMP: Complication BTA: Blood transfusion average, MRT: Mortality

Blood transfusion was needed for 38% of the patients and the average need per patient was 4.8 units erythrocyte suspension. Intensive care follow-up was required for 38.2% of the patients and length of intensive care unit was 5.57 days on the average (Table 1). Complications developed at 42 (24%) of patients. They were wound infections in 18 (10%), pulmonary complications (4 atelectasias, 2 pneumonias, 1 embolism) in

7(4%), anastomotic leak in 3(1.8%), evisceration in 2 (1.2%), bleeding in 3(1.8%), intra-abdominal abscess in 4(2.3%) and urinary fistula in 5(2.9%) of the patients. Intra-abdominal injured organ distribution and the treatments implemented were given in Table 3. 15(88.3%) of 17 dying patients were under 50 years old and 2 (11.7%) of them were over 50 years.5 (29%) of 17 patients died of hemorrhagic shock and 12 (%71) died of sepsis. Mortality was 3.2% for patients with intra-abdominal single organ injury, 14.6% for the ones with two organ injuries, 23% for the ones with three organ injuries and 33.3% for 4≥ organ injuries (Table 2). 9 of 17 patients who died had colon, 3 had duodenum, 3 had liver and 2 % had vessel injuries.

Table 3. Intra-abdominal injured Organ Distribution and The Treatments Implemented.

Injured Organ	(n, %)	Treatments Implemented	(n, %)
Liver	25(8.8)	Primary repair	16(64)
		Packing	7(27)
		Non-operative	2(9)
Stomach	4(1.4)	Primary repair	4(100)
Duodenum	8(2.8)	Primary repair	8(100)
Small Bowel (jejunum and/ or ileum)	66(23.5)	Primary repair	40(60)
		Resection + anastomose	21(32)
		Jejunostomy or ileostomy	5(8)
Colon	89(31.5)	Primary repair	22(24.7)
		Resection + anastomose	12(13.5)
		Colostomy	53(59.5)
		Primary repair + ileostomy or rez-anst.+ileostomy	2(2.3)
Rectum	9(3.1)	Primary repair	3(33.3)
		Primary repair + colostomy	6(66.7)
Spleen	17(6)	Splenectomy	11(65)
		Splenorraphy	6(35)
Diaphragma	19(6.7)	Primary repair	19(100)
Gall bladder	5(1.7)	Cholecystectomy	5(100)
Choledoch	1(0.4)	Primary repair	1(100)
Pancreas	2(0.8)	Non-operative	2(100)
Major Abdominal Vessels	4(1.6)	Primary repair	4(100)
Kidney	10(3.5)	Nephrorrhaphy	7(70)
		Total nephrectomy	3(30)
Ureter	9(3.1)	Primary repair	9(100)
Bladder	13(4.5)	Primary repair	13(100)
Femoral Venous	1(0.3)	Primary repair	1(100)
Penis	1(0.3)	Primary repair	1(100)
TOTAL	283(100)		

Discussion

Our study is an important serie in terms of containing the data that exhibit the points of abdominal injury, organ damages, treatment strategies and mortality numbers of the patients, who were transported to a 3rd level hospital after they have taken the first intervention in the border regions. After Gunshot wounds are an important problem in places, where violence, terror and particularly wars continue. Given the regions throughout the world, where wars continue, particularly the Middle East, it can be understood how big problem it is. People will encounter increasingly with this type of wounding. While abdominal region body surface area is 11%, the rate of abdominal injuries varies between 8-9.4 % [4]. it was determined in a higher rate of 10.1% (175/1721) in our study. Moreover, abdominal injuries increased gradually in wars since the 2nd World War [4]. The rate of multiple organ injuries reach up to 90% in abdominal injuries by firearm [2, 5]. And this rate was found 44.6% (n=78) in our study.

The intra-abdominal organs of liver, small bowel and colon are the organs injured most in injuries by firearm in the literature [2-7]. The injured intra-abdominal organs in our cases were 31.5% colon, 23.5% small bowel and 8.8% liver injuries similarly with the literature.

Complication is one of the important problems in injuries by firearm and it is known that the trauma-appeal time longer than 6 hours, existence of shock during appeal, operation lengths of more than 6 hours, existence of abdominal organ injuries more than 2, existence of extra-abdominal organ injuries more than 2 and multiple blood transfusion increased complication rates [7-9]. We observed that complications affected these factors in our serie as well. It was encountered with complications in 24% of the cases. The most frequently seen complications were the wound site injection, bleeding and pulmonary complications [2-6]. In addition, intra-abdominal abscess developed in 4 patients and all of them were cured successfully through percutaneous drainage.

In the literature, while the cause of death of the patients with abdominal injuries by firearms was bleeding in early period, it is seen that it was infection related sepsis in next periods [2, 3]. While the most frequent cause of death was haemorrhagic shock in previous series [1, 2, 10-13], 12 of the cases in our study died of sepsis and 5 died of haemorrhagic shock. So we observed that the deaths of sepsis were higher for the patients with colon and small bowel injuries, who were intervened 6 hours after wounding, and that wound site infections were higher than normal. And this makes us think that injuries perforating gastrointestinal system should be treated more carefully, due to the fact that they could progress toward sepsis. It was seen that abdominal aortas were affected in 2, and thorax, pelvis and lower extremity, which are non-abdominal body regions, were affected in 3 of the patients died of hemorrhagic shock; and the tendency to hemorrhagic shock increased in these organ and tissue injuries and treatment should be planned in accordance to that.

In the literature, mortality increases up to 45% in injuries by firearm [10-13]. One of the factors affecting these results is the time to reach from the site of injury to the hospital. This time is short in Kuwait, Korea and Vietnam war so that mortality rate is short; but in the Afghanistan war, mortality rate is high because it took few days to reach a hospital (16.7%) [7,11,12].

And in our study, the rate of mortality was found as 9.7%. We think that the mortality rate to be lower in our study is dependent on patients to have hemodynamic stability to endure more than 6 hours time elapsed during transportation from the wounding site to our hospital and the possible deaths of seriously wounded patients during this transportation. In addition, we associate liver injuries to be third in our serie to that, where hemorrhagic shock is frequently seen.

Many factors can have influence on mortality in injuries by firearm. And two of these factors are multiple organ and multiple

system injuries [14]. In our study, mortality was found as 13.8% for patients with more than one system injuries, and as 18% for patients with more than one organ injuries. It was determined that the increase in number of injured intra-abdominal organs and injured systems raised the rate of mortality.

One of the important factors that affects mortality is advanced age and the rate mortality is higher for the patients over the age of 50 [1]. However, in our study, only 2 of 17 patients died were over the age of 50. The reason for this can be shown as crusaders attending to war to be young people below the age of 50.

Diagnosis of intra-abdominal penetration existence is hard for tangential and thoraco-abdominal injuries by firearm. This may cause negative laparoscopies [5]. The diagnostic accuracy of laparoscopy was excellent for retroperitoneal hematomas, hemoperitoneum, solid organ injuries and diaphragmatic lacerations [15,16]. In our study, it was hesitated in determining intra-abdominal penetration in 21 cases. Diagnostic laparoscopy was implemented to all cases. It was determined that intra-abdominal organ injuries existed in 16 and did not exist in 5 of these cases. Negative laparoscopy was determined as 2.9% by us in our study [2, 3].

Conclusions

Abdominal injuries by firearm are the injuries with high morbidity and mortality. If these injuries occur as multiple organ and multiple system injuries, than morbidity and mortality become higher. Besides, intensive care support, length of intensive care unit and the need for blood transfusion increase in such cases. If treatment is started in patients with abdominal injuries by firearm later than 6 hours, the number of infection related complications and mortality increase. Due to the injuries occurring in war times are mostly multiple system and multiple organ injuries, early, fast and efficient intervention in a full-fledged hospital with an experienced staff can decrease morbidity and mortality significantly.

Ethical standard

The study was approved from the Regional Ethics Committee (136/28.08.2014).

Competing interests

The authors declare that they have no competing interests.

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Predicting Risk of Type 2 Diabetes Mellitus: A Population-Based Study

Tip-2 Diyabet Risk Tahmini: Toplum Tabanlı Bir Çalışma

Tip-2 Diyabet Risk Tahmini / Predicting Risk of Type 2 Diabetes Mellitus

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Özet

Amaç: Dünyada ölümlere neden olan majör risk faktörlerinden biri de tip-2 diyabettir (DM). Türkiye'de toplumun DM'ye yakalanma riskini tahmin eden formülüze edilmiş bir araç bulunmamaktadır. Araştırmanın amacı, Finnish Diyabet Risk Skoru (FINDRISC) aracı kullanılarak Türk toplumunda DM risk düzeyini belirlemektir. Gereç ve Yöntem: Kesitsel nitelikteki bu çalışmanın verileri, Yozgat il merkezinde 2011 yapılan "Kronik hastalıklar için davranışsal risk faktörleri" adlı araştırmadan elde edilmiştir. Araştırma grubu, 25-79 yaşlarında, daha önce kan şekerini ölçtürmüş ancak DM tanısı almamış 825 kişiden oluşmaktadır. DM risk düzeyi, FINDRISC aracı kullanılarak hesaplanmıştır. Ölçek skoru 0-26 arasında olup, ≥15 puan alanlar yüksek riskli (risk oranı 1/3) olarak kabul edilmektedir. Verilerin analizinde, t testi, ANOVA, ki-kare testi ve binary lojistik regresyon kullanılmıştır. Bulgular: Araştırmaya alınanların 10 yıllık DM riski puan ortalaması 8.8±4.6'dır. FINDRISC puanı düşük/orta ve yüksek olarak 2 gruba ayrıldığında, yüksek risk grubunda olanların oranı %11.5'dir. Bu oran, Türkiye için hesaplanan 10 yıllık DM insidansı (%11-12.4) ile benzerdir. Bu çalışmada da, FINDRISC hesaplamasına alınan faktörlerin tamamı istatistiksel olarak önemli bulunmuştur (p<0.01). Tekli analizde, cinsiyete, medeni duruma, öğrenim düzeyine, ekonomik düzeye, yaşam memnuniyetine, çalışma durumuna ve sigara içme durumuna göre DM riski farklı iken, çok değişkenli lojistik analizde bu değişkenler önemli bulunmamıştır (p>0.05). Tartışma: Türk toplumunda DM riski hesaplamasında FINDRISC kullanılabilir. Her on yetişkinden biri, 10 yıl içinde DM'ye yakalanma açısından yüksek risk altındadır. Bu sorunu önlemek için bireysel ve toplumsal düzeyde çeşitli programların acilen uygulanması gerekmektedir.

Anahtar Kelimeler

Diyabet; Risk Tahmini; Toplum

Abstract

Aim: One of the major risk factors that can cause death in the world is also type-2 diabetes mellitus (DM). Turkey does not have a vehicle in the society has been formulate predicting the risk of developing DM. The purpose of this study is to determine the level of DM risk in Turkish society using the Finnish Diabetes Risk Score (FINDRISC) tool. Material and Method: This is a cross-sectional study. The data has been obtained from "behavioral risk factors for chronic diseases study" that was made in the province of Yozgat, in 2011. The study population included 825 subjects between 25 to 79 years old who had measured their blood sugar before, but who were not diagnosed DM. DM risk level was calculated using FINDRISC tool. The scale score is between 0-26, ≥15 points are considered high risk (risk ratio 1/3). In analyzing the data, t-test, ANOVA and chi-square test and binary logistic regression were used. Results: Of the subjects 10 years of DM risk score's mean was 8.8 ± 4.6. When FINDRISC score low / medium and high divided into 2 groups, the proportion of those in the high risk group is 11.5%. This rate is similar to the 10-year incidence of DM calculated (11-12.4%) for Turkey. In this study, all of the factors taken into FINDRISC calculations were statistically significant (p <0.01). In univariate analysis, DM risk differently according to gender, marital status, education level, economic level, life satisfaction, employment status, and smoking status while in logistic analysis of these variables were not significant (p> 0.05). Discussion: FINDRISC used to be in the DM risk calculations of Turkish population. One out of every ten adults are at high risk of developing DM in 10 years. To avoid this problem urgently needs to be implemented by the various programs on an individual and societal level.

Keywords

Diabetes Mellitus; Risk Assessment; Community

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Giriş

Dünya Sağlık Örgütü'nün Bulaşıcı olmayan hastalıkların Küresel Durum Raporu 2010'a göre, diyabetin (DM) kontrol altına alınmasıyla fatal ve non-fatal kardiovasküler olguların en az %30 azalacağı tahmin edilmektedir. Bulaşıcı olmayan hastalıkların majör nedenlerinden biri de yüksek kan şekeridir. DM hastaları, diyabet sorunu olmayanlara göre en az iki üç kat daha fazla sağlık hizmeti kullanmakta ve ulusal sağlık harcamalarının yaklaşık olarak %15'i DM hastalarının bakımı için harcanmaktadır. Bozulmuş glikoz toleransı ve bozulmuş açlık glikozu, DM ve kardiovasküler hastalıkların gelişmesinde önemli risk faktörüdür. Gelişmiş ülkelerdeki DM hastalarında sorunu olmayanlara göre inme gelişme riskinin iki kat, alt ekstremite ampütasyon riskinin ise 10 kat daha fazla olduğu görülmüştür [1]. Dünyada 2013 yılında 382 milyon DM'li kişi olduğu ve bu sayının 2035'de 592 milyona ulaşacağı, bu vakalarının çoğunluğunun düşük ve orta gelirli ülkelerde olacağı tahmin edilmektedir [2]. DM hastalarının %46'sı tanı konmadan yaşamaktadır. Dünyada 2013 yılında 20-79 yaş grubunda DM prevalansının %8.3 olduğu, yine aynı yılda DM'nin 5.1 milyon kişinin ölümüne neden olduğu ve en az 548 milyar $ sağlık harcamasına neden olduğu tahmin edilmektedir [3]. Kanada Diyabet Derneği, 30 yaşından itibaren kan şekerinin 3 yılda bir ölçülmesini önermektedir [4]. Türkiye Hastalık Yükü Çalışması 2004'e göre, ülkemizdeki ölüm nedenlerinden sekizincisi (%2.2), yine bulaşıcı olmayan hastalıklar içinde altıncısı DM'dir [5]. TEKHARF çalışmasının 1997/98'den 2004/05 yıllarına kadar izlenen kohortuna göre ise, Türkiye'de 35 yaş üstü nüfusta diyabet prevalansı %11 olarak tahmin edilmiş ve bunun 3,3 milyon kişiye karşılık geldiği hesaplanmıştır [6]. 1997-1998 yıllarında Türkiye genelinde 20 yaş üstü bireyler arasında yapılan "Türkiye Diyabet Epidemiyoloji Çalışması"nın (TURDEP-I sonuçlarına göre DM prevalansı %7,2, bozulmuş glukoz toleransı prevalansı ise %6,7 iken [7], TURDEP-II'de (2010) standardize DM prevalansı %13,7'ye ve bozulmuş glukoz toleransı %7.1'e yükselmiştir [8]. Bu prevalansa göre, ülkemizde 6,5 milyon kişinin DM hastası olduğu tahmin edilmektedir. TURDEP-II çalışması, 1998'de yapılan TURDEP-I çalışmasıyla kıyaslandığında, ülkemizde DM ve bozulmuş glukoz toleransı sıklığı sırasıyla %90 ve %6'lık bir artış göstermiştir [9]. Türkiye (2011) %8.1'lik DM prevalansı [10] ve bilinen 3.6 milyon DM vakası ile Avrupa ülkeleri içinde 4. sırada yer almaktadır [11]. Yine 2012 yılında Türkiye genelinde yapılan Chronic Diseases and Risk Factors Survey çalışmasında, DM prevalansı %11 ve BAG prevalansı ise %16 olarak saptanmıştır. DM farkındalığı, TURDEP-II'ye göre %54.5, CDRFS'ye göre %74 olup, DM'si kontrol altında olanların oranı sırasıyla %35.5 ve %29'dur [9,12].

Hastalıkların insidansını hesaplamak için kohort araştırmalarının yapılması gerekmektedir, ancak ınsıdans araştırmaları pahalı ve uzun zaman alan çalışmalardır. Dünyada kohort araştırmalarından yararlanarak toplumdaki DM riskini tahmin eden birçok ölçek geliştirilmiştir. Geliştirilen bu ölçekler yardımıyla toplumun DM risk düzeyi kesitsel araştırmalarla hesaplanabilmektedir. Kesitsel araştırmalar, insidans araştırmalarına göre daha kısa sürede yapılan ve maliyeti daha düşük olabilen araştırmalardır. Yapılan bir derleme çalışmasında (2009), DM riskini tahmin etmeye çalışan 56 adet araştırma saptanmıştır [13]. Ülkemizde bugüne kadar DM risk tahmini için bir ölçek/araç kullanılmamıştır. Bu çalışmada, DM riskini hesaplamada Finnish Diyabet Risk Skoru (Finnish Diabetes Risk Score [FINDRISC]) kullanılmıştır. [14-16]

Araştırmanın amacı, Finnish Diyabet Risk Skoru (FINDRISC) aracı kullanılarak Türk toplumunda DM risk düzeyini belirlemektir.

Gereç ve Yöntem

Bu araştırmanın verileri, retrospektif ve kesitsel türde bir araştırma olan "Kronik hastalıklar için davranışsal risk faktörleri" adlı çalışmadan elde edilmiştir. Araştırma, 2011 yılında Yozgat il merkezinde yaşayan 18 yaş ve üzeri kişiler arasında yapılmıştır. Türkiye İstatistik Kurumu 2010 yılı verilerine göre, Yozgat il merkezi nüfusu 75012 ve 18 yaş ve üzeri nüfus yaklaşık olarak 51000'dir (22). Örneklem seçiminde sistematik örnekleme yöntemi kullanılmıştır. Konut ve iş yerlerinden 25'te biri örnekleme alınmıştır. İş yerlerinde, 25 kişi ve daha az çalışan varsa hepsi örnekleme alınmıştır. Eğer iş yerinde 25'ten fazla kişi varsa, basit rastgele örnekleme ile yalnız 25 kişisi örnekleme alınmıştır.

Veriler, araştırmacı tarafından literatüre dayalı olarak hazırlanan anket formunun görüşmeciler aracılığıyla doldurulmasıyla toplanmıştır. Görüşmeci olarak araştırmacı tarafından eğitilen intörn hemşireler görev yapmıştır. Araştırmaya katılanların boy, ağırlık ve bel çevresi ölçümleri intörn hemşireler tarafından yapılmıştır. Araştırma, sözlü onam vererek araştırmaya katılmayı kabul eden 1837 yetişkin üzerinde yapılmıştır. Araştırmanın kurum izni Yozgat Valiliği'nden, etik kurul onayı ise Yozgat Devlet Hastanesi Etik Kurulu'ndan alınmıştır.

DM geliştirme riski, FINDRISC ölçeği kullanılarak hesaplanmıştır. FINDRISC ölçeği hesaplamasına uygun olan 25-79 yaş grubundaki 825 kişinin verileri değerlendirmeye alınmıştır. Daha önce hekim tarafından DM tanısı konanlar ile daha önce kan şekerini ölçtürmediğini belirtenler değerlendirmeye alınmamıştır. Kişiler, FINDRISC ölçeğinden 10 yıllık DM risk puanı olarak minimum 0, maksimum 26 puan alabilir. 10 yıllık DM risk skoru hesaplamasına; yaş (18-44: 0, 45-54: 2, 55-64: 3, ≥65: 4), beden kitle indeksi (<25: 0, 25-29.9: 1, ≥30: 3), bel çevresi (kadın ve erkekte sırasıyla <80-94: 0, 80-88/94-102: 3, >88/102: 4) yetersiz egzersiz yapmak (haftada 3 gün ve 150 dk daha az): 2, her gün sebze-meyve tüketmemek: 1, hipertansiyon ilacı kullanmak: 2, gebelik dönemi dahil kan şekeri yüksek saptanma: 5, ebe/dede, amca/dayı, hala/teyze DM varlığı: 3, anne/ baba/ kardeş/ evlatta DM varlığı: 5 puan alınarak hesaplanmıştır. Toplam puan; düşük risk: 0 – 11 puan (10 yıllık DM riski ≤1/7), orta risk: 12 – 14 puan (10 yıllık DM riski 1/6), yüksek risk: 15 – 20 puan (10 yıllık DM riski 1/3) ve çok yüksek risk: ≥21 puan (10 yıllık DM riski 1/2) olarak sınıflandırılmıştır [14-16]. Canadian Task Force on Preventive Health Care (CTFPHC), DM riski hesaplamasında FINDRISC ölçeğini veya bu ölçek üzerine oturan Canadian Diabetes Risk Assessment Questionnaire (CANRISK) kullanılmasını ve risk tahmininde kesim noktası olarak 15 ve üzerinde puan alanları yüksek riskli olarak kabul edilmesini uygun görmüştür [17].

Veriler, SPSS paket programında değerlendirilmiştir. İstatistiki değerlendirmede, aritmetik ortalamaları karşılaştırmada Student t testi ve One way ANOVA, risk düzeyini karşılaştırmada ki-kare testi ve çok değişkenli analizde binary lojistik regresyon (BLR) kullanılmıştır. BLR analizi öncesinde modelin uyum iyiliğine Hosmer and Lemeshow Test ile ($p>0.05$) ve modelin önemliliğine Omnibus Test ile ($p<0.05$) bakılmıştır [18]. BLR analizine bağımlı değişken olarak 10 yıllık DM riski 2 grup (<15 puan;

düşük/ orta risk:0 ve ≥15 puan; yüksek risk:1) halinde alınmıştır. FINDRISC hesaplamasına dahil edilmeyen ancak ki-kare testine göre önemli bulunan bağımsız değişkenler BLR analizine alınmıştır. Cinsiyet, medeni durum, çalışma durumu ve günlük sigara içme durumu kategorik türde, öğrenim düzeyi, yaşam memnuniyeti ve ekonomik düzey ordinal türde bağımsız değişkenler olarak alınmıştır. Bu değişkenler ile yaş ve beden kitle indeksi arasında genelde bir ilişki olduğu için modele yaş ve beden kitle indeksi tekrar dahil edilmiştir.

Bulgular

Araştırmaya katılanların sosyo-demografik özelliklerine bakıldığında; %55.8'i, kadın, %88.8'i evli olduğunu, %35.3'ü 5 yıl ve daha az öğrenim gördüğünü, %26.5'i lisans mezunu olduğunu, %74.2'si yaşamından memnun olduğunu, %57.0'si halen bir işte çalıştığını, %25.9'u her gün sigara içtiğini, %26.4'ü ekonomik durumunun iyi olduğunu belirtirken, %9.2'si ise kötü olduğunu belirtmiştir (Tablo 2).

Araştırmaya katılanların FINDRISC hesaplamasına alınan özelliklerine bakıldığında, %62.8'i 25-44 (%29.9'u 25-34) yaş grubunda, %6.9'u 65 ve üzeri yaşında olup yaş ortalaması 42.4±12.0'tür. Deneklerin %32.1'inin obez olduğu ve %46.1'inin bel çevresinin riskli düzeyde olduğu saptanmıştır. Yine deneklerin %32.1'i aile bireylerinden en az birinde DM olduğunu, %7'si kan şekerinin daha önce yüksek saptandığını, %17.8'i her gün sebze-meyve tüketmediğini, %74.1'i yeterli egzersiz yapmadığını ifade etmiştir (Tablo 3).

Araştırma grubunun 10 yıllık FINDRISC puan ortalaması 8.82±4.62 (%95 güven aralığı, 8.51-9.14)'dir. FINDRISC puanı 3 gruba ayrıldığında 10 yıllık DM risk düzeyi; düşük, orta ve yüksek riskli olanların oranı sırasıyla %71, %17.5 ve %11.5'dir (Tablo 1).

Tablo 1. Araştırma grubunda 10 yıllık DM risk düzeyi ve FINDRISC ortalaması.

				%95 GA	
Risk düzeyi	Sayı	%	X	Alt sınır	Üst sınır
Düşük: <12 (≤1/25)	586	71.0	6.50	6.25	6.75
Orta:12 – 14 (1/6)	144	17.5	13.04	12.90	13.19
Yüksek: 15 – 20 (1/3)	92	11.2	16.55	16.22	16.89
Çok yüksek: ≥ 21 (1/2)	3	0.4	22.33	18.54	26.13
Toplam	825	100.0	8.82	8.51	9.14

X : Aritmetik ortalama, GA: Güven aralığı

FINDRISC hesaplanmasına dahil edilmeyen cinsiyet, medeni durum, öğrenim düzeyi, ekonomik düzey, çalışma durumu, günlük sigara içime durumu ve yaşam memnuniyeti değişkenlerine göre 10 yıllık DM risk düzeyi istatistiksel olarak farklı bulunmuştur (Tablo 2). DM risk düzeyini yüksek (≥15 puan) ve yüksek olmayan (<15 puan) olarak 2 gruba ayırıp çok değişkenli olarak BLR analizinde incelendiğinde; bu 7 değişkenin hiçbiri de istatistiksel olarak önemli bulunmamıştır (p>0.05). Bu faktörler ile yaş ve beden kitle indeksi arasında ilişki olduğu için BLR analizine yaş ve beden kitle indekside dahil edilerek analiz yapılmıştır (Tablo 3).

Yaş, beden kitle indeksi ve bel çevresi arttıkça FINDRISC puanı ve risk düzeyi artmaktadır. Yüksek risk grubunda (risk oranı 1/3) olanların oranı, 45 yaş altında %4.3 iken, 65 yaş ve üzerinde bu oran %38.6'ya çıkmaktadır. Obezler (%27.9), hafif obez olanlara (%4.6) göre 6 kat, bel çevresi riskli olanlar (%21.9) sınırda riskli olanlara (%5.3) göre 4 kat daha yüksek risk altındadır. Birinci derece akrabalarında DM sorunu bulunan kişilerin (%29.8), diğer kişilere (%4.5) göre 6.5 kat, daha önce kan şekeri yüksek saptananların (%46.6) saptanmayanlara (%8.9) göre 5 kat, hipertansiyon ilacı kullananların (%32.9) kullanmayanlara (%7.2) göre 4.5 kat, günlük sebze-meyve tüketmeyenler (%19) her gün tüketenlere (%9.9) göre yaklaşık 2 kat, yetersiz egzersiz yapanlar (%14.2) yeterli egzersiz yapanlara (%3.7) göre yaklaşık 4 kat daha yüksek risk altındadır. FINDRISC hesaplamasına dahil edilen faktörlere göre, hem FINDRISC puan ortalaması hem de risk düzeyi istatistiksel olarak önemli bulunmuştur (Tablo 4). Bu çalışmada da, FINDRISC hesaplamasına dahil edilen faktörlerin DM için temel risk faktörleri olduğu görülmüştür.

Tablo 2. Sosyo-demografik özelliklere göre 10 yıllık DM düzeyi ve FINDRISC ortalaması.

Çeşitli özellikler	Denek Sayısı	Düşük ve orta risk	Yüksek risk	FINDRISC
Cinsiyet	n (%)	n (%)	n (%)	X (SS)
Erkek	365 (44.2)	341 (93.4)	24 (6.6)	7.68 (4.33)
Kadın	460 (55.8)	389 (84.6)	71 (15.4)	9.73 (4.64)
Medeni durum		X2 =15.68	p <0.001	t=6.48, p<0.001
Evli	733 (88.8)	656 (89.5)	77 (10.5)	8.75 (4.49)
Bekâr	44 (5.3)	43 (97.7)	1 (2.3)	5.59 (3.63)
Eşi ölmüş/ eşinden ayrılmış	48 (5.8)	31 (64.6)	17 (35.4)	12.85 (4.71)
Öğrenim durumu		X2 =31.34	p <0.001	F=31.25, p<0.001
≤İlkokul	291 (35.3)	228 (78.4)	63 (21.6)	11.32 (4.19)
İlköğretim	83 (10.1)	73 (88.0)	10 (12.0)	9.58 (4.03)
Lise	131 (15.9)	119 (90.8)	12 (9.2)	7.97 (4.49)
Ön lisans	101 (12.2)	95 (94.1)	6 (5.9)	7.60 (4.42)
Lisans	219 (26.5)	215 (98.2)	4 (1.8)	6.29 (3.76)
Çalışma durumu		X2 =53.33	p <0.001	F=51.17, p<0.001
Halen çalışan	470 (57.0)	444 (94.5)	26 (5.5)	7.27 (4.26)
Çalışmayan	355 (43.0)	286 (80.6)	69 (19.4)	10.87 (4.27)
Ekonomik durum		X2 =38.38	p <0.001	t=12.01, p<0.001
İyi	218 (26.4)	209 (95.9)	9 (4.1)	6.76 (4.12)
Orta	531 (64.4)	461 (86.8)	70 (13.2)	9.44 (4.54)
Kötü	76 (9.2)	60 (78.9)	16 (21.1)	10.43 (4.73)
Yaşam memnuniyeti		X2 =19.91	p <0.001	F=33.59, p<0.001
Memnun	612 (74.2)	549 (89.7)	63 (10.3)	8.57 (4.53)
Notr/ memnun değil	213 (25.8)	181 (85.0)	32 (15.0)	9.55 (4.81)
Her gün sigara içme		X2 =3.47	P= 0.06	t=2.69, p=0.008
Hayır	611 (74.1)	528 (86.4)	83 (13.6)	9.22 (4.68)
Evet	214 (25.9)	202 (94.4)	12 (5.6)	7.69 (4.25)
		X2 =9.90	P< 0.001	t=4.42, p<0.001
Toplam	8 2 5 (100.0)	730 (88.5)	95 (11.5)	8.82 (4.62)

Düşük ve orta risk: 0-14 puan, Yüksek risk: ≥15 puan, X: Aritmetik ortalama, SS: Standart sapma

Tablo 3. DM ile ilişkili olabilecek değişkenlerin binary lojistik regresyon ile analizi

				%95 GA.	
Önemli bulunan bağımsız değişkenler	β	p	O.R.	Alt sınır	Üst sınır
Yaş	.068	.000	1.070	1.041	1.101
BKI	.169	.000	1.185	1.125	1.247
Öğrenim düzeyi	-.056	.668	.946	.734	1.219
Ekonomik düzey	-.073	.483	.930	.759	1.139
Yaşam memnuniyeti	.259	.106	1.295	.947	1.771
Cinsiyet (ref. kadın)	.609	.098	1.839	.894	3.785
Medeni durum (ref. evli)		.821			
Bekâr	-.263	.805	.769	.095	6.195
Eşinden ayrı/ eşi ölmüş	-.267	.560	.766	.313	1.877
Çalışma durumu (ref. çalışmayan)	.327	.413	1.386	.634	3.030
Günlük sigara içme (ref. içmeyen)	-.310	.393	.734	.361	1.492
Sabit	-10.819	.000	.000		

Hosmer ve Lemeshow test: p=0.812, O.R. Odds ratio, GA: Güven aralığı
Bağımsız değişkenler: Cinsiyet, medeni durum ve çalışma durumu kategorik türde, öğrenim düzeyi, yaşam memnuniyeti ve ekonomik düzey ordinal türde, yaş ve BKI sürekli türde alınmıştır.

Tartışma

Bu araştırmada, FINDRISC kullanılarak Yozgat il merkezinde yaşayan 25-79 yaş aralığındaki kişilerin DM risk düzeyi incelenmiştir.

Araştırma grubunun FINDRISC puan ortalaması 8.8±4.6 olup, %11.5'i 10 yıl içinde DM'ye yakalanma açısından yüksek risk (RO ≥1/3) altındadır (Tablo 1). İsveç'te FINDRISC ile yapılan bir çalışmada, risk puan ortalaması 8.5±4.5, yüksek risk grubunda olanların oranı ise %9.6 olarak saptanmıştır [19]. Onat ve ark. yaptığı araştırmaya göre, DM insidansı kadınlarda binde 11, erkeklerde binde 12.4'tür [20]. Yani 10 yıllık DM insidansı %11-12.4 olacaktır. Bu çalışmadaki yüksek risk grubunun 10 yıllık DM insidansı, İsveç'te ve Onat et al (2006) saptadığı insidansla benzerdir. International Diabetes Federation [3] göre dünyada 20-79 yaş grubunda DM prevalansı %8.3 iken, Türkiye'de 15 yaş ve üzeri kişiler arasında yapılan CDRFS (2012) araştırmasında %11 olduğu belirtmektedir [12].

Türkiye'de 2013'ten 2035 yılına kadar yetişkin nüfusun (20-79 yaş grubu) %32.3 oranında, DM'li kişi sayısının ise bu oranın iki katı kadar daha (%67.3) artacağı ve her yıl 216 bin kişinin DM hastalığına yakalanacağı tahmin edilmektedir [2]. CDRFS (2012) araştırmasına göre, DM sorunu olduğunu belirtenlerin oranı %8 olup, kadınlarda (%9) erkeklerden (%7) biraz daha fazladır. DM farkındalık oranı %74 olup, kadınlarda (78%) erkeklere (69%) göre daha yüksektir [12].

İngiltere'de 1993-2008 yılları verilerini kullanarak QDSCORE ölçeği ile 10 yıllık DM riski hesaplanmış ve DM insidansıyla benzer bulunmuştur. QDSCORE ölçeği ile DM risk hesaplaması insidans çalışmasına gerek olmadan yapıldığı için maliyet etkinlik açısından uygun bulunmuştur. Bu çalışmada kadın ve erkeklerde gözlenen risk ile tahmin edilen risk benzer bulunmuştur. Yalnız 55 ve üzeri yaştakilerde tahmin edilen risk, gözlenen riske göre biraz daha düşük saptanmıştır. Ancak bu fark hafif bir düzeydedir. QDSCORE'un hem klinikte hem de toplum taramalarında rutin olarak kullanılması önerilmektedir [21]. Yine Bulgaristan'da

Tablo 4. FINDRISC'teki risk faktörlerine göre 10 yıllık DM risk puan ortalaması ve risk düzeyi.

Çeşitli özellikler	Denek sayısı	DM risk düzeyi		FINDRISC
		Düşük ve orta risk	Yüksek risk	
Yaş grupları	n (%)	n (%)	n (%)	X (SS)
25 – 44	518 (62.8)	496 (95.8)	22 (4.2)	7.12 (4.08)
45 – 54	171 (20.7)	139 (81.3)	32 (18.7)	10.79 (4.08)
55 – 64	79 (9.6)	60 (75.9)	19 (24.1)	12.33 (3.77)
≥ 65	57 (6.9)	35 (61.4)	22 (38.6)	13.53 (3.44)
BMI (kg/m2)		X2=88.76	p<0.001	F=91.15, p<0.001
<25	234 (28.4)	228 (97.4)	6 (2.6)	5.16 (3.50)
25 – 29.9	326 (39.5)	311 (95.4)	15 (4.6)	8.29 (3.68)
≥30	265 (32.1)	191 (72.1)	74 (27.9)	12.72 (3.42)
Bel çevresi (kadın/erkek)		X2=103.73	p<0.001	F=288.41, p<0.001
< 80/ 94 cm	233 (28.2)	233 (100.0)	0 (0.0)	4.32 (3.04)
80-88/ 94-102 cm	208 (25.2)	197 (94.7)	11 (5.3)	8.15 (3.14)
> 88/ 102 cm	384 (46.5)	300 (78.1)	84 (21.9)	11.91 (3.59)
Ailede DM		X2=78.68	p<0.001	F=382.61, p<0.001
Ailede DM yok	560 (67.9)	535 (95.5)	25 (4.5)	7.31 (4.09)
Ebe/dede, amca/dayı, hala/teyzede	37 (4.5)	35 (94.6)	2 (5.4)	8.86 (3.07)
Anne/baba / kardeş/çocukta	228 (27.6)	160 (70.2)	68 (29.8)	12.54 (3.91)
Kan şekeri yüksek saptanma		X2=103.69	p<0.001	F=138.24, p<0.001
Hayır	767 (93.0)	699 (91.1)	68 (8.9)	8.42 (4.43)
Evet	58 (7.0)	31 (53.4)	27 (46.6)	14.16 (3.71)
Hipertansiyon ilacı kullanma		X2=75.16	p<0.001	t=11.19, p<0.001
Hayır	685 (83.0)	636 (92.8)	49 (7.2)	7.96 (4.26)
Evet	140 (17.0)	94 (67.1)	46 (32.9)	13.06 (3.96)
Her gün sebze-meyve tüketme		X2=73.37	p<0.001	t=13.07, p<0.001
Evet	678 (82.2)	611 (90.1)	67 (9.9)	8.53 (4.59)
Hayır	147 (17.8)	119 (81.0)	28 (19.0)	10.18 (4.56)
Egzersiz yapma		X2=9.96	p=0.002	t=3.96, p<0.001
Yeterli	214 (25.9)	206 (96.3)	8 (3.7)	7.43 (4.40)
Yetersiz	611 (74.1)	524 (85.8)	87 (14.2)	9.31 (4.60)
		X2=25.42	p<0.001	t=5.18, p<0.001
Toplam	825 (100.0)	730 (88.5)	95 (11.5)	8.82 (4.62)

Düşük ve orta risk: 0-14 puan, Yüksek risk: ≥15 puan, X: Aritmetik ortalama, SS: Standart sapma

FINDRISC kullanılarak yapılan bir çalışmada, tanı konmamış diyabet vakalarını ortaya çıkarmada FINDRISC tarama aracının duyarlılığı %78, seçiciliği %62 olarak saptanmıştır [22]. Buda bize, DM riski hesaplaması için geliştirilen araçların geçerlik ve güvenirliklerinin uygun olduğunu göstermektedir.

TURDEP-I çalışmasında, DM riskini artıran faktörlerin; erkek olmak, yaş artışı, ailede DM varlığı, kişide HT varlığı, yetersiz fiziksel aktivite, sigara içme ve geniş bel çevresi olduğu saptanmıştır [7]. TURDEP-I'de önemli bulunan cinsiyet ve sigara içme değişkenleri, bu çalışmada yapılan çoklu lojistik analizinde önemli bulunmamıştır (Tablo 3). Yine CDRFS çalışmasında da DM prevalansı cinsiyete göre farklı bulunmamıştır [12]. Bu araştırmada

FINDRISC hesaplamasına alınan risk faktörlerinin çoğu, TURDEP, QDSCORE, Avustralya Diyabet Risk Değerlendirme Aracı (AUSDRISK) ve diğer risk araştırmalarında da kullanılmaktadır [23,24]. Canadian Task Force on Preventive Health Care, DM belirtileri olmayan yetişkinlerin 3-5 yılda bir FINDRISC aracı ile taramalarının yapılmasını, ölçekten kesim noktası olan 15 ve üzerinde puan alanları yüksek riskli olarak kabul edilmesini uygun görmüştür [17]. Ülkemizle coğrafi ve kültürel olarak benzer bir ülke olan Yunanistan'da DM taramasında FINDRISC aracının kullanımı uygun bulunmuştur [25].

Tüm bu açıklamalara göre, Türkiye'de DM risk tahmininde FINDRISC aracından yararlanılabilir. Sağlık kuruluşlarına -özellikle de aile hekimlerine- başvuran yetişkinlerin kan şekeri ölçümü sorgulanmalı, kişilerin DM riski hesaplanmalı ve risk düzeyine göre kan şekeri ölçülmeli, riski yüksek olanlara risk faktörlerini nasıl kontrol altında tutabileceği konusunda danışmanlık verilmelidir.

Teşekkür: Bu araştırmanın yapılması ve yazılması sürecinde, herhangi bir kişi veya kuruluştan finansal bir destek, bağış vb. yardım alınmamıştır. Ayrıca bu çalışma ile ilgili olarak, herhangi bir kişi veya kuruluşla bir çıkar ilişkisi bulunmamaktadır.

Çıkar Çakışması ve Finansman Beyanı

Bu çalışmada çıkar çakışması ve finansman destek alındığı beyan edilmemiştir.

Kaynaklar

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Peripherally Inserted Intravenous Catheters in Children: One Year

Çocuk Hastalarda Damar İçi Kateter Kullanımı: Bir Yıllık Deneyim

Çocukta Kateter Kullanımı / Catheter Usage in Children

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Özet

Amaç: Damar içi kateter yerleştirilmesi gerek yoğun bakım üniteleri gerekse servislerde hasta çocukların yönetiminde giderek artan sıklıkta kullanılmaktadır. Bu çalışmada amaç, kateter yerleştirilmesi ile ilişkili komplikasyonlar ve risklerin değerlendirilmesidir. Gereç ve Yöntem: Ağustos 2014 ile Ağustos 2015 tarihleri arasında İstanbul Üniversitesi Çocuk Yoğun Bakım Ünitesinde damar içi kateter yerleştirilen 105 hasta ve yerleştirilen 171 kateter geriye dönük olarak dosya kayıtları ile incelendi. Bulgular: Ortalama kateter takılma yaşı 4,45±5,48 yıl, dağılımı 3 gün-228 ay, 78'i (%45,6) kız, 93'ü (%54,4) erkek idi. Yüz on beş kateterin (%67,3) kalış süresi 7 gün ve üzeri, ortalama kalış süresi 20,33±38,80 idi. En sık altta yatan hastalık metabolik hastalıktı (n=43, %25,1). Kateterler en sıklıkla damar yolu bulunamaması nedeni ile takılmıştı (n=77, %45). Kateter tipleri en sık santral venöz kateter (n=110, %64,3) ve hemodiyaliz kateteri (n=51, %29,8) idi. Hastalara 98 femoral (%57,3), 48 juguler (%28,1) ve 22 subklaviyan kateter (%12,9) yerleştirildi. Kateterlerin 107'si (%62,6) sadece yoğun bakım ünitesinde, 30'u (%17,5) yoğun bakımdan sonra serviste ve 34'ü (%19,9) serviste kullanılmak üzere takıldı. Hastaların 13'ünde (%7,6) kateter ilişkili enfeksiyon gözlendi. Hastaların 6'sında (%3,5) işlem sırasında ya da sonrasında enfeksiyon dışı komplikasyon gözlendi. Kateterlerin 95'i (%55,6) gereksinimin ortadan kalkması nedeniyle çekildi. Kateter tipi, boyu ve takıldığı bölge karşılaştırıldığında enfeksiyon sıklığı açısından anlamlı bir farklılık bulunmazken (p>0,05), kateter kalış süresi uzadıkça enfeksiyon sıklığının anlamlı olarak arttığı görüldü (p<0,05). Serviste takip edilen kateterlerde enfeksiyon sıklığı anlamlı olarak yüksek saptandı (p<0,05). Tartışma: Çocuk hastaların izleminde önem taşıyan kateterlerin tecrübeli kişiler tarafından yerleştirilmesi ve bakımı ile komplikasyon oranları azaltılabilmektedir.

Anahtar Kelimeler

Çocuk; Damar İçi Kateter; Kateter Komplikasyonları; Kateter İlişkili Kan Akımı Enfeksiyonları

Abstract

Aim: Intravascular catheters are used in intensive care units as well as the services with increased frequency in the management of children. The aim of this study is to evaluate the complications and risk factors associated with intravascular catheterization. Material and Method: Between the years 2014-2015 Augusts, in Medical Faculty of Cerrahpasa, University of Istanbul, Pediatric Intensive Care Unit, 105 patients and placed 171 intravascular catheters analyzed retrospectively by the patients' medical records. Results: Average age of catheter insertion was 4,45±5,48 years, ranging between 3 days-228 months. 78 of the patients (45.6%) were female, 93 (54.4%) were male. One hundred and fifteen catheters (67.3%) were used 7 days or more, the average length of usage was 20.33±38.80. The most common underlying disease was metabolic disease (n = 43, 25.1%). Catheters were inserted most often because of the absence of a peripheral venous route (n = 77, 45%). The most common catheter types were central venous catheter (n = 110, 64.3%) and hemodialysis catheters (n = 51, 29.8%), respectively. Ninety eight femoral (57.3%), 48 jugular (28.1%) and 22 subclavian (12.9%) catheters were placed. Hundred and seven of the catheters (62.6%) were used only in intensive care unit, 30 (17.5%) in services after intensive care unit and 34 catheters (19.9%) were placed for the usage in services. Catheter-related infections were observed in 13 patients (7.6%). Noninfectious complications were observed in 6 cases (3.5%) during or after insertion. Ninety five catheters (55.6%) withdrew due to no more remaining requirement. As catheter type, size and location had no risk for catheter related infections (p> 0.05), increased time length for the usage of catheters showed a significant increase in infection incidence (p <0.05). The frequency of infection of catheters followed in services was significantly higher (p <0.05). Discussion: The insertion and care of catheters by skilled persons reduce the complication rates.

Keywords

Children; Intravascular Catheter; Catheter Complications; Catheter Related Infections

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Giriş

Günümüzde çocuk yoğun bakımların önemi ve sayısındaki artışa paralel olarak yatan hasta sayısı ile hastaya yapılan girişimler artmaktadır. Çocuklarda damar yolu bulma sorunları, parenteral beslenme, kan ürünlerinin verilmesi, ekstrakorporeal tedavilerin uygulanması, hemodinamik parametrelerin takibi ve kan örneklemesinin yapılması gibi nedenler ile kateterizasyon işlemleri daha sık olarak uygulanmaktadır. Birtakım ön yargılardan dolayı bazı merkezlerin kateter kullanımında halen çekinceleri vardır. Bu çekincelerden en önemlisi de mortalite ve morbiditesi yüksek olan kateter ilişkili enfeksiyonlardır. Özellikle subklaviyan ve internal juguler kateterler yerleştirilmesi sırasında pnömotoraks, hemotoraks, tromboemboli gibi yaşamı tehdit edici komplikasyonlar gelişebilmektedir. Bu çalışmanın amacı kateter kullanımının tecrübeli ellerde güvenilir olduğunu göstermektir.

Gereç ve Yöntem

İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Çocuk Yoğun Bakım Ünitesi'nde Ağustos 2014-Ağustos 2015 tarihleri arasında takılan tüm kateterler geriye dönük olarak incelendi ve hasta bilgileri toplandı. Kateter takılan hastaların yaş, cinsiyet, tanı, yoğun bakım yatış ve çıkış tarihleri, yoğun bakımda kalış süreleri, kateter takılma endikasyonları, takılma yeri ve kalış süresi, kateter takılma sırasında ve sonrasında gelişen komplikasyonlar, enfeksiyon oranları, üreyen mikroorganizmalar, kateterin çekilme nedeni ve kateter enfeksiyonuna bağlı ölümler incelendi.

Hemodiyaliz ve santral venöz kateterizasyon (SVK) için femoral, internal juguler ve subklaviyan venler kullanıldı. Arter kateterizasyonu için femoral ve radyal arterler kullanıldı. Kateter takılma öncesinde hastalara sedasyon ve analjezi uygulandı. Sedasyon ve analjezi için midazolam, ketamin, remifentanil ve propofol tercih edildi. Lokal anestezik olarak da lidokain kullanıldı. Nöromusküler blokör kullanılmadı. Hiçbir hastaya cerrahi kateter takılmadı. Tüm kateterler tek bir uzman tarafından takıldı.

Kateter takıldığı sırada aseptik teknik kullanıldı. Girişim yeri %10 povidon iyot ile steril edildikten sonra kuruması beklendi. Tüm vücudu örtecek şekilde tek kullanımlık steril örtü kullanıldı. İşlem sırasında steril önlük, maske ve bone giyildi. Ultrasonografi (USG) kullanılmadı. Kateterler Seldinger tekniği ile takıldı ve 2.0 keskin uçlu ipek ile cilde sabitlendi. Üzeri ilk gün steril gazlı bezle kapatıldı. Ertesi gün pansuman yenilendi ve günlük pansuman yapıldı. Juguler ve subklaviyan kateterlerin takılma işlemi sonrasında akciğer grafisi çekildi. Kateter takılma işlemi sırasında heparin kullanılmadı. İşlem sonrasında kilit solüsyonu veya antibiyotikle kapatma uygulanmadı. Diyaliz kateterleri dışında heparinli kapatma yapılmadı. Kateter giriş yerine lokal antibiyotik uygulanmadı. Kateter setleri lipid içeren sıvılar kullanılıyorsa 24 saatte bir, diğerleri ise 48 saatte bir değiştirildi.

Sepsis kliniği ve laboratuvar bulguları olan hastalardan kültür örneklemeleri yapıldı. Kateterden ve periferden alınan kan kültürlerinde aynı mikroorganizmanın üremesi kateter ilişkili kan akımı enfeksiyonu, kateterden alınanda üreme olup periferden alınan kan kültürlerinde üreme olmaması kolonizasyon olarak kabul edildi. Giriş yerinde kızarıklık, akıntı ve ısı artışı olması lokal enfeksiyon olarak değerlendirildi. Tüm bu enfeksiyon durumlarında kateterler çekildi. Kateter kaynaklı enfeksiyon, katetere bağlı komplikasyon ya da lümende tıkanıklık olmadıkça kateterler rutin olarak değiştirilmedi. Kateter enfeksiyonu düşünülmedikçe rutin olarak kateter ucu kültürü gönderilmedi. Kateterlerin hepsi steril koşullarda çocuk hekimi tarafından çekildi.

İstatistiksel analizde SPSS programı (15.0. sürüm, Chicago, SPSS Inc.) kullanıldı. Sayısal veriler ortalama±standart sapma, kategorik veriler ise sıklık (n) ve yüzde (%) ile belirtildi. Sayısal verilerin değerlendirilmesinde normal dağılım gösteriyorsa Student-t testi, normal dağılım göstermiyorsa Mann-Whitney U testi ve kategorik verilerin değerlendirilmesinde Ki-Kare testi kullanıldı. İstatistiksel anlamlılık p değerinin 0,05'in altı olarak kabul edildi.

Bulgular

Ağustos 2014 ile Ağustos 2015 tarihleri arasında çocuk yoğun bakım ünitesine yatırılan 105 hastaya 171 adet kateter yerleştirildi. Kateterlerin 78'i (%45,6) kız, 93'ü (%54,4) erkek hastaya takılmıştı. Hastaların yaş dağılımları 3 gün ile 228 ay arasında olup ortalama kateter takılma yaşı 4,45±5,48 yıldı. Hastaların tartıları 2,5 ile 110 kilogram arasında idi. Kateterlerin 43 'ü (%25,1) metabolik hastalık tanısı ile yatırılan hastalara takıldı (Hastaların dağılımı ayrıntılı olarak Tablo I'de gösterilmiştir). Hastaların 82'sinde (%48) başvuru anında enfeksiyon vardı. Takılma nedenlerinden en sık üç neden 77 kez (%45) damar yolu bulunamaması, 53 kez (%31) hemodiyaliz uygulanması ve 34 kez (%19,9) ilaç ve sıvı tedavisi idi. En sık kateter tipi olarak hastalara 110 (%64,3) santral venöz kateter (SVK) ve 51 (%29,8) hemodiyaliz kateteri yerleştirildi. İki hastanın hemodiyalizi uygun boyda kateter olmadığı için SVK ile yapıldı. Kan ürünü aktarımı 124 kateter (%72,5) aracılığı ile yapıldı. Hastalara 98 (%57,3) femoral, 48 (%28,1) juguler ve 22 (%12,9) subklaviyan kateter yerleştirildi. Yüz sekiz kateter (%63,2) acil şartlarda takıldı. En sık (n= 86, %50,3) kullanılan kateter 4 french iki lümenli geçici kateter idi (Seldiflex 4F-2L, PU 8 cm, 1,3 mm). Kateterlerin 107 tanesi (%62,6) sadece yoğun bakım ünitesinde izlendi. 30 kateter (%17,5) yoğun bakımdan sonra serviste kullanılmaya devam edildi. 34 kateter (%19,9) serviste kullanılmak üzere takıldı. Kateterlerin 95'i (%55,6) gereksinimin ortadan kalkması nedeniyle çekildi. Yüz on beş kateterin (%67,3) kalış süresi 7 gün ve üzeri, ortalama kalış süresi 20,33±38,80 idi.

Hastaların 6'sında (%3,5) işlem sırasında ya da sonrasında enfeksiyon dışı komplikasyon gözlendi. Bir hastada juguler ven kateteri takılırken arter ponksiyonuna bağlı transfüzyon gerektiren hematom, bir hastada subklaviyan ven kateteri takılırken pnömotoraks gelişti ve tüp torakostomi yapıldı. Dört hastanın femoral vende tromboz gelişmesi nedeniyle kateterleri çekildi, düşük molekül ağırlıklı heparin tedavisi uygulandı. Kateter takılma sırasında ölen hastamız olmadı.

Hastaların 6'sında (%3,5) kateter sepsisi, 4'ünde (%2,3) lokal enfeksiyon ve 3'ünde (%1,8) kolonizasyon saptandı. Bin kateter gününe düşen kateter enfeksiyon sayısı 3,38 olarak hesaplandı, bu sayı sadece yoğun bakım ünitesinde izlenen hastalar için 1,88 idi. Katetere bağlı sepsisten iki hasta kaybedildi. Hastaların ikisi de ağır malnütre ve uzun süreli total parenteral beslenme alan hastalardı. Kateterler de uzun süreli beslenme için takılmıştı. Hastaların birinde karbapenem dirençli Klebsiella Pneumoniae, diğerinde ise Enterobacter Cloacae üremesi oldu. Kateter ilişkili enfeksiyonlarda üreyen mikroorganizmalar Tablo II'de gösterilmiştir.

Kateter tipi, boyu ve takıldığı bölge karşılaştırıldığında enfeksiyon sıklığı açısından anlamlı bir farklılık bulunmadı (p>0,05). Kateter takılma yaşı ile enfeksiyon ya da komplikasyon gelişme sıklığı arasında anlamlı fark bulunmadı (p>0,05). Başvuruda enfeksiyon varlığı ile kateter enfeksiyonu gelişme sıklığı arasında anlamlı bir ilişki bulunmadı (p>0,05). Kateter kalış süresi uzadıkça enfeksiyon sıklığının anlamlı olarak arttığı görüldü (p=0,001). Serviste takip edilen kateterlerde enfeksiyon sıklığı anlamlı olarak yüksek saptandı (p=0,008).

Tartışma

Çocuk hastalarda damar içi kateter kullanımı kan örneklemesinin yapılması, ilaç ve sıvı tedavisinin uygulanması, hemodinamik bulguların takibi, ekstrakorporeal tedavilerin uygulanması gibi pek çok amaçla gerek yoğun bakım üniteleri gerekse yataklı servislerde giderek artan sıklıkta kullanılmaktadır1,2,3. Ayrıca kateter uygulaması ile zor damar yolu bulmanın gerek sağlık çalışanı gerekse çocuk ve aile üzerinde yarattığı stres ortadan kalkmakta ve verilen sağlık hizmetinin kalitesi artırılmaktadır. Teknik zorluklar ve işleme bağlı komplikasyonlar gözlenebilse de deneyimli kişiler tarafından takılan ve bakımı uygulanan kateterlerde komplikasyonların azaldığı vurgulanmakta ve kullanım alanları genişletilmektedir4,5.

En sık görülen komplikasyonlar mekanik, enfeksiyöz ve trombotik komplikasyonlar olarak gruplandırılabilir4,6. Bu komplikasyon oranları çeşitli girişimlerle, örneğin USG rehberliğinde kateter takılması, antibiyotik ile kapatma yapılması ya da fibrinolitik kullanımı gibi, azaltılmaya çalışılmaktadır. Bizim yoğun bakımımızda USG cihazı olmadığı için klasik yöntem ile kateterizasyon uygulandı.

Mekanik problemler kateterde tıkanıklık, kateterin kıvrılması, kırılması, yırtılması ya da yanlışlıkla yerinden çıkmasıdır ve nadiren hayatı tehdit edicidir. En ciddi problem oldukça nadir görülse de kateterin kırılıp parçasının emboli atmasıdır. Çalışmamızda bir hastada transfüzyon gerektiren hematom ve bir hastada pnömotoraks gelişti. Hastaların acil müdahalesi yapıldıktan sonra farklı bölgeye takılan kateterlerde problem yaşanmadı.

Çocuklarda kateter ilişkili enfeksiyonlar 1000 kateter gününe 0,5 ile 2,8 aralığında bildirilmiştir7. Enfeksiyonun önlenmesinde birçok yayınlanmış rehber bulunmaktadır8,9,10. Enfeksiyonun belirlenmesinde periferden ve kateterden alınan kan örneği ve kateter ucu kültürlerinin yapılması önem taşımaktadır. Böylece kateter kaynaklı kan akımı enfeksiyonu tanısı konulabilmekte ve kateterin çekim kararı verilebilmektedir. Bakteriyeminin raporlanmasında, 1000 kateter gününe denk gelen kateter ilişkili enfeksiyon sayısının hesaplanması ile enfeksiyon riskinin belirlenmesi önemlidir11. Mclaws ve ark.'nın yaptığı çalışmada 1-5 gün arasında kalan kateterlerin enfeksiyon sıklığı 1000 kateter gününe 2,1 iken 16-30 gün arasında kalan kateterlerde 10,2'ye yükseldiği görülmüştür12. Ancak 2015'te yayınlanan Cochrane analizinde 72-96 saatte bir kateterlerin düzenli değiştirilmesinin kateter ilişkili komplikasyonları azaltmadığı sonucuna ulaşılmış ve kateterlerin klinik olarak gereklilik halinde değiştirilmesi önerilmiştir13. Kateter kalış süresinin 21 günden uzun olması, parenteral beslenme için kateter takılması, kronik metabolik bozukluğun olması, yoğun bakım ünitesinde kalma ve tekrarlayan kateter uygulanması kateter ilişkili enfeksiyonları artıran en önemli risk faktörlerindendir4,6,7,8. Çalışmamızda da olduğu gibi eskiden sanılanın aksine kateter takılma yeri ile enfeksiyon sıklığı arasında bir ilişki bulunmamıştır14. En sık saptanan mikrobiyolojik etkenler gram pozitif koklardır (Koagülaz negatif stafilokok, Stafilokok Aureus). Gram negatif etkenler ve mantarlar da sık görülen enfeksiyon etkenleridir15. Enfeksiyonun tedavisinde kateterler çekilmeli ve uygun sistemik antibiyotikler uygulanmalıdır. Yoğun bakım ünitemizde rutin kateter değişimi yapılmadı, antibiyotik ya da kilit solüsyonu ile kapatma yapılmadı, ancak komplikasyon ya da tıkanıklık gelişmiş ise kateterler değiştirildi. Ayrıca Yoğun bakımımızda HEPA (High Efficiency Particulate Air) filtre bulunmamakta idi. Aseptik teknikle takılan kateterlerin aynı özenle bakımları yapıldı, giriş yerleri kontrol edildi. Günlük pansumanları değiştirildi. Bin kateter gününe düşen kateter enfeksiyon sayısı 3,38 olarak hesaplandı, bu sayı sadece yoğun bakım ünitesinde izlenen hastalar için 1,88 bulundu. Serviste takip edilen kateterlerde enfeksiyon sıklığı anlamlı olarak yüksek saptandı. Bu farkın bizce nedeni yoğun bakım hemşire ve personelinin kateter bakımı ile takibi konusunda eğitim almış olmasıdır. Hastaların 6'sında (%3,5) kateter sepsisi, 4'ünde (%2,3) lokal enfeksiyon ve 3'ünde (%1,8) kolonizasyon saptandı. Ağır malnütre, uzun süreli total parenteral beslenme alan ve bu amaçla santral venöz kateter yerleştirilen iki hasta katetere bağlı sepsisten kaybedildi. Birinde karbapenem dirençli Klebsiella Pneumoniae, diğerinde ise Enterobacter Cloacae üremesi oldu. Her iki hasta da kateterleri takıldıktan sonra servise devredilmişti. Servis izlemi sırasında septik şoka girmeleri üzerine yoğun bakıma alındılar. Enfeksiyon saptandığında birinin kateteri 48.gününde subklaviyan, diğeri ise 10. gününde femoral kateterdi. Kateter enfeksiyonu nedeniyle toplamda 8 hastanın (%4,7) kateteri çekildi. Kalış süresi uzadıkça enfeksiyon sıklığının anlamlı olarak arttığı görüldü. Kan ürünü verilmesi ile kateter infeksiyonu arasında da istatistiksel anlamlı farklılık bulunmadı. Zaten hastaların büyük çoğunluğuna kan ürünü aktarımı yapılmıştı.

Kateter kullanımında en önemli çekincelerden biri de tromboz gelişimidir. Risk faktörleri konjenital olarak tromboza yatkınlık oluşturan hastalıklar, öncesinde bilinen kateterde tıkanıklık ve kateter ilişkili enfeksiyonların varlığıdır. Trombozu öngörmek ve önlemek amacıyla çocukta ve ailede tromboz sorgulanmalı, tromboz riskinin artıracak altta yatan hematolojik ve onkolojik hastalıklar belirlenmelidir; ayrıca damar boyutuna uygun kateterler kullanılmalı, kateterin kullanım süresi göz önünde tutulmalıdır. Düzenli antikoagülan tedavi ile profilaksi önerilmemektedir. Tromboz açısından yüksek riski olan ve kanama riski düşük olan çocuklarda tromboprofilaksi yapılabilir16. Kateter ilişkili derin ven trombozu enfeksiyon, posttrombotik sendromlar ve pulmoner emboliye neden olabilir. Bulgu vermeyebildiğinden ya da geç bulgu verebildiğinden düzenli Doppler USG yapılması ya da düşük molekül ağırlıklı heparin profilaksisi etkinliği açısından da birçok çalışma mevcuttur17,18. Ayrıca bulgu vermeyen trombüslerde tedavi trombüsün yeri, büyüklüğü, damarı tıkama derecesi, hastanın mevcut koagülasyon durumu gibi çok faktöre bağlı olarak klinisyenin kararıdır. Tedavide düşük molekül ağırlıklı heparin güvenle kullanılabilir. Ünitemizde sadece uzun süreli femoral kateteri olan ya da ekstremite dolaşımı bozulan hastalardan doppler USG istedik. Dört hastada (%2,3) tromboz gelişti, tromboz gelişen tüm kateterler femoral vende yerleşimli idi. Hastaların kateterleri çekilip düşük molekül ağırlıklı heparin te-

davisi uygulandıktan sonra problem yaşanmadı.

Özetle; bu çalışmada çocuk yaş grubunda damar içi kateter kullanımı ve bakımının deneyimli ekip tarafından uygulanmasının komplikasyonları azaltacağını son bir yıllık deneyimimiz ile göstermek istedik. Bununla birlikte çocuk hastalarda bu görüşümüze destek olacak daha kapsamlı ileriye dönük çalışmalara ihtiyaç vardır.

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Antibiotic Resistance in Staphylococcus aureus Strains Isolated from Clinical Specimens

Klinik Örneklerden İzole Edilen Staphylococcus aureus Suşlarında Antibiyotik Direnci

Staphylococcus aureus ve Antibiyotik Direnci / Staphylococcus aureus and Antibiotic Resistance

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Özet

Amaç: Bu çalışmada 2011-2014 yılları arasında çeşitli klinik örneklerden izole edilen S.aureus suşlarının antibiyotik duyarlılıklarının belirlenmesi ve yıllar içerisindeki değişiminin incelenmesi amaçlanmıştır. Gereç ve Yöntem: Suşların identifikasyonu ve antibiyotik duyarlılık testleri Vitek 2 compact otomatize sistemi (bioMérieux, Fransa) ile yapılmıştır. Vankomisine ve teikoplanine orta duyarlı bulunan suşlar E-test yöntemiyle test edilmiştir. Bulgular: S.aureus suşları (n=1442) en sık yara, idrar ve kan örneklerinden izole edilmiştir. Yatan hastalardan MRSA izole edilme oranlarının ayaktan hastalara göre anlamlı ölçüde yüksek olduğu saptanmıştır. Tüm suşlar vankomisin, teikoplanin, linezolid ve tigesikline duyarlı bulunmuştur. MRSA suşlarının toplam dört yıllık eritromisin, klindamisin, siprofloksasin, moksifloksasin, gentamisin, ko-trimoksazol, fusidik asit direnç oranları metisiline duyarlı S.aureus (MSSA) suşlarına göre istatistiksel olarak anlamlı derecede yüksek bulunmuştur. MSSA suşlarının antibiyotik direnç oranlarında yıllar içinde istatistiksel olarak anlamlı bir değişiklik saptanmazken, MRSA suşlarında yıllar içinde eritromisin, klindamisin, siprofloksasin, moksifloksasin ve gentamisin direncinde anlamlı bir azalma saptanmıştır. Tartışma: Glikopeptidler, linezolid ve tigesiklin S.aureus suşlarına karşı en etkili antibiyotikler olarak saptanmıştır. İnfeksiyonların kontrolü ve direnç gelişiminin önlenebilmesi için etkin sürveyans çalışmalarıyla antimikrobiyal direnç profillerinin tespit edilmesi ve yıllar içinde ortaya çıkan değişikliklerin izlenmesinin gerekli olduğu düşünülmüştür.

Anahtar Kelimeler

Staphylococcus aureus; Antibiyotik Direnci; MRSA; MSSA

Abstract

Aim: The aim of this study was to determine the antibiotic susceptibilities of S.aureus strains isolated from various clinical specimens between the years 2011-2014 and to investigate the changes of these susceptibilities over the years. Material and Method: Identification and antibiotic susceptibility testing of the strains were performed by Vitek 2 compact automated system (bioMérieux, France). The strains found to be intermediate susceptible to vancomycin and teicoplanin were also tested by E-test method. Results: S.aureus strains (n=1442) were most commonly isolated from wound, urine and blood samples. The isolation rates of methicillin-resistant S.aureus (MRSA) in hospitalized patients were significantly higher than the isolation rates of MRSA in outpatients. All strains were susceptible to vancomycin, teicoplanin, linezolid and tigecycline. The total of four years resistance rates of MRSA strains to erythromycin, clindamycin, ciprofloxacin, moxifloxacin, gentamicin, co-trimoxazole, fusidic acid were significantly higher than the resistance rates of methicillin-sensitive S.aureus (MSSA). The changes in the rates of antibiotic resistance were not statistically significant in MSSA strains over the years, and statistically significant decrease was found in erythromycin, clindamycin, ciprofloxacin, moxifloxacin and gentamicin resistance in MRSA strains. Discussion: Glycopeptides, linezolid and tigecycline were the most effective antibiotics against S.aureus strains. It was considered as necessary to detect antimicrobial resistance profiles by effective surveillance studies and monitor the changes occurred over the years in order to prevent the development of resistance and control of infections.

Keywords

Staphylococcus aureus; Antibiotic Resistance; MRSA; MSSA

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Giriş

Staphylococcus aureus, morbidite ve mortalitesi yüksek toplum ve hastane kaynaklı infeksiyonlara yol açabilen önemli bir patojendir. Başta deri ve yumuşak doku infeksiyonları olmak üzere osteomyelit, septik artrit, pnömoni, endokardit ve bakteriyemiye neden olan S. aureus, hastane infeksiyonu etkenleri arasında ilk sıralarda yer almaktadır [1-3]. Özellikle metisiline dirençli suşların neden olduğu infeksiyonların tedavisinde büyük sorunlar yaşanmaktadır. Metisiline dirençli S.aureus (MRSA) suşları tüm beta laktam grubu antibiyotiklere dirençli olmakla birlikte makrolidler, linkozamidler, kinolonlar ve aminoglikozidlere de direnç gösterebilmektedir [3,4]. MRSA'ya bağlı infeksiyonların tedavisinde glikopeptid grubu antibiyotiklerin özellikle de vankomisinin sık kullanımı sonucunda; vankomisine orta düzeyde duyarlı (VISA), heterojen orta düzeyde duyarlı (hVISA) ve dirençli (VRSA) suşlarının ortaya çıktığı bildirilmektedir. Son yıllarda artış gösteren bu çoklu antibiyotik direnci, ciddi MRSA enfeksiyonlarında antimikrobiyal tedavi seçeneklerini kısıtlayabilecek boyutlara ulaşmıştır [1,2].

Antibiyotik direnç profillerinin düzenli olarak izlenmesi, ampirik tedavide seçilecek ilaçların belirlenmesi ve direnç gelişiminin önlenebilmesi açısından önemlidir. Bu retrospektif çalışmada hastanemizde dört yıllık süre içinde çeşitli klinik örneklerden izole edilen S.aureus suşlarının antibiyotik duyarlılıklarının belirlenmesi ve yıllar içerisindeki değişiminin incelenmesi amaçlanmıştır.

Gereç ve Yöntem

Ocak 2011-Aralık 2014 tarihleri arasında çeşitli klinik örneklerden izole edilen 1442 S.aureus suşu çalışmaya alınmıştır. Ayaktan ve yatan hastalardan alınan örnekler kanlı, Eosine Methylene Blue (EMB) ve çikolata agar besiyerlerine ekilmiş, kan kültürleri BacT/Alert 3D (bioMérieux, Fransa) otomatize kan kültürü sisteminde değerlendirilmiştir. İzole edilen suşlar konvansiyonel yöntemlerin (koloni morfolojisi, gram boyama, katalaz, lam ve tüpte koagülaz, sefoksitin tarama testi) yanısıra Vitek 2 compact (bioMérieux, Fransa) otomatize sistemi ile tür düzeyinde tanımlanmıştır. Suşların antibiyotiklere karşı duyarlılıkları Clinical Laboratory Standards Institute (CLSI) ve üretici firmanın önerileri doğrultusunda Vitek 2 compact otomatize sistemi ile araştırılmıştır. CLSI onaylı standart sınır değeri olmayan fusidik asit ve tigesiklin için European Committee on Antimicrobial Susceptibility Testing (EUCAST) kriterlerine göre minimum inhibitör konsantrasyon (MİK) değeri sırasıyla ≤1 µg/ml ve ≤0.5 µg/ml olanlar duyarlı olarak değerlendirilmiştir. Vankomisine ve teikoplanine orta duyarlı bulunan suşlar E-test (bioMérieux, Fransa) yöntemiyle de test edilmiştir. Kontrol suşu olarak S.aureus ATTC 25923 standart suşu kullanılmıştır. Tekrarlayan üremelerde, aynı hastaya ait tek örnek çalışmaya dahil edilmiştir. Orta duyarlı olarak saptanan suşlar dirençli olarak kabul edilmiştir. Çalışmamıza ait veriler retrospektif olarak elde edilmiş ve incelenmiştir. Antibiyotik duyarlılıklarının istatistiksel olarak karşılaştırılmasında ki-kare ve Fisher's exact testi kullanılmıştır. $p<0.05$ değeri anlamlı olarak kabul edilmiştir.

Bulgular

Dört yıllık süre içinde izole edilen 1442 S.aureus suşunun 1303'ü metisiline duyarlı, 139'u metisiline dirençli olarak belirlenmiştir. Metisiline duyarlı S.aureus (MSSA) ve MRSA suşlarının örneklere göre dağılımı Tablo 1'de gösterilmiştir. S.aureus suşlarının sırasıyla en sık yara (%43.4), idrar (%26.4) ve kan (%22.7) örneklerinden izole edildiği görülmüştür.

Ayaktan ve yatan hastalarda MSSA ve MRSA suşlarının yıllara göre dağılımı Tablo 2'de gösterilmiştir. MSSA suşlarının (n=1303) en sık ayaktan hastalardan (n=713), MRSA suşlarının (n=139) ise en sık yatan hastalardan (n=104) izole edildiği görülmüştür. Yatan hasta örneklerinden MRSA izole edilme oranının ayaktan hasta örneklerine göre anlamlı ölçüde yüksek olduğu saptanmıştır (p=0.000). Ayaktan hastalarda MRSA suşu izolasyon oranları 2011, 2012, 2013, 2014 yıllarında sırasıyla %5.2, %4.8, %3.0, %6.1 olarak saptanmış olup yıllar içindeki değişiklikler istatistiksel olarak anlamlı bulunmamıştır (p>0.05). Yatan hastalarda ise MRSA suşu izolasyon oranları 2011, 2012, 2013, 2014 yıllarında sırasıyla %18.0, %17.2, %12.6, %12.1 olarak saptanmıştır. Yatan hastalarda yıllar içinde MRSA suşu izolasyon oranlarında bir azalmanın olduğu görülmesine rağmen fark istatistiksel olarak anlamlı bulunmamıştır (p>0.05).

Tablo 1. MSSA ve MRSA suşlarının örneklere göre dağılımı [n (%)]

Örnek	MSSA	MRSA	Toplam
Yara	548 (42.1)	78 (56.1)	626 (43.4)
İdrar	367 (28.2)	14 (10.1)	381 (26.4)
Kan	295 (22.6)	33 (23.8)	328 (22.7)
Trakeal aspirat	39 (3.0)	10 (7.2)	49 (3.4)
Balgam	19 (1.5)	1 (0.7)	20 (1.4)
Kulak	16 (1.2)	-	16 (1.1)
Vajen	6 (0.5)	-	6 (0.4)
BOS	4 (0.3)	-	4 (0.3)
Konjonktiva	4 (0.3)	-	4 (0.3)
Boğaz	3 (0.2)	2 (1.4)	5 (0.4)
Kateter	2 (0.1)	1 (0.7)	3 (0.2)
Toplam	1303 (100)	139 (100)	1442 (100)

Tablo 2. Ayaktan ve yatan hastalarda MSSA ve MRSA suşlarının yıllara göre dağılımı [n (%)].

Yıllar	Ayaktan		Yatan	
	MSSA	MRSA	MSSA	MRSA
2011	184 (94.8)	10 (5.2)	137 (82.0)	30 (18.0)
2012	179 (95.2)	9 (4.8)	154 (82.8)	32 (17.2)
2013	196 (97.0)	6 (3.0)	146 (87.4)	21 (12.6)
2014	154 (93.9)	10 (6.1)	153 (87.9)	21 (12.1)
2011-2014	713 (95.3)	35 (4.7)	590 (85.0)	104 (15.0)

MSSA ve MRSA suşlarının yıllara göre antibiyotik direnç oranları Tablo 3 ve 4'te gösterilmiştir. Vitek 2 compact otomatize sisteminde vankomisine orta duyarlı bulunan 6 MRSA suşu ve teikoplanine orta duyarlı bulunan 9 MRSA suşu E-test yöntemi ile vankomisine ve teikoplanine duyarlı olarak saptanmıştır. MSSA suşlarının antibiyotik direnç oranlarında yıllar içinde istatistiksel olarak anlamlı bir değişiklik saptanmazken, MRSA suşlarında yıllar içinde eritromisin, klindamisin, siprofloksasin, moksifloksasin ve gentamisin direncinde istatistiksel olarak anlamlı bir azalma saptanmıştır (Tablo 3,4). MRSA suşlarının toplam dört yıllık eritromisin, klindamisin, siprofloksasin, moksifloksasin, gentamisin, ko-trimoksazol, fusidik asit direnç oranlarının

MSSA suşlarının direnç oranlarına göre istatistiksel olarak anlamlı derecede yüksek olduğu görülmüştür (tümü için p=0.000).

Tablo 3. MSSA suşlarının yıllara göre antibiyotik direnç oranları (%)

Antibiyotikler	2011 (n=321)	2012 (n=333)	2013 (n=342)	2014 (n=307)	2011-2014 (n= 1303)	p değeri
Penisilin	88.7	86.8	81.5	83.6	85.1	0.062
Eritromisin	15.3	13.8	18.4	12.7	15.1	0.355
Klindamisin	12.8	11.5	13.5	10.2	12.0	0.307
Siprofloksasin	5.7	6.9	7.6	4.2	6.2	0.412
Moksifloksasin	1.9	2.4	2.7	1.6	2.2	0.818
Gentamisin	3.1	2.7	2.6	2.0	2.6	0.359
Ko-trimoksazol	3.4	4.5	4.7	2.6	3.9	0.563
Fusidik asit	5.9	4.5	3.6	2.9	4.2	0.070
Tigesiklin	0	0	0	0	0	-
Vankomisin	0	0	0	0	0	-
Teikoplanin	0	0	0	0	0	-
Linezolid	0	0	0	0	0	-

Tablo 4. MRSA suşlarının yıllara göre antibiyotik direnç oranları (%)

Antibiyotikler	2011 (n=40)	2012 (n=41)	2013 (n=27)	2014 (n=31)	2011-2014 (n=139)	p değeri
Eritromisin	57.5	50.0	44.4	32.3	47.1	0.034
Klindamisin	54.1	47.5	37.0	30.0	43.2	0.037
Siprofloksasin	63.2	51.2	44.4	35.5	49.6	0.030
Moksifloksasin	55.0	48.7	36.0	29.0	43.8	0.029
Gentamisin	57.9	47.5	40.7	31.0	45.5	0.029
Ko-trimoksazol	12.8	14.6	23.1	17.9	16.4	0.568
Fusidik asit	10.5	12.5	7.7	6.7	9.8	0.577
Tigesiklin	0	0	0	0	0	-
Vankomisin	0	0	0	0	0	-
Teikoplanin	0	0	0	0	0	-
Linezolid	0	0	0	0	0	-

Tartışma

S.aureus suşlarında metisilin direnci, ilk kez 1961 yılında tanımlandıktan sonra giderek yaygınlaşarak tüm dünyada önemli bir sorun haline gelmiştir [2,3]. MRSA görülme sıklığı ülkeler, bölgeler, hastaneler ve hatta aynı hastanenin servisleri arasında değişkenlik gösterebilmektedir. Avrupa'da 2002-2008 yılları arasında yapılan sürveyans çalışmasının verilerine göre ülkeler arası MRSA oranları %5-100 arasında değişmektedir. European Antimicrobial Resistance Surveillance System (EARSS) tarafından yürütülen bu çalışmada MRSA oranları Kuzey Avrupa ülkelerinde ve Hollanda'da %5'in altında saptanırken aralarında Türkiye'nin de bulunduğu Balkan ülkelerinde, İtalya ve İspanya gibi Güney Avrupa ülkelerinde, İngiltere ve İrlanda'da %25 ve üzerinde tespit edilmiştir. Malta ve Portekiz'de ise bu oranın %50'lere ulaştığı görülmüştür [5]. Bununla birlikte aynı sürveyans çalışmasının 2002-2009 verilerinin değerlendirildiği EARS-net raporunda Almanya, Fransa, Belçika, Avusturya, İngiltere ve İrlanda'da saptanan MRSA oranlarının yıllar içinde azaldığı bildirilmiştir [6]. Dünyanın diğer farklı bölgelerinde yapılan çok merkezli çalışmalarda; Gales ve ark. [7] Brezilya'da MRSA oranını %31, Janagihara ve ark. [8] Japonya'da %50.5, Tillotson ve ark. [9] ABD'de %57 olarak saptamışlardır.

Ülkemizde de çeşitli hastanelerde yapılan çalışmalarda %10.9-76.7 aralığında farklı MRSA oranlarının bildirildiği görülmektedir [10-18]. Gülmez ve Gür [13], 2000-2011 yılları arası çocuk hastaların kan kültürlerinden izole ettikleri S.aureus suşlarında metisilin direncinin yıllar içinde azaldığını ve 2011 yılında oranın % 0 olduğu bildirmişlerdir. Çetinkol ve arkadaşlarının [14] yaptığı çalışmada, kan kültürlerinden izole edilen S.aureus suşlarında metisiline direncin yıllar içinde azaldığı ve 2008 yılında % 35.1 iken bu oranın 2012 yılında % 18.5'e düştüğü belirlenmiştir. Çalışmamızda da benzer şekilde yatan hastalarda metisilin direnç oranları 2011, 2012, 2013 ve 2014 yıllarında giderek azalan oranlarda sırasıyla %18.0, %17.2, %12.6, %12.1 olarak bulunmuştur. Ancak yıllar içinde gözlenen bu direnç azalması istatistiksel olarak anlamlı bulunmamıştır. Toplum kaynaklı MRSA infeksiyonları, hastane kaynaklı MRSA infeksiyonlarına göre daha az sıklıkla görülmektedir. Son yıllarda ABD'de toplum kaynaklı MRSA infeksiyonlarının sıklığında ciddi artışlar görülürken Avrupa'da halen düşük oranlarda seyretmektedir. Uzun süreli hospitalizasyon, ileri yaş, altta yatan ciddi hastalıklar, malignansi, önceden antibiyotik kullanımı ve en önemlisi uygulanan invaziv işlemler bu bakterilerle gelişen hastane infeksiyonları için başlıca risk faktörleridir [1,3,11]. Literatür bilgileriyle uyumlu olarak çalışmamızda yatan hastalardan MRSA izolasyon oranının, ayaktan hastalardaki izolasyon oranına göre istatistiksel olarak anlamlı ölçüde yüksek olduğu görülmüştür.

Metisilin direncinin yaygınlaşmasıyla birlikte MRSA suşlarının neden olduğu ciddi infeksiyonların tedavisinde vankomisinin sıklıkla kullanılmaya başlanması, vankomisine duyarlılığı azalmış suşların ortaya çıkmasına neden olmuştur. İlk VISA suşu 1996 yılında Japonya'da, vankomisine dirençli ilk S.aureus suşu ise 2002 yılında ABD'de tanımlanmıştır [1-3]. Ülkemizde yapılan çeşitli çalışmalarda S.aureus suşlarında vankomisin direncine rastlanmamıştır [10-12,15,19-23]. FDA tarafından 2000 yılında kullanım onayı alan linezolid, metisiline dirençli suşlarda glikopeptidlere alternatif antimikrobiyal ajan olarak görülmektedir. S.aureus suşlarında linezolid direncine çok nadir rastlanmaktadır. İlk kez 2001 yılında yayınlanan linezolid direncinden bu yana yapılan çeşitli çalışmalarda linezolid direnci <%0.1 olarak bulunmuştur [3,4,7-9,20,21,23]. Çalışmamızda izole ettiğimiz S.aureus suşlarında glikopeptidlere ve linezolide direnç saptanmamıştır.

Beta-laktam grubu antibiyotiklere karşı görülen direnç ve penisilin allerjisi nedeniyle özellikle toplum kökenli S.aureus infeksiyonlarının tedavisinde sıklıkla makrolid ve linkozamid grubu antibiyotikler kullanılmaktadır [18,22]. Ülkemizde ve yurt dışında yapılan çalışmalarda MSSA suşlarında eritromisin ve klindamisin direnci sırasıyla %6.4-25.5 ve %1.7-10, MRSA suşlarında ise daha yüksek olmak üzere sırasıyla %56-99 ve %10.1-87.9 arasında değişmektedir [4,7,8,10,12,15,18,19]. Çalışmamızda MSSA suşlarında toplam dört yıllık eritromisin ve klindamisin direnci sırasıyla %15.1 ve %12.0 olarak bulunmuş olup yıllar içinde istatistiksel olarak anlamlı bir değişiklik saptanmamıştır. MRSA suşlarında ise dört yıllık eritromisin ve klindamisin direnci sırasıyla %47.1 ve %43.2 olarak bulunmuş olup yıllar içinde istatistiksel olarak anlamlı bir azalma saptanmıştır.

S.aureus suşlarında metisilin direnci ile kinolon direnci arasında doğrudan bir ilişki olduğu bilinmektedir [17,22]. Çalışmamızda MRSA suşlarında kinolon direncinin MSSA suşlarına göre daha yüksek olduğu ve MRSA suşlarında yıllar içinde istatistiksel olarak anlamlı bir azalmanın olduğu görülmüştür (Tablo 3, 4). Moksifloksasinin, MSSA suşlarına siprofloksasine göre daha etkili olduğu birçok çalışmada saptanmıştır [8,17,18]. Çalışmamızda da benzer şekilde MSSA'da toplam dört yıllık siprofloksasin direnci (%6.2) moksifloksasin direncinden (%2.2) daha yüksek bulunmuştur. MSSA infeksiyonlarının tedavisinde, antibiyotik duyarlılık testlerinin sonuçları da göz önünde bulundurularak kinolonlar alternatif bir ilaç grubu olarak değerlendirilebilir.

Ülkemizde ve yurt dışında yapılan çalışmalarda gentamisin direnci MSSA suşlarında %0.4-8.2, MRSA suşlarında %41.3-90.2 arasında bildirilmektedir [4,8-12,15,18-20]. Çalışmamızda toplam dört yıllık gentamisin direnci MSSA ve MRSA suşlarında sırasıyla %2.6 ve %45.5 olarak bulunmuştur. MRSA'da gentamisin direncinin daha yüksek olduğu ve yıllar içinde istatistiksel olarak anlamlı derecede azaldığı saptanmıştır. Çalışmamızın bulgularına benzer şekilde, Holmes ve ark. [24] 1999-2006 yılları arasında MRSA suşlarında gentamisin ile birlikte siprofloksasin ve klindamisin dirençlerinin, Sipahi ve ark. [16] 2001-2005 yılları arasında S.aureus suşlarında metisilin, eritromisin, klindamisin, levofloksasin ve gentamisin dirençlerinin istatistiksel olarak anlamlı şekilde azaldığını bildirmişlerdir.

Ko-trimoksazol, yaşamsal risk taşımayan stafilokok infeksiyonlarının tedavisinde kullanılması önerilen bir antibiyotiktir [25]. Çalışmamızda dört yıllık ko-trimoksazol direnci MSSA suşlarında %3.9, MRSA suşlarında %16.4 olarak bulunmuştur. Ülkemizde ve yurt dışında yapılan çalışmalarda S.aureus suşlarında ko-trimoksazol direnci %0-74 aralığında bildirilmiştir [4,7,9,10,12,15,18,19,22,24]. Toplum kökenli ve komplike olmayan S.aureus infeksiyonlarının ampirik tedavisinde kotrimoksazol alternatif bir antibiyotik olarak düşünülebilir.

Fusidik asit bakteriyemi, endokardit, osteomyelit olgularının tedavisinde tercih edilmeyen ancak komplike olmayan ve oral yolla tedavi edilebilecek S.aureus infeksiyonlarda sıklıkla kullanılan bir antimikrobiyal ajandır [25]. Ülkemizde yapılan çalışmalarda, fusidik asit direncini Ekşi ve ark. [11] MSSA'da %2.4, MRSA'da %9.2, Yaman ve ark. [19] MSSA'da %4, MRSA'da %6, Yıldız ve ark. [20] MRSA'da %8.1 olarak bildirmişlerdir. İzole ettiğimiz MSSA ve MRSA suşlarında toplam dört yıllık fusidik asit direnci sırasıyla %4.2 ve %9.8 olarak bulunmuş olup yıllar içinde istatistiksel olarak anlamlı bir değişiklik saptanmamıştır. Fusidik asit, antibiyotik duyarlılık testlerinin sonuçlarına göre komplike olmayan MSSA ve MRSA infeksiyonlarının tedavisinde kullanılabilecek alternatif bir antibiyotik olarak değerlendirilebilir.

Ülkemizde 2008 yılında kullanıma girmiş olan tigesiklinin MRSA suşlarının neden olduğu komplike deri ve yumuşak doku infeksiyonlarının tedavisinde etkin bir şekilde kullanılabileceği bildirilmiştir [3,21,25]. Son zamanlarda yapılan çalışmalarda tigesikline karşı direnç bildirilmeye başlanmıştır. Öksüz ve ark. [21] tigesiklin direncini %2, Cesur ve ark. [23] %3 olarak bildirmişlerdir. Çalışmamızda S.aureus suşlarında tigesiklin direnci saptanmamıştır. Tigesiklin, MSSA ve MRSA suşlarına karşı glikopeptidler ve linezolidden sonra en etkili antibiyotik olarak bulunmuştur. Sonuç olarak, 2011-2014 yılları arasında çeşitli klinik örneklerden izole ettiğimiz S.aureus suşlarında glikopeptid, linezolid ve tigesiklin direncine rastlanmamış olup MRSA suşlarında yıllar içinde eritromisin, klindamisin, kinolon ve gentamisin direncinde azalmanın olduğu görülmüştür. İnfeksiyonların kontrolü ve direnç gelişiminin önlenebilmesi için tüm merkezlerin etkin sürveyans çalışmalarıyla antimikrobiyal direnç profillerini tespit etmeleri, yıllar içinde ortaya çıkan değişiklikleri izlemeleri ve buna göre antibiyotiklerin tercih edilmesi gerektiği düşünülmüştür.

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Foot Disability in Patients with Ankylosing Spondylitis: A Clinical and Ultrasonographic Assessment

Ankilozan Spondilitli Hastalarda Ayak Dizabilitesi: Klinik ve Ultrasonografik Değerlendirme

Ankilozan Spondilitli Hastalarda Ayak Dizabilitesi / Foot Disability in Patients with Ankylosing Spondylitis

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Bu çalışma 11. Türk Romatoloji Sempozyumu'nda poster olarak sunulmuştur.

Özet

Amaç: Bu çalışmanın amacı ankilozan spondilitli hastalarda ayak dizabilitesi ve ilişkili faktörleri klinik ve ultrasonografik olarak değerlendirmektir. Gereç ve Yöntem: Çalışmaya modifiye New York kriterlerine göre ankilozan spondilit (AS) tanısı konulan 40 hasta ve 30 sağlıklı kontrol alındı. Hastalık aktivitesi (BASDAI) ve fonksiyonel durumun (BASFI) yanı sıra Ayak Fonksiyon İndeksi (AFİ) ile ayak fonksiyonları, Ankylosing Spondylitis Quality of Life (ASQoL) anketi ile yaşam kalitesi değerlendirildi. Her iki grupta ultrason ile plantar fasya (PF) ve aşil tendon (AT) kalınlıkları, ekojenite değişiklikleri, kemik erozyonları, entezofit ve bursit varlığı değerlendirildi. Bulgular: Hastaların yaş ortalaması 39,9±10,4 yıl, hastalık süresi medyan 48 (1-288) ay idi. Onaltı (%40) hastada ayak ağrısı mevcuttu. Onüç (% 32,5) hastada klinik entezit bulguları saptandı. Otuz (% 75) hastada ultrasonografik incelemede en az bir patolojik bulgu gözlendi. AS'li grubun ortalama AFİ skoru kontrol grubuna göre yüksekti (p<0,001). Hasta grubunda ortalama PF ve AT kalınlıklarının fazla olduğu saptandı (Sırasıyla p<0,05, p<0,001). Hastaların AFİ skorları ile BASDAI, ASQoL ve BASFI skorları arasında anlamlı pozitif ilişki olduğu görüldü (Tüm p değerleri<0,001). Tartışma: AS'li hastalarda ayak tutulumu önemli bir dizabilite nedenidir. Ayak dizabilitesi aktif hastalık ile ilişkili olup, yaşam kalitesinde azalmaya yol açmaktadır.

Anahtar Kelimeler

Ankilozan Spondilit, Ayak Dizabilitesi, Entezit, Yaşam Kalitesi

Abstract

Aim: The objective of this study was to perform a clinical and ultrasonographic assessment of foot disability and related factors among patients with ankylosing spondylitis. Material and Method: The study enrolled 40 patients diagnosed with ankylosing spondylitis (AS) according to the modified New York criteria and 30 matched healthy controls. In addition to the assessments for Disease activity (BASDAI) and functional status (BASFI), foot functioning was evaluated using the Foot Function Index (FFI) and quality of life using the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire. Thickness of plantar fascia (PF) and Achilles tendon (AT), changes in echogenicity and presence of bone erosions, entesophytes and bursitis were examined using ultrasound. Results: The mean age of patients was 39.9 ± 10.4 years and median disease duration was 48 (1-288) months. Sixteen patients (40%) had foot pain. Thirteen patients (32.5%) had clinical evidence for enthesitis. Thirty patients (75%) showed at least one pathological finding at ultrasonographic examination. Mean FFI score was higher in the AS group versus control group (p<0.001). Mean PF and AT thickness values were found to be greater in the patient group (p<0.05 and p<0.001, respectively). A significant positive correlation was found between FFI scores and BASDAI, ASQoL and BASFI scores among patients (all p values<0.001). Discussion: Foot involvement is a major cause of disability in AS patients. Foot disability is associated with active disease and results in reduced quality of life.

Keywords

Ankylosing Spondylitis, Enthesitis, Foot Disability, Quality of Life

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Giriş

Ankilozan spondilit spinal, articular ve entesal tutulumlar nedeni ile mobilite azalması ve fonksiyonel kayıplara yol açan enflamatuar bir hastalıktır. Ankilozan spondilit (AS) seyrinde entezisler enflamatuar sürecin en fazla etkilediği bölgelerdendir. Entezit; ligament, tendon ve eklem kapsüllerinin kemiğe yapışma yerlerindeki enflamasyon olarak tanımlanmaktadır. Periferik entezit tanısı sıklıkla lokalize ağrı, şişlik ve hassasiyet gibi klinik bulgular ile konulmaktadır. Ancak olguların büyük kısmının asemptomatik olması nedeni ile entezit tanısında fizik muayenenin yetersiz kalabildiği gösterilmiştir [1, 2].

Non-invazif, ucuz ve hızlı bir yöntem olan ultrason (US) entezit tanısında manyetik rezonans görüntüleme (MRG) ile karşılaştırılabilir düzeydeki başarısı ile son yıllarda ön plana çıkmıştır [3]. Erozyonlar, tendon kalınlaşması, tendonun fibriler yapısının bozulması, ekojenite değişiklikleri, lokal kalsifikasyonlar ve entezofit'ler gibi yapısal ve enflamatuar lezyonları göstermede ultrason çok duyarlı bir yöntemdir [4]. Geliştirilen skorlama sistemleri sayesinde ultrason entezitlerin semikantitatif olarak değerlendirilmesine de imkan sağlamaktadır [1].

Aşil tendonu ve plantar fasyanın kemiğe yapışma yerleri spondiloartropatilerde (SpA) en sık etkilenen entezis bölgelerindendir [5, 6]. Bu lezyonlara bağlı gelişebilecek topuk ağrısı tanı kriterleri arasında da yer almaktadır. AS'li hastalarda entezitlere bağlı olarak yaşam kalitesinin azaldığı bilinmektedir [7, 8]. Ancak AS'in önde gelen klinik problemlerinden olan enflamatuar ayak lezyonlarının yol açtığı ayak dizabilitesi ve bunun yaşam kalitesi üzerine etkileri incelenmemiştir.

Bu çalışmada ankilozan spondilitli hastalarda ayak dizabilitesini, dizabilite düzeyini etkileyen faktörleri ve yaşam kalitesi ile fonksiyonel kapasite üzerine etkilerini araştırmayı amaçladık.

Gereç ve Yöntem

Çalışmaya fizik tedavi ve rehabilitasyon polikliniklerimizde takip ve tedavi edilmekte olan 40 ankilozan spondilitli hasta alındı. AS tanısı 1984 modifiye New York tanı kriterlerine göre konuldu. Eklem ve yumuşak dokuya yönelik cerrahi operasyon geçiren hastalar, ayaktaki entezitler veya eklemlere kortikosteroid enjeksiyonu yapılmış olan hastalar, ayak fonksiyonlarını etkileyebilecek pes planus, pes cavus gibi primer ayak problemleri olan hastalar ile nörolojik, metabolik, ağır kardiyak, pulmoner ve malign hastalığı olanlar çalışma dışında bırakıldı. Vücut kitle indeksi (VKİ), yaş ve cinsiyetin tendon kalınlıklarını etkilediği bilinmektedir [9]. Bu nedenle kontrol grubu için yaş, cinsiyet ve VKİ olarak eşleştirilmiş, primer ayak problemi olmayan 30 sağlıklı kişi alındı. Çalışma hastanemizin lokal etik kurulunun onayı ile yapıldı. Hasta ve kontrol grubundaki katılımcıların çalışma öncesinde yazılı onamları alındı.

Klinik değerlendirmeler: Hastaların lomber lateral fleksiyon, tragus-duvar mesafesi, modifiye Schober testi, servikal rotasyon ve intermalleoler mesafe ölçümleri yapıldı. Bu ölçümler kullanılarak ASAS tarafından önerilen basamaklı tanımlama yöntemi ile Bath Ankylosing Spondylitis Metrology Index (BASMI) skorları hesaplandı [10]. Hastalık aktivitesini değerlendirmek için Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [11] ile C-reaktif protein (CRP) ve eritrosit sedimantasyon hızı (ESR) değerleri kullanıldı. Bath Ankylosing Spondylitis Functional Index (BASFI) ile hastaların fonksiyonel kapasiteleri değerlendirildi [12]. Hastaların yaşam kalitelerinin değerlendirilmesi için Ankylosing Spondylitis Quality of Life (ASQoL) anketi Türkçe versiyonu kullanıldı [13].

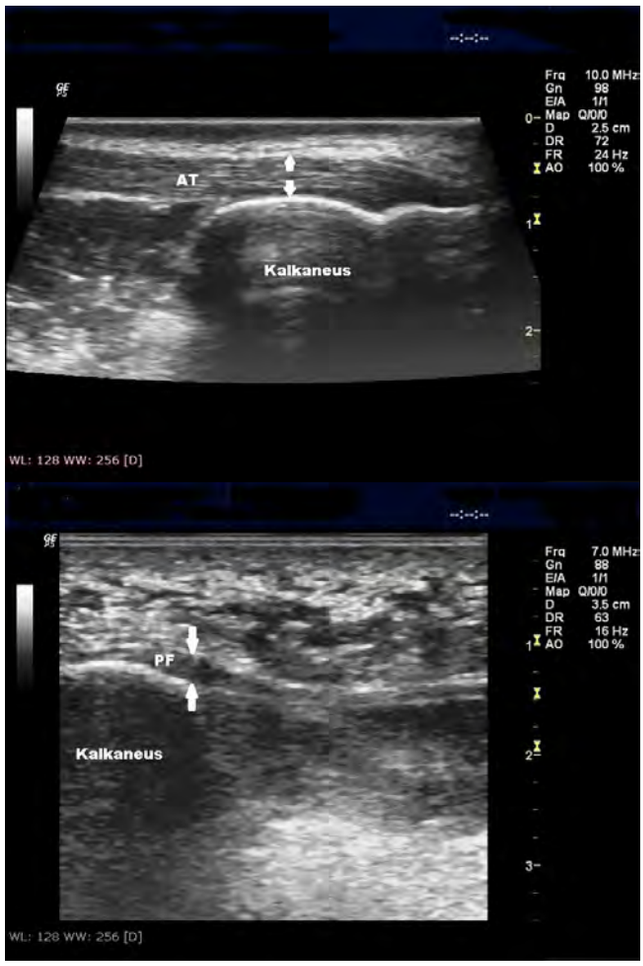
Hasta ve kontrol gruplarında ayak fonksiyonları Ayak Fonksiyon İndeksi (AFİ) ile değerlendirildi. AFİ ayak ağrısını değerlendiren 9, yetersizliği değerlendiren 9 ve kısıtlılığı değerlendiren 5 olmak üzere toplam 23 sorudan oluşan bir ölçektir. Katılımcıların son bir hafta içindeki durumlarını göz önüne alarak tüm soruları 0-10 arası ölçeklendirilmiş görsel analog skala ile skorlamaları istenmektedir. Bütün soruların aldığı skorlar toplandıktan sonra bu soruların alabileceği toplam maksimum skora bölünüp, elde edilen sayı 100 ile çarpılarak indeks toplam skoru hesaplanır. İndeksin yüksek skorları artmış ayak dizabilitesini göstermektedir. Bu çalışmada ölçeğin Türkçe versiyonu kullanılmıştır [14]. Plantar fasya (PF) ve aşil tendon (AT) yapışma yerleri şişlik, kızarıklık, hassasiyet gibi klinik entezit bulguları açısından muayene edildi. Ayak eklemleri periferik artrit varlığı açısından değerlendirildi. Bütün klinik değerlendirmeler deneyimli fiziatrist tarafından yapıldı.

Ultrasonografik incelemeler: Ultrasonografik inceleme muskuloskeletal ultrason konusunda deneyimli fiziatrist tarafından yapıldı. İncelemeler için GE marka, Logiq P5 model US cihazı ve 7-12 MHz lineer prob kullanıldı. Hasta grupta her iki ayaktaki plantar fasya ve aşil tendonlarına ait toplam 160 entezis bölgesi US ile değerlendirildi. İncelemeler 22-24 ºC ısıdaki odada, hasta yüzüstü yatar durumda ve ayak bileği nötral pozisyonda iken yapıldı. İlk olarak Gri skala US ile tendonlarda fokal değişiklikler (hipoekojenite), tendon kalsifikasyonları, kemik erozyonları, entezofitler, bursitler ile aşil tendonu ve plantar fasya kalınlıkları değerlendirildi. Aşil tendonu ve plantar fasya kalınlığı ölçümleri kalkaneus'a yapışma yerlerinden yapıldı (Resim 1a ve 1b). Aşil tendonu ve plantar fasya kalınlık ölçümleri iki kez yapılarak elde edilen ortalamalar değerlendirmeye alındı.

US ile elde edilen bulguların aşil ve plantar fasya entesopatisi olarak kabul edilebilmesi için OMERACT tarafından tanımlanan entesopati bulguları esas alındı [15]. Elde edilen entesopati bulgularının semikantitatif olarak değerlendirilmesi amacı ile Glasgow Ultrasound Enthesitis Scoring System (GUESS) kullanıldı. GUESS ile her iki ayak için alınabilecek toplam skor 0 ile 14 arasında değişmektedir [1]. Gri skala incelemeden sonra aynı bölgelerde power doppler ile anormal lokal vaskülarizasyon araştırıldı. Power doppler ayarları; vuru tekrarlama sıklığı (pulse repetition frequency) 0.5-1.0 kHz, power doppler frekansı 5-6.7 MHz ve düşük duvar filtresi şeklinde yapıldı. Power doppler ultrason (PDUS) ile inceleme longitudinal ve transvers planlarda yapıldı. İnceleme sırasında anatomik yapıların bası altında kalmaması için proba aşırı basınç uygulanmamasına özen gösterildi.

İstatistiksel incelemeler

Çalışmada elde edilen bulgular değerlendirilirken, istatistiksel analizler için SPSS (Statistical Package for Social Sciences) for Windows 19.0 programı kullanıldı. Çalışma verileri değerlendirilirken tanımlayıcı istatistiksel metodların (normal dağılım gösteren veriler için ortalama ve standart sapma, normal dağılım göstermeyen veriler için medyan ve minimum-maksimum) yanı sıra normal dağılım gösteren niceliksel verilerin gruplar arası karşılaştırmaları için Student-T Testi, normal dağılım göstermeyen niceliksel verilerin gruplar arası karşılaştırmaları için ise



Resim 1. Kalkaneal entezis bölgesinde aşil tendonu kalınlık ölçüm lokalizasyonu (Beyaz oklar), AT: Aşil tendonu (A). Kalkaneal entezis bölgesinde plantar fasya kalınlık ölçüm lokalizasyonu (Beyaz oklar), PF: plantar fasya (B).

Mann-Whitney U testi kullanıldı. Ayak fonksiyon indeksi ile diğer parametreler arasındaki ilişkiler spearman korelasyon analizi ile değerlendirildi. Sonuçlar % 95'lik güven aralığında, anlamlılık p<0.05 düzeyinde değerlendirildi.

Bulgular

Ankilozan spondilitli hastaların 26'si TNF-alfa antagonisti (anti-TNF), 7'si sulfasalazin (SLZ), 3'ü nonsteroid antienflamatuar ilaç (NSAEİ) kullanmakta, 4'ü ise ilaçsız takip edilmekte idi. Hastalar 1 ile 288 ay arasında değişen hastalık sürelerine sahiplerdi. Onaltı (%40) AS'li hasta ayak ağrısından şikayetçi idi. Yapılan klinik değerlendirme ile 13 (%32,5) hastada entezit (Entezis bölgelerinde şişlik ve/veya hassasiyet) bulgusu saptandı. AS'li hastaların diğer klinik ve laboratuar karakteristikleri tablo 1'de görülmektedir. Ankilozan spondilit ve kontrol grupları arasında yaş, vücut kitle indeksi ve cinsiyet oranları arasında fark yoktu (Tablo 1). AS grubundaki hastaların ayak fonksiyon indeksleri medyan değeri kontrol grubuna göre ileri derecede anlamlı olacak şekilde yüksek bulundu (p = 0,000).

AS'li hastaların sağ ve sol plantar fasya kalınlıkları median değerleri kontrol grubuna göre istatistiksel olarak anlamlı olacak şekilde artmış bulundu (Tablo 2). Sağ ve sol aşil tendon kalınlıkları ise AS grubunda kontrol grubuna göre ileri düzeyde anlamlı olacak şekilde yüksekti (p = 0,000). En az bir patolojik ultrason bulgusu saptanan kişi sayısı AS grubunda 30 (%75) iken, kontrol grubunda sadece 5 (%16,7) olarak saptandı (Tablo 2). Üç AS'li hastada (%7,5) power doppler ile patolojik sinyal izlendi.

Tablo 1. Grupların karakteristik özellikleri

	AS (n=40)	Kontrol (n=30)	P değeri
Yaş, yıl	39.9 ± 10.4	38.8 ± 7.9	0.637
Cinsiyet (% kadın)	13 (%32.5)	10 (%33.3)	0.941
VKİ, kg/m2	27.4 ± 4.4	26.4 ± 3.6	0.284
AFİ	17.4 (0-59.1)[a]	0 (0-8.6)[a]	0.000*
Hastalık süresi (ay)	48 (1-288)[a]		
ESH, mm/h	15 (4-68)[a]		
CRP, mg/L	0.32 (0.01-7.9)[a]		
GUESS	2.5 (0-7)[a]		
BASDAI	4 (0-8.1)[a]		
BASFI	2.5 (0-9.3)[a]		
BASMI	2.8 (0.8-8.4)[a]		
ASQoL	7 (0-18)[a]		
Tedavi, n (%)			
NSAEİ	3 (%7.5)		
Sulfasalazin	7 (%17.5)		
Anti -TNF	26 (%65)		
İlaçsız takip	4 (%10)		

[a] Medyan (minimum-maksimum), * p<0.001, AFİ: ayak fonksiyon indeksi, AS: ankilozan spondilit, ESH: eritrosit sedimantasyon hızı, NSAEİ: non steroid antienflamatuar ilaç, GUESS: glasgow ultrasound enthesitis scoring system. VKİ: vücut kitle indeksi

Tablo 2. Ankilozan spondilit ve kontrol gruplarında ultrason bulgularının karşılaştırması

	AS (n=40)	Kontrol (n=30)	P değeri
PF kalınlığı (R), mm	3.2 (2.6-4.9)[a]	3.0 (2.2-3.8)[a]	0.016*
PF kalınlığı (L), mm	3.4 (2.3-4.8)[a]	3.0 (2.2-4.5)[a]	0.011*
AT kalınlığı (R), mm	5.0 (3.6-7.4)[a]	4.1 (3.6-5.2)[a]	0.000**
AT kalınlığı (L), mm	4.9 (3.7-7.3)[a]	4.1 (3.0-5.4)[a]	0.000**
Patolojik US, n (%)	30 (%75)	5 (%16.7)	0.000**

[a]Medyan (minimum-maksimum). * p<0.05, ** p<0.001, AT: aşil tendonu, PF: plantar fasya

AS'li hastaların GUESS skorları ile ayak fonksiyon indeksi skorları arasında çok iyi derecede korelasyon saptandı (p = 0,000). GUESS skorları ile ASQoL ve BASFI skorları arasında iyi derecede, GUESS ve BASDAI skorları arasında ise orta derecede korelasyon mevcuttu (Tablo 3). Ayak fonksiyon indeksi skorları ise ASQoL, BASDAI ve BASFI skorlarının tümü ile çok iyi derecede korele bulundu (Tüm p değerleri = 0,000). Gerek GUESS, gerekse AFİ skorları BASMI skorları ile korele değildi (Tablo 3). Ayrıca CRP, ESR düzeyleri, yaş ve hastalık süreleri de GUESS skorları ve ayak fonksiyon indeksi ile ilişkili bulunmadı (Tüm p değerleri > 0,05). Hastaların BASDAI ve ASQoL skorları arasında da çok iyi derecede korelasyon mevcuttu (p = 0,000).

Tablo 3. Ayak dizabilitesi ve diğer parametrelerin korelasyon analizi

		GUESS	AFİ	ASQOL	BASDAI	BASFI	BASMI
GUESS	r	1,000	,695	,495	,336	,485	,201
	P		,000 ***	,002 **	,036 *	,002 **	,233
AFİ	r	,695	1,000	,789	,647	-,710	,205
	P	,000 ***		,000 ***	,000 ***	,000 ***	,223

* p<0,05, ** p<0,01, *** p<0,001. AFİ: ayak fonksiyon indeksi, ASQoL: Ankylosing Spondylitis Quality of Life, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, GUESS: Glasgow Ultrasound Enthesitis Scoring System

Tartışma

Ayaklar tendon ve ligamentlerin önemli katkıları ile vücudu dinamik ve statik olarak dengede tutan kompleks yapılardır. Bu nedenle entesopatik lezyonlar ağrı yanında önemli dizabiliteye de neden olmaktadır [16].

AS'li hasta grubumuzun yaklaşık üçte birinde fizik muayene ile ayaklarda entezit saptanmıştır. Ultrason ile en az bir entesopati bulgusu saptadığımız hasta oranı ise %75'tir. Bu oranlar literatür ile karşılaştırılabilir düzeydedir. D'Agustino ve ark. [5] tüm SpA'lar içinde en sık aşil (%79), ikinci sıklıkta plantar fasya (%74) entezitine rastlandığını bildirmişlerdir. Aydın ve ark. [2] AS'li hastaların %83'ünde aşil tendon lezyonu saptamışlardır. Balint ve ark.'a [1] göre alt ekstremitedeki 5 entezis bölgesi değerlendirildiğinde SpA'lı hastaların %22'sinde klinik, %56'sında sonografik entesopati saptanmıştır. Borman ve ark. [17] SPA'lı hastaların %56,8'inde US ile ayakta entezit bulgusuna rastlamışlardır. Aynı çalışmada klinik entezit oranı ise %37'dir. Kiriş ve ark.'nın [18] AS'de klinik ve ultrasonografik aşil enteziti oranları ise literatüre göre biraz yüksektir (Sırasıyla %45, %96). Klinik entezit sıklığının %10 - %60 arasında değiştiği bildirilmektedir [19].

Sonuçlarımız AS'li hastalarda entezis düzeyindeki AT ve PF kalınlıklarının sağlıklı kontrollere göre artmış olduğunu göstermiştir. Entezit tanısı için en karakteristik bulgunun çalışmaların %94'ünde saptanan tendon kalınlık artışı olduğu bilinmektedir [20]. Aydın ve ark. [9] seronegatif spondiloartropatili hastalarda entezis düzeyinde aşil tendonu kalınlıklarının kontrollere göre artmış olduğunu göstermişlerdir. Genç ve ark. [21] ise AS'li hastalarda ortalama aşil tendonu kalınlığını kontrol grubuna göre artmış bulmakla birlikte PF kalınlıklarını kontrollerden farklı bulamamışlardır.

Bulgularımız ayak dizabilitesinin (AFİ) GUESS skorları ve hastalık aktivitesi (BASDAI) ile belirgin biçimde ilişkili olduğunu göstermiştir. Hastalık aktivitesi arttıkça GUESS skoru ve ayak dizabilitesi artmaktadır. Laatris ve ark.'a [22] göre BASDAI skorları Mander Enthesis Index (MEI) ve Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) ile ilişkilidir. Hamdi ve ark. [23] ise BASDAI ile doppler skoru arasında ilişki olduğunu göstermişlerdir.

Çalışmamızda AFİ ile GUESS skorları ESR, CRP, BASMI ve hastalık süresi ile ilişkili bulunmamıştır. GUESS skorları diğer çalışmalarda da ESR ve CRP düzeyleri ile ilişkili bulunmamıştır [1, 17]. Literatür sonuçları klinik entezit şiddetinin de ESR ve CRP düzeyleri ile ilişkili olmadığı yönündedir [22]. Entezit şiddetinin hastalık süresi ile ilişkili olmadığı yönündeki bulgularımız Laatris ve ark.'nın [22] çalışması ile uyumludur.

Yaptığımız literatür araştırmasına göre çalışmamız AS'li hastalarda klinik ve ultrasonografik ayak tutulumunun yol açtığı ayak dizabilitesini ve klinik etkilerini değerlendiren ilk çalışmadır. AS'li hastaların günlük yaşam aktivitelerinin kısıtlandığı ve yaşam kalitelerinin azaldığı bilinmektedir. Özellikle yüksek hastalık aktivitesi durumunda yaşam kalitesinin belirgin biçimde etkilendiği gösterilmiştir [24]. Bizim çalışmamızda da bu bulguları destekler şekilde BASDAI ve ASQoL skorları arasında çok iyi derecede korelasyon saptanmıştır. SpA'lı hastalarda yürüme limitasyonları da sık görülmektedir [25]. Entesopatilerin AS'de yaşam kalitesini bozan en önemli faktör olduğu bildirilmiştir [7]. Yüksek MASES ve MEI skorlarının düşük yaşam kalitesi ile ilişkisi bilinmektedir [8, 22]. Laatris ve ark.'a [22] göre yüksek MASES ve MEI skorları fonksiyonel disabilite (BASFI) artışı ile sonuçlanmaktadır. Bizim bulgularımız da AFİ ve GUESS skorları arttıkça fonksiyonel kapasite (BASFI) ve yaşam kalitesinin azaldığı yönündedir. Literatürde sonografik indekslerin klinik parametrelerle ilişkili olmadığını bildiren bazı çalışmalara da rastlanmaktadır [6, 17].

Ayaktaki entesopatik lezyonlar TNF-alfa antagonisti tedavilere çok iyi cevap vermektedir. TNF-alfa antagonisti tedavi sonrasında US skorlarında anlamlı azalmalar olduğu gösterilmiştir. Aşil tendonundaki entesopatik bulguların US ile takibinin anti-TNF tedavilere cevabın monitörize edilmesinde kullanılması önerilmektedir. [2].

SpA'lı hastalarda kemik erozyonları ve entesopatik değişikliklerin erken dönemde görülmesinin prognoz açısından olumsuz bir gösterge olabileceği bilinmektedir. Bu nedenle ayaktaki entesopatik lezyonların US ile erken dönemde saptanabilmesi prognoz tahmini ve tedavi seçimi için önemli görünmektedir [17].

Görülmektedir ki AS'li hastaların büyük bir çoğunluğunda aşil ve/veya plantar fasya entezis bölgeleri enflamasyondan etkilenmektedir. Bu durum AS'de ayak sağlığının ne kadar önemli olduğunu göstermektedir. Ne yazık ki AS takip ve tedavi stratejileri içinde ayak problemleri çoğu zaman gözardı edilmektedir. Klinik önemlerine rağmen entezitlerin tedavi seçenekleri de sınırlıdır.

Çalışmamızın kısıtlılıkları arasında hasta grubumuzun farklı tedaviler alması nedeni ile entesopatik lezyonların farklılık göstermesi ile ultrasonografik ölçümlerin bir kişi tarafından yapılması ve gözlemci içi geçerlilik değerlendirmesinin yapılmamış olması sayılabilir.

Sonuç olarak ankilozan spondilitli hastalarda başta entezitler olmak üzere ayakta oluşan enflamatuar lezyonlar önemli disabilite nedenidir. Ayak tutulumu fonksiyonel kapasitenin azalması ve yaşam kalitesi kayıbına yol açmaktadır. Tedavi sürecinde genellikle ihmal edilen ayak patolojilerinin; lokal enjeksiyonlar, ayakkabı modifikasyonları, splintleme, ortezler, fizik tedavi ajanları gibi lokal tedavi seçeneklerini de kapsayacak şekilde etkin tedavisi ile hastaların mobilite, fonksiyonel kapasite ve yaşam kalitelerinin artırılabileceği açıktır. Entezopatilerin erken tanısı yanında, aşil entezitlerinin US ile takibi yoluyla anti-TNF tedavi etkinliğinin monitörize edilebilmesi gibi yeni kullanım alanlarının olması da tanısal ayak ultrasonunun spondiloartropatilerde etkin kullanılmasının önemini göstermektedir.

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Kaynaklar

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Distribution of Interstitial Cells of Cajal in the Esophagus of Fetal Rats with Esophageal Atresia

Özefagus Atrezili Rat Fetüs Özefagusunda İnterstisyel Cajal Hücrelerinin Dağılımı

Özefagusda İnterstisyel Cajal Hücrelerinin Dağılımı / Distribution of Interstitial Cells of Cajal in the Esophagus

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Özet

Amaç: İnterstisyel Cajal hücrelerinin (İCH) azalmış olması intestinal motilite bozuklukları ile ilişkilendirilmektedir. Bu çalışmada deneysel özefagus atrezisi (ÖA) rat modelinde, rat fetüs özefaguslarındaki İCH dağılımının değerlendirilmesi amaçlanmıştır. Gereç ve Yöntem: Elde edilen rat fetüsleri üç grupta toplanarak kontrol grubu, özefagus atrezisi eşlik etmeyen ve özefagus atrezisi eşlik eden adriyamisin grupları oluşturuldu. Adriyamisin grubu ratlara 6 ve 9. gebelik günlerinde 4 doz, 2 mg/kg'dan intraperitoneal adriyamisin enjekte edildi. Rat fetüslerinin özefagusunda, immünohistokimyasal yöntemle (c-kit, CD117) İCH varlığı değerlendirildi. Mikroskobik değerlendirme ortalama İCH sayılarına göre, 1'den 3'e kadar olan görsel bir skorlama sistemi kullanılarak yapıldı. Bulgular: Her gruba 7 fetüs dahil edildi. Gruplardaki İCH skor 3 alan fetüslerin sayısı, kontrol grubunda 5 (%72), ÖA eşlik etmeyen adriyamisin grubunda 3 (%42), ÖA eşlik eden adriyamisin grubunda 1 (%14) olarak belirlendi. ÖA'nin eşlik ettiği adriyamisin grubu ile kontrol grubu karşılaştırıldığında, ÖA'nin eşlik ettiği adriyamisin grubunda İCH dağılımında anlamlı bir azalma olduğu belirlendi ($p < 0.05$). Konrol grubu ile ÖA'nin eşlik etmediği adriyamisin grubu karşılaştırıldığında İCH dağılımında anlamlı bir fark olmadığı belirlendi ($p > 0.05$). Tartışma: ÖA'li rat fetüslerin İCH yoğunluğunun ÖA olmayan rat fetüsler ile karşılaştırıldığında daha düşük olduğu görüldü. Bu bulgular ÖA'de İCH dağılımının konjenital olarak anormal olduğunu gösterebilir. Bu durum, ÖA'ne bağlı ameliyat olmuş özefaguslarda görülen dismotilite ile ilişkilendirilebilir.

Anahtar Kelimeler

Özefagus Atrezisi; İnterstisyel Cajal Hücresi; C-Kit

Abstract

Aim: Scarcity of the interstitial cells of Cajal (ICC) is related to motility disorders. In the study, we aimed to evaluate the number and density of ICCs in the fetal rat esophagus in the adriamycin - esophageal atresia (EA) model. Material and Method: Rat fetuses were divided into three groups as a control, adriamycin group without EA and adriamycin group with EA. Four doses of adriamycin, 2 mg/kg each, were injected intraperitoneally to the adriamycin group rats between on 6 and 9 days of gestation. The presence of ICCs in the esophagus of the rat fetuses was determined by using an immunohistochemistry technique (c-kit, CD117). The average numbers of ICCs were calculated with microscopic evaluation by using a visual scoring system (range1 to 3). Results: Seven fetuses were included in each group. The ICCs score 3 distributions of fetuses were 5 (72%) fetuses in the control group, 3 (43%) fetuses in the adriamycin group without EA, 1 (14%) fetus in the adriamycin group with EA. It have been found that there was a marked reduction of ICCs distribution in the adriamycin group with EA compared to control group ($p < 0.05$). There was no significant difference the ICCs distribution between the control group and the adriamycin group without EA ($p > 0.05$). Discussion: ICCs density was significantly decreased in the rat fetuses with EA compared to the fetuses without EA. These findings support the idea that ICCs density may be congenitally abnormal in EA. This may be led to dismotility seen in the operated esophagus due to EA.

Keywords

Esophageal Atresia; Interstitial Cells of Cajal; C-Kit

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Introduction

The current treatment approach for esophageal atresia (EA) and tracheoesophageal fistula (TEF) is esophago-esophagostomy [1]. The motility problems in the patients who underwent an esophageal atresia repair can appear during postoperative period and 60-90% of the patients suffer from dysphagia, vomiting and gastroesophageal reflux disease (GERD) depended on the motility disorder [1-4]. It was determined that the motility disorders seen in the patients with esophageal atresia may result from primary malformation of the neural structures or neural tissue injuries secondary to atresia repair [5-7].

The control of the esophageal motility is provided by the intrinsic and extrinsic innervations of the esophagus that regulate the muscle activity [8,9]. It has been believed that the interstitial cells of Cajal (ICCs) have critical roles in intrinsic innervations of the gastrointestinal system [10]. Distribution and maturation of the intrinsic pacemaker cells are determined as abnormal in some gastrointestinal system diseases related to peristalsis and motility disorders [11-15]. It is likely to be seen a relation between the density of ICCs and esophageal dismotility in the patients operated for EA.

The development of EA/TEF in rat fetuses has been observed experimentally when adriamycin that is known to have a teratogenic effect, was given to pregnant rats [16,17]. In the current study, we aimed to evaluate the number and density of ICCs in the fetal rat esophagus using adriamycin-induced EA rat model.

Material and Method

All procedures involving animals were reviewed and approved by The Institutional Ethics Committee for Animal Experiments (no: 60/2010-24/12/2010). The animal protocol was designed to minimize pain or discomfort to the animals. This study was conducted in the Experimental Animal Department and Pathology Department of Dokuz Eylül University between April and July 2012.

Animal model

Primigravida female Wistar albino rats, weighing 200-250g, kept on standard laboratory chow and with free access drinking water and eating food, were used throughout the experiments. Couples were kept together for 24 hours. After mating, the female rats that had the vaginal plate plaque and sperm in their vaginal smears were accepted as the #0 day of their pregnancy and they were included in the study. The pregnant rats were kept in plastic bathtubs in laboratories in which the humidity and the temperature were controlled. The rats were housed in separate cages with controlled temperature (23°C), humidity (50%) and 12 hour light/dark cycle.

In this study, 2 main groups were created. These are the control group and the adriamycin groups. The control group includes normal rat fetuses that did not undergo any intervention. The adriamycin groups included two subgroups; with EA and without EA groups. Four doses of adriamycin (Adriblastina; Deva, Istanbul, Turkey), 2mg/kg each, were injected intraperitoneally to the adriamycin group rats between the embryologic day (E) E6 and E9 days of gestation.

Tissue Handling

At the E20, all dams were general anesthesia (pentobarbital 50 mg/kg body wt intraperitoneal injection) with ether and the surviving fetuses were harvested by cesarean section, then the dams were euthanized by cervical dislocation and the rat fetuses were killed by decapitation. Then, the fetuses were dissected under the microscope with x10 magnification and the fetuses in the adriamycin group were divided into two groups; fetuses with EA and fetuses without EA. The fetal distal esophagus was dissected starting from the gastroesophageal junction up to the tracheal bifurcation region and harvested. A full-thickness biopsy from the lower one third of the esophageal tissue was obtained from the fetuses of all groups. The study continued until we obtained 7 fetuses in each group.

Tissue preparation and immunohistochemical staining

The 4 µm sections were obtained from the tissues. They were embedded into the paraffin blocks and incubated 48 h in the Bouin's solution for the histopathological examination. The sections were deparaffinized with xylene. The dehydration of the sections was performed with alcohol (1x5 min). The samples were boiled in the microwave oven (56˚C, 5 min) in ethylenediamine-tetraacetic acid (EDTA) buffer in order to expose the antigen. The samples were treated with polyclonal primer antibody (A4502: CD117, c-kit, DAKO, California, USA) at 1:100 dilution at room temperature for 45 min. Then, the chromogenic material with peroxidase and the labeled secondary antibody (ACT500: DAB Chromogen/Substrate Kit, Scy-Tek, Utah, USA) was applied to the samples. Upon waiting 20 min at room temperature, the emergence of the brown color was considered as positive staining. The counterstaining of the samples was performed with Hematoxylin-eosin for the morphological evaluation. ICCs were evaluated morphologically as a result of microscopic observations by staining the cells with Hematoxylin-eosin. The c-kit (CD117) positive cells were detected in all groups according to the immunohistochemical findings.

Under x40 magnification light microscope, ICCs were counted in 10 different microscopic sites which were selected randomly by the pathologist and expressed as count per unit area (100 µm2). The pathologist was blinded with respect to experimental groups when preparing and evaluating the specimens. Morphological differences were used to distinguish the ICCs from the mast cells. The counting results of the ICCs were scored from 1-3, according to the average number of ICCs. The scoring system was as follows: score 1= if cell count is between 0 and 2, score 2= if cell count is 3 or 4, Score 3= if cell count is more than 4 (Table1).

Table 1. The visual scoring system for the evaluation of the ICC distributions in fetal rat esophagus

Visual scoring system
Score 1= if cell amount is between 0-2
Score 2= if cell amount is between 3-4
Score 3= if cell amount is more than 4

Statistical analysis

The statistical differences between the groups were evaluated by using chi-square and Kruskal-Wallis test. The p-value less

than 0.05 were considered as statistically significant.

Results

Macroscopic observations

In this study, 28 fetuses was obtained from 5 pregnant rats in which there were one pregnant rat in the control group and four pregnant rats in the adriamycin group. Seven fetuses were obtained in the control group. In the adriamycin group, EA and distal TEF (Type C) were determined in 10 (47%) out of 21 fetuses. Seven fetuses from each group were included to the study. In the adriamycin group, three out of 10 fetuses with EA, and four out of 11 fetuses without EA in which did not obtained convenient esophageal tissue were excluded from the study. Biopsy specimens could only be obtained from the distal esophagus, since the proximal esophagus was embedded in the neck and it was not technically possible to obtain a proper tissue for biopsy. Therefore, tissue samples were taken from the 1/3 distal esophagus of the control and experimental group fetuses without EA and the distal esophagus of the fetuses with EA (Figure 1).

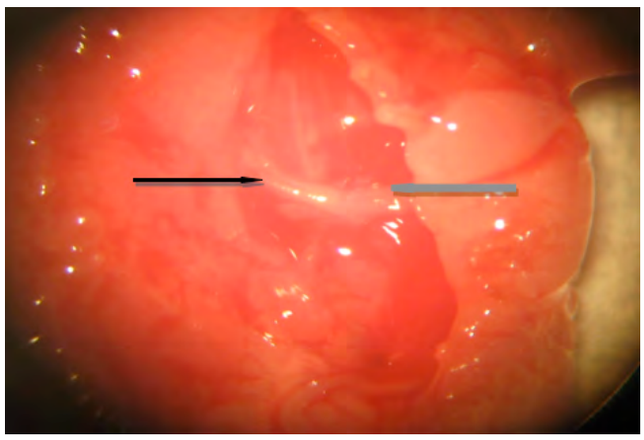


Figure 1. Type-C esophageal atresia in a rat fetus (x10 magnification), tracheoesophageal fistula (black arrow), gastroesophageal junction (gray arrow)

Changes in the number and density of ICCs

The ICCs score distributions of fetuses were as follows: the score was 2 (28%) in 2 fetus and score 3 was (72%) in 5 fetus of the control group whereas the score was 1 (14%) in 1 fetus, score 2 was (43%) in 3 fetus and score 3 was (43%) in 3 fetus of the adriamycin group without EA. There was no c-kit (-) sections in the both control and adriamycin group without EA. In the adriamycin group with EA, the score was 1 (72%) in 5 fetus, score 2 was (14%) in 1 fetus and score 3 was (14%) in 1 fetus (In the adriamycin group with EA, there were 3 sections which were stained c-kit (-) (Figures 2-4).

When the ICCs scores of each group were evaluated, we have found that there was a marked reduction curve of ICCs distribution of the group with EA ($p < 0.05$). When we compared the control group and the group without EA, there was no statistically significant difference between them regarding the ICCs scores distributions ($p > 0.05$) (Table 2).

Discussion

ICCs had been first described in the gastrointestinal tract that was thought to be originating from the precursors of the smooth muscle cells serving as a pacemaker to initiate peristalsis [10]. ICCs in the gastrointestinal system are located in the myenteric plexus, inside the circular muscle layer and between the muscle fibers on the gut wall [10]. Intrinsic pacemaker cells included ICCs maintain an electrical activity for the peristaltic waves [10]. ICCs are important cells for organs with peristaltic

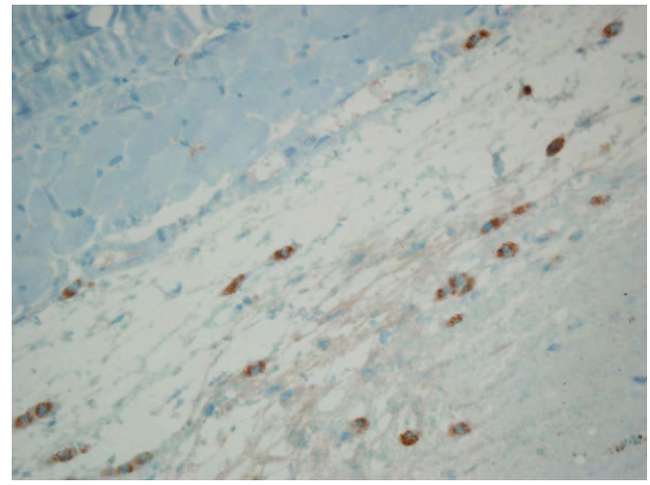


Figure 2. ICCs were not observed between muscles of the esophageal tissues in the rat fetuses with EA, while there are many mast cells staining c-kit positive (c-kit, x40)

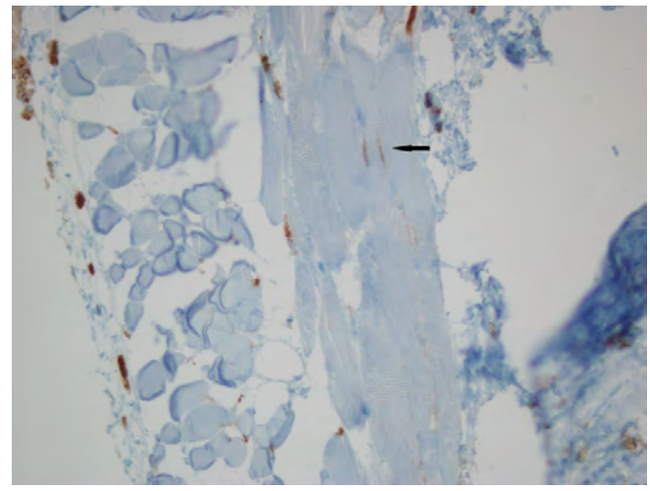


Figure 3. C-kit (CD117) positive ICCs (arrow) in intermuscular area of the fetal rat esophagus in the control group (c-kit, original magnification x40)

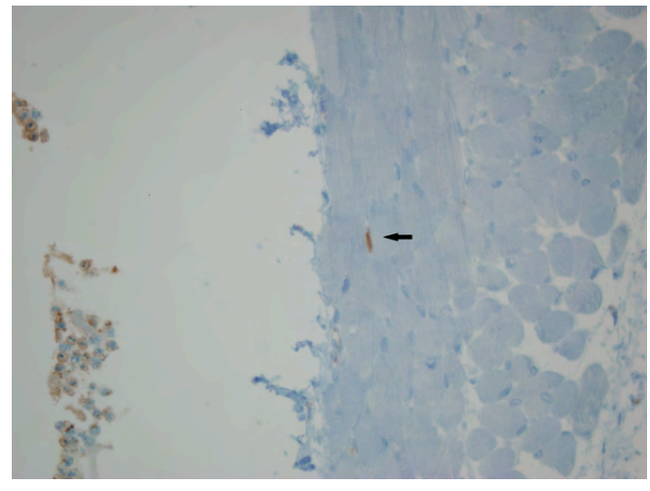


Figure 4. C-kit (+) ICCs (arrow) in the rat fetus esophagi of the adriamycin group without EA in the intermuscular area (c-kit, original magnification x40)

Table 2. The visual scores distribution of the interstitial cells of Cajal in the fetal rat fetuses

Groups	Score 1 (n)	Score 2 (n)	Score 3 (n)
Control	0	2	5
EA atresia (-)†	1	3	3
EA atresia (+)*	5	1	1

Esophageal atresia (EA)
† p = 0.427 when the atresia (-) group compared with control group
* p = 0.018 when the atresia (+) group compared with control group

function. ICCs produce signals for rhythmic contractions and their absence is associated with peristaltic dysfunction. ICCs show c-kit positivity by means of tyrosine kinase surface receptors which can be stained with c-kit antibodies [18]. Peristaltic dysfunction is closely related with the aplasia, hypoplasia or dysplasia of these cells. ICCs have been shown to be absent or decreased in some gastrointestinal system diseases related to peristalsis and motility disorders such as Hirschsprung's disease, neuronal intestinal dysplasia, infantile hypertrophic pyloric stenosis [11-15,19]. It is demonstrated that a remarkable decrease of ICC in small bowel wall of patients with intestinal atresia [14,15].

It is reported in some studies that esophageal motility failure in EA is associated with the neural damage due to operation, anatomical branching defects of the vagus nerve and Auerbach plexus hypoplasia [5-9,20,21]. The motility defects seen in the esophagus of EA-TEF cases, in which surgical dissection is limited at the lower esophagus, strongly suggests that the motility problems may result from the innervation deficiency of the esophagus [22]. Additionally, the detection of the irregular peristaltic pattern and accompanying GERD before the corrective operation in isolated TEF cases is also showed that innervation defects of the esophagus may be congenital [23].

It has been recently stated that ICCs are closely contact with smooth muscle cells and nerve endings [10,18]. Thus, it is possible that ICCs numbers and the distributions may also be affected in the EA in which smooth muscle structure is disrupted congenitally.

After the animal models of EA were described, several studies have been conducted regarding the pathophysiology of the EA [8,9]. Romeo et al [20] have showed that a decline in the relaxation response in the lower esophageal segments of the babies who had not surgery for EA with manometer in the newborn period. In an experimental EA rat model, Turgay et al [24] have showed a decline in the relaxation response in the lower esophageal segments of the rat fetuses with adriamycin induced EA. However, there is no data about the relation between the ICCs and the insufficient esophageal relaxation response in EA. Midrio et al [25] have performed a post-mortem study investigating the ICCs numbers and distributions in the esophagus of the babies with EA. They have found that the density of the ICCs was significantly decreased in the biopsy samples obtained from both distal and proximal segments of the atretic esophagus [25].

In the current study, we have found that ICCs numbers and densities significantly decreased in the rat fetuses with EA compared to the fetuses without EA. These findings support the idea that ICCs density may be congenitally abnormal in EA. We conclude that a decline in the ICCs density may negatively affect the esophageal peristaltic activity in the EA by decreasing the relaxation response in the smooth muscle tissue. This may be related to dismotility seen in the operated esophagus due to EA and TEF.

In conclusion, the scarcity of the ICCs in EA may result in the esophageal motility problems with different clinical findings observed after the operation. Nevertheless, further histological and physiological studies should be done to determine the relation between the absence of ICCs and esophageal peristalsis disorders. Additionally teratogenic effects of adriamycin on the fetal esophagus should also evaluated.

Competing interests

The authors declare that they have no competing interests.

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Treatment of Clarithromycin-Induced Rhabdomyolysis with Continuous Renal Replacement Therapy

Klaritromisine İkincil Gelişen Rabdomyolizin Sürekli Renal Replasman ile Tedavisi

Klaritromisine İkincil Gelişen Rabdomyoliz / Clarithromycin-Induced Rhabdomyolysis

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Özet

Rabdomiyoliz yaygın ve şiddetli kas yaralanması ile karakterize nadir görülen, hayatı tehdit eden bir hastalıktır. Rabdomiyolizin kliniği asemptomatik hastalıktan akut böbrek yetmezliği gelişimine kadar değişkenlik göstermektedir. Sık kullanılan makrolid grubu bir antibiyotik olan klaritromisin sitokrom p 450 enzim sistemini inhibe ederek rabdomiyolize neden olabilir. Erişkinlerde makrolit ve statinlerin birlikte kullanımı sonrası rabdomyoliz gelişimi bildirilmiştir. Ama çocuklarda özellikle de tek başına klaritromisin kullanımı sonucu nadir görülmektedir. Bu yazıda 8 yaşında bir hastada klaritromisin kullanımını takiben gelişen ağır rabdomyoliz ve akut böbrek yetersizliği ile ilgili deneyimimizi sunmaktayız.

Anahtar Kelimeler

Rabdomyoliz; Klaritromisin; Renal Replasman

Abstract

Rhabdomyolysis is a rare, life-threatening syndrome characterized by a diffuse and severe muscle injury. Clinical presentation is variable, ranging from asymptomatic disease to acute renal failure. Clarithromycin, a commonly used macrolide antibiotic, can cause rhabdomyolysis by inhibiting CYP450 enzyme system. Rhabdomyolysis related to combination of macrolide and statins has been previously reported in adults. However, it is rare in children, especially with clarithromycin monotherapy. Herein we report our experience with a severe rhabdomyolysis and acute renal failure following clarithromycin administration in a 8-year-old patient.

Keywords

Rhabdomyolysis; Clarithromycin; Renal Replacement

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Introduction

Rhabdomyolysis is a clinical and laboratory syndrome caused by myocyte necrosis that impairs the integrity of the cell membrane and leads to the release of myoglobulin and toxic intracellular constituents containing electrolytes and proteins into the bloodstream [1]. Assessment of serum creatine kinase is the most sensitive confirmatory laboratory test. Rhabdomyolysis may be associated with toxins, crush injury, overexertion, seizures, genetic disorders, and metabolic disorders. The most common cause of rhabdomyolysis in children is viral myositis, whereas medications in adults [2]. It is important to recognize drug induced rhabdomyolysis early because it is usually reversible. Rhabdomyolysis secondary to concomitant use of macrolides and statins has been reported previously in adult [3], but it is uncommon in children, especially in clarithromycin monotherapy [2]. We report the successful treatment of rhabdomyolysis and acute renal failure related to administration of clarithromycin with continuous veno-venous hemodialysis therapy in a 8-year-old boy. Clarithromycin was suspected to be the cause of rhabdomyolysis, as no other precipating factor or drug interaction were identified.

Case Report

A 8-year-old previously healthy boy was referred for diffuse and severe muscle pain, weakness and dark urine. He had been administered clarithromycin twice daily (15 mg/kg/day) for 5 days due to fever, cough and rinorrhea. His muscle pain had started after the second day of clarithromycin. He did not have any concomitant medication. Physical examination revealed a body temperature of 36.60C, heart rate 142 beats/min, arterial blood pressure 115/72 mmHg, and blood oxygen saturation 96%. Muscle strength was 3/5 in all extremities and deep tendon reflexes were hypoactive. Laboratory studies showed creatine kinase (CK) 58722 U/L (normal range, 55-170 U/L), lactate dehidrogenase 4271 U/L, alanine aminotransferase 1435 U/L , aspartate amino transferase >10000 U/L, glucose 89 mg/dl, urea 85 mg/dl, creatinine 1.9 mg/dl, uric acid 8.9 mg/dl, sodium 142 mmol/L, potasium 6.5 meq/L, calcium 6.1 mg/dl, phosphorus 7.2 mg/dl and blood pH 7.34, base excess -11,2 mmol/L, HCO3 14,5 mmol/L, pCO2 27,4 mmHg and thyroid-stimulating hormone 2.2 mIU/mL. Urine output was diminished. It was brown in colour and myoglobin was detected. There was no calculi and its culture was sterile. Complete blood count, peripheral blood smear and other serum electrolyte tests were all in normal ranges. Serum lactate, pyruvate, ammonia, tandem mass spectroscopic analysis and urine organic acide levels were all normal. Influenza A (H1N1) or other respiratory tract viruses were not detected in nasopharyngeal swab by rRT-PCR assay. Serologic studies determined Ebstein-Barr immunglobulin M (IgM), herpes simplex virus IgM, cytomegalovirus IgM and mycoplasma IgM as negative. The probability that the symptoms of rhabdomyolysis that occurred after clarithromycin treatment were an adverse drug reaction (ADR) was assessed using the Naranjo ADR probability scale. The total Naranjo score for the patient was 5, which is in the “probable” range. So, clarithromycin was considered a probable cause of rhabdomyolysis and was immediately stopped. Agresive intravenous hydration was initiated. Because of impaired renal function, (and) high potassium and phosphorus levels and fluid overload, the patient received continuous veno-venous hemodialysis (CVVHD) with a dialysate flow rate of 900 mL/hour, in which multibic 0 was used. The blood flow rate was 90 mL/min. After 3 days of treatment, by recovery of renal function and electrolyte imbalance, urine output improved and CVVHD was stopped.

Discussion

Clarithromycin, like the other macrolides inhibits CYP450 enzyme system. Clarithromycin is also involved in the CYP3A4 component of this pathyway which is responsible for statins and ıts own metabolism. Beside pharmacokinetic interactions clarithromycin might cause direct muscle toxicity [3]. Rhabdomyolysis due to interaction of macrolides and statins is reported in adults [3]. To date, there are only two pediatric cases in the literature reporting rhabdomyolysis after monotherapy with clarithromycin [2,4].

The infections, especially acute viral infections, metabolic disorders, seizures, immobility and drugs can lead to rhabdomyolysis. Viral myositis is the most common cause of rhabdomyolysis in children [2]. The symptoms of viral myositis are nonspecific and child may not have the classic symptoms of rhabdomyolysis. Therefore we cannot completely rule out viral infections in our patients, although viral markers are negative. An objective causality assessment using the Naranjo probability scale suggested that clarithromycin was the probable cause of rhabdomyolysis in our patient [5].

Rhabdomyolysis ranges from asymtomatic elevation of muscle enzymes to acute renal failure (ARF) due to obstruction of renal tubules with myoglobulin. Acute renal failure is the most serious complication of rhabdomyolysis. The rate of ARF due to rhabdomyolysis is lower in children compared with adults. Wu et al reported the prevalence of ARF as 5% among 191 children and only 3 of them required renal replacement therapy (RRT) [6].

Although there is not a definite correlation between eleveted serum CK levels and rate of ARF, high CK levels can suggest the severity of rhabdomyolysis. In a recent study, it is reported that if a peak value of CK >5000 U/L the risk of ARF increases and if a peak value of CK>10 000 U/L the probability of RRT increases [7].

For the recovery of renal function, complete removal of myoglobulin from circulaton is required. Continuous veno-venous hemodialysis (CVVHD) is more effective than hemodialysis in reducing serum myoglobulin levels [8]. We used CVVHD in the treatment of acute renal failure in our patient and after hemodialysis for 3 days he completely recovered. The two other reported pediatric cases after clarithromycin usage improved only with intravenous fluid and drug withdrawal. None of them had acute renal failure and recieved CVVHD. Our patient may be the only pediatric case who had get CVVHD for severe rhabdomyolysis after clarithromycin administration.

In conclusion, it is important for clinicians to recognise rhabdomyolysis early in patients treated with clarithromycin because the clinical process due to drugs is usually reversible. We reported this case both to remind clinians to be aware of this adverse effect of clarithromycin which is commonly used in daily practice and also to consider continuous renal replacement treatment as a remedy of rhabdomyolysis.

Competing interests

The authors declare that they have no competing interests.

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Acute Renal Failure due to Non-Traumatic Rhabdomyolysis

Non-travmatik Rabdomyolize Bağlı Akut Böbrek Yetmezliği

Nontravmatik Rabdomyoliz / Non-Traumatic Rhabdomyolysis

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Özet

Rabdomiyoliz iskelet kasının travmatik ve nontravmatik nedenlere bağlı olarak görülen klinik ve biyokimyasal sendromudur ve kelime olarak kas erimesi anlamını taşımaktadır. Ezilme tipi travmayı takiben gelişen rabdomiyoliz (Crush sendromu) nadir görülen ancak ABY etyolojisinde iyi tanınan bir klinik durumdur. Nontravmatik rabdomiyoliz ise nadirdir. Bu yazıda akut böbrek yetmezliği (ABY) kliniğinde başvurarak rabdomiyoliz tanısı konulan ve tekrarlayan diyaliz uygulanan bir olgu sunulmaktadır.

Anahtar Kelimeler

Akut Böbrek Yetmezliği; Diyaliz; Nontravmatik; Rabdomiyoliz

Abstract

Rhabdomyolysis is a musculoskeletal clinical and biochemical syndrome which is seen associated with traumatic and non-traumatic causes and is known as muscular dystrophy. Rhabdomyolysis which develops following crush-type trauma (Crush syndrome) is rarely seen but is a well-known clinical event in the etiology of acute renal failure. Non-traumatic rhabdomyolysis is rare. The case is here presented of a patient who was diagnosed with rhabdomyolysis on presentation with acute renal failure and to whom repeated dialysis was applied.

Keywords

Rhabdomyolysis; Non-Traumatic; Dialysis; Acute Renal Failure

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Introduction

Rhabdomyolysis is known as a syndrome which destroys the integrity of the sarcolemma as a result of musculoskeletal damage from traumatic or non-traumatic reasons [1]. In 5-7% of cases that develop acute renal failure, musculoskeletal breakdown is responsible [2]. Reasons in the etiology include medications such as colchicine, lithium and statins, hereditary muscle enzyme deficiencies, trauma, viral infections, excessive exercise and hyothyroidism [3]. The aim of this case presentation was to draw attention to the necessity of keeping in mind the diagnosis of rhabdomyolysis in a patient with no trauma history who presentedwith acute renal failure.

Case Report

An 11-year old male presented at the pediatric emergency polyclinic with the complaint of dark brown coloured urine which had been ongoing for 4 months. From the history it was learned that the patient had had diarrhoea for one week and on the day of presentation had started to experience pain on walking and difficulty standing. In the physical examination, the patient was conscious and co-operative with a weak appearance, pulse 98/min, respiratory count 24/min, and TA 120/85 mmHg. The eyeballs were sunken, the skin had reduced turgor and there was a herpetic lesion on the lower lip. In the apex 3/6 systolic murmur could be heard. Deep tendon reflexes were normo-active and muscle strength in the lower and upper extremities was 3/5. Values in the full blood count were Hb: 11 g/dL, PLT: 136.000/µL, WBC: 6600/µL, RBC: 6.3x106/µL, MCV: 85 fl, MCHC: 34 g/dL, RDW: 13% and in the peripheral blood smear, thrombocyte aggregation, leukocyte and erythrocyte morphology was normal and there was 5% reticulocytosis. In the full urine test, density was 1035, protein 3+ and abundant erythrocytes were determined in microscopy. In the biochemical tests, the values were determined as BUN 20 mg/dL, creatinine 1.28 mg/dL, uric acid 10.5 mg/dL, sodium 123 mmol/L, potassium 5 mmol/L, phosphorus 8 mg/dL, AST 6953 U/L, ALT 721 U/L, lactic dehydrogenase (LDH) 331.910 U/L, creatinine clearance 13.5 mL/min. Complements (C3, C4) and IgA values were within the normal range. Prothrombin time was determined as 15.1 secs, aPTT 62.3 secs, fibrinogen 281 mg/dL, D-Dimer 1278 (normal değer) ng/ml, and the direct Coombs test was negative. Blood gas values were pH 7.42, pCO2 29, HCO3 20.9, and BE -5.1.

The patient was admitted to the pediatric intensive care unit with findings of acute renal failure (ARF), thrombocytopenia and impaired liver function tests. The echocardiographic evaluation was found to be normal, the size of the kidneys was normal on the urinary system ultrasonography and there was seen to be increased parenchyma echogenity (consistent with Grade 2 parenchymal disease). Three times (20 cc/kg) 0.9% NaCl was administered intravenously because of hyponatremic dehydration. Together with parenteral fluid therapy and diuretic treatment, treatments for the raised levels of uric acid and phosphorus were started. Under observation, the patient developed hyperkalemia (K+: 6.3 mg/dL) and hypocalcemia (Ca++: 6.7 mg/dL), which recovered with the administration of 2 cc/kg iv calcium gluconate.

From the history and the acute muscle weakness determined in the physical examination and the determination of creatine kinase (CK) 38.350 U/L, blood and urine myoglobin >3000 ng/mL, the clinical table was thought to be consistent with rhabdomyolysis. There were no findings of hemolysis in the peripheral smear and under observation the thrombocyte count did not decrease. Blood electrolytes recovered with fluid treatment but creatine continued to rise and urine output continued to fall. In the kidney biopsy, acute tubular damage was determined consistent with rhabdomyolysis. The thyroid functions were normal and in viral serology, EBV, CMV, HSV, HIV and toxoplasma were found to be negative, perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) negative, antinuclear antibody negative, cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA) and anti-ds-DNA negative. Proteinuria was determined at 64 mg/m2/hour in 24 hours of urine. Four times hemodialysis and pulse steroid treatments were administered to the patient. Polyuria which had developed under observation receded and renal functions returned to normal. With improvement of the clinical and laboratory values, the patient was administered oral steroid treatment, referred to the polyclinic for follow-up and was discharged.

Discussion

Following damage to the striated muscle cells, intracellular elements pass into systemic circulation resulting in the clinical and laboratory findings of rhabdomyolysis. This situation can show variations from a table of temporary hypocalcemia, hyperkalemia, increased creatin kinase and myoglobin as far as a Crush syndrome table characterised by hypovolemic shock, cardiac arrest and ARF. When muscle cells are damaged, proteins such as myoglobin, CK, aldolase, LDH, potassium, and AST and cellular components apart from proteins are expressed into the plasma [2, 4]. Determination of myoglobin at high levels in the serum may be an indicator of early stage damage in the muscle or the muscle membrane.

Rhabdomyolysis may occur for traumatic reasons such as earthquakes, electric shocks or mining accidents or for many different reasons such as alcoholism and medication use (especially statins), excessive physical activity, long-term lack of movement, epileptic seizures, hyperthermia, hypothermia, infections, electrolyte imbalances (especially hypokalemia, hypophosphatemia). Rhabdomyolysis is also seen in many congenital diseases of the metabolism, in glycolytic enzyme deficiency diseases, in some diseases with abnormal lipid metabolism and in malignant hyperthermia [2].

Frequently seen complications of rhabdomyolysis are cardiac arrest, hypovolemia, arrythmia, compartment syndrome, widespread intravascular coagulation and ARF. As the most common complication, ARF develops associated with impaired renal perfusion and myoglobin damage. Of all ARF cases, 5-25% are known to be associated with rhabdomyolysis and approximately 10-40% of rhabdomyolysis cases develop ARF. The most significant laboratory finding of rhabdomyolysis is the increased level of serum myoglobin. With a normal plasma level of <0.003 mg/dL, myoglobin is completely cleared from the plasma in approximately 6 hours with a very short half life of 1-3 hours. As the half life is short, the level is generally found to be normal on presentation [5]. In healthy individuals, as approximately 50-85% is associated with plasma globulins, the transfer of myo-

globin to the urine is negligible. Myoglobinuria has been seen to be much greater in muscle mass which has suffered necrosis. The main factors affecting the formation of myoglobinuria are the level of blood myoglobin, the glomerular filtration rate and urine flow rate [6]. Although the current patient had impaired kidney function, the myoglobin level in the urine was found to be >3000 ng/mL.

Sometimes rhabdomyolysis may develop without any trauma and this is known as non-traumatic rhabdomyolysis. The current case was thought to be non-traumatic rhabdomyolysis and the fluid loss due to diarrhea and reduced oral intake were considered to have facilitated acute renal failure.

The most practical and meaningful test in the diagnosis of rhabdomyolysis is an increase in creatin kinase showing muscle damage. As 70% of potassium in the body is found in the muscles, severe hyperpotassemia may be seen in rhabdomyolysis cases. In the current case potassium was determined at 6.1 mg/dL. While the ARF table is initially prerenal character in rhabdomyolysis patients, at an advanced stage, acute tubular necrosis occurs [7]. In the current patient, despite sufficient appropriate fluid treatment, oliguria continued suggesting acute tubular necrosis.

In patients developing ARF asociated with Crush syndrome, it is not necessary to perform a kidney biopsy in all cases but in cases that do not start the recovery process of ARF, a biopsy can be performed to ascertain the underlying cause. Due to the raised levels of creatinine in the current case, kidney biopsy was performed and acute tubular necrosis associated with rhabdomyolysis was determined.

Conclusion

Rhabdomyolysis, which develops for various reasons and becomes evident with widesprread muscle damage, must be kept in mind for patients presenting with ARF table even if there is a history of trauma. It should not be forgotten that despite appropriate treatment, it may lead to 2-5% mortality [8].

Competing interests

The authors declare that they have no competing interests.

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Spontaneous Fracture and Vaginal Expulsion of the Arm of Intra-Uterine Device: Case Report

Rahim İçi Aracın Spontan Olarak Kırılması ve Kolunun Vajinal Olarak Atılması: Olgu Sunumu

Rahim İçi Araç Kırılması / Fracture of Intrauterine Device

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Özet

Rahim içi araç (RIA) dünya çapında yaygın olarak kullanılan etkin ve güvenilir bir doğum kontrol yöntemidir. Ancak kullanım sırasında nadiren kendiliğinden veya iatrojenik olarak kırılabilirBiz 30 yaşında bir kadında 2 yıl önce takılmış bakırlı RIA'nın tek kolunun kendiliğinden kırıldığı ve atıldığı olguyu sunulmuştur. Hasta kliniğimize vajinal çıkımda yabancı bir cisim tarileyerek başvurmuştur. Yapılan transvajinal incelemede RIA'nın yerinden oynadığı ve sol kola ait ekojenitenin olmadığı izlenmiştir.Rahim içi araç kırılması nadir görülse de özellikle RIA'nın dislike olduğu vakalarda akılda tutulmalıdır. Rutin kontrollerde ultrasonografik olarak fundustan uzaklık ve lokalizasyonun yanı sıra ekojenitenin devamı ve bütünlüğü de değerlendirilmelidir.

Anahtar Kelimeler

Rahim İçi Araç; Doğum Kontrolü; Ultrasonografi

Abstract

Intrauterine device (IUD) is an effective and safe contraceptive method which is commonly used worldwide. However, spontaneous or iatrogenic IUD fracture was rarely occurred during usage. We present the case about spontaneous fracture of one arm of copper IUD and the spontaneous expulsion of the broken piece in a 30-year-old woman 2 years after insertion. The patient recoursed to our clinic due to finding of a foreign body at vaginal outlet. Copper IUD was dislocated in transvaginal ultrasonographic (TVUSG) examination and echogenicity of left transverse arm was not identified in transvers section.Although IUD fracture seems rarely, it must be born in mind especially when dislocation exists. Distance to fundus and its location, besides the continuity of its echogenicity and integrity should be observed during routine controls.

Keywords

Intauterine Device; Contraception; Ultrasonography

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Introduction

Intrauterine device (IUD) is a cost efficient, effective, long acting and reversible contraceptive method which is preferred by an increasing number of women worldwide [1]. The use of IUD may be associated with abnormal uterine bleeding, pelvic pain, dysmenorrhea. Also dislocation, expulsion and perforation can be seen [2, 3].

Spontaneous or iatrogenic IUD fracture is seen rarely in literature as case presentations. Here we present the case about spontaneous fracture of one arm of copper IUD and the spontaneous expulsion of the broken piece in a 30-year-old woman 2 years after insertion. The patient recoursed to our clinic due to finding of a foreign body at her vagina outlet. At transvaginal ultrasonography (TVUSG) copper IUD was dislocated and echogenicity dependent to left transverse arm was not identified in transvers section. This is the first case reported in the literature about the spontaneous breakage of one arm of copper IUD and subsequent spontaneous expulsion of the broken piece.

Case Report

A 30 years old patient who gave her first birth by cesarean section 2 years ago recoursed to our clinic due to finding of a foreign body at her vagina outlet. The foreign body was determined to be a piece of copper IUD. Copper IUD (Copper T380A) was inserted in the postpartum 2nd month easily, without any complication. It was in its place at the controls in the 3rd and 18th months. The patient complained from blot hemorrhage for 20 days and pelvic pain for 2 days. During the gynecologic examination the string of IUD was seen and minimal blood was observed in cervical ostium. In TVUSG examination, copper IUD was seen as dislocated. Left transverse arm echogenicity was not identified in transvers section (Fig. I). It was found out that copper IUD has broken at the joint of left transverse arm and vertical body. It was removed easily by pulling the string. Additional intervention was not necessitated because the broken piece and the piece taken out had complemented each other and echogenicity dependent to copper IUD was not identified at control TVUSG (Fig. II).



Fig I. Absence of the left arm echogenicity



Fig II. Broken and removed part of IUCD

Discussion

IUD is an effective and safe contraception method which is commonly used worldwide [1]. Its ease of use and very rarely observed systemic side effects provide an advantage as to the other contraception methods [4]. It may cause abnormal uterine bleeding, pelvic pain and dysmenorrhea. Also dislocation, expulsion and uterine perforation can be observed [2, 3].

Spontaneous or iatrogenic fracture of IUD is a quite rarely seen situation. In the reported cases breakage and retention of IUD has been occurred during removal[4]. In the first spontaneous fracture of copper IUD case, the vertical piece of it was expelled 5 weeks after its easy postpartum placement; the remaining piece was removed by hysteroscopy[5]. To the best of our knowledge this is the first case of spontaneous fracture of one arm of copper IUD and the spontaneous expulsion of the broken piece.

Emerging of a stress on T-junction due to imposing excessive force to the arms during placement, increase in the stress resulting from uterine contractions developed during menses and manufacturing defects are considered being responsible from breakage of IUD [6]. To understand fracture mechanisms, force imposed to different IUD types during the insertion, removal and breakage are measured [6, 7]. According to the results of these measurements, a force of 1.5-4 N and 5-6 N is needed for an easy IUD placement and removal, respectively. However for the breakage of IUD 15-22 N force is needed [6, 8]. Moreover it was shown that, as the time period in uterus is extended, the pressure for breakage gets lower [9]. Because uterus can create 20 N magnitude force, uterine forces seems to be more effective factor on fracture mechanism than the forces applied during routine IUD insertion and removal [6, 8]. In fact most of the fractures identified during removal might occur previously. Unless routine ultrasonography is performed before removal or continuity of IUD echogenicity is examined carefully, intrauterine fractures can be overlooked. In our case, if the broken piece had not been expelled spontaneously and it had not been realized by the patient, it could be perceived as broken during removal.

Uterine forces resulting in IUD fracture and dislocation seems to be same [8]. In our case, coexistence of dislocation and fracture and spontaneous expulsion of the broken piece gave rise to the thought of the effects of the uterine contractions in the foreground. However, determining whether dislocation or fracture was occurred first was not possible. Due to dislocation, more pressure might be imposed on the joint of the left arm and the body and that may cause fracture or; after the fracture, stabilization of IUD might be disconcerted and this might be the cause of dislocation. For this reason, when dislocation is determined, to eliminate the fracture risk, dislocated IUD should be removed as soon as possible. In addition, retention of the broken piece can cause adhesion, infection, perforation and infertility [4, 5]. In our case, because the broken piece was spontaneously expelled and the remaining piece was removed easily, additional intervention was not necessitated.

In conclusion, IUD fracture possibility must be born in mind especially when dislocation exists. During routine controls, distance of the IUD to fundus and its location, besides the continuity of its echogenicity and after removal its integrity should be observed. The patients should be informed about this rare but important condition and checked periodically. Moreover, IUD manufacturers must be informed on the fracture cases to improve the manufacturing quality.

Competing interests

The authors declare that they have no competing interests.

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Hyponatremic-Hypertensive Syndrome in an 18-Month-Old Male Child

Hiponatremik-Hipertansif Sendromlu 18 Aylık Erkek Çocuk

Hiponatremik-Hipertansif Sendrom / Hyponatremic-Hypertensive Syndrome

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Özet

Poliüri, polidipsi, hipertansiyon, ciddi hiponatremi, metabolik alkaloz ve nefrotik sınırda proteinürisi olan, 18 aylık erkek olgu sunuldu. Hipertansiyon ilaca dirençliydi. Angiografide, sağ renal arter tıkanıklığı saptandı. Böbreğin nükleer taramasında, afonksiyone sağ böbrek tespit edildi. Perkütan renal arter anjiyoplasti, hastamız için uygun olmadığından nefrektomi yapıldı. Tüm bulgular sağ nefrektomiden sonra düzeldi. Çocuklarda hiponatremik hipertansif sendromun nadir olması, onun yeterli bilinmediğini gösterir. Poliürik, hipertansif ve hiponatremik çocuklarda, renal hasarı ve yaşamı tehdit eden komplikasyonları önlemek amacıyla, hiponatremik hipertansif sendromun farkındalığının arttırılması amaçlandı.

Anahtar Kelimeler

Hiponatremi; Hipertansiyon; Renal Arter Darlığı; Poliüri; Hiponatremik-Hipertansif Sendrom

Abstract

An eighteen-month-old boy presented with polyuria, polydipsia, hypertension, severe hyponatremia, metabolic alkalosis and nephrotic-range proteinuria. Hypertension was drug resistant. Renal artery angiogram revealed right renal artery occlusion. Nonfunctional right kidney was also detected on the nuclear renal scan. As percutaneous transluminal renal artery angioplasty was not appropriate for our patient, nephrectomy was performed. Right nephrectomy resulted in the resolution of all the symptoms. Rarity of hyponatremic hypertensive syndrome in children may project its under-recognition. We aimed to increase awareness of early diagnosis of HHS among polyuric, hypertensive and hyponatremic children in order to prevent renal damage and life-threatening complications.

Keywords

Hyponatremia; Hypertension; Renal Artery Stenosis; Polyuria; Hyponatremic-Hypertensive Syndrome

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Introduction

Hyponatremic hypertensive syndrome (HHS) is a condition characterized by severe hypertension, hyponatremia or hypochloremia caused by unilateral renal artery stenosis or occlusion [1]. In children, 5-25% of the cases with secondary hypertension are due to renovascular hypertension. Although information about HHS in adults is well-known since 1950 [2], there are only a few cases available in the literature regarding this condition in children [1, 3-4]. However, some reports emphasized that rarity of this disease in children might be the result of the lack of its recognition [1, 5].

Activation of renin and angiotensin II system by the ischemic kidney causes hypertension and pressure diuresis from nonstenotic kidney. On the other hand, increase in aldosterone and antidiuretic hormone (ADH) secretion and thirst also cause hyponatremia and hyokalemia [1, 5].

HHS may be accompanied by weight loss, polyuria, polydipsia, hypertension, enuresis, fatigue, unconsciousness and personality changes [1, 3, 5]. Associated laboratory findings may include hyponatremia, hypokalemia, hypochloremic alkalosis, hyperreninemia, hyperaldosteronism, high sodium levels in the urine, and sometimes high nephrotic level of proteinuria, hypercalciuria and glycosuria [5-6]. The aim of this study was to report an infant who presented with polyuria and was diagnosed with hyponatremic hypertensive syndrome.

Case Report

An 18-month-old boy was referred to the Pediatrics department with symptoms of drinking large volumes of water, with frequent urination and weakness, as well as growth retardation for three months. It was reported that his fluid intake was 2000-4000 ml/day and daily urine output was 3000 ml/day since two months. The family history indicated that parents were third-degree relatives. The physical examination showed the infant's body weight to be 9800 g (<3 percentile), height 84 cm (50 percentile), and blood pressure of 180/100 mmHg (>99 percentile) (Table 1). He displayed symptoms of 10% dehydration, such as sunken eyes, dry mucus membranes and mild delay in skin turgor elasticity. All peripheral pulses were evident. Neurological, eye and all other system examinations were normal. No papilledema was found in the eye examination.

Complete blood count and renal function tests (blood urea 25 mg/dl, serum creatinine 0.34 mg/dl) were within normal ranges. Hyponatremia (125 mEq/L), hypochloremia (90 mEq/l), hypokalemia (2.9 mEq/L), hypoalbuminemia (2.9 gr/dl) and hypercholesterolemia (293 mg/dl) were detected. Analysis of blood gases howed metabolic alkalosis (pH: 7.50, bicarbonates 29.8 mEq/L). Urinalysis indicated Ph of 7, density:1005 and +3 proteins. The 24-hour urine protein test result showed 159 mg/m2/hr and the fractional excretion of sodium (FENa) was calculated to be 10% while the fractional excretion of potassium (FEK) was 14%. No glycosuria or hypercalciuria was found. The renin test performed in bed revealed 2500 pg/ml (2.77-61.80 pg/ml) and aldosterone was determined at 745 (30-350 pg/ml). The antidiuretic hormone was not evaluated.

Echocardiogram revealed left ventricular hypertrophy. Evidence of end-organ damages, secondary to hypertension was detected. The dimercaptosuccinic acid (DMSA) revealed a non-functional right kidney (<10% functioning). Renal Doppler ultrasound revealed left hydronephrosis and possible right renal artery stenosis. The left kidney showed normal vascular structure. Magnetic Resonance (MR) angiography revealed hypoplastic right kidney with occlusion in the right renal artery, 2 mm from the aorta outlet. The angiographic examination revealed that the right renal artery was almost completely constricted and the blood circulation in the kidney was via the collateral circulation (Fig. 1). The infant was diagnosed as having HHS with clinical findings of resistant hyponatremia and hypertension with unilateral renal artery stenosis.



Fig. 1. Very little filling or full stenosis of the right renal artery on the renal arteriograph (thin arrow) and normal filling of the left renal artery (bold arrow)

On admission rehydration and sodium chloride treatment were started. The serum sodium was corrected on the 7th day post treatment, with 20-30 mEq/kg/day of sodium chloride. Although maximum doses of nifedipine, enalapril and beta-blocker were administered, no response was observed. As percutaneous transluminal renal artery angioplasty (PTRA) could not be performed in this case, the only option available right nephrectomy, which was performed. One day post nephrectomy, diuresis decreased to 4 cc/kg/hour and blood pressure began to drop. Symptoms like hypertension, polyuria, polydipsia, hyponatremia, alkalosis and nephrotic proteinuria were all resolved by one week post nephrectomy (Table 1). During the follow up of 18 months after nephrectomy, no pathologic clinical or laboratory findings were observed.

Discussion

Hyponatremic hypertensive syndrome is a rare and special type of renovascular hypertension with hyponatremia, hypokalemia, polyuria, proteinuria and high renin activity [4-5]. It occurs more often in adults than in children, a few studies are available on children diagnosed with HHS [3, 6]. HHS could be underdiagnosed in children due to inadequate information and awareness regarding the disease [4-5].

Table 1. Clinical and laboratory parameters of a patient with hyponatremic hypertension syndrome

Variable	Preoperation	Postoperation
Blood Pressure (mmHg)	180/100	85/55
Daily urine volume (ml)	3000	650
Body weight (kg)	9.8	12
Serum parameters Na (meq/l)	125	136
K (meq/l)	2.9	3.7
CI (meq/l)	90	110
Bicarbonate (meq/l)	29.8	23
Albumin (g/dl)	2.9	3.8
Urinary parameters FENa (%)	10	2
FEK (%)	14	3.8
Urinary protein excretion (mg/m2/h)	159	8
Urine osmolarity (mOsm/kg)	169	350
Urinary Na (mmol/l)	90	27
Urinary K(mmol/l)	3	1

FENa=Fractional excretion of sodium; FEK=fractional excretion of potassium

Our patient revealed weight loss, polyuria, polydipsia, drug-resistant hypertension, resistant hyponatremia, hypokalemia, hypochloremic alkalosis, hyperreninemia, hyperaldosteronism, high sodium levels in the urine and nephrotic level of proteinuria. These symptoms are indicators of hyponatremic hypertensive syndrome. Although our patient had polyuria and growth retardation for three months, he was unrecognized as mentioned in the literature [4-5].

For a patient to develop HHS, the condition of unilateral renal artery stenosis is observed, with the other kidney displaying normal perfusion and function [1]. In the pathogenesis of the disease, the main problem is the release of high quantities of renin from the ischemic kidney due to renovascular stenosis [4]. Our patient had right renal artery occlusion. It was thought that renal ischemia in our patient caused hyperreninemia resulting with hypertension and pressure diuresis. Stimulation of thirst, causing polyuria, together with pressure diuresis was the reason of sodium loss in urine resulted with hyponatremia (Table 1). Direct renal action of angiotensin II and ADH secretion might also have role in hyponatremic renin angiotensin system activation caused hyperaldosteronism resulted with hypokalemia [1, 5].

Measurement of blood pressure in children with unexplained polydipsia and polyuria is important. Late diagnosis of hypertension in our patient caused end organ damage both in hearth as left ventricular hypertrophy and kidney as glomerular hyperfiltration. Nephrotic-range proteinuria in our patient similar to that reported by Trivelli [4] was probably due to the glomerular hyperfiltration, deriving from hyperreninemia and hypertension. Quick resolution of proteinuria after right nephrectomy demonstrated reversible nonstenotic kidney hyperfiltration.

Trivelli et al. [4] reported hypercalciuria in two children with HHS which lasted for several months after surgery. We supposed that in our patient, not having hypercalciuria, distal convoluted tubules were not involved.

The first choice for the antihypertensive treatment of cases with HHS should be the angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers. Except potent diuretics, which may exacerbate the disorder, additional antihypertensive drugs can be used [5]. No response was observed to the antihypertensive agents used.

For the achievement of cure, surgical correction of the underlying renal ischemia is necessary Percutaneous transluminal renal angioplasty with or without stenting or uninephrectomy can be used [5, 7]. Nephrectomy is necessary if the ischemic kidney contributes less than 10% of the renal function or if PTRA fails [6, 8]. It is impossible to perform PTRA in our patient, because his right renal artery was almost completely constricted and DMSA revealed a non-functional (10 %) right kidney. Therefore, we performed to threat our patient with unilateral nephrectomy of the affected kidney.

In conclusion, clinicians should be careful in differantial diagnosis of the children with polyuria and unexplained electrolyte abnormalities. This case, with the other few reports, indicated that HHS may also be seen in renovascular hypertension in children. Our case report also emphasizes the importance of early diagnosis in preventing life-threatining complications and preserving renal function of the non-stenotic kidney.

Competing interests

The authors declare that they have no competing interests.

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Darier's Disease: Two Familial Case Reports

Darier Hastalığı: Ailesel İki Olgu Sunumu

Darier's Disease / Darier Hastalığı

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Özet

Darier hastalığı (Darier-White hastalığı, keratozis follikülaris), özellikle seboreik bölgeleri tutan, keratinizasyon bozukluğu ile karakterize, otozomal dominant geçişli, nadir gözlenen bir hastalıktır. Bu makalede, klinik ve histopatolojik bulgular ile Darier's disease tanısı konulan 47 ve 28 yaşlarında ki anne ve kız iki kadın hasta, bu hastalığın nadir görülmesi nedeniyle sunulmuştur.

Anahtar Kelimeler

Darier Hastalığı; Keratozis Follikülaris; Keratotik Papüller

Abstract

Darier's disease (Darier-White disease, keratosis follicularis) is a rare autosomal dominant disease particularly involving the seborrheic areas and characterized by impaired keratinization. Herein, two cases of this rare disease in a mother and her daughter, aged 47 and 28 years, are reported, together with clinical and histopathological findings.

Keywords

Darier's Disease; Keratosis Follicularis; Keratotic Papules

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Introduction

Darier's disease, also known as Darier-White disease or keratosis follicularis, is a rare, autosomal dominant keratinization disorder first reported in 1889 by Darier and White. It is observed equally in both sexes [1-3]. Impairment in desmosomes and the tonofilament-desmosome complex, and compromise of epidermal homeostasis resulting from damage in ATP2A2 gene on the 12q23-24 1 chromosome that codes the calcium pump have been implicated in the pathogenesis of the disease [4]. Darier's disease is an entity that should be considered in the differential diagnosis of dermatoses progressing with keratotic papular lesions.

This report presents two familial cases of Darier's disease of a mother and her daughter.

Case Report 1

A 47-year-old woman presented to our clinic with numerous mildly itching brown eruptions on the trunk and skin folds, having persisted and worsened for about 30 years. Her symptoms increased with sunlight and sweating and improved in the winter. Her history revealed that she had hepatitis B infection for 12 years, and she had been receiving telbivudine therapy for 14 months. In addition, she had generalized anxiety disorder for 4 years, and was using paroxetine for 2 years. Further investigation revealed that her daughter had similar eruptions. Physical examination findings were normal. Dermatological examination revealed numerous brown hyperkeratotic papular lesions on the bilateral axillary regions, beneath the breasts and on the trunk (Figure 1). Complete blood count and routine biochemical tests were within normal limits. A punch biopsy from a keratotic papular lesion on the trunk was performed. Histopathologically, a parakeratotic plug accompanying hyperkeratosis was detected in the stratum corneum (Figure 2). Beneath the parakeratotic plug, mild papillomatosis, irregular acanthosis, and focal suprabasal acantholysis were observed in the epidermis, by performing serial sections (Figure 3). In addition, dyskeratotic cells were present in the formation of "corps ronds" and "grains" in the upper part of the epidermis (Figure 3). Mild rete hyperplasia in the upper dermis was detected. There were mild perivascular chronic inflammation and melanophages in the upper dermis. The histopathological features were evaluated as compatible with Darier's disease. After clinicopathological correlation, the case was diagnosed as Darier's disease. Treatment with acitretin (25 mg/day) was started.



Figure 1. Brown hyperkeratotic papules on the trunk in Case 1.

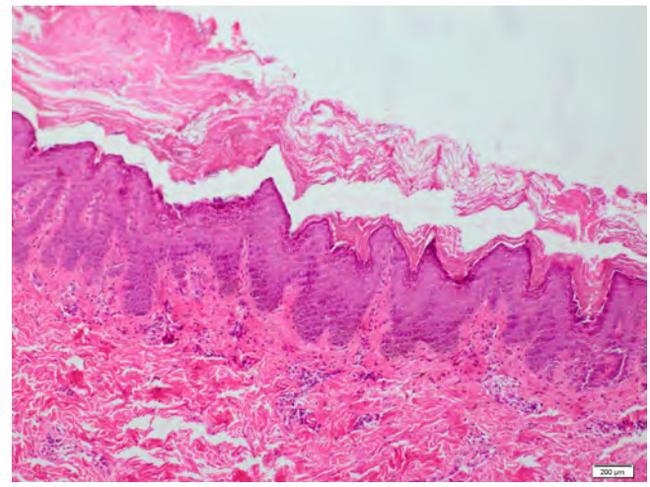


Figure 2. The microscopic photo of Case 1 showing focal suprabasal acantholysis (H&E, x40).

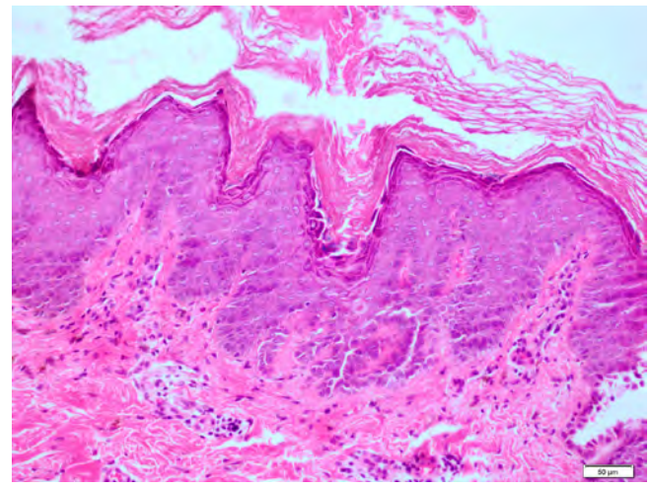


Figure 3. The higher-power microscopic view of Case 1 illustrating focal suprabasal acantholysis, dyskeratotic cells as "corps ronds", and "grains" (H&E, x200).

Case Report 2

The 28-year-old daughter of Case 1 had eruptions extending from the neck to the trunk for approximately 10 years. These eruptions increased in size and number in the summer, and itching occurred. No characteristic finding was determined in her clinical history. Physical examination findings were normal. Dermatological examination revealed brown hyperkeratotic papular lesions on both sides of the neck, and both beneath and

between the breasts (Figure 4). Complete blood count and routine biochemical tests were within normal limits. A punch biopsy from a keratotic papular lesion on the neck was performed. The histopathological findings were similar but more striking and characteristic than Case 1. In the present case suprabasal acantholysis was extensive and formed suprabasal clefts (Figure 5). Dyskeratotic cells as "corps ronds" and "grains" in the upper part of the epidermis were also present (Figure 6). There was mild perivascular chronic inflammation accompanying a few eosinophils and melanophages in the upper dermis. The histopathological features were reported as consistent with Darier's disease. On the basis of clinical and histopathological findings, the case was diagnosed as Darier's disease. Topical 0.1% adapalene gel and moisturizing cream treatment was started. Since the patients did not attend to regular follow-up, the efficiency of the treatment could not be determined.



Figure 4. Brown hyperkeratotic papules on the neck of Case 2.

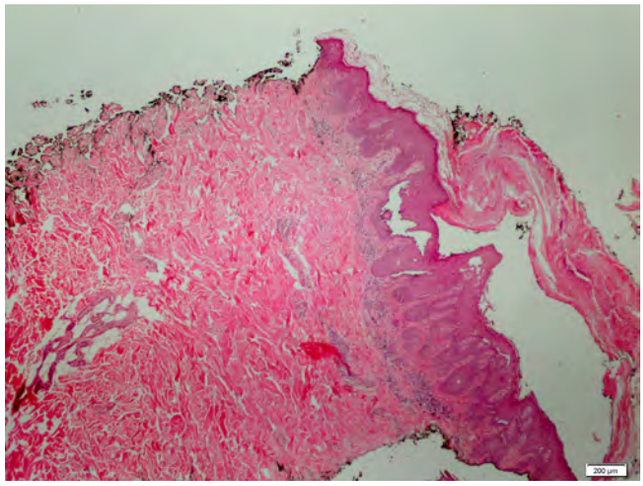


Figure 5. The microscopic photo of Case 2 showing extensive suprabasal acantholysis forming suprabasal clefts (H&E, x40).

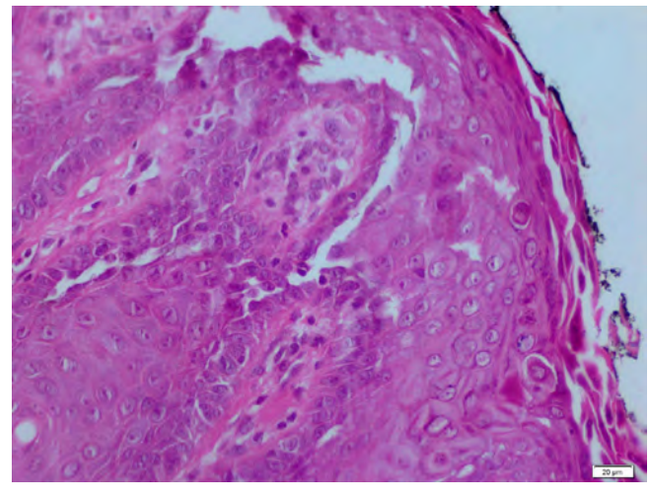


Figure 6. The high-power microscopic view of Case 2 illustrating suprabasal clefts, dyskeratotic cells as "corps ronds", and "grains" (H&E, x400).

Discussion

The characteristic features of Darier's disease are fatty, hyperkeratotic hard lesions located at the anterior part of the chest, the middle part of the back, and seborrheic areas such as the hair margins and flexural areas. In general, the lesions are itching. The symptoms usually begin between the ages of 6 and 20 years, and peak in puberty. Clinically, Darier's disease may be confused with seborrheic dermatitis and acne. The triggering factor initiating pathogenesis is unknown, but increased sebum secretion in puberty and changes in bacterial flora are thought to play significant roles. Symptoms may worsen with sunlight and sweating, as in our cases. This is attributed to solar injury induced inflammation [1, 5].

Hair is generally normal in Darier's disease, while hairy skin is frequently covered with thick, fatty squames and crusts. Acral involvement in the form of punctate, keratotic papules is seen on the hands and feet in 95% of patients [1, 6]. Nail involvement manifests as fragility in the nails, subungual hyperkeratosis and splinter hemorrhage. Longitudinal white ridges may appear, and V-shaped nicks are seen at the free edge of the nail. Oral mucosal involvement may occur in about 15% of the cases as mucosal plaques and/or a cobblestone appearance in the hard palate [2, 4, 5]. In our cases there was no hairy skin, acral area, nail or oral mucosa involvement.

Darier's disease is a disorder of epidermal maturation and keratinization showing acantholytic dyskeratosis, histopathologically. The most strikingly characteristic features are suprabasal acantolysis forming clefts or lacunae, and dyskeratotic cells called "corps ronds" and "grains", histopathologically (1, 7). The histopathological appearance also supported diagnosis in our cases.

No relation is determined between Darier's disease and other medical problems in the literature. However, accompanying neuropsychiatric problems such as bipolar affective disorder, mental retardation, schizophrenia, recurrent depression, attempted suicide and epilepsy have been reported in some families [5, 6]. Our first case had a history of paroxetine use due to generalized anxiety disorder. Although Darier's disease exhibits a progressive course, it has no important complications. The most common complications are secondary skin infections such as widespread viral, bacterial, and dermatophyte infections [7].

No complication was observed in our cases.

The main approach for the treatment of Darier's disease includes avoiding heat and sunlight, and using emollients. Antiseptics, retinoids, tacrolimus, and 15% fluorouracil are used in topical treatment. Isotretinoin and acitretin therapies are more popular in widespread and serious cases [1, 5]. Alitretinoin, an endogenous retinoid used in severe, chronic hand eczema resistant to topical potent steroids, has recently been reported to be more beneficial in Darier's disease [8]. Oral treatments including prednisolone, cyclosporine, oral contraceptives, and essential fatty acids are the alternative therapies that are used rarely. Surgical procedures such as laser and dermabrasion may be tried if there is no response to oral therapies [6].

In conclusion, Darier's disease is an inherited rare entity that is a member of the acantholytic dyskeratosis family. It should be kept in mind in the differential diagnosis of dermatoses progressing with keratotic papular lesions, clinically. In the present report, a mother and her daughter with Darrier's disease are presented emphasizing the rarity of this disorder, the significance of the detailed clinical history, and a summary of the basic diagnostic and therapeutic approaches.

Competing interests

The authors declare that they have no competing interests.

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Magnetic Resonance Imaging of Unusual Intramedullary Spinal Cord Lesions

Nadir Intrameduller Spinal Kord Lezyonlarında Manyetik Rezonans Görüntüleme

Spinal Kord Lezyonlarında Manyetik Rezonans Görüntüleme / Magnetic Resonance Imaging of Spinal Cord Lesions

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Özet

Manyetik rezonans görüntüleme, miyelopatik semptomlar ile başvuran spinal kord lezyonu araştırılan hastaların değerlendirilmesi için tercih edilen geçerli görüntüleme yöntemidir. Erken tanı, bu lezyonların tedavisinde önemli bir rol oynar, prognozu ve hastanın sonucunu etkileyebilir. Bu derlemede infarkt, kavernöz malformasyon (CM), arteriovenöz malformasyon (AVM), tüberküloma, brusella apsesi, hemangioblastoma, dermoid, epidermoid tümörler, ve metastazı içeren nadir intramedüller spinal kord lezyonları klinik bulgular ve manyetik rezonans sinyal özellikleri sunulmuştur.

Anahtar Kelimeler

MR Görüntüleme; Spinal Kord; İntrameduller Lezyon

Abstract

Magnetic resonance imaging is the current imaging modality of choice for evaluating patients presenting with myelopathic symptoms in the search for spinal cord lesions. Early diagnosis plays an important role in the management of these lesions and can affect the prognosis and final outcome of the patient. In this review article, the clinical presentation and magnetic resonance signal characteristics of unusual intramedullary spinal cord lesions, including infarction, cavernous malformation (CM), arteriovenous malformation (AVM), tuberculoma, brucella abscess, hemangioblastoma, dermoid, epidermoid tumors, and metastases, are presented.

Keywords

MR Imaging; Spinal Cord; Intramedullary Lesions

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Introduction

Spinal cord lesions are rare; magnetic resonance imaging should be performed as soon as possible and as the first technique whenever an intrinsic spinal cord lesion is suspected clinically. In this pictorial essay, unusual intramedullary spinal cord lesions, including vascular lesions of the spinal cord (such as infarction, cavernous malformation (CM), arteriovenous malformation (AVM), spinal cord abscess (including tuberculoma and brucella abscess) and rare intramedullary neoplasms (including hemangioblastoma, dermoid, epidermoid tumors, and metastases) are presented. The clinical presentation and magnetic resonance signal characteristics of these unusual intramedullary lesions are discussed.

Vascular Diseases of the Spinal Cord

Vascular diseases affecting the spinal cord, while a relatively rare occurrence, compared with cerebrovascular events, can cause substantial neurological morbidity. They include various pathologies, including structural issues (e.g., infarction, cavernous malformation (CM), arteriovenous malformation (AVM).

Spinal Cord Infarction

The key to distinguishing spinal cord infarction from other entities that can have a similar appearance on imaging is the clinical history. Spinal cord infarction is characterized clinically by sudden motor and sensory loss below the level of the spinal cord injury [1]. Underlying causes include aortic disease and surgery, atherosclerosis, degenerative spinal disease, systemic hypotension, vertebral artery dissection, coag¬ulopathy, trauma, and cocaine abuse. However, the cause has been reported to be idiopathic in 28-74% of cases [2].

Infarction occurs most commonly in the thoracic and thoracolumbar cord, which has a tenuous blood supply. Spinal cord infarction typically manifests in MRI as focal cord swelling, including intramedullary hyperintensity on T2-weighted images (Fig. 1). Diffusion-weighted imaging demonstrating focal restricted diffusion has become increasingly sensitive for the diagnosis of spinal cord infarcts, but its sensitivity is not as high as in the brain. Infarction may show minimal enhancement (typically after 5 days). Contrast enhancement may persist for up to 3 weeks after onset. Mild cord expansion is often present. However, as described in several studies, conventional MRI may appear normal in some patients, especially in the acute phase [1-4].

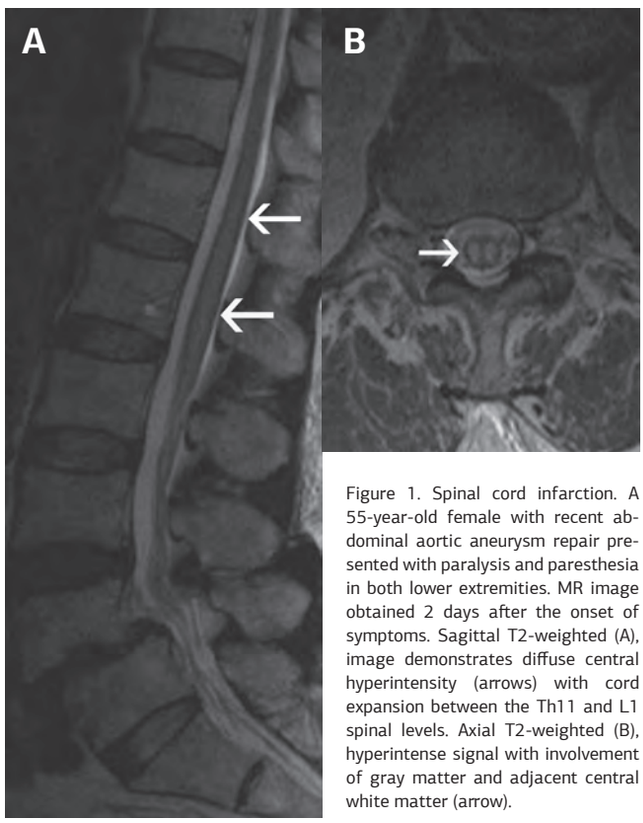


Figure 1. Spinal cord infarction. A 55-year-old female with recent abdominal aortic aneurysm repair presented with paralysis and paresthesia in both lower extremities. MR image obtained 2 days after the onset of symptoms. Sagittal T2-weighted (A), image demonstrates diffuse central hyperintensity (arrows) with cord expansion between the Th11 and L1 spinal levels. Axial T2-weighted (B), hyperintense signal with involvement of gray matter and adjacent central white matter (arrow).

Cavernous Malformation

Cavernous malformation (CM) is also known as cavernous angioma, cavernous hemangioma, and cavernoma. CMs are angiographically occult vascular malformations, defined by abnormal, enlarged vascular channels but without interposing neural or glial tissue. Intracerebral CMs are more common than spinal lesions; coexisting intracranial CMs can be found in a quarter of cases and even more frequently in familial cases [3]. The clinical presentation is variable, and patients may receive a diagnosis of an asymptomatic intramedullary CM. The acute presentation is likely due to hemorrhage within the vascular spaces or into the spinal cord parenchyma [1].

The diagnosis of spinal CM requires MRI. CM typically demonstrates a speckled "popcorn" heterogeneous signal intensity on both T1- and T2-weighted images due to blood products in various stages of evolution. The lesion may demonstrate a peripheral rim of hemosiderin of low signal intensity on T2-weighted images. Gradient echo sequences may demonstrate the "blooming" susceptibility artifact from the presence of blood products (Fig. 2) [1,3,4]. CT may also be of value, because some cavernomas demonstrate extensive calcification. In acutely hemorrhaging cavernomas, however, spinal angiography should be performed to rule out small glomerular AVM [1].

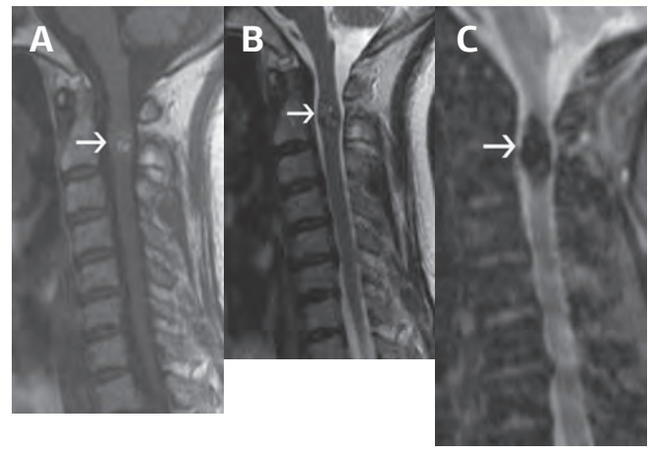


Figure 2. Cavernous malformation. A 61-year-old female with an incidentally revealed spinal cord cavernous malformation (CM). Sagittal T1- weighted (A) and T2- weighted (B) spinal MR images show a focal area of hyperintensity with a hypointense rim on the right side of the cervical cord (arrow). (C) The lesion "blooming" artifact on a sagittal gradient echo image (arrow).

Spinal AVMs

Spinal cord AVMs are congenital lesions resulting from a defect in early vascular embryogenesis. Spinal AVMs are a rare clinical phenomenon, although precise estimates of the incidence are lacking for all but a specific subset called "spinal dural AV fistulae" (sdAVF), which has been reported to affect 5 10 patients per million population annually [3] . Spinal dural AV fistulae are the most frequent vascular malformations of the spine and rep-

resent upwards of 70% of all spinal AVMs [1]. Both sdAVFs and AVMs are predominantly thoracolumbar, but may develop at any level of the cord, including the filum terminale. They cause symptoms primarily from venous hypertension, which then produces cord edema and, eventually, infarction. Spinal MRI and angiography are essential in establishing a diagnosis of spinal AVM. Spinal MRI has excellent sensitivity and specificity for the detection of spinal AVMs and sdAVF, as long as it includes all necessary sequences and is interpreted by experienced neuroradiologists [3]. MRI of the entire spine should be performed, be it in the setting of a progressive myelopathy or spinal subarachnoid hemorrhage, because neurological signs and symptoms do not correspond well with the level of the vascular lesion. MRI characteristics of the myelopathy associated with sdAVF include longitudinally extensive T2 hyperintensity within the central aspect of the spinal cord, involving the conus medullaris in as many as 95% of patients. Spinal cord enlargement and dilated perimedullary veins may also be seen, most prominently on sagittal T2 sequences. The cord becomes swollen and may demonstrate patchy or diffuse enhancement as a sign of chronic venous congestion [4] (Fig. 3).



Figure 3. Spinal dural AV fistula: A 46-year-old male presented with bilateral lower extremity weakness for 2 months. Sagittal T2- weighted (A) spinal MR images, intramedullary high-intensity area (arrow) and dilated perimedullary vessels (open arrow), which are present as a flow void in these images. The combination of pathologically dilated vessels and edema of the cord is pathognomonic for spinal dural AV fistulae. Gadolinium-enhanced fat-suppressed T1 -weighted image (B) the cord is swollen, demonstrating patchy enhancement (arrow).

Spinal Cord Abscess

Intramedullary abscess of the spinal cord is a rare infection of the central nervous system. It is associated with high morbidity and mortality. Early recognition and treatment are important [5]. Multiple organisms have been shown to cause intramedullary abscess; we discuss tuberculoma and brucella abscess.

Tuberculoma

The most common form of spinal tuberculosis is meningitis, but involvement of spinal cord in the form of intramedullary tuberculoma is rare and the concurrent occurrence of cranial and intramedullary tuberculomas is extremely rare [6]. Central nervous system tuberculosis occurs because of the hematogenous spread of the bacilli from a distant focus. Additionally, in spinal tuberculosis, the tuberculous bacilli may gain entry through the subarachnoid space or central canal and produce a local inflammatory response, which can evolve into an intramedullary granulomatous lesion [6,7]. The clinical presentation of intramedullary tuberculoma is progressive myelopathy, with or without sphincter disturbances [6,8].

The MRI findings in cases of spinal intramedullary tuberculoma can vary during the different phases of the tuberculoma. In the early phase, there are severe infective reactions and variable degrees of edema around the lesion. During this phase, tuberculoma appears isointense on both T1WI and T2WI and is homogenously enhanced. Subsequently the tuberculoma capsule becomes richer in collagen. As a result, T1WI shows equal signal intensity and T2WI shows equal or low signal intensity. After enhanced scanning, there is rim enhancement and a low signal in the central region (Fig. 4). The center of the tuberculoma



Figure 4. Co-occurrence of intracerebral tuberculoma with spinal cord tuberculoma. A 31-year-old female with a history of tuberculous meningitis with weakness right lower limb for 2 days. Sagittal T2- weighted (A) MR image showing an intramedullary lesion with extensive surrounding edema. Enhanced sagittal T1- weighted image (B) shows obvious ring enhancement of the intramedullary lesion (arrow).

becomes hyperintense on T2WI with the development of caseation. The solid parts of granulomas may appear as hypo- to hyperintense on T2WI with the development of caseation; also, T2WI typically shows a "target sign" [7,8].

Brucella Abscess

Brucellosis is an infectious disease caused by a Gram-negative intracellular coccobacillus.

Brucella reaches the CNS via the hematogeneous route or by direct extension from spondylitis. Nervous system complications of neurobrucellosis include meningitis, encephalitis, brain abscess, epidural abscess, demyelization syndromes, and meningovascular syndromes. Meningitis has been reported as the most frequent presentation, occurring in ~50% of cases, but abscess and granuloma development generally have rarely been reported [9,10]. Neurobrucellosis can be diagnosed by raised brucella titers in the CSF, which were also detected in the present case. The lesion exhibits a hypointense signal on T1-weighted sequences and a hyperintense signal on T2-weighted sequences with associated spinal cord edema (Fig. 5). Intramedullary abscesses may show restricted diffusion on diffusion-weighted images [5].



Figure 5. Intramedullary Brucella abscess. A 15-year-old male with a history of brucellosis presented with progressive upper and lower extremity pins and needles symptoms. Pretreatment: Sagittal T2-weighted MR image (A) showing intramedullary isointense lesion with surrounding edema. Enhanced sagittal and axial T1-weighted (B,C) showed obvious homogeneous enhancement of the intramedullary lesion. The lesion is hyperintense on axial DWI (D). Restricted diffusion is seen on the ADC map (E).

Rare Intramedullary Neoplasms

We discuss hemangioblastomas, dermoid and epidermoid tumors, and metastases.

Hemangioblastoma

Hemangioblastomas are benign WHO grade I tumors. Hemangioblastomas of the spinal cord tend to be solitary (80%), with multiple lesions being suggestive of VHL syndrome (autosomal-dominant cerebelloretinal hemangioblastomatosis, renal cell carcinoma, multiple renal and pancreatic cysts, pancreatic cystadenocarcinoma, and epididymal cysts) [1]. These neoplasms are slow-growing and may present with sensory changes, pain, and motor dysfunction [11]. On MRI, hemangioblastomas are well-circumscribed nodular masses with variable T1 intensity (typically isointense), prominent enhancement with gadolinium, and hyperintensity on T2-weighted imaging. Flow voids, adjacent cysts, and hemorrhage are also common findings. The signal within the cyst may vary depending on the protein content within the cyst fluid. A syrinx may be present, and there may also be long segment cord edema without a syrinx [11,12]. Some cases may have the classic "cystic mass with an enhancing mural nodule" appearance characteristic of cerebellar hemangioblastoma (Fig. 6) (1).

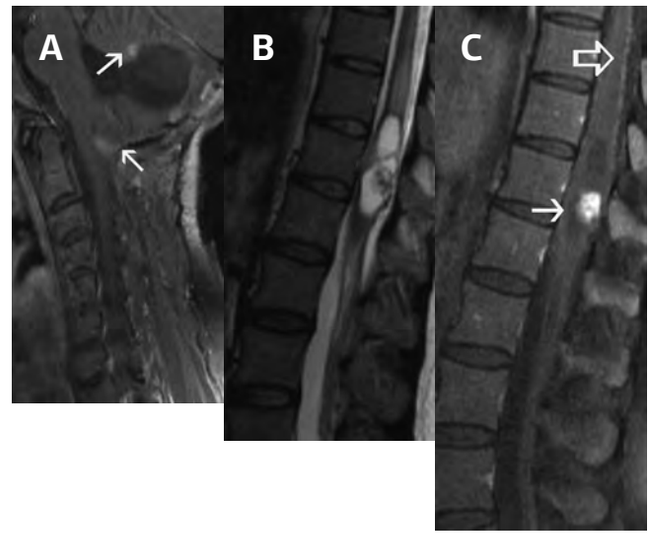


Figure 6. A 29-year-old female with multiple hemangioblastoma lesions in the spinal cord and cerebellum in von Hippel-Lindau (VHL) syndrome. Sagittal postcontrast T1- weighted images (A) show enhanced nodule posterior aspects of the cord and cerebellum (arrows). Sagittal T2-weighted (B) consistent with edema and a cystic mass. Sagittal postcontrast T1-weighted images (C) enhanced nodule (arrow) and open arrow show a hyperintense linear structure consistent with a vessel posterior to the cord.

Dermoid Tumor

Dermoid tumors or dermoid cysts are rare, congenital, benign, slow-growing tumors composed of more than one of the three primitive germ cell layers that produce skin and its appendages (hair follicles, sweat gland, and sebaceous glands). Dermoid cysts can be associated with dermal sinus (20%), vertebral abnormalities, and closed dysraphism [1]. Patients may present with slowly progressive compressive radiculopathy and myelopathy or cauda equina syndrome. These tumors may often become acutely symptomatic after rupture or infection [1,13]. On MR imaging, the signal intensity characteristics are variable, depending on the cystic contents, with the two major components being fluid and lipid. The lipid components appear hyperintense on T1- weighted MR images and exhibit low signal in¬tensities on gadolinium-enhanced fat-suppressed

T1-weighted MR images (Fig. 7). The lesion can also appear

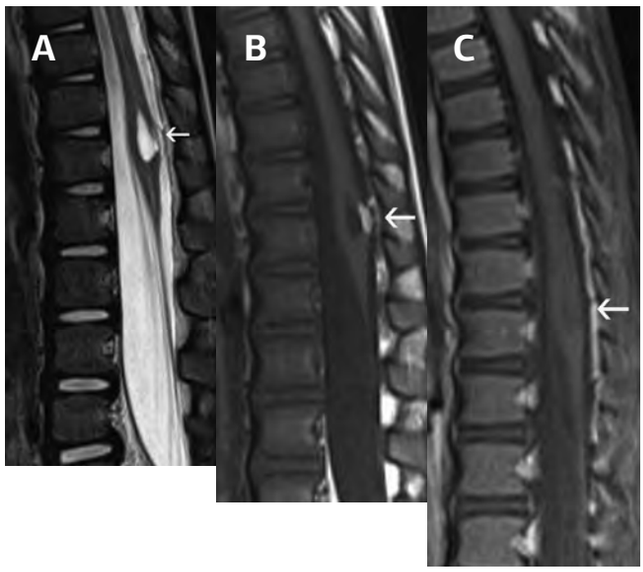


Figure 7. Intramedullary dermoid tumor. A 3-year-old female patient with previous history of occult spinal dyraphism. Sagittal MRI of spine: T2-weighted (A), T1-weighted (B) and gadolinium-enhanced fat-suppressed T1-weighted images (C). There is a well-defined intramedullary cystic mass, expanding the dorsal spinal cord. The dorsal component (arrows) is hyperintense on T1-weighted and T2 -weighted images and shows suppression on gadolinium-enhanced fat-suppressed T1-weighted MR image, consistent with fat.

hypointense on T1-weighted MR images because of increased water content. On T2 weighted MR images, the fluid components are hyperintense. The soft-tissue component usually enhances after administration of intravenous contrast [1,13].

Epidermoid Cysts

Epidermoid cysts are benign tumors originating from ectoderm remnants. Intramedullary epidermoid cysts are very rare entities. They can be congenital, and are frequently associated with other spinal malformations, such as spina bifida [14]. Patients may present with non-specific presentations and symptoms, such as numbness, weakness, spasticity, and paraparesis of the lower extremities [15]. On MRI, where the absence of peritumoral edema and sharp boundaries between the lesion and surrounding parenchyma confine the diagnosis, there is minimal peripheral enhancement with gadolinium, and an inhomogeneous signal is usually observed on both T1 and T2WI [14,15]. At MR imaging, epidermoid tumors can mimic cystic lesions with fluid content, such as arachnoid cysts. DWI can help in obtaining a correct diagnosis. Arachnoid cysts exhibit elevated diffusion with low signal on trace DWI and high ADC values, whereas epidermoid cysts show high signals on DWI (Fig. 8). ADC measured in the tumor was lower than that reported in intracranial epidermoids [14].

Metastasis

Intramedullary spinal cord metastases (ISCM) are rare. Although lung and breast cancers are the most common tumor sites in ISCM, melanoma, renal, colorectal, and lymphoma have also been reported [1,12]. The prognosis of patients with ISCM is very poor and nearly all patients present with motor weakness and pain, as well as bowel and bladder dysfunction (60%) and parasthesias (50%) [1]. At MR imaging, metastatic intramedullary lesions often show cord expansion due to associated edema, which is usually out of proportion to a seemingly focal small cord lesion, usually extending over several vertebral segments. Postcontrast images may show either a ring-enhancing or a homogenously enhancing lesion (Fig. 9). The presence of hemorrhage may produce heterogeneous enhancement [1,12].

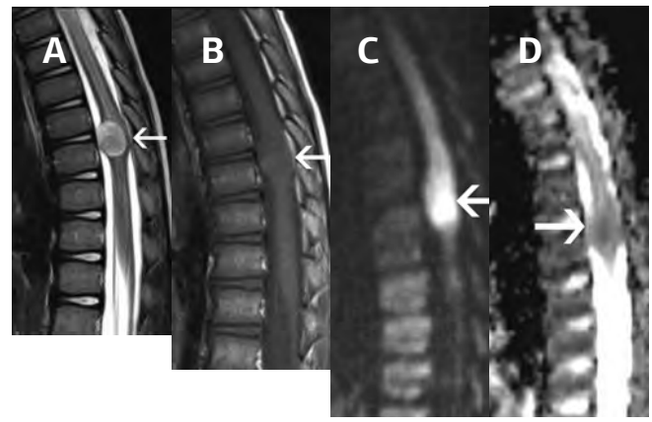


Figure 8. Intramedullary epidermoid cysts. A 3-year-old male patient who presented with bilateral lower extremity weakness for 4 days. MRI of the thoracolumbar spine shows an intramedullary mass at the T8-9 level. On sagittal T2-weighted image (A), the intramedullary lesion appeared hyperintense and well-defined (arrow). Sagittal T1-weighted image(B) lesion hypointense (arrow). On sagittal DWI (C), a marked high signal with low apparent diffusion coefficient value (D) is demonstrated.

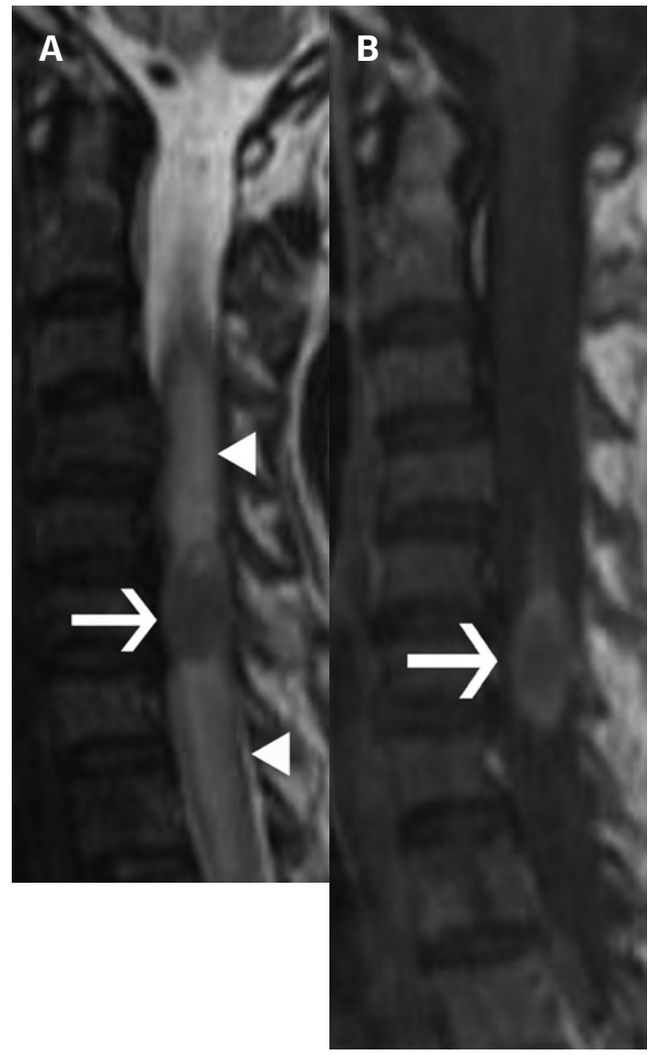


Figure 9. Intramedullary metastasis (primary, lung). A 45-year-old female with lung cancer with a known history of metastatic disease presents with bilateral lower and upper extremity paresthesia and weakness. On sagittal T2-weighted image (A), the intramedullary lesion appears isointense (arrow), there is a diffuse increased T2 signal, consistent with edema with enlargement of the cord (arrow head). Postcontrast sagittal (B) images show a lesion (arrow) of homogeneous enhancement in the cervical cord.

Conclusion

We have briefly reviewed clinical presentation and magnetic resonance signal characteristics of unusual intramedullary lesions, including infarction, CM, AVM, tuberculoma, brucella abscess, hemangioblastoma, dermoid, epidermoid tumors, and metastases. When spinal cord diseases are suspected, MRI should constitute the first diagnostic modality to identify the lesion and rule out potential differential diagnoses.

Competing interests

The authors declare that they have no competing interests.

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Minimal Invasive Management of Small Renal Masses: State of Art and New Trends

Küçük Renal Kitlelerin Minimal İnvazif Yönetimi: Son Gelişmeler ve Yeni Trendler

Küçük Renal Kitlelerin Minimal İnvazif Yönetimi / Minimal Invasive Management of Small Renal Masses

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Özet

Ultrasonografi, bilgisayarlı tomografi ve manyetik rezonans görüntüleme gibi radyolojik görüntüleme yöntemlerinin yaygın kullanımı ile birlikte özellikle 2 cm'den küçük, klinik olarak lokalize böbrek tümörlerinin insidansında göze çarpan bir artış olmuştur. Dahası, bu lezyonların kesin patoloji sonuçları %30'lara kadar iyi huyludur. Probların gelişmesi ve eş zamanlı görüntüleme yeteneği gibi sürekli yenilikler ile birlikte ablasyon tekniklerinin (radyofrekans ablasyon [RFA], krioablasyon [CA], yüksek yoğunlukla odaklanmış ultrasonografi [HIFU], microwave ablasyon [MWA]) gelişmesi özellikle T1 renal tümörlerin tedavisinde bu tekniklere olan ilgiyi arttırmıştır. RFA ve CA'nın nefrektomi ile karşılaştırıldığında benzer kanser-spesifik sağkalım, hastalıksız sağkalım, nükssüz sağkalım ve genel sağkalım oranları vardır. MWA ve HIFU düşük hasta sayıları ve yetersiz klinik deneyim ile hala deneyseldir. Minimal invazif teknikler pek çok komorbiditesi ile yüksek cerrahi ve anestezik riske sahip, VHL gibi sistemik hastalıklara bağlı birçok tümörü olan ya da cerrahiye gitmek istemeyen hastalar için uygun bir teknik olabilir. Özellikle rölatif kısa yaşam beklentisi ve düşük performans durumlu yaşlı hastalar bu işlemler için iyi birer aday olabilirler.

Anahtar Kelimeler

Böbrek Tümörü; RFA; HIFU; MWA

Abstract

With the widespread use of abdominal imaging modalities such as ultrasound (US), computerized tomography (CT) and magnetic resonance imaging (MRI), there has been a pronounced increase in the incidence of renal tumors especially clinically localized, small < 2 cm ones. Moreover the final pathology of these lesions is benign up to 30%. The development of ablation techniques (radiofrequency ablation, cryoablation, high-intensity focused ultrasound and microwave ablation) with continuous innovations such as refinement of probes and real-time imaging capabilities has pioneered the great interest in these techniques, especially for the treatment of T1 renal malignancies. RFA and CA have similar cancer specific survival, disease-free survival, recurrence free survival and overall survival rates compared to nephrectomy. MWA and HIFU remain still experimental due to low patient volume and insufficient clinical experience. Minimal invasive techniques can be a feasible treatment alternative for patients who have high surgical and anesthetic risk with multiple comorbidities, have multiple tumors due to a systemic disease like VHL or do not want to undergo extirpative surgery. Especially elderly patients can be good candidates for these procedures with their relatively short life expectance and impaired performance status.

Keywords

Renal Masses; RFA; HIFU; MWA

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Introduction

With the widespread use of abdominal imaging modalities such as ultrasound (US), computerized tomography (CT) and magnetic resonance imaging (MRI), there has been a pronounced increase in the incidence of renal tumors especially clinically localized, small < 2 cm ones [1]. It is estimated that more than 50% of renal cell carcinomas (RCCs) are being identified incidentally [2]. This exaggerated utilization of modern technology has led to the alteration of clinical landscape of renal tumors. At the present time, majority of renal tumors are detected incidentally with small dimensions (<4cm), low grade and low malignant potential. Moreover the final pathology of these lesions is benign up to 30% [3].

The surgical management of RCC has evolved impressively subsequent to description of radical nephrectomy (RN) and ipsilateral adrenalectomy as gold standard treatment in 1969 [4]. The data supporting that surgically induced chronic kidney disease may increase cardiovascular and metabolic risk factors has led a shift toward nephron preserving treatment options [5]. Currently, partial nephrectomy (PN) has became the gold standard for the management of small renal masses (SRMs) because it preserves the normal renal parenchymal tissue and has similar oncologic outcomes to radical nephrectomy [6]. While PN has similar oncologic outcomes to RN, it is related with increased complications [5]. Another management choice in SRMs is active surveillance (AC). AC surveillance is postulated as an appropriate initial strategy for SRMs. It is especially convenient for elder patients with multiple or serious comorbidities thus unfit for surgery [7].

Minimal invasive treatment modalities like thermal ablations (cryotherapy or radiofrequency ablation) and high intensity focused ultrasound (HIFU) can be a good choice for those patients who are unsuitable for or not willing to undergo extirpative surgery, elderly or have multiple tumors due to systemic diseases like Von-Hippel Lindau (VHL) disease. The development of ablation techniques with continuous innovations such as refinement of probes and real-time imaging capabilities has pioneered the great interest in these techniques, especially for the treatment of T1 renal malignancies. Ablation procedures also have some superiority in terms of cost compared to both open and radical nephrectomy [8].

On the other hand, the maximum tumor size for such ablative techniques still remains controversial. While EAU guidelines restricts it use with tumors smaller than 3 cm some studies have reported success in pT1b (4-7 cm) tumors [3].

The purpose of the following section is to overview the current literature to provide the reader a point-view about most often applied ablative procedures.

Radiofrequency Ablation (RFA) of Renal Tumors

RFA or radio thermal ablation is a tissue-destruction technique, which uses thermal energy produced by alternating high-frequency electric current between 100-500 kHz. The current reaching the tissue via needle electrode causes the resistive heating of adjacent tissue known as Joule effect. Alteration of tertiary structure of intracellular protein occurs at 60° C which causes the denaturation of collagen and lipid bilayer damage. Thermal coagulation starts at 70° C while the drying of the tissues takes places at about 100° C. Higher temperatures are not suggested due to increase in impedance and diminish in the efficacy of the treatment caused by the tissue charring [9]. RFA can be performed either laparoscopic (L/S) or percutaneous.

RFA has been widely accepted as an affective nephron-sparing procedure in the management of small RCCs. The AUA guidelines recommended RFA as a treatment option especially for clinical T1a RCC patients. Multiple retrospective studies have demonstrated that RFA has a similar cancer-specific survival (CSS) and disease-free survival (DFS) rates compared to nephrectomy in clinical T1a RCCs [10].

Chang et al. conducted a study with 268 patients providing us information on perioperative and long-term outcomes of RFA and PN. As perioperative outcomes they found larger estimated blood loss (243.3 ±284.8 mL vs. 74.8± 50.8 mL, P < 0.001), longer operative time (171.5± 32.4 min vs. 132.6± 24.9 min, P < 0.001) and larger GFR percentage change in PN patients. There was no statistically significant difference between the two groups regarding to hospital stay and major complications (Clavien system: ≥ IIIa). After minimum 5 years of follow up no significant difference was found in the oncologic outcomes between the two groups as having similar 5-year overall survival (OS) and 5-year CSS [10].

İn another study comparing local recurrence-free survival (LRFS), metastases-free survival (MFS) and OS among patients treated with PN, percutaneous RFA and percutaneous cryoablation (PCA) demonstrated similar local control among the three groups, inferior MFS for RFA and superior OS for PN [11].

Young et al. reported favorable results for L/S RFA for T1b renal tumors. They performed L/S RFA on 51 patients with a 5.1±0.6 cm mean tumor size. The initial ablation success rate was 90.2%. They reported the 3-year disease-free survival as 84.7%. Mild complications like postoperative fever and perinephric hematoma was seen in 6 patients. No significant difference has found between pre and post RFA estimated GFR [12].

In their retrospective study conducted with 165 patients, Wah et al. performed 200 RFA for renal tumors with a mean size of 2.9 (1-5.6) cm. The patients had 46.1 months of mean follow-up. All tumors <3 cm has ablated completely (133/133), 1 patient through 63 with 3-5 cm tumor and 2 of 4 with >5 cm tumor has ablated incompletely with a single RFA session. The independent predictors of successful RFA in a single session were tumor size and exophytic location. They found a significant difference between the GFR measurements before and after RFA, where the GFR was higher before treatment (54.7 vs. 52.7-mL/min/1.73 m2). 10 major complications were reported as 6 ureteric injuries, 1 calyceal-cutaneous fistula, 1 acute tubular necrosis and 2 abscesses. The OS, 5-year CSS, LRFS and MFS rates were 75.8%, 97.9%, 93.5% and 87.7% respectively [13].

Takaki et al. compared RFA to radical nephrectomy for T1b RCC. They have found OS rate significantly lower in RFA group than RN group (48% vs. 97% at 10 years). RCC-related survival rate and DFS rate was comparable between the two groups. The percentage of decrease in the GFR was significantly higher in the RN group than in the RFA group (32.3% ±20.8 vs. 12.5%± 23.4). Major complication rates found similar between the two groups [14].

Miller et al. stated that percutaneous thermal ablation both RFA and CA, is safe and effective in the management of octogenarian and nonagenarian patients with clinical T1a tumors [15].

A recent paper by Ma et al. [16] showed durable oncological and functional outcomes for T1a tumor patients who underwent RFA. The 5- and 10-year recurrence free survival (RFS) rate was reported 94.2%.

Some researchers focused on the radiation exposure and its

effects on life expectancy (LE) during the CT-guided ablation of renal masses and their follow-up. Eisenger et al. found that cumulative RFA radiation exposures (up to 305.2 mSv for one session plus surveillance) exceed from surgery (up to 87.2 mSv). They estimated that increased LE loss associated with RFA compared to surgery, related to differences in radiation exposure is 1-2 weeks in 65-year old patients. They emphasize that this value increases with decreasing age thus dose-reduction strategies must take into consideration in young patients especially in post-RFA follow-up CT scans [17].

Cryoablation (CA) of Renal Tumors

Cryoablation directly damages tissue by producing intra and extracellular ice, which disrupts the cell membrane. This damage leads to coagulation necrosis, fibrosis and scarring over the time. Temperatures between -40 and -20 C are ideal for the procedure. These low temperatures also leads to a indirect tumor killing due to microvasculature thrombosis [18]. Cryoablation of renal tumors can be performed either laparoscopic or percutaneous. Many studies have evaluated the outcomes of those CA techniques.

Larcher et al. stated the long-term oncologic outcomes of laparoscopic cryoablation (LCA) as primary treatment for cT1a RCC in 174 patients. In that study median tumor size was 20 mm and median follow-up was 48 months. Local recurrence was recorded in 4 biopsy-proven RCC patients. They reported the 10-year RFS rate as 95% and the 10-year systemic progression-free survival (PFS) rate as 100% [19].

Babaian et al. reported clinical outcomes of 114 patients who underwent cryoablation for small renal masses. 72 tumors were biopsy-proven RCC, 18 benign tumors (BT= angiomyolipoma or oncocytoma) and the remaining 27 were non-diagnostic (ND). 9 patients (12.5%) in biopsy=proven RCC group developed recurrent disease. The 2-year and 5-year RFS rates for this group were 90.2% and 81.2%, respectively as well as the RFS rate for the remaining two groups was 100% [20].

In a recent study conducted by Lai et al. , feasibility of CT-guided percutaneous cryoablation (PCA) in renal tumors was investigated. 7 patients experienced (23.3%) complications < Grade 4 based on Clavien-Dindo classification. They noted incomplete ablation in 2 patients and local tumor recurrence in another 2. Local tumor control was reported as 86.4% [21].

Theoretical advantages of laparoscopic approach are insertion of probes under direct visualization and treatment of anterior tumors. On the other hand percutaneous approach presents shorter recovery time, ability to be performed on an outpatient basis and avoidance of general anesthetıc. Several studies compared percutaneous with laparoscopic cryoablation. Zargar et al. analyzed 275 patients who underwent LCA and 137 patients who underwent PCA for small renal masses. They found that the overall and major complications were similar. 36 patients (13.1%) in LCA group and 20 patients (14.6%) in PCA group reported to have a local recurrence. They found no significant difference in OS and RFS at 5-years between the 2 groups. Oncologic outcomes were found equivalent between the 2 techniques. Also there was no significant difference in median GFR preservation between LCA and PCA [22].

One meta-analysis compared LCA to laparoscopic PN (LPN) for the treatment of SRMs. This analysis included 555 cases and 642 controls. They found LCA was associated with shorter operative time, less blood loss and major complications on the other hand LPN is related with significantly lower local recurrence and distant metastasis rate [23].

In another systematic review and meta-analysis compared LCA to LPN showed similar results. LCA was associated with significantly shorter operative time (weighted mean difference [WMD] 35.45 minutes), lower estimated blood loss (WMD 130.11 ml), shorter length of hospital stay (WMD 1.22 days) and a lower risk of total and urological complications. At the same time LCA represents a sıgnıfıcantly rısk of local and metastatic tumor progression [24].

Schmit et al. focused on complications of renal CA. They found that maximal tumor diameter and central tumor location, prior myocardial infarction, complicated diabetes mellitus were significantly associated with major complications [25].

Microwave Thermal Ablation (MWA)

MWA is an actual ablative therapy used for soft tissue destruction. Microwave energy applied into the tissue via an antenna. Microwave energy constitutes a electromagnetic field, causes high-frequency ion vibration and intermolecular collision that creates frictional heat, by this way leads to high temperatures as well as coagulation necrosis [26]. In addition to its similarity to RFA it has some superiority such as higher intratumoral temperatures, larger ablation zone, less treatment time, less dependence on electrical conductivities of tissue and more entire tumor destruction [26, 27]. It could be considered in treating small SRM percutaneously or laparoscopically.

Bai et al. reported results of 22 patients with cT1a patients who underwent retroperitoneoscopic MWA. The mean tumor size was 2.8 cm. Mean ablation time for per tumor was about 12.4 minutes. Mean estimated blood loss was 72 ml and the mean operative time was 99 minutes. No intraoperative complications were occurred. There was no significant change in creatinine level and glomerular filtration rate after the treatment or during follow-up. Successful MWA was documented in 17 (94.4%) of 18 tumors (Table 1) [26] .

Carrafiello et al. conducted a retrospective observational study with 12 patients who had RCCs smaller than 3 cm and treated with percutaneous MWA. They reported technical success rate and clinical effectiveness as 100%. No tumor recurrence was seen on follow-up. Also no major complications reported during or shortly after MWA. The ablation volume ranged between 10.2 and 25.1 cm3 [28].

In contrast Castle et al. found poor oncologic outcomes with a significant complication rate at an intermediate term follow up in their percutaneous MWA series. The recurrence rate of 10 patients with a mean tumor size of 3.65 cm who underwent percutaneous MWA as 38% and the intraoperative and postoperative complication rate was 20% and 40%, respectively [29].

Yu et al. reported the outcomes of 46 patients with 49 RCC who underwent US guided percutaneous MWA. Complete ablation rate was 98% and metastasis-free and cancer specific survival rates were 100% [30]. In another study Yu et al compared 65 patients who underwent MWA and 98 patıents who underwent open RN for SRM. They found MWA group overall survival significantly lower than open RN, 67.3% and 97.8%, respectively. But 5-year RCC-related survival rates for MWA and open RN were comparable, 97.1% and 97.8, respectively [27].

Moreland et al. evaluated 53 consecutive patients with biopsy-proven RCC≤ 4 cm who were treated with percutaneous MWA. The mean tumor size was 2.6 cm. There was significant difference between preoperative and postoperative GFRs. Six low-grade (Clavien 1-2) complications was documented. With

Table 1. The Outcomes of Recently Published Studies on Minimal Invasive Treatment Modalities

	Authors		References	No. Patients	No. Tumors	Mean/Median follow-up	İnitial/Technical success (%)	RFS (%)	CSS (%)	DFS (%)	OS (%)
RFA	Chang, et al		J Endourol 2015.	45	Na	67.6±6.0	Na	95.4	95.6	86.7	90.2
	Yang, et al		J Endourol 2014	51	Na	31.5	90.2	Na	Na	84.7 (3yr)	Na
	Wah, et al		BJU Int 2014;	165	200	47.6	95.5	93.5	97.9 (5yr)	Na	75.8 (5yr)
	Takaki, et al		Radiology 2014	21	Na	46.1±32.1	81	Na	94 (10yr)	88 (10yr)	48 (10yr)
	Ma, et al		BJU Int 2014;	52	58	60	100	94.2	100	Na	95.7
	Larcher, et al		Urol Oncol 2015	109 *	Na	48	98	95	100	90 (5yr)	95(5yr)
CA	Babaian, et al		Urology 2015	72*	Na	26.5	98.6	81.2(5yr)	Na	Na	Na
	Lai, et al		J Chin Med Assoc 2015.	30	32	15.2	91*	90.9 (6mth)	Na	80.9	95.2
	Zargar, et al	LCA	Urology 2015.	275	Na	52.9	93.1	79(5yr)	Na	Na	89(5yr)
		PCA		173	Na	37.8	93.4	80(5yr)	Na	Na	82(5yr)
MWA	Bai, et al		J Endourol 2010	22	23	20**	94.4**	Na	Na	Na	Na
	Yu, et al		Radiology 2014	65	69	20.3	85.5	Na	97.8	Na	67.3(5yr)
	Carrafiello, et al		Cardiovasc Intervent Radiol 2010;	12	Na	6	100	Na	Na	Na	Na
	Castle, et al		Urology 2011	10	Na	17.9	Na	62	Na	Na	Na
	Yu, et al		Radiology 2012	46	49	20.1	98		100	92.3(3yr)	97.8(3yr)
HIFU	Moreland, et al		J Endourol 2014	53	55	8	100***	100***	Na	Na	Na
	Ritchie, et al		BJU Int 2011	12	Na	15	58.3	100	Na	Na	Na
	Hacker, et al		BJU Int 2006.	19	19	Na	Na	Na	Na	Na	Na

* Biopsi proven RCC
**Available 17 patients
***Available 38 patients
Na: Not available

a median follow-up of 8 months none of 38 patients (0%) demonstrated evidence of local recurrence or metastasis. 98% of patients were able to discharge on the day following the operation [31].

High-İntensity Focused Ultrasound (HIFU)

High- intensity focused ultrasound (HIFU) technique uses physical effect of ultrasound (US) energy to cause coagulation necrosis on the tissue. A focused US beam leads to mechanical vibrations in the tissues, which produce heat. Rapidly increased heat results in protein denaturation thus cell destruction and coagulation necrosis with a threshold of 60° C. The efficacy of this thermal necrosis depends on several factors such ultrasound frequency, absorption coefficient, perfusion rate in the targeted tissue, acoustic reflection and refraction, exposure time and transducer characteristics. HIFU can be applied both extracorporeally and laparoscopically. HIFU is considered the most minimally invasive technique among the ablative treatments such there is no need of insertion of a probe into the tissue, which may result in hemorrhage and tumor spillage. Other possible advantages include decreased morbidity, reduced postoperative pain, shorter hospitalization, preservation of renal function, and no need of general anesthesia or skin incision [32, 33]. To avoid tissue attenuation and respiratory movement of the kidney, a laparoscopic approach can be preferred. By attaching a HIFU transducer to a laparoscopic probe; US energy can be apply directly to the renal tumor surface.

Briones et al. suggested HIFU as a promising but investigational method due to small number of treated patients and technologic incompetence in their review article [34]. In a study conducted with 12 patients, HIFU was found a safe and feasible technique for ablation of renal tumors with comparable oncologic efficacy with other options [35].

Hacker et al. reported the outcomes of 19 patients requiring RN for renal tumors who underwent extracorporeal HIFU prior to nephrectomy. They found no systemic adverse effects during or after the procedure. Two patients had a localized grade 3 skin burn. Pathologic examinations revealed no subcapsular or perirenal hematomas and no thermal injury to the ureter, renal pelvis or renal vascular pedicle. Various morphological signs of tissue ablation were noticed in 15 kidneys and there was no correlation with administered US energy [36].

Klingler et al. reported promising results from their phase I clinical study. They treated ten kidneys with solitary kidneys ranging from 12 mm to 90 mm. Laparoscopic nephrectomy was performed subsequent to HIFU in 2 patıents with 9 cm tumors. The remaining seven underwent laparoscopic partial nephrectomy and one was managed with post-HIFU biopsies and radiologic follow-up. Four of seven tumors extirpated after HIFU showed complete ablation of the whole tumor. Two had 1 to 3 mm viable tissue adjacent to HIFU targeted area and one tumor possessed vital tissue about 20% of its central area. They reported no intra or postoperative complications related to HIFU [37].

Discussion

The development of technology leads new techniques in the field of health. The refinement of laparoscopy and then the use of robot-assisted surgery have created great excitement in the management of renal masses. On the other hand, both patients and physicians have become more concerned with minimally invasive techniques along this time. Minimally invasive techniques offer a less debilitating treatment process even they can be performed on an outpatient base. Minimal invasive techniques can be a feasible treatment alternative for patients who have high surgical and anesthetic risk with multiple comorbidities, have multiple tumors due to a systemic disease like VHL or do not want to undergo extirpative surgery. Especially elderly patients can be good candidates for these procedures

with their relatively short life expectance and impaired performance status.

As we discuss previously minimal invasive treatment of small renal masses consist of various ablative techniques such as RFA, CA, MWA and HIFU. The clinical studies on MWA and HIFU are less compared to RFA and CA. Thus MWA and HIFU remain still experimental due to low patient volume and insufficient clinical experience. The methodology of the studies in the literature varies which makes it difficult to make a comparison between these techniques.

In many clinical studies, it is postulated that minimal invasive techniques particularly RFA and CA have similar CCS, DFS, RFS and OS rates compared to nephrectomy. Besides their favorable oncologic outcomes, their complication profile is acceptable and even less compared to extirpative surgery. The preservation of renal function, shorter operative times, smaller estimated blood loss and easy application comprise other potential advantages. These techniques also present an improved patient procedural tolerance with a shorter hospital stay and more comfortable postoperative course. Using laparoscopic approach may improve technical success but it hampers the minimal invasive aspect of these techniques.

The follow-up procedures may require consecutive CT imaging. Physicians must be aware of the secondary neoplasms related to that radiation exposure. Thus, definitive follow-up schemes must be establish.

In conclusion, aforementioned techniques for the management of small renal masses are promising with their high efficacy and good short and intermediate term results. Controlled randomized trials with large patient volume and long-term follow-up are mandatory particularly for MWA and HIFU.

Competing interests

The authors declare that they have no competing interests

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Role of the Otolaryngologist in Children with Mucopolysaccharidose; Review

Mukopolisakkaridozlu Çocuklarda KBB Uzmanının Rolü; Derleme

Mukopolisakkaridoz'da KBB'nin Rolü / Role of the Otolaryngologist in Mucopolysaccharidoses

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Özet

Mukopolisakkaridozlar (MPS) nadir bir hastalık grubu olmasına karşın otolaringolojik semptom ve bulgular oldukça yüksektir. Multidisipliner yaklaşımda kulak burun boğaz uzmanı MPS'li çocukların tanı ve tedavisinde tamamlayıcı bir rol oynar. MPS'li çocuklar tipik semptomlar olmadan doğar ve geçen zamanla belirtiler gelişir. Adenotonsiller hipertrofi, otolojik sorunlar ve hava yolu sorunları özellikle otolaryngolojik şikayetler olabilir. Bu makalede MPS hastalarında otolaringolojik sorunlar ve tedavileri değerlendirilmiştir.

Anahtar Kelimeler

Mukopolisakkaridoz; KBB; Adenotonsil Hipertrofisi; Otolojik Problemler; Havayolu Problemleri

Abstract

Mucopolysaccharidoses (MPSs) is a rare group of disorders with a very high percentage of otolaryngologic symptoms and signs. Otolaryngologists play an integral role in the multidisciplinary approach to the diagnosis and management of many children with MPSs disorders. Children with MPSs are born without typical symptoms and develop a variety of symptoms over time. Otolaryngological manifestations of MPSs disorders may be especially considered adenotonsillar hypertrophy, otological problems, and airways problems. Otolaryngologic problems and their treatments evaluated on MPSs patients in this article.

Keywords

Mucopolysaccharidoses; Otolaryngology; Adenotonsillar Hypertrophy; Otological Problems; Airways Problems

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Intraduction

Mucopolysaccharidoses (MPSs) represent a clinically diverse group of metabolic disorders within genetically inherited lysosomal storage diseases [1]. This disorders have an overall incidence reported as anywhere from 1 in 150,000 to as high as 1 in 10,000 live births with geographical differences in the frequencies of specific types [1,2]. Although MPSs are rare, the structures of the head and neck are nearly always involved. As a result, otolaryngologists are commonly the first clinicians to whom these individuals present. Otolaryngological manifestations certainly exert an effect on quality of life issues, perhaps more important is the recognition and management of upper airway obstruction, which may range from varying degrees of obstructive sleep apnea to life-threatening airway emergencies [3]. The aim of this article is to evaluate otolaryngologic problems (hearing, adenoid and tonsil hypertrophy, upper airway obstruction) and their treatments in MPSs patients.

Pathophysiology

MPSs are lysosomal storage disorders caused by deficiency of enzymes involved in the degradation of glycosaminoglycans (GAGs). The primary GAGs (dermatan sulfate, heparan sulfate, keratan sulfate, and hyaluronic acid) are an important constituent of the extracellular matrix, joint fluid, and connective tissue throughout the body [4,5]. This metabolic block leads to the accumulation of GAGs in lysosomes, resulting in cell, tissue and organ dysfunction. Musculoskeletal system, nervous system, heart, lung, eye and otolaryngologic involvement are common effected [3,6]. Hence clinical manifestations may be quite variable and are often multisystem.

MPSs are heterogeneous group of autosomal-recessive disorders (except for MPS II, which is X-linked-recessive) [3]. Seven types have been described to date (Table 1). Each disorder is caused by a deficiency of a specific enzyme required for GAG degradation [3]. It has a continuum of clinical manifestations from mild form to severe. The ubiquitous nature of GAGs in the body's connective tissues gives rise to a wide phenotypic spectrum usually characterized by coarse facial features, liver and spleen enlargement, bone deformities with subsequent reduction of joint mobility, variable mental retardation and cardiac and ophthalmologic involvement [3,7]. Predominantly a disease of childhood, clinical features are frequently absent at birth, appearing gradually as the disease progresses along an unrelenting course that commonly ends with death before adulthood [4].

Importance of the otolaryngology

MPS is a rare group of disorders with a very high percentage of otolaryngologic symptoms and signs [6]. Otolaryngologists play an integral role in the multidisciplinary approach to the diagnosis and management of many children with MPS disorders. The most common otolaryngologic complaints of MPS patients are airway problems include obstructive sleep apnea (OSA), otitis media with effusion, sinusitis, frequent respiratory infections, adenotonsillar hypertrophy, irregular nasal septum, turbinate hypertrophy, speech disorders, dyspnea, restricted temporomandibular joint motion, thickened pharyngeal wall, laryngeal abnormalities, tracheomalacia, tracheal stenosis and short neck [3,5,8,9]. Otolaryngological disorders are extremely frequent, mostly in MPS I, II and VI, and are often the earliest clinical manifestations of these diseases [3]. Mesolella et al. [10] concluded that ear, nose and throat manifestations in all types of MPS; in particular, recurrent otitis media was present in 30% of cases, hearing loss in 75% (mixed in 43.33%, conductive in 43.33%, sensorineural in 13.33%), adenotonsillar hypertrophy in 75%, frequent infections of the upper airway in 75% and obstructive sleep apnea syndrome in 45% of cases.

Otolaryngologists are commonly the first clinicians to whom these individuals present [11-13]. Increased awareness of the features of MPS by otolaryngologists will lead to earlier diagnosis. Early diagnosis, as well as having important implications for the affected individual and surgical treatment of processes often significantly enhances the quality of life of these children. They often have a number of the patients undergo adenoidectomy, tonsillectomy or ventilation tube insertion prior to diagnosis the histological examination of the tissue could lead to an earlier diagnosis [12,14]. Children with MPSs are born without typical symptoms and develop a variety of symptoms over time. Otolaryngological manifestations of MPSs disorders may be especially considered adenotonsillar hypertrophy, otological problems, and airways problems.

Otological problems

Hearing loss is often present at the time of diagnosis in nearly all patients with MPS which is characterized by both conductive and sensorineural involvement. Otitis media with effusion (OME) is a recurrent problem in a great majority of patients with MPS [10,13]. It is particularly important to identify and treat hearing loss in MPS, as it has been demonstrated that children with hearing loss in the context of multiple disabilities experience improvements in communication ability, language development, social and emotional development, and behavioral regulation when a hearing loss is actively managed.

Hearing loss was present in literature data, in which the percentage varies from 59.7% to 89%, especially those with MPS I and II [6,15,16]. In this international cohort of patients with MPS II (HOS) over two thirds were identified to have a degree of hearing loss by the age of 5 years, of which 22% had severe hearing loss [11]. Conductive hearing loss (CHL) is usually secondary to recurrent upper respiratory tract infection and serous otitis media, or a deformity of the bony ossicles. MPS patients display an increased risk of otitis media with effusion (OME) due to the pathologic deposition of GAGs in the post-nasal space, eustachian tubes and middle ear [5]. There is some evidence to suggest that tympanomastoid abnormalities may contribute to conductive hearing loss as well. Temporal bone examination in a patient with MPS II and found that there was a marked absence of mastoid pneumatisation, the middle ear cleft was filled with fibrous tissue, and the tympanic membrane was of three to four times normal thickness as the disease progresses, patients with CHL may develop SNHL, resulting in a mixed hearing loss [11]. Motamed et al. [13] reported that young patients often undergo repeated insertions of short-term ventilation tubes before MPS is diagnosed.

Nearly three-quarters of the patients with otolaryngological data in HOS had a positive history of at least one episode of otitis (either acute otitis media or chronic otitis media), and about half had undergone adenoidectomy and/or insertion of ventilation tubes. About 60% of cases experienced improvement in hearing after surgical treatment [11]. Some practitioners may choose to use long-term ventilation tubes when CHL is seen because these patients will likely not outgrow their need for ventilation tubes and because patients with MPS have a substantially increased risk of adverse events when anaesthesia is attempted [17]. Whereas long-term ventilation tubes do

Table 1. Mucopolysaccharidoses syndrome

MPS type	Subtypes	Eponym	Enzyme deficiency	Storage material
MPS I	MPS I H	Hurler	Iduronidase	Dermatan sulphate, Heparan sulphate
	MPS I S	Scheie	Iduronidase	Dermatan sulphate, Heparan sulphate
	MPS I H/S	Hurler—Scheie	Iduronidase	Dermatan sulphate, Heparan sulphate
MPS II		Hunter	Iuronidate sulphate sulphatase	Dermatan sulphate, Heparan sulphate
MPS III	MPS III A	Sanfilippo A	Heparan-N-sulphatase	Heparan sulphate
	MPS III B	Sanfilippo B	N-acetylglucosaminidase	Heparan sulphate
	MPS III C	Sanfilippo C	Acetyl-CoA-glucosaminidase acetyltransferase	Heparan sulphate
	MPS III D	Sanfilippo D	N-acetylglucosamins-6-sulphatase	Heparan sulphate
MPS IV	MPS IV A	Morquio A	Galactosamine-6-sulphatase	Keratan sulphate
	MPS IV B	Morquio B	B-galactosidase	Keratan sulphate
MPS VI		Maroteaux-Lamy	N-acetylgalactosamine-4-sulphatase	Dermatan sulphate
MPS VII		Sly	B-glucuronidase	Dermatan sulphate Heparan sulphate, Chondroitin sulphate
MPS IX		Natowicz	Hyaluronidase	Hyaluronic acid

confer a higher risk of persistent perforation and subsequent chronic otitis media [18].

Sensorineural hearing loss (SNHL) aetiology remains unclearin hovewer it may result from GAGs accumulation in the cochlea, auditory nerve, and brainstem MPS. Excessive GAGs deposition may occur within the cochlear duct, stria vascularis, and cochlear nerve sufficient to disrupt function and result in anywhere from a mild to profound loss bilaterally [19,20]. Although auditory brainstem response (ABR) is an objective test of hearing threshold that does not require the patient's cooperation, the risks of sedation for MPS patients make it difficult to use in routine clinical practice [11]. It is reasonable to conduct an ABR directly after the insertion of ventilation tubes while the patient is still under general anesthesia, but it is known that the results of the ABR in this situation are not as reliable.

Insertion of ventilation tubes can improve CHL resulting from chronic otitis media with effusion but ventilation tubes with or without adjuvant adenoidectomy will obviously not ameliorate SNHL, either alone or as a component of mixed hearing loss [21]. Rehabilitation of hearing loss in MPS disorders may be achieved by fitting conventional hearing aids for mild to moderate conductive, mixed or sensorineural hearing loss. Cochlear implant (CI) is an established method of rehabilitating profound hearing loss in children [22]. However, technique is being developed to facilitate MR imaging in the presence of a CI it is more likely that the risks of surgery and general anesthesia will be considered acceptable

Adenotonsillar hypertrophy

Adenotonsillar hypertrophy is almost universal in this group of patients due to the deposition of GAGs [6]. Therefore, adenoidectomy and tonsillectomy are among the most commonly performed operations in patients with MPS, often prior to diagnosis [12]. Patients with MPS had significantly smaller retropalatal and retroglossal spaces compared to healthy persons [9]. Radiological and endoscopic examination may play an important role by evaluating backward displacement of posterior tonsillar pillars toward the posterior oropharyngeal wall; thus, during endoscopy may determine the percentage of oropharynx tonsils are occupying in sagittal axis [12]. Gönüldaş et al. [6] discovered that most of the tonsillar enlargement was toward the tonsillar bed instead of the lumen in MPS patients; thus indicating that actual tonsil size might be larger than it appeared on oropharyngeal examination. Therefore more careful oropharyngeal examination on MPS patients whose tonsils appear to be grades 1 and 2, because tonsils contribute a lot to airway obstruction.

MPS patients also have odontoid hypoplasia which predisposes them to atlantoaxial dislocation. Therefore, the surgeon has to be careful while inserting mouth gag and extending head on neck during adenotonsillectomy [6]. Tonsillectomy should not be performed on MPS patients with severe mouth opening restriction. In case of possible postoperative hemorrhage intubation of the patient and control of bleeding may be very difficult or even impossible [6].

After adenoidectomy in normal population recurrence rate is between 0.55 and 1.5% [23]; however, the recurrence rate in our MPS population is 56% [6]. Despite recurrence the need for revision surgery is rather low in MPS patients. Althought this mechanism does not appear to explain Monroy at al claimed that recurrent adenoid did not as much obstruct choana as preop adenoid tissue [24].

Upper-airway obstruction

MPS patients have airway narrowing due to GAGs accumulation in airway walls [6,25]. Deposition of the GAGs in the walls of the pharynx and larynx can cause alterations of normal airway function [5]. This changes in soft tissues including tonsils, adenoids, tongue, lingual tonsils, larynx and trachea are responsible for most respiratory problems. As the disease progresses, pharyngomalacia and tracheomalacia may develop and become severe, leading to significant airway obstruction [26]. Additionaly, facial features, predominantly found in MPS I, II, VI and VII, include the macro- and retroglossia and the unfavourable ratio of tongue size to oral cavity predispose to pharyngeal collapse (pharyngomalacia) and obstructive sleep apnea [15].

Involvement of the larynx is almost universal in severe forms of MPS I and II, whereas it is less severe in other forms of MPS [15]. Laryngomalacia, typically caused by the GAGs deposits in epiglottis and arytenoid mucosa was expanded and flaccid, so that it prolapsed into the laryngeal inlet causing glottic stenosis seem to be related to respiratory problems in MPS patients [25]. Hypertrophy of the false vocal cords reduces the glottic space and was one of the reasons for obstructive sleep apnea in MPS patients, but was not related to dysphagia.

OSA evaluation should begin with history and physical examination. However, airway evaluation is very difficult, typically non-uniform among different providers and varies from case to case

the degree of ostruction should be studied with polysomnography and rhino-oro-laryngoscopy. Lin et al. [27] determined 88% moderate to severe OSA, while Yeung et al determined 55% moderate to severe OSA on MPS patients depending on polysomnographic data [28]. Addionaly, Mesolella et al. [10] determined upper airway obstruction in 75% of cases while literature data describes percentages varying from 38% to 48% to 92% [29]. Pelley et al. [30] concluded that symptoms during sleep were not associated with PSG findings, which suggested that this population should undergo routine PSG as early as possible. Adenotonsillectomy is the initial treatment of choice, although it does not always resolve the condition due to the multifactorial origin of the obstruction, with nocturnal noninvasive ventilation being recommended in such cases [5]. Despite adenotonsillectomy being a routine procedure in most children, the risks are usually higher in an MPS child including post-operative hemorrhage, airway edema, and failure to extubate [31]. The initial intervention is often adenotonsillectomy, which may provide temporary improvement. Subsequent steps in MPS patient may include continuous positive airway pressure or bi-level positive airway pressure. Ultimately tracheotomy may be required to relieve severe upper airway obstruction during wakefulness [15].

Tracheotomy

Tracheotomy, which is typically performed for severe upper airway obstruction, may alleviate tracheal narrowing by stenting the component caused by tracheal collapse. Tracheal stenos is also be narrowing of the tracheal lumen due to GAG deposition in the wall and may lead to tracheomalacia [8,32]. With progressive tracheomalacia a regular tracheostomy tube may be insufficient and attempts have been made to bypass the obstruction with longer and wider tracheostomy tubes [8]. These carry the risk of mucosal irritation and injury potentially resulting in granulation tissue and further accumulation of GAG deposits.

Tracheotomy is also a difficult operation in MPS patients; because the neck is short and with neck extension and lowest possible cervical incision the surgeon only reaches cricoid cartilage, thus high tracheotomy is almost unavoidable, carrying the risk of laryngotracheal stenosis [6]. Additionally, MPS patients also have odontoid hypoplasia which predisposes them to atlantoaxial dislocation. Therefore, the surgeon has to be careful while giving the position on head and neck during tracheotomy [6].

Finally, otolaryngologists must be familiar with the symptoms and signs related to MPS. They should have a basic knowledge of MPS in order to avoid the possible complications of otolaryngologic treatments.

Competing interests

The authors declare that they have no competing interests.

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The Role of Platelet-Rich Plasma in Peripheral Nerve Injuries

Periferik Sinir Yaralanmalarında Trombosit Zengin Plazmanın Tedavideki Yeri

Sinir Yaralanması ve Trombosit Zengin Plazma / Nerve Injury and Platelet-Rich Plasma

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Özet

Sinir rejenerasyon ve reinnervasyon süreci, nöronla ilişkili sayısız faktörü içeren karmaşık bir olaydır. Sinir rejenerasyonunun geliştirilmesi için birçok büyüme faktörü kullanılmıştır. Koagülasyon kaskatında önemli rolleri ile bilinen trombositler, içerdikleri büyüme faktörleri ile doku tamirinde de rol oynamaktadır. Bu büyüme faktörlerinin özelliği, farklılaşmamış hücrelerin kemotaktik ve mitotik özelliklerini arttırarak anjiogenezi başlatması ve dokunun iyileşmesine katkıda bulunmasıdır. Trombosit Zengin Plazma (TZP), tam kanın santrifüj edilmesi ile elde edilen ve suprafizyolojik dozlarda büyüme faktörü içeren plazma komponentidir. Başlıca maksillofasiyal ve kardiyovasküler cerahi olmak üzere tıbbın birçok dalında uzun zamandır kullanılmakta olan TZP, son yıllarda tendon ve kıkırdak doku rejenerasyonunu arttırıcı etkisi ile kas iskelet sistemi hastalıklarında da uygulanmaya başlanmıştır. TZP'nin perferik sinir iyileşmesine olan katkısı ise daha yakın dönemde araştırılmaya başlanmış ve umut verici sonuçlar elde edilmiştir.

Anahtar Kelimeler

Trombosit Zengin Plazma; Periferik Sinir Yaralanması; Sinir Rejenerasyonu

Abstract

Nerve regeneration and reinnervation process is a complex event involving numerous neuron-related factors. Many growth factors have been used to stimulate nerve regeneration. In addition to their well-know role in hemostasis, platelets also play an important role in tissue repair due to the growth factors they contain. These growth factors initiate angiogenesis by increasing the chemotactic and mitotic characteristics of the undifferentiated cells, thus contributing to tissue healing. Platelet-rich plasma (PRP) which is obtained by centrifugation of whole blood is a plasma component that contains supraphysiological doses of growth factors. PRP has been used in many branches of medicine including maxillofacial and cardiovascular surgery in particular and is currently being used in musculoskeletal system disorders due to its effect on increasing tendon and cartilage tissue regeneration. Evaluation of the contribution of PRP to peripheral nerve healing has started more recently and encouraging results have been obtained.

Keywords

Platelet-Rich Plasma; Peripheral Nerve Injury; Nerve Regeneration

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Introduction

The main objective in the treatment of peripheral nerve injuries is ensuring functional improvement of the nerve by re-establishing structural integrity at the lesion site. Despite the developments in understanding the regeneration mechanisms and technical improvements and modern surgical equipment in microsurgery, functional improvement in peripheral nerves following serious injuries commonly presents unsatisfactory results [1]. This review includes information regarding the role of platelet-rich plasma (PRP) which has an increasingly widespread use in the treatment of peripheral nerve injuries, its biological mechanism of action, and review of the literature for relevant studies.

The Pathophysiology of Peripheral Nerve Damage

Injury to the peripheral nerve causes wallerian and axonal degeneration distal to the damaged segment. Wallerian degeneration is a pathological process that results when a nerve fiber is cut or crushed, in which the part of the axon separated from the neuron cell's body degenerates distal to the injury. The axonal degeneration is followed by degradation of the myelin sheath. Regeneration process starts following degeneration and regeneration occurs through Schwann cells [2]. Regenerations starts at the distal end of the portion of the nerve fiber proximal to the lesion. Sprouts are sent to the neurolemma of the injured nerve and if it the gap is not too wide it reaches the end, grows into it and advances between the nerve sheaths reinnervating the target tissue growth factors such as nerve growth factor, brain-derived neurotrophic factor, ciliary neurotrophic factor and glial cell-derived neurotrophic produced by Schwann cells play a role in the modulation of healing [3,4]. However, this improvement depends on many factors. Regeneration usually develops slowly and the healing may not be complete. Axonal degeneration develops due to metabolic disorders at the axon of the nerve fibers and this effects commonly result in axon destruction at the distal regions [3].

Platelet-Rich Plasma

PRP; which is obtained by centrifugation of whole blood is a plazma component containing higher concentration of platelets than the whole blood. In addition to their primary role in hemostasis, platelets play an instrumental role in the initiation and regulation of healing with the growth factors, cytokines and other bioactive factors they contain [5]. They trigger an inflammatory response, chemotaxis, atherothrombosis, coagulation and cellular differentiation regulation with autocrine and paracrine self-activation. They contain three types of granules; alpha, lysosomal and dense core granules. The cytokines, chemokines, clotting factors and growth hormones that are found especially in the alpha and core granules play a main role in hemostasis and injury healing [6,7]. Resting platelets at the injury site are activated with thrombin within a 10-minute period after coagulation and secrete the coagulation and growth factors within their alpha granules [5]. An important point here is that the growth factors become activated prior to their release. If the platelets are damaged during the PRP preparation, activation of the growth factors fail resulting in an ineffective PRP administration. Acid citrate dextrose type A anticoagulant and low gravitational power is therefore necessary during centrifugation [8,9]. Alpha granules of the platelets contain mitogenic and chemotactic growth factors such as insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) [10]. These factors play a role in cell regulation, differentiation, proliferation, chemotaxis, angiogenesis and matrix synthesis during healing following injury [5]. Their common characteristics are initiating angiogenesis by increasing the chemotactic and mitotic characteristics of the undifferentiated cells and making a positive contribution to tissue healing [1].

The Characteristics of Growth Factors

PRP contains growth factors in supraphysiological amounts and can be called as a regenerative treatment like stem cell, prolotherapy and nitric oxide treatments. The aim of PRP is to activate the repair mechanisms of the body. Unlike conventional treatments, the general principle is to trigger inflammation rather than suppress it. PRP has been in use for about 30 years. It was first used in 1987 by Ferrari et al [11] to decrease the transfusion of homologous blood products following open heart surgery. Use in maxillofacial and plastic surgery started in the 1990s followed by application in musculoskeletal problems [12]. PRP's effect of accelerating the healing process in tendon, ligament, cartilage and muscle injuries has been demonstrated in various animal trials and clinical studies [13,14]. Although the relevant factors are not classical neurotrophic factors other than IGF-1, their effect on nerve regeneration is being investigated in recent years and promising results have been reported. IGF-1 was reported to play a role as a neurotrophic factor after nerve incisions and increase the protein and lipid synthesis necessary for regeneration in in vivo studies. The positive effects of local IGF-1 administration on the nerve lesion have been shown in several studies [10]. Experimental data show that growth factors such as TGF-β, FGF and PDGF stimulate axonal growth and increase Schwann cell proliferation and mitogenesis [15].

IGF-1

IGF-I is an important mediator in all stages of healing and especially in the inflammatory and proliferative stages and has many effects such as protein synthesis, myoblast and fibroblast proliferation, and matrix and collagen synthesis stimulation [16]. IGF-I can be secreted in various structures such as Schwann cells, skeletal muscle and capillaries. Its receptors are present especially in the axons, nerve endings and motor neuron cell bodies in the peripheral nervous system [17]. IGF-I has been shown to stimulate initial sprouting and subsequent elongation of axons in the motor, sensory and sympathetic nerves by acting as a neuropathic factor and providing protection from apoptosis [18]. Systemic IGF-1 treatment has been reported to increase muscle reinnervation and prevent motor neuron death after neonatal sciatic nerve axotomy [19], furthermore increased axonal sprouting and axonal regeneration rate have been shown at the damaged nerve following local IGF-I administration [17]. Tiangco et al [20] reported that local IGF-I infusion improves muscle functions quicker than placebo in the end-to-side nerve repair model. IGF-I has also been suggested to play a role in repair after hypoxic ischemic damage in many tissues and also to be of critical importance for myelinization, which will not occur in its absence [17].

VEGF

VEGF is a potent angiogenic factor. It has been reported to stimulate proliferation and migration of endothelial cells and play a role in angiogenesis and increasing vascular permeabil-

ity. VEGF has also been shown to stimulate axonal sprouting and increase Schwann cell proliferation in experimental studies [21]. VEGF has been reported to play a role in axon growth and Schwann cell proliferation and act as a neurotrophic factor and enhance nerve cell survival through FLK-1 activation. Additionally, VEGF increases the survival of motor neurons with the deletion of the element responsible for hypoxia within VEGF that causes motor neuron degeneration [4].

TGF- β

TGF-β is a pro-inflammatory factor which plays a role as an immunosuppressant at the inflammatory phase. It can activate or inhibit growth of many cells in the presence of other growth factors and plays a role in macrophage chemotaxis [22]. It has many biological effects such as enhancing cell migration, fibroblast count and type I and III collagen expression. TGF-β also plays a role in angiogenesis and improves mechanical structure of the tendon during the healing process [5]. TGF-β has been shown to be secreted from the damaged nerve following injury. TGF-β2 and TGF-β3 regulate Schwann cell proliferation and differentiation [23].

bFGF

bFGF plays a key role in cell proliferation and migration. It stimulates angiogenesis and capillary endothelial cell proliferation. It is also involved in the formation of granulation tissue [24]. bFGF has been shown to play a role in nerve regeneration. bFGF can be synthesized and secreted from damaged axon, Schwann cell, endothelial cell, fibroblast and macrophages. bFGF and FGF-3 receptors have been shown to be upregulated at the lesion site at L5 sensory neurons and sciatic nerve after peripheral nerve injury [25]. An animal study conducted by Toledo et al [26] showed better functional results in facial nerve recovery in the group that received topical bFGF compared to the control group on the 6th day, while there was no difference between the two groups on the 16th day.

PDGF

PDGF plays an important role in embryonic development, cell proliferation, migration and angiogenesis. PDGF has been shown to be a potent mitogen for fibroblasts, muscle cells and mesenchymal cells [3]. PDGF-β is also a mitogenic factor for Schwann cells with its trophic activity on neurons. The increased expression after peripheral nerve injury supports that it plays a role in peripheral nerve regeneration [15].

PRP Therapy and Its Effectiveness

Recent studies have investigated the effect of PRP on peripheral nerve regeneration due to the factors it contains. Ding et al [27] applied local PRP following a crush injury they created in bilateral cavernous nerves of 24 rats in their study. The authors found functional and histological parameters of the PRP group to be significantly better and reported that PRP has a positive effect on cavernous nerve regeneration and functional improvement. The positive effects of PRP were demonstrated in a similar study conducted by Emel [17] et al where crush injury was formed at the sciatic nerve. Farrag et al [28] reported an improved functional outcome with the use of PRP in comparison with fibrin sealant or no bioactive agents on facial nerve regeneration in a rat model. Sarıgüney et al [10] suggested that the PRP following an ideal surgical repair in a peripheral nerve incision model provided a significant improvement in myelin thickness and latency, but had no marked positive effect on axonal regeneration. The authors also reported PRP to be ineffective if surgical repair was inadequate.

Besides studies reporting positive effects, there are also some studies which do not confirm a positive effect of PRP on healing process. Pişkin et al [29] reported that PRP had no positive effect on nerve regeneration in their studies where they reconstructed the nerve lesion with collagen tubes. Welch et al [30] suggested that PRP has no significant effect on healing after direct repair in a nerve transection model.

Despite the presence of animal studies investigating the effects of PRP on peripheral nerve improvement, we did not find any clinical studies on this subject in the literature. Ultrasound guided intraneural PRP injection in a 28-year-old male who had developed drop foot due to peroneal nerve paralysis after multiple ligament injury resulted in partial improvement in clinical and electrophysiological parameters 21 weeks later. The patient was able to walk and run without an orthosis [15].

PRP injection in or around a peripheral nerve plays a role in regeneration. The suggested mechanisms of action in various studies are as follows:

1. It increases the number of regenerating nerve fibers by improving the biological environment and thus supports axonal sprouting and remyelination;
2. It enhances migration of undifferentiated cells at the injury site and induces mitosis and angiogenesis;
3. Another possible effect is that the growth factors has a role in shifting the histological property of extra- and intraneural tissues from “stiff scar tissue or fibrosis” to “bening sof scar tissue” where axonal sprouting and reinnervation is possible [15,31].

In conclusion, PRP treatment has become common in musculoskeletal problems in recent years and has been shown to have positive effects also on nerve regeneration. Controlled long-term studies could be planned for its use in tendon and cartilage damage, chronic wound treatment and also peripheral nerve injury, and this is an open area for future research. PRP treatment seems to have a promising future when accompanied by proper rehabilitation once the ideal PRP preparation technique, correct dose and the correct timing are determined. Further studies are needed to guide the development of standard PRP injection procedures and to decide when they should be used.

Competing interests

The authors declare that they have no competing interests.

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Neuropathic Pain Following Spinal Cord Injury: Mechanism, Assessment and Treatment

Medulla Spinalis Yaralanması Sonrası Görülen Nöropatik Ağrı: Mekanizma, Değerlendirme ve Tedavisi

Medulla Spinalis Yaralanması Sonrası Görülen Nöropatik Ağrı / Neuropathic Pain Following Spinal Cord Injury

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Özet

Medulla spinalis yaralanması (MSY); fiziksel, psikolojik ve sosyal fonksiyon bozukluklarına neden olabilen yıkıcı bir hastalıktır. MSY sonrası nöropatik ağrı (NPA) sıktır, değişik derecelerde görülebilir ve MSY sonrası oluşan tedavisi en zor problemlerden biridir. MSY sonrası fonksiyon kayıplarına NPA'nın da eklenmesiyle hastaların uyku düzenleri, duygudurumları ve günlük yaşam aktiviteleri olumsuz etkilenir. Ağrıyı etkili bir şekilde tedavi edebilmek için MSY sonrası görülen ağrının sınıflandırması dikkatli ve doğru yapılmalıdır. Uluslararası Ağrı Çalışma Grubu'nun oluşturduğu sınıflamaya göre MSY sonrası görülen ağrı nosiseptif ve NPA olarak iki ana gruba ayrılır MSY sonrası görülen nosiseptif ağrı, musküloskeletal ya da visseral kaynaklı olabilir. NPA "somatosensoriel sistemi doğrudan etkileyen bir lezyon veya hastalık sonucu ortaya çıkan ağrı" olarak tanımlanmaktadır. MSY sonrası görülen NPA görüldüğü anatomik bölgeye göre sınıflandırılır (lezyon seviyesinin üstünde, lezyon seviyesinde, lezyon seviyesinin altında). MSY sonrası görülen NPA tedavisi çoğu zaman zordur ve tedaviye yanıt almak da uzun zaman alabilir. Bu nedenle MSY sonrası NPA'nın tedavisi multidispliner olmalıdır. Tedavi seçenekleri farmakolojik tedaviyi, transkutanöz elektriksel sinir stimülasyonu uygulamasını, psikiyatrik tedavi yaklaşımlarını ve seçili olgularda cerrahi yaklaşımları içerir. Farmakolojik tedavide ilk sırada yer alan ajanlar trisiklik antidepresanlar, pregabalin ve gabapentin yer alır. Bu derlemede MSY sonrası görülen NPA'nın mekanizmaları, değerlendirilmesi ve tedavisi güncel literatür eşliğinde tartışılacaktır.

Anahtar Kelimeler

Medulla Spinalis Yaralanması; Nöropatik Ağrı; Mekanizma; Değerlendirme; Tedavi

Abstract

Spinal cord injury (SCI) is a devastating disease which may cause physical, psychological and social dysfunction. Neuropathic pain (NP) after SCI is common, can be seen in varying degrees and is one of the most difficultly treated problems developing after SCI. With the addition of the NP to loss of function after SCI, sleep patterns, moods and daily activities of patients are adversely affected. In order to treat pain effectively, classification of pain after SCI must be done carefully and correctly. According to classification of International Pain Study Group, pain after SCI is divided into two main groups as nociceptive and neuropathic pain. Neuropathic pain is defined as "pain occuring as a direct result of a disease or lesion directly affecting somato-sensorial system". NP after SCI can be classified according to anatomical region (above the level of lesion, at the level of lesion, below the level of lesion). Treatment of NP after SCI is often challenging and receiving response to treatment may take long time. Therefore, treatment of NP after SCI should be multifactorial. Treatment options include pharmochologic treatment, application of transcutanous electrical nerve stimulation, psychiatric treatment approaches, and surgical approaches in selected cases. In pharmachologic treatment, first line agents are tricyclic antidepresants, pregabalin and gabapentin. In this review, mechanisms and assessment and treatment of NP after SCI is discussed with the guide of current literature.

Keywords

Spinal Cord Injury; Neuropathic Pain; Mechanism; Assessment; Treatment

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Giriş

Medulla spinalis yaralanması (MSY) sonrası görülen ağrı sıktır ve hastaların uyku düzenini, yaşam kalitesini ve günlük yaşam aktivitelerinin olumsuz etkilemektedir [1]. MSY sonrası kronik ağrı prevalansı %11 ile %94 arasında değişmektedir. MSY sonrası nöropatik ağrı (NPA) sıklığı ise %18.3 ile %53 arasında değişmektedir [2-4]. Ülkemizde ise MSY sonrası ağrı sıklığı %61, NPA sıklığı ise %53 olarak bildirilmiştir [4,5]. Yine Türkiye'den bildirilmiş bir çalışmada MSY sonrası kronik ağrısı olan hastaların %88.6'sında NPA saptanmıştır [6].

Ağrı tedavisini etkin bir şekilde gerçekleştirebilmek için MSY sonrası görülen ağrının sınıflandırmasının dikkatli ve doğru yapılması şarttır. MSY'na bağlı kronik ağrı sınıflamasında en çok kabul gören Uluslararası Ağrı Çalışma Grubu'nun oluşturduğu sınıflamaya göre MSY sonrası görülen ağrı nosiseptif ve NPA olarak iki ana gruba ayrılır [7]. Nosiseptif ağrı serbest sinir uçlarındaki ağrı reseptörlerinin uyarılmasıyla ortaya çıkar. MSY sonrası görülen nosiseptif ağrı, musküloskeletal (kemik/eklem/kas dokularında travma ya da enflamasyon, kas spazmı, aşırı kullanım, mekanik instabilite) ya da visseral (böbrek/bağırsak/sfinkter disfonksiyonu, disrefleksif başağrısı) kaynaklı olabilir [8].

NPA ise"somatosensoriel sistemi doğrudan etkileyen bir lezyon veya hastalık sonucu ortaya çıkan ağrı" olarak tanımlanmaktadır [9]. MSY sonrası görülen NPA görüldüğü anatomik bölgeye göre sınıflandırılır (lezyon seviyesinin üstünde, lezyon seviyesinde, lezyon seviyesinin altında). Lezyon seviyesinin üstündeki NPA kompresif mononöropatileri, kompleks bölgesel ağrı sendromunu, lezyon seviyesindeki NPA sinir kökü kompresyonlarını, post travmatik siringomyeliyi, spinal kord travma/iskemisini, lezyon seviyesinin altındaki NPA spinal kord travma/iskemisini içerir [8]. NPA'sı olan MSY'li hastalar sıklıkla allodini ve hiperaljezi gibi duyusal bozukluklardan şikayet ederler [10].

MSY sonrası görülen NPA genelde şiddetli ve uzun sürelidir [11]. Bu nedenle de hem emosyonel hem fiziksel açıdan MSY'li hastaların yaşam kalitesini olumsuz etkilediği bulunmuştur [12]. Finnerup ve arkadaşları da MSY sonrası NPA'sı olan hastalarda yaptıkları çalışmalarında hastaların %90'ında NPA'nın günlük yaşam aktivitelerini olumsuz etkilediğini bulmuşlardır [13].

Bu derlemede MSY sonrası görülen NPA'nın mekanizmaları, değerlendirilmesi ve tedavisi tartışılacaktır.

Medulla Spinalis Yaralanması Sonrası Görülen Nöropatik Ağrının Mekanizmaları

MSY sonrasında spinal kordda, beyinde ve periferik dokularda bir takım patolojik değişiklikler meydana gelir. NPA'nın da bu değişimler sonucunda ortaya çıktığı düşünülmektedir [14,15].

Spinal Kord

Akut iskemik ya da travmatik hasar sonucunda spinal korda bir dizi anatomik, nörokimyasal, eksitotoksik ve enflamatuar patolojik olay meydana gelir. Bu olaylar spinal nöron fonksiyonunda değişime ve ağrıya yol açar [14]. Cinsiyet, ırk ve hormonal faktörler de kaskadın işleyişine etki ederler [16]. Enflamatuar (sitokinler, prostoglandinler, reaktif oksijen radikalleri) ve nöromodülatör (glutamat, GABA, opioidler, serotonin, noradrenalin) ajanlar spinal kordda nöronal fonksiyonda üç ana etkiyle değişime yol açarlar [17]:

1. İstirahat halindeki astrositleri ve mikroglial hücreleri aktive ederler [18].
2. Nöronal ateşleme yaparak stimülasyon sonrası artmış nöronal rekrütmana, artmış düzensiz arka plan aktivitesine, sodyum kanal akımlarında değişkenliğe yol açarlar [19,20].
3. Modifiye sinaptik bağlantıların kurulması, protein sentezinde değişiklikler meydana gelmesi, apoptozun indüklenmesi, modifiye gen transkripsiyonu/translasyonunun indüklenmesi ile uzun süreli sinaptik plastisite sağlarlar [21,22].

Beyin

MSY sadece spinal kordda değil primer motor ve duyusal kortekste de atrofiye yol açar [23]. Kortekste vucüt temsil alanlarında değişimler meydana gelir [24]. Dahası MSY sonrası özellikle talamusta nöronal ateşlemede değişiklikler olduğu bulunmuştur [25]. MSY sonrası beyinde fonksiyonel reorganizasyon iki aşamada meydana gelir. İlk olarak hızlı bir mekanizma ile inaktif durumdaki sinapslar aktifleşirler, ikinci daha yavaş ama etki süresi daha uzun olan mekanizma ile de deafferente korteks bölümlerinde kalınlaşma meydana gelir [11].

Perifer

Literatürde MSY sonrası yüzeyel dokulardaki morfolojik ve fonksiyonel değişimleri inceleyen az sayıda çalışma bulunmaktadır [26,27]. MSY'lı hastalarda rezidüel spinotalamik yolların stimülasyonu ile periferik ağrı jeneratörleri aktive olabilir, bu da MSY sonrası NPA'nın eksaserbasyonunda rol oynayabilir [28]. Daha önce hayvan çalışmalarında MSY sonrası görülen lezyon seviyesi üzerindeki NPA'da hasar görmemiş primer afferent liflerde artmış duyarlılık olduğu bulunmuştur. Bu sonuçlar da MSY sonrası periferik sinir liflerinde artmış sensitizasyon olması ile tarif edilen "periferik sensitizasyon" teorisini desteklemektedir [15,29]. İnsanlarda da MSY sonrası mekanik ve termal uyaranlara karşı uyarılma eşiğinin düşmesi de insanlarda da bu teorinin varlığının göstergesi olarak kabul edilmektedir [30].

Medulla Spinalis Yaralanması Sonrası Görülen Nöropatik Ağrının Değerlendirilmesi

Uluslararası NPA tedavi kılavuzlarında NPA'nın değerlendirilmesine yönelik yaklaşımlar da yer almaktadır [31,32]. MSY sonrası görülen NPA değerlendirmesinde de aynı yolun izlenmesi önerilmiştir [33].

MSY sonrası NPA değerlendirilmesinde ilk basamak NPA tanımını doğru yaparak diğer ağrı sebeplerini dikkatli bir şekilde dışlamaktır. NPA hastalar tarafından yanma, zonklama, uyuşma, karıncalanma, hissizlik, iğnelenme ya da künt bir ağrı diye tarif edilebilir [34]. NPA'ya dizestezi, allodini (ağrı oluşturmayacak bir uyaranla ağrı duyulması) ya da hiperaljezi (ağrılı bir uyaran için ağrı eşiğinin azalması) gibi duyu bozuklukları eşlik etmektedir [35]. Uluslararası Ağrı Çalışma Grubu NPA terimleri Tablo 1'de verilmiştir. Türkiye'den bildirilmiş bir çalışmada da MSY sonrası NPA karakterini hastaların % 39.1'i yanıcı, %37.7'si acıma, %5.8'i kesici, %4.3'ü iğneleyici ve %4.3'ü ise kramp olarak tariflemişlerdir [36].

MSY olan her hastada olduğu gibi NPA'sı olan hastalar da en son 2011 yılında American Spinal Injury Association (ASIA) tarafından revize edilen ve International Spinal Cord Society (ISCoS) tarafından da kabul edilmiş olan omurilik yaralanması nörolojik sınıflaması için uluslararası standartlara göre muayene edilmeli ve sınıflandırılmalıdır [37]. Sonrasında da refleks muayenesi, duyusal bozuklukların muayenesi, kas spazmı, spastisite ve klonus değerlendirmesi yapılmalıdır. Hem aktif hem pasif eklem hareket açıklıkları ölçülmelidir. Ağrı bölgesi inspeksiyon ve palpasyonla değerlendirilmelidir. Ayrıca hastanın ambulasyon durumuna göre tekerlekli sandalye kullanımı, postür ve yürüyüş paterni açısından da gözlem yapılmalıdır [38].

Ayrıca MSY sonrası görülen NPA'nın ayırıcı tanısında Leeds nö-

Tablo 1. Uluslararası Ağrı Çalışma Grubu Nöropatik Ağrı Terimleri

Ağrı terimi	Tanım
Allodini	Ağrılı olmayan bir stimulusun neden olduğu ağrı
Hiperaljezi	Ağrılı stimulusa artmış cevap
Hiperpati	Uyarıya anormal ağrılı cevap ile karakterize ağrılı sendrom
Parestezi	Spontan veya uyarılma ile oluşan, rahatsız edici olmayan anormal duyu
Dizestezi	Spontan veya uyarılma ile oluşan hoş olmayan, rahatsız edici anormal duyu
Anestezi	Ağrılı stimulus ile ağrının yokluğu
Hiperestezi	Stimulusa artmış duyarlılık
Hipoaljezi	Ağrılı stimulusa azalmış cevap
Hipoestezi	Stimulusa azalmış duyarlılık

ropatik semptom ve bulgu değerlendirme testi ya da NPA DN-4 Anketi kullanılabilir [39]. Her iki testin de Türkçe dilinde geçerlilik çalışması da yapılmıştır [40,41]. NPA DN-4 Anketi klinikte kolayca uygulanabilecek pratik bir değerlendirme yöntemidir. Toplam 10 maddeden oluşur, 7 madde hastaya sorulan sorulardan 3 madde ise fizik muayene bulgularından oluşur (Tablo 2). 10 maddeden en az dördünün pozitif olması NPA varlığını gösterir [41].

Tablo 2. Nöropatik Ağrı DN4 Anketi

Hasta ile görüşme		
Soru 1: Ağrı aşağıdaki bir veya daha fazla özelliğe sahip mi?		
1. Yanma	Evet	Hayır
2. Ağrılı soğuk hissi	Evet	Hayır
3. Elektrik çarpması	Evet	Hayır
Soru 2: Ağrı, aynı bölgede aşağıdaki yakınmalardan bir veya daha fazlasıyla ilişkili mi?		
4. Karıncalanma	Evet	Hayır
5. İğnelenme	Evet	Hayır
6. Hissizlik	Evet	Hayır
7. Kaşınma	Evet	Hayır
Hastanın Muayenesi		
Soru 3: Ağrı fizik muayenenin yapıldığı bir alana lokalize ve aşağıdaki özelliklerden bir veya daha fazlasını açığa çıkarıyor mu?		
8. Dokunma hipoestezisi	Evet	Hayır
9. İğne hipoestezisi	Evet	Hayır
Soru 4: Ağrılı bölgede ağrıya neden olabiliyor ya da ağrıyı artırabiliyor mu?		
10. Fırçalama	Evet	Hayır

İkinci basamakta VAS (Vizuel ağrı skalası) ya da NAS (Numerik ağrı skalası) kullanarak ağrının şiddeti ölçülmelidir. Bu skalalar ile ağrının şiddeti hastalar tarafından subjektif olarak değerlendiriliyor olsa da NPA'nın şiddetinin zaman içerisindeki değişimini izlemek ve tedaviye cevabı değerlendirmek açısından önemlidirler [11]. NPA'nın klinik değerlendirmesi uyku düzeni, duygudurum ve yaşam kalitesi değerlendirmelerini de içermelidir [42]. Üçüncü basamakta laboratuar testler yapılabilir ancak bu testlerin kullanımı sınırlıdır. Elektronöromiyografi periferik sinir hasarını göstermek için kullanılabilir [43]. Magnetik rezonans görüntüleme ile spinal kord hasarının düzeyi ve buna bağlı gelişen patolojik durumlar (post-travmatik siringomiyeli gibi) değerlendirilebilir [44].

Medulla Spinalis Yaralanması Sonrası Görülen Nöropatik Ağrının Tedavisi

MSY sonrası görülen NPA tedavisi çoğu zaman zordur ve tedaviye yanıt almak da uzun sürebilir. MSY sonrası NPA'nın tedavisi multidisipliner olmalıdır. Tedavi planı; farmakolojik tedaviyi, fizik tedavi modalitelerinden transkutanöz elektriksel sinir stimülasyonu (TENS) tedavisini ve psikiyatrik tedavi seçeneklerini içerir, dirençli olgularda cerrahi tedaviler de gündeme gelebilir [45]. MSY sonrası görülen NPA'nın tedavisinde antidepresanlar, antikonvülzanlar, baklofen, non-opioid ve opioid analjezikler, alfa adrenerjik agonistler ve ketamin gibi çok sayıda ilaç araştırılmıştır. Ancak bazı ilaçların tedavide etkinlikleri düşük kaldığından bazılarının ise şiddetli yan etkileri olduğundan kullanımları sınırlı kalmıştır [46].

MSY sonrası görülen NPA'nın tedavisinde ilk sırada trisiklik antidepresanlar, pregabalin ve gabapentin yer almaktadır. Bir trisiklik antidepresan olan amitriptilinin 50-150 mg arasında, pregabalinin 150-600 mg arasında, gabapentinin 900-3600 mg arasında kullanılması önerilmektedir. İkinci sırada tramadol, opioidler ve lamotrijin yer almaktadır [32]. Avrupa Nöroloji Dernekleri Federasyonu'nun 2010'da en son kılavuzunda yayınlanan MSY sonrası NPA'daki ilaç tedavisi için kanıtların ilaç önerileriyle birlikte sınıflaması tablo 3'de verilmiştir.

Tablo 3. Avrupa Nöroloji Dernekleri Federasyonu'nun MSY Sonrası Görülen Santral Nöropatik Ağrıda İlaç Tedavisi için Kanıtların, İlk ve İkinci, Üçüncü Sıra İlaç Önerileriyle Birlikte Sınıflaması

A düzeyi değer	B düzeyi değer	C düzeyi değer veya A/B düzeyi kanıtlarla zayıf/tutarsız sonuçlar	İlk sıra için öneriler/ ilaç dozları	İkinci/üçüncü sıra için öneriler/ ilaç dozları
Pregabalin	Trisiklik antidepresanlar Tramadol Opioidler	Gabapentin Lamotrijin Karbamezapin Levatiresetam Valproat Meksiletin S-Ketamin iontoforezi	Amitriptilin/ (50-150 mg) Pregabalin/ (150-600 mg) Gabapentin/ (900-3600 mg)	Tramadol/ (100-400 mg) Opioidler-oksikodon/ (10-80 mg) Lamotrijin/ (200-400 mg)

MSY sonrası cerrahi tedaviler yapısal problemlerin giderilmesine yönelik olarak yapılır. Travma sonrası spinal stabilizasyon cerrahisi yapılmasıyla sinir dekompresyonu sağlanabilir. Diğer cerrahi yöntemler genelde farmakolojik tedavi yetersiz kaldığında uygulanır. Bunlardan DREZ (Dorsal Root Entry Zone) operasyonu ile dorsal boynuzdaki hasar seviyesine yakın hiperaktif sinir hücresini tahrip edilerek ağrının tedavisi hedeflenir. Ancak DREZ için etkinlik sonuçları farklı bildirilmiştir [8]. Ciddi spastisite varlığında intratekal baklofenden faydalanılabilir. Kordotomi, kordomiyelotomi spinal kord stimülasyonu, derin beyin stimülasyonu, motor korteks stimülasyonu diğer daha az kullanılan cerrahi tedavilerdir [8,47].

Son yıllarda transkranial doğru akım uyarımı (TDAU) da MSY sonrası NPA tedavisinde en çok araştırılan tedavi seçeneklerinden birisi olmuştur. 2015 yılında yayınlanan bir meta-analizde TDAU'nun MSY sonrası NPA tedavisinde ortalama bir etkisi olduğu ancak zamanla bu etkinin azaldığı bildirilmiştir [48]. Bu konuyla ilgili yapılacak daha fazla sayıda çalışmaya ihtiyaç vardır. MSY sonrası NPA'da fizik tedavi modalitelerinden TENS etkinliği çeşitli çalışmalarda gösterilmiştir [49]. TENS uygulaması kapı kontrol mekanizması ile ağrıyı azaltmaktadır. TENS kalp pili varlığında, gebeliğin ilk üç ayında, hasta koopere olamadığında, kardiyak sorunu olan hastalarda göğüs ön duvarı üzerine, epilepsi, geçici iskemik atak ve serebrovasküler olay geçiren hastaların baş ve boyun bölgelerine, gözler üzerine, karotis si-

nüs üzerine ve mukozalar üzerine uygulanmamalıdır [50]. TENS tedavisi, etkinliği gösterildiğinden ve uygulaması kolay olduğundan kontraendikasyonları da göz önünde bulundurularak MSY sonrası NPA tedavisinde seçenekler arasında yer almalıdır.

Sonuç

MSY sonrası NPA sıktır ve hastaların yaşam ve uyku kalitelerini olumsuz etkilemekte, depresyona yol açmaktadır. Fizik muayene, ağrının karakterinin ve şiddetinin belirlenmesi ve gerekli durumlarda elektronöromiyografi ve magnetik rezonans görüntüleme gibi yöntemlerle MSY sonrası NPA değerlendirmesi yapılır. MSY sonrası NPA tedavisinde multidisipliner yaklaşım önemlidir. Tedavi seçenekleri farmakolojik tedaviyi, TENS uygulamasını, psikiyatrik tedavi yaklaşımlarını ve seçili olgularda cerrahi tedaviyi içerir. Farmakolojik tedavide ilk sırada trisiklik antidepresanlar, pregabalin ve gabapentin yer alır. MSY sonrası NPA'nın patogenezi ve tedavisi ile ilgili büyük hasta gruplarında yapılacak uzun takipli prospektif randomize kontrollü çalışmalara ihtiyaç vardır.

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For books: Savaş Z, Batuhan M, editors. Vascular and endovascular surgery. London: W. B. Saunders; 1999. p. 87-93
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