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Original Article

Does insulin-like growth factor influence prognosis ten months after myocardial infarction?

İnsülin benzeri büyüme faktörü miyokard infarktüsünden on ay sonra prognozu etkiler mi?

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ABSTRACT

Background: We investigated the levels of insulin-like growth factor-1 (IGF-1) in acute myocardial infarction (AMI) patients, and we determined whether a decrease in IGF-1 could influence long-term prognosis.

Methods: In total, 65 patients who were admitted to our hospital for AMI and 25 healthy controls were included in this study. Fasting blood samples were obtained from all patients immediately after AMI and 10 months later to determine their IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3) levels. Fasting blood samples were obtained from the control group. The patients were also evaluated for cardiac events 10 months after AMI.

Results: The IGF-1 levels were higher in the AMI patients than in the healthy controls (p=0.002); after 10 months, both the IGFBP-3 and IGF-1 levels were higher. No differences were found in cardiac event occurrence between patients with low and high IGF-1 and IGFBP-3 levels (for both the baseline and 10-month values).

Conclusions: The serum total IGF-1 and IGFBP-3 levels were higher in the AMI patients compared to the control patients; however, there was no correlation between the IGF-1 and IGFBP-3 levels and cardiac events during the 10-month period after AMI. Additional studies are needed to clarify the time required for IGF-1 and IGFBP-3 level normalization after AMI, and to determine the effects of IGF-1 and IGFBP-3 on the long-term prognosis of patients after AMI.

Keywords: acute myocardial infarction, cardiac events, insulin-like growth factor-1

ÖZ

Amaç: Akut miyokard infarktüslü (AMİ) hastalarda insülin benzeri büyüme faktörü-1 (İGF-1) düzeylerini araştırdık ve IGF-1'de bir azalmanın uzun vadeli prognozu etkileyip etkilemeyeceğini belirlemeyi amaçladık.

Yöntemler: AMİ nedeniyle hastanemize başvuran 65 hasta ve 25 sağlıklı kontrol birey çalışmaya dahil edildi. İGF-1 ve insülin benzeri büyüme faktörü bağlayıcı protein-3 (IGFBP-3) seviyelerini belirlemek için AMİ' den sonra en erken zamanda ve 10 ay sonra tüm hastalardan ve kontrol grubundan kan örnekleri alındı. Hastalar AMİ' den 10 ay sonra kardiyak olayları açısından değerlendirildi.

Bulgular: İGF-1 düzeyleri, AMI hastalarında sağlıklı kontrollerden daha yüksekti (p = 0,002); 10 ay sonra, hem İGFBP-3 hem de İGF-1 seviyeleri daha yüksekti. Düşük ve yüksek İGF-1 ve IGFBP-3 düzeyleri olan hastalarda kardiyak olay oluşumunda anlamlı fark bulunmadı (hem başlangıç hem de 10 aylık değerler için).

Sonuç: Serum total İGF-1 ve İGFBP-3 düzeyleri, AMİ hastalarında kontrol hastalarına göre daha yüksekti; ancak, İGF-1 ve iGFBP-3 seviyeleri ile AMİ sonrası 10 aylık dönemde kardiyak olaylar arasında korelasyon bulunamadı. AMİ sonrası İGF-1 ve İGFBP-3 düzey normalleşmesi için gereken süreyi netleştirmek ve AMİ sonrası hastaların uzun dönem prognozu üzerindeki etkilerini belirlemek için ilave çalışmalara ihtiyaç vardır.

Anahtar kelimeler: akut miyokard infarktüsü, kardiyak olay, insülin benzeri büyüme faktörü-1

INTRODUCTION

Insulin-like growth factor-1 (IGF-1) plays a pivotal role in the regulation of cellular growth, proliferation, and differentiation, and in the inhibition of apoptosis and necrosis. It also contributes to tissue remodeling and energy metabolism [1]. IGF-1 is transported in the circulation by carrier proteins known as IGF binding proteins (IGFBPs).

Low IGF-1 and high IGFBP-3 levels are associated with increased cardiovascular risk [2,3]. Previous studies reported that serum IGF-1 was related to heart failure [4,5] and coronary artery disease (CAD) [3, 6], and in particular with myocardial infarction [7,8]. IGF-1 may play an important role after acute myocardial infarction (AMI) in the protection of myocardial function [9-11]. However, only one previous study examined IGF-1/IGFBP-3 levels and their relationship with long-term mortality in AMI patients. Therefore, this study investigated long-term IGF-1/IGFBP-3 levels and determined their effects on mortality.

METHODS

In total, 65 patients who were admitted to our hospital for AMI (mean age: 52±9 years; range: 31-75 years; 59 males) were included in this study. In addition, 25 patients (mean age: 52±8 years; range: 40-73 years; 21 males) without CAD that met the exclusion criteria were also enrolled as controls. The inclusion criteria were a diagnosis of AMI, which was established according to World Health Organization criteria [12]. Sixty two patients were evaluated for cardiac events and laboratory parameters 10 months later again.

Patients with uncontrolled hypertension (systolic blood pressure [SBP] of 140 mmHg and/or diastolic blood pressure [DBP] of ≥90 mmHg based on their history), diabetes mellitus, acromegaly, history of CAD or heart failure, thyroid deficiency, hepatic dysfunction, Killip score of 3-4, aortic or mitral valve dysfunction, cardiomyopathy, history of acute pericarditis or myocarditis, acute or chronic renal failure, systemic infection, musculoskeletal disease, or cancer, and those who were on medications that would affect serum IGF-1/IGFBP-3 levels were excluded from the study. All patients were informed of the study details, and the study protocol was approved by a regional ethics committee.

Study Protocol

Fasting blood samples were obtained from all patients in the hospital and after about 10 months to establish their IGF-1 and IGFBP-3 levels. In the control group, fasting blood samples were obtained to measure their parameters.

Laboratory Studies

IGF-1 and IGFBP-3 levels were measured by immunoradiodynamic measurement in serum separated from whole blood. For measurement of the IGF-1 levels, a DSL-5600 ACTIVE® IGF-1 with EXTRACTION (Diagnostic System Laboratories, Inc.®, Webster, TX, USA) kit was used; for measurement of the IGFBP-3 levels, a DSL-6600 ACTIVE® IGFBP-3 (Diagnostic System Laboratories, Inc.®) kit was used.

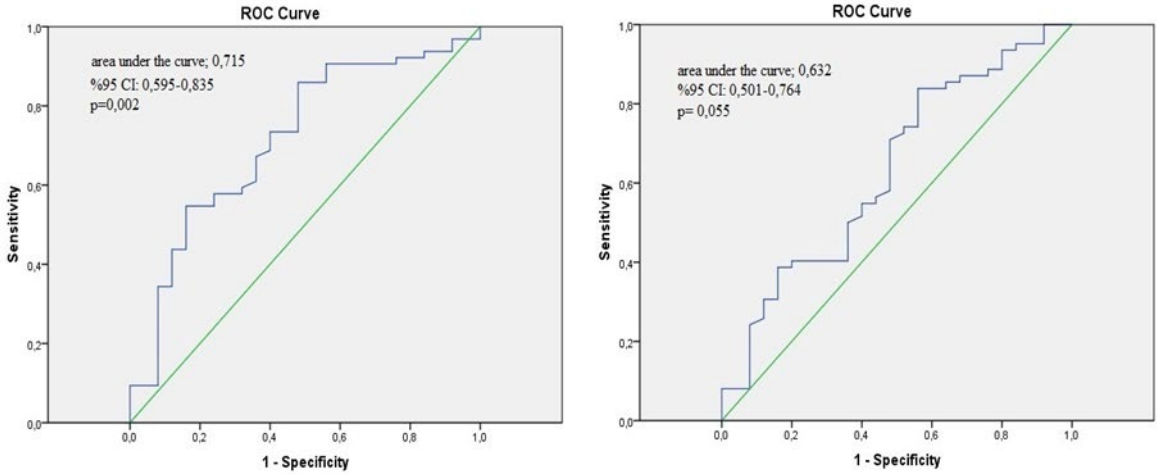

Figure 1. The receiver operating characteristic (ROC) curve of IGF-1 for baseline and 10th month

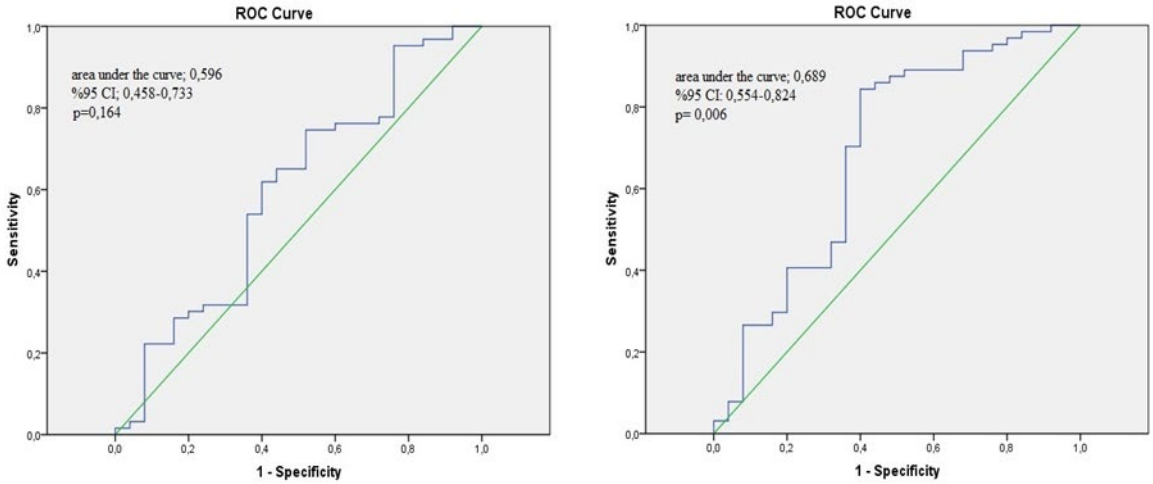

Figure 2. The receiver operating characteristic (ROC) curve of IGFBP-3 for baseline and 10th month

Statistical Analysis

All analyses were performed using SPSS v16.0 for Windows. Quantitative variables were expressed as the mean value±SD for parametric variables and as median or minimum-maximum levels for non-parametric variables. Comparisons of parametric values between the two groups were performed using the independent samples *t*-test. Comparisons of non-parametric values were performed using the Mann-Whitney U test. Categorical variables were compared using the chi-squared test. The Pearson test was used to determine the correlation between parametric variables; the Spearman test was used for non-parametric variables. A two-tailed p-value <0.05 was considered statistically significant. A receiver operating characteristic (ROC) analysis was also performed; the best cut-off value, and the sensitivity and specificity at that point were determined (**Figures 1** and **2**).

RESULTS

In the AMI patients, the IGF-1 levels were higher whereas the SBP was lower compared with the control group (p=0.002 and 0.03, respectively). All other parameters were similar between the two groups. After 10 months, the levels of IGFBP-3 remained significantly higher than in the control group; even though the IGF-1 levels tended to be higher, the values did not reach statistical significance (p=0.006 and 0.05, respectively) (**Table 1**). The 10-month IGF-1 and IGFBP-3 levels were similar the baseline values (p>0.05).

The predictive value for serum IGF-1 levels (sensitivity of 64% and specificity of 67%; area under the ROC curve=0.715) was 214 mg/dl at baseline and 156 mg/dl after 10 months (sensitivity of 52% and specificity of 71%; area under the ROC curve=0.632) (**Figure 1**). The predictive value of serum IGFBP-3 levels (sensitivity of 56% and specificity of 65%; area under the ROC curve=0.596) was 2738 mg/dl at baseline and 2836 mg/dl after 10 months (sensitivity of 60%

Table 1. A comparison of the laboratory and epidemiological parameters between the patients with AMI and the control group at baseline and the 10th month

	Baseline			10th month		
	Patients (n=65)	**Controls (n=25)**	**P**	**Patients (n=62)**	**Controls (n=25)**	**P**
Age (years)	52±9	52±8	0.5	53±8	52±8	0.6
HR/min	71.5±9.5	72.1±7.1	0.4	68.8±10.5	72.1±7.1	0.05
SBP mmHg	102.6±13	109±10.9	0.03	111.8±15.1	109±10.9	0.2
DBP mmHg	55.2±9.1	57.9±9.3	0.2	61±11	57.9±9.3	0.1
HgA1c mg/dl	5.7±0.5	5.6±0.3	0.2	5.9±0.7	5.6±0.3	0.05
TC mg/dl	186.4±36.3	185.4±37.8	0.7	164.7±35.6	185.4±37.8	0.05
TG mg/dl	147.3±124	153.2±91.2	0.2	150.6±81.2	153.2±91.2	0.8
HDL mg/dl	47.5±12.8	46.2±11.1	0.9	42.2±12.1	46.2±11.1	0.06
LDL mg/dl	109.6±30	108.5±35.1	0.5	92.4±29.3	108.5±35.1	0.06
IGF-1	243.6±82.4	180.3±82	0.002	219.6±87.2	180.3±82	0.05
IGFBP-3	3185.3±930.2	2813.6±1071.3	0.1	3501.3±760.4	2813.6±1071.3	0.006

Abbreviations: AMI: acute myocardial infarction; IGF-1: insulin-like growth factor -1; IGFBP-3: IGF-binding protein-3; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein; TC: total cholesterol; TG: triglyceride; NS: not significant. A value of $p<0.05$ was considered to be statistically significant

Table 2. A comparison of cardiac events between the AMI patients with low or high IGF-1 and the IGFBP-3 levels at baseline and the 10th month

		Complication (n)	p
IGF-1 at baseline	High	7	0.782
	Low	4	
IGF-1 at 10th month	High	8	0.788
	Low	2	
IGFBP-3 at baseline	High	6	0.281
	Low	2	
IGFBP-3 at 10th month	High	7	0.557
	Low	2	

Abbreviations: AMI: acute myocardial infarction; IGF-1: insulin-like growth factor-1; IGFBP-3: IGF- binding protein-3; NS: not significant. A value of $p<0.05$ was considered to be statistically significant

and specificity of 84%; area under the ROC curve=0.689) (**Figure 2**). At the 10th month, only 11 cardiac events were detected in 62 evaluated patients. No differences were found in the number of cardiac events between patients with low and high IGF-1 and IGFBP-3 levels (for both the baseline and 10-month values) (**Table 2**).

DISCUSSION

Several studies have suggested that low serum IGF-1 levels contribute to the pathogenesis of atherosclerosis [13-17]. Low serum IGF-1 and high IGFBP-3 levels were associated with an increased risk of CAD and mortality [2,3,11,18-20]. However, Kaplan et al. reported that low IGFBP-3 levels were significantly associated with an increased risk of coronary events. However, the same study found no association between IGF-1 levels and coronary event incidence [21].

A literature search revealed a limited number of studies investigating the relationship between serum IGF-1/IGFBP-3 levels and myocardial infarction, and the results of these studies were controversial. Investigators showed that the serum IGF-1 levels were low in patients with manifest CAD; however, this was not consistent in all studies [8, 22–26]. Sekuri et al. reported that the IGF-1 levels were significantly decreased only in ST segment elevation myocardial infarction (STEMI) patients, and that there was no difference in patients with unstable angina pectoris and non-ST segment elevation. There were no significant differences in IGFBP-3 levels between the two groups [27]. Yamagushi et al. reported that serum IGF-1 levels were decreased during the acute phase in patients with myocardial infarction [28]. However, the serum IGF-1 concentrations of the patients increased during the chronic phase (approximately 1 month later), similar to the IGF-1 concentrations in control subjects. However, Lee et al. reported that the total IGF-1 levels trended towards being higher (p=0.17) and that the free IGF-1 levels were significantly higher in patients with AMI [8]. In the present study, the serum total IGF-1 levels were significantly higher in patients with AMI compared to the healthy controls. The serum IGFBP-3 levels were also higher, but the values did not reach significance.

Previous studies showing that IGF-1 has beneficial effects on CAD have suggested different underlying mechanisms.

IGF-1 is important for tissue repair and cell proliferation; therefore, it may be involved in the pathogenesis of atherosclerosis. IGF-1 plays a critical role in cell cycle regulation and has mitogenic effects; additionally, it inhibits apoptosis and necrosis, which increases plaque stabilization [29,30]. In addition, IGF-1 facilitates neovascularization, increases nitric oxide production in the endothelium and muscle cells, and reduces cardiomyocyte loss post-AMI [31,32]. Thus, substantial evidence suggests a cardioprotective role for IGF-1. Growth hormone (GH) and insulin are major stimulating factors for IGF-1 secretion [33]. In this study, increased levels of GH and insulin may have sustained the increase in IGF-1.

The time required to return to normal IGF-1 levels and the association with long-term cardiac events are controversial. Sekuri et al. showed that serum IGF-1 levels were significantly increased after 3 months in the STEMI patient group, but did not reach the values in the control group [27]. Furthermore, no correlation was found between IGF-1 and IGFBP-3 levels and cardiac events during the 90-day follow-up period. Yamagushi et al. reported that the mean IGF-1 level on admission declined sharply and then promptly returned to baseline after 1 month, and that serum IGF-1 on admission was the most significant predictor of 90-day mortality in AMI patients [28]. Conti et al. found that low IGF-1 levels were associated with 90-day cardiac events and appeared to return to the normal range after 1 year [1]. In our study, the IGF-1 levels decreased while the IGFBP-3 increased after 10 months, but neither value was significantly different from the baseline value (p=0.5 and 0.5, respectively). After 10 months, both the IGF-1 and IGFBP-3 levels were statistically higher in the patient group than in the control group (p=0.05 and 0.006, respectively). In our study, no correlation between IGF-1 and IGFBP-3 levels and cardiac events was found during the 10-month follow-up period. Based on cross-sectional studies, we expected that the IGF-1 levels would be equal to or lower than those in the control group over time. Therefore, we hypothesize that to achieve the levels of IGF-1 found in cross-sectional studies, the follow-up period should be longer than 1 year.

Based on the mechanisms of IGF-1 and the studies mentioned above, we expected that the occurrence of cardiac events in patients with high IGF levels would be lower than in those with low levels of IGF-1 after 10 months. However, this was not the case. These results may be explained by the limitations of the current study. For example, the ejection fraction, rate of myocardial necrosis, performance index, and drugs used by the patients were not evaluated. Unfortunately, the design of our study did not allow us to perform a valid multivariate analysis. We were surprised by the finding that IGF-1 levels were not related to cardiac events. We believe that if the patients were followed for a longer period of time, we would obtain different results concerning the association between IGF-1, IGFBP-3, and cardiac events.

CONCLUSIONS

The serum total IGF-1 and IGFBP-3 levels were higher in AMI patients compared to the controls, but there was no correlation between IGF-1 and IGFBP-3 levels and cardiac events in the 10-month follow-up period after AMI. Additional studies are needed to clarify the levels of IGF-1 and IGFBP-3 and the time required to return to normal levels, and to clarify the long-term relationship between IGF-1, IGFBP3, and cardiac events in patients with AMI.

DECLARATION OF CONFLICT OF INTEREST

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Olgu Sunumu

Derin ven trombozu tablosu ile seyreden bir tifo olgusu

A case of typhoid fever with deep vein thrombosis

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ÖZ

Tifo, *Salmonella typhi*'nin neden olduğu sistemik bir hastalıktır. Yiyecek ve su kaynaklı oluşan bir hastalık olup gelişmekte olan ülkelerde önemli bir halk sağlığı sorunudur. Ateş, grip benzeri semptomlar, baş ağrısı, öksürük, kırgınlık, bulantı ve miyalji en sık görülen semptomlardır. Venöz tromboz sıklıkla hastalığın dördüncü haftasında ortaya çıkmaktadır ve antibiyotik döneminden önce yaygın bir komplikasyondu. Bu yazıda yüksek ateş, baş ağrısı, halsizlik, ishal şikayetleriyle başvuran, tetkikler sonucunda derin ven trombozu saptanan, kan kültüründe *Salmonella typhi* üreyen ve seftriakson tedavisiyle kür sağlanan bir olgu sunuldu.

Anahtar kelimeler: *Salmonella typhi,* tifo, tromboz

ABSTRACT

Typhoid fever is a systemic infection caused by *Salmonella typhi*. It is a disease caused by food and water sources and is an important public health problem in developing countries. Fever, flu-like symptoms, headache, cough, malaise, nausea and myalgia are the most common symptoms. Venous thrombosis often occurs in the fourth week of the disease and was a common complication before the antibiotic era. In this article, we present a case who presented with high fever, headache, fatigue, diarrhea, had deep vein thrombosis as a result of the tests, *Salmonella typhi* produced in blood culture and healing with ceftriaxone treatment.

Keywords: *Salmonella typhi,* typhoid fever, thrombosis

GİRİŞ

Tifo, *Salmonella typhi* bakterisinin neden olduğu sistemik bir enfeksiyon hastalığı olup sadece insanlara özgü bir hastalıktır [1]. *Salmonella* serotipleri çoğunlukla gastroenterit, enterik ateş, bakteriyemi, vasküler enfeksiyon, lokalize enfeksiyonlar ve kronik taşıyıcılık olmak üzere karakteristik klinik sendromlara neden olmaktadır [2]. Antibiyotik döneminden önce yaygın bir komplikasyon olan venöz tromboz sıklıkla hastalığın dördüncü haftasında ortaya çıkmaktadır. Etkili antimikrobiyal tedavi seçeneklerinin kullanıma girmesinden sonra tromboz ve flebit olguları nadiren bildirilmiştir [3]. Bu yazıda düşmeyen ateş şikayeti olan, alt ekstremitede yaygın tromboz saptanan ve kan kültürlerinde *Salmonella typhi* üreyen tifo olgusu sunulması amaçlandı.

OLGU

On yedi yaşında erkek olgu, yaklaşık bir ay önce ateş, baş ağrısı, halsizlik ve ishal şikayetleri nedeniyle özel bir hastanede yatırılarak takip edilmiş. Altta yatan hastalığı olmayan olgu yapılan tetkikler sonucunda derin ven trombozu saptanarak hastanemiz Kalp Damar Cerrahisi bölümüne sevk edilmiş. Hastanın bu klinikteki takibinde ishal şikayeti düzelirken; ateş, baş ağrısı, sol bacak ağrısı ve şişliği, devam etmekteydi. Fizik muayenesinde genel durumu iyi, şuuru açık, vücut ısısı 39,3 °C, kan basıncı 90/60 mmHg, kalp tepe atımı 108 atım/dk idi. Batın muayenesine hepatomegali ve splenomegali saptandı. Ayrıca sol alt ekstremitede ısı artışının olmadığı, ağrılı şişlik mevcuttu. Başvuru sırasında beyaz küre 7400/ml, C-reaktif protein (Crp):238 mg/l, alanin aminotransferaz (Alt) 85 U/L, aspartat aminotransferaz (Ast) 134 U/L, kreatinin 0,7 mg/dl, D-dimer 6,6 ug/ml, fibrinojen 691 mg/dl idi. Sol alt ekstremite venöz renkli doppler ultrasonografi (USG) incelemesinde; common femoral, superfisiyal femoral, derin femoral ve popliteal ven total tromboze izlendi. Batın USG'de hepatosplenomegali mevcuttu. Gruber widal ve brusella wright aglütinasyon serolojik testleri negatifti. Ateş yüksekliğinin devam etmesi üzerine kan kültürleri alındı ve olguya ampirik olarak ampisilin-sulbaktam 4x2 gr/intravenöz (iv)/gün tedavisi başlandı. İki kan kültüründe de *Salmonella typhi* üredi. Kültür antibiyogramında ampisilin, ampisilin/sulbaktam, trimetoprim/sulfametoksazole karşı dirençli iken, amikasin, siprofloksasin, sefoksitin, sefuroksim, seftriakson, sefepim, imipenem ve meropeneme duyarlıydı. Olgu devralınarak tedavisi siprofloksasin 2x400 mg/intravenöz/gün olarak değiştirildi ve anti-trombotik tedaviye devam edildi. Siprofloksasin tedavisinin 5. gününde ateş yanıtı olmaması üzerine seftriakson 2x1 gr/iv/gün tedavisine geçildi ve bu tedavinin 4. gününde düzelme görüldü. Kontrol doppler USG'de trombotik lezyonlarda belirgin regresyon izlendi. Seftriakson tedavisinin 9. gününde (yatışının 22. gününde) klinik ve laboratuvar değerlerinde belirgin düzelme görülen olgu seftriakson (intravenöz olarak iki haftaya tamamlanacak şekilde) ve anti-trombotik ile taburcu edildi.

TARTIŞMA

Tifo, Gram negatif enterik bakterilerden *Salmonella enterica serovar typhi*'ye bağlı gelişen sistemik bir hastalıktır. Yiyecek ve su kaynaklı olan bu hastalık tablosu, zayıf hijyen yanısıra nüfusun yoğun olduğu bölgelerde kötü hijyen ile kuvvetle ilişkilidir. Gelişmekte olan ülkelerde tifo hastalığı önemli bir halk sağlığı sorunu olmaya devam etmekte ve başlıca mortalite ve morbidite nedenlerinden biridir [4]. Tifonun dünyada her yıl, özellikle gelişmekte olan bölgelerde 20 milyondan fazla kişiyi etkilediği tahmin edilmektedir. Ülkemizde ise Sağlık Bakanlığı verilerine göre tifo vakalarında son yıllarda önemli bir düşüş olduğu gözlenmiştir (2008 yılında 2214 tifo vakası bildirilirken 2011 yılında yeni tifo vaka sayısı 123'e gerilemiştir) [5].

Tifo 11-30 yaş arası büyük çocuk ve genç erişkinlerde daha sık görülmektedir. İnkübasyon süresi genel olarak 7-14 gün arasında olup, 60 güne uzayabilen hastalığın klinik görünümü ve ciddiyeti çok değişkenlik göstermektedir. Ateş, grip benzeri semptomlar, baş ağrısı, kuru öksürük, kırgınlık, iştahsızlık, bulantı ve miyalji en sık görülen semptomlardır. Klasik hastalık periyodu dört hafta olup, hastalığın ilk haftasında yüksek ateş, kabızlık, toksemi, ikinci haftasında diyare, üçüncü haftasında splenomegali, nötropeni, lökopeni, ensefalopati, intestinal hemoraji ve intestinal perforasyon gibi bulgu ve komplikasyonların görülmesi tipiktir [6]. Venöz tromboz, antibiyotik döneminden önce genellikle hastalığın dördüncü haftasında gelişen ve görülen sık bir komplikasyondu [3]. Dehidratasyon ve uzun süre yatakta yatmanın tromboz gelişimine yol açtığı düşünülmekteydi; fakat bazı olgularda *Salmonella typhi* pıhtıdan da izole edilmiştir [7]. Endotoksinin tifo hastalarında görülen hematolojik değişikliklerde arabulucu olduğu ve aslında koagülasyonun esas indükleyicisi olduğu düşünülmektedir. Akut enfeksiyon, koagülasyonun sistemik aktivasyonu ile sonuçlanabilir. Tifo ateşinde, enflamasyonun sonucu olarak koagülasyon kaskadının aktivasyonu ve fibrin ürünlerinin birikimi ortaya çıkmaktadır. Trombüsün immünolojik fonksiyonları trombositlere bağlıdır [8]. Olgumuzda tromboz gelişmeden 3-4 hafta önce semptomları başlandığı öğrenildi ve ilk olarak yüksek ateş, baş ağrısı, halsizlik ve ishal şikayetleri olup ilerleyen günlerde sol bacak ağrısı ve şişliği gelişmesi üzerine yapılan doppler USG görüntülemesinde sol alt ekstemitesinde tromboz saptanmıştı.

Hastalığın kesin tanısı kan, kemik iliği, idrar ve dışkıdan *Salmonella typhi*'nin üretilmesi ile konmaktadır. Birden fazla alınan kan kültüründen etkenin izole edilme oranı %73-93'e kadar çıkabilmektedir. Bu oran, hastalığın üçüncü haftasında %50, antibiyotik alan hastalarda ise %40'a kadar düşebilir [9]. Baran ve ark. [10] yaptığı çalışmada daha önceden antibiyotik tedavisi almış (sevk edildiği merkezde tedavi uygulanmış) olguların %17'sinde, antibiyotik tedavisi verilmeden kan kültürü alınmış olguların %78'inde kan kültürü pozitifliği saptamışlardır. Olgumuzun ateş yüksekliğinin devam etmesi üzerine tekrarlanan kan kültürlerinde *Salmonella typhi* üremesi görüldü.

Gruber widal, tanısal değeri sınırlı olsa da gelişmekte olan ülkelerde yaygın olarak kullanılan, kullanımı basit ve ucuz bir testtir. Bununla birlikte testin standardizasyon eksikliği, özgüllüğünün düşük olması ve uygun olmayan sonuçların yorumlanması gibi sorunları da mevcuttur. Ayrıca endemik bölgelerde normal popülasyonda da düşük titrede antikor pozitifliği olması, pozitif sonuçlar için uygun cut-off noktasının belirlenmesini zorlaştırmaktadır. Enterik ateş tanısını koymak amacıyla widal test sonuçlarının doğru bir şekilde yorumlanması, her ülkenin uygun titreyi belirlemesini gerektirir [11]. Olgumuzun bakılan Widal testi negatif olarak sonuçlanmıştı. Olgumuzda da görüldüğü üzere Widal test negatifliği tifo tanısını ekarte ettirmemektedir. Testin duyarlılığı ve özgüllüğü düşüktür. Tanı alan hastaların bir bölümünde antikor seviyesinde artış görülmemektedir.

Hastaların çoğunda laboratuvar bulgusu olarak lökopeni, eritrosit sedimantasyon hızında artış saptanırken, fiziki muayene bulgularında yüksek ateş, splenomegali, hepatomegali ve rölatif bradikardi saptanabilir [9]. Baran ve ark. [10] yaptığı çalışmada olguların %66,7'sinde hepatomegali, %57,1'sinde splenomegali, %33,3'ünde lökopeni, %9,5'inde anemi, %42,9'ünde trombositopeni, %52,4'ünde ALT yüksekliği, %76,2'sinde AST yüksekliği, %100'ünde CRP yüksekliği, %90,5'inde sedimentasyon yüksekliği saptamışlardır. Olgumuzun fizik muayenesinde yüksek ateş, hipotansiyon, taşikardi, hepatomegali ve splenomegali vardı. Laboratuvar tetkiklerinde ise ALT, AST, d-dimer ve CRP yüksekliği mevcuttu.

Kloramfenikol, trimethoprim-sulfametoksazol ve ampisillin yıllarca tifo hastalığının tedavisinde kullanılmıştır; fakat direnç gelişiminden dolayı artık kullanılmamaktadır. Siprofloksasin ve ofloksasin gibi florokinolonlar seftriaksona tercih edilen ilaçlardır. Ne yazık ki, florokinolonlara dirençli *Salmonella typhi* suşlarının ortaya çıkması artan tedavi başarısızlığına, hastalık şiddetine ve hatta ölümlere neden olmaktadır [11]. Beş Asya ülkesini kapsayan prospektif bir çalışmada multidrug rezistan (MDR) (kloramfenikol, ampisilin, trimetoprim-sulfametoksazol) oranı 23% bulunmuştur [12]. Olgumuza da tifo teşhisi konduktan sonra ilk olarak siprofloksasin başlanmış klinik ve laboratuvar tetkiklerinde düzelme görülmemesi üzerine tedavisi seftriakson olarak revize edilmiş ve fayda sağlanmıştır. Olgumuzun kültür antibiyogramında siprofloksasine karşı direnç olmamasına rağmen klinik belirti ve bulgularında düzelme olmaması siprofloksasine karşı azalmış duyarlılıkla veya tromboz ile komplike olmasından ötürü klinik iyileşmenin uzun sürebileceğiyle ilişkili olabileceği düşünüldü.

SONUÇ

Tifo, ülkemizde endemik olarak görülen multisistem tutulumu gösterebilen bir hastalıktır. Tifo hastalığında erken ve uygun antibiyoterapi ile komplikasyonların görülme sıklığı ve mortalite belirgin bir şekilde azalmıştır. Derin ven trombozu eski dönemlere nazaran nadir görülen bir komplikasyondur. Derin ven trombozu nedeniyle takip edilen olgularda tifo hastalığının da etiyolojik nedenlerden birinin olabileceğinin akılda tutulması, erken medikal tedavi uygulanması ve gerekli vakalarda cerrahi tedavi uygulanması uygun bir yaklaşımdır.

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Original Article

The role of pesticides in the etiology of lymphoma: A systematic review

Lenfoma etiyolojisinde pestisitlerin rolü: Sistematik derleme

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ABSTRACT

Aim: It is known that non-Hodgkin lymphoma risk increases in agricultural workers and it is thought that pesticides have an effect on this increase. The aim of this systematic review is to evaluate the role and effect of pesticides in the etiology of lymphoma.

Material and Methods: This systematic review was conducted in accordance with the Centre for Reviews and Dissemination 2009 guide developed by York University National Institute of Health Research. It was carried out in the databases Science Direct, EBSCO (CINAHL Complete), PUBMED, Wiley Interscience, Springer Link databases to cover the years 2014-2019.

Results: As a result of the review, six studies were included in the research and presented in "year of study, research type and sample characteristics, measurement tools used, results obtained, and level of evidence".

Conclusion: It was found that pesticide use was associated with the risk of non-Hodgkin lymphoma and its subtypes. Occupational exposures should be assessed in communities whose main livelihood is agriculture and this group should be trained by health professionals on the use of personal protective equipment and protective behaviors.

Keywords: lymphoma, non-Hodgkin lymphoma (NHL), pesticide, systematic review

ÖZ

Amaç: Tarım çalışanlarında non-Hodgkin lenfoma riskinin arttığı bilinmektedir ve bu artışta pestisitlerin rolü olduğu düşünülmektedir. Bu sistematik derlemenin amacı lenfoma etiyolojisinde pestisitlerin rolünü ve etkisini değerlendirmektir.

Gereç ve Yöntemler: Bu sistematik derleme York Üniversitesi Ulusal Sağlık Araştırmaları Enstitüsü tarafından geliştirilen Derleme ve Yaygınlaştırma Merkezi 2009 kılavuzuna uygun olarak yürütülmüştür. Çalışmaya ilişkin taramalar 2014-2019 yıllarını kapsayacak şekilde Science Direct, EBSCO (CINAHL Complete), PUBMED, Wiley Interscience ve Springer Link veri tabanlarında yapılmıştır.

Bulgular: Tarama sonucunda, kriterlere uyan altı çalışma araştırma kapsamında alınmıştır. Sonuçlar "Çalışmanın yılı, araştırma tipi ve örneklem özellikleri, kullanılan ölçüm araçları, elde edilen sonuçlar ve kanıt düzeyi" başlıkları altında tablo olarak sunulmuştur.

Sonuç: Pestisit kullanımının non-Hodgkin lenfoma ve alt tipleri ile ilişkili olduğu bulunmuştur. Tarımın ana geçim kaynağı olduğu toplumlarda mesleki maruziyet değerlendirilmeli ve bu grup kişisel koruyucu ekipman kullanımı ve koruyucu davranışlar konularında sağlık profesyonelleri tarafından eğitilmelidir.

Anahtar kelimeler: lenfoma, non-Hodgkin lenfoma (NHL), pestisit, sistematik derleme

INTRODUCTION

Pesticides are commonly used with the purpose of preventing the loss of yield in food sources to meet the needs of the growing world population, and these products have serious negative impacts on human health. The length of stay in nature of pesticides may vary between 3-17 years. Pesticides entering the body through digestion, respiration or skin can easily cross the white blood cell and red blood cell membrane by binding to serum lipoproteins through blood circulation and may damage the health by accumulating in different tissues and organs of the body such as liver, brain, adrenal glands, muscle tissue and especially fatty tissue [1].

It is known that the risk of Non-Hodgkin's Lymphoma (NHL) increases in agricultural workers [2-5]. Different exposures may contribute to this increased risk, and pesticides are considered to have a significant role [6]. Despite the widespread use of pesticides, there are a limited number of studies examining the relationship between the risk of NHL and pesticides in the general population. The International Agency for Research on Cancer study group classified organochlorine pesticides as NHL-associated carcinogens [7,8]. The same study group reported that there was a positive relationship between dichloro diphenyl trichloroethane (DDT) and liver, testis, and NHL [8]. In another study, it was found that high DDT level increased the risk of NHL [9]. Although most studies reported increased NHL risk with organochlorine exposure [10-12], there are also studies indicating that there is no relationship [13-15].

Organophosphate and carbamate group pesticides have serious negative effects on human health such as cancer [16,17]. The International Agency for Research on Cancer classified organophosphates as possible human carcinogens [18]. In large prospective cohort studies, it was reported that there was a positive relationship between the use of organophosphate group pesticides and NHL [19,20]. The aim of this systematic review was to investigate the role of pesticides in the etiology of lymphoma. This systematic review was initiated with the question "Do pesticides have effects on the formation of lymphoma?"

MATERIAL AND METHODS

This study is a systematic review carried out to investigate the role of pesticides in the etiology of lymphoma. The review was carried out in accordance with the Center for Reviews and Dissemination (CRD) 2009 guide developed by the York University National Institute for Health Research. The literature review was conducted in the "Science Direct, EBSCO (CINAHL Complete), PUBMED, Springer Link, Wiley Interscience" databases covering the years between 2014 and 2019. The review was carried out between April and August 2019. The key words "Lymphoma" "Pesticide", "Lymphoma and pesticide" were used in the review. While the inclusion criteria of this systematic review were case-control and cohort studies carried out in those who used or were exposed to pesticides regardless of age group and gender, the exclusion criteria were determined as the

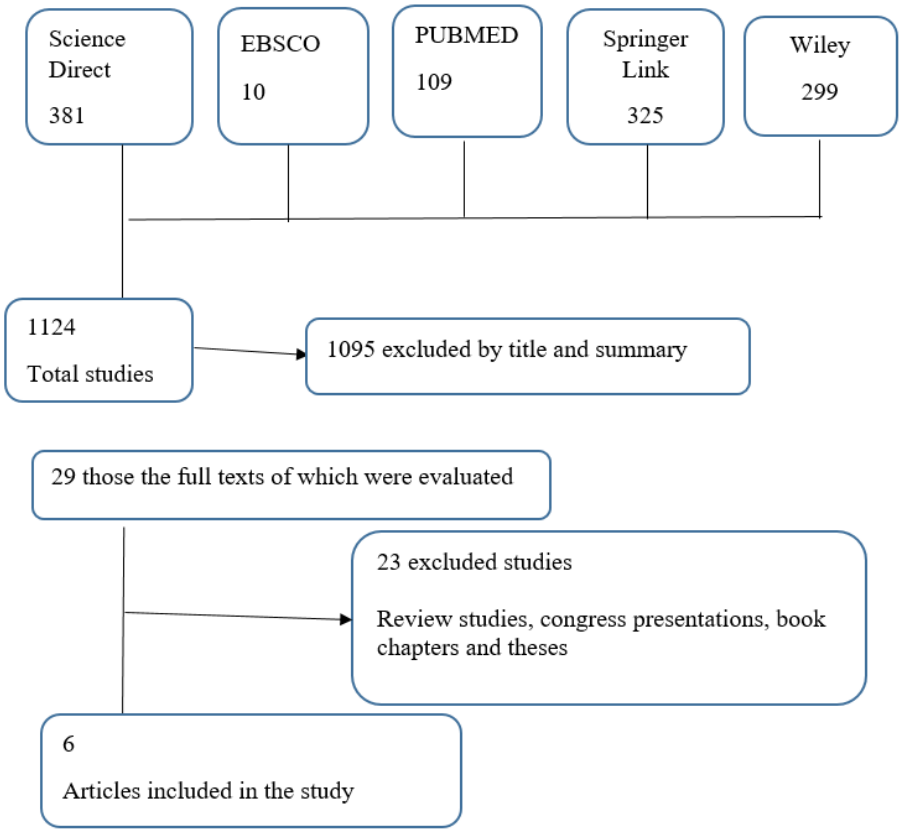

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart

reviews, congress reports, theses, and book chapters. As a result of the review, a total of 1124 (Science Direct: 381, EBSCO (CINAHL Complete): 10, PUBMED: 109, Springer Link: 325, Wiley Interscience: 299) studies were reached. At the end of the eliminations made in accordance with the criteria, six studies were included in the study (**Figure 1**).

The level of evidence of each study was evaluated according to the Melnyk and Fineout-Overholt classification: Systematic review or meta-analysis (Level I), Randomized controlled trial (Level II), Controlled trial without randomization (Level III), Case-control or cohort study (Level IV), Systematic review of qualitative or descriptive studies (Level V), Qualitative or descriptive study (Level VI), Expert opinion or consensus (Level VII) [21]. This review followed the recommendations proposed by Preferred Reporting Items for Systematic Reviews and Meta-analyses [22].

RESULTS

As a result of the review, six studies that met the inclusion criteria were included in the systematic review (Figure). The results obtained from the studies are presented by being grouped under the headings of "Study/Year, Research Type/Sample Characteristics, Measurement Tools Used, Results Obtained, and Level of Evidence" (**Table 1**).

Sample Characteristics

The studies under review were cohort and case-control studies and all of them were observational studies. When sample characteristics were examined, the cases diagnosed with lymphoma and one of its subtypes on a yearly basis regardless of age group and gender were reviewed. The participants in the case-control group were usually selected from the existing hospital/health records or from the results of prospective cohort studies. It was determined that the minimum and maximum numbers of samples were 158 [23] and 1690 [24], respectively.

Measurement Tools Used

Different measurement tools and methods were used in the studies included in the review. Cancer records [19], SEER coding scheme for the classification of NHL and its subtypes [19], WHO Lymphoma Classification [23], International Classification of Oncology [24], InterLymph Consortium Classification [6], socio-demographic information questionnaire form [19,23,24], questionnaire form examining the use of pesticides [6,19,24], CAREX database [23] were used. Gas chromatograph and chemistry analyzer were used to perform laboratory analyses in two studies [25,26].

Table 1. Scientific Researches on the Relationship between Lymphoma and Pesticide*

Study/Years	Research Type / Sample Characteristics	Measurement Tools Used	Results Obtained	Level of Evidence
Alavanja et al., 2014	Prospective cohort study. 523 NHL cases.	- State Cancer Records - SEER coding scheme in the classification of NHL and its subtypes (based on Pathology Working Group of the International Lymphoma Epidemiology Consortium) -Socio-demographic information questionnaire - Algorithm questioning whether to mix pesticides, method of application, repair of equipment or use of personal protective equipment	It was found that the use of herbicides had a small but significant effect on the risk of some NHL subtypes, however, it did not affect the risk of NHL in general. Lindane was the only pesticide with a statistically significant increase for the risk of NHL with both exposure measurements. DDT indicated that there was a significant trend for the risk of NHL on the days of lifetime use. For follicular lymphoma, lindane showed a non-significant relationship. Lifelong use of lindane was found to be associated with the risk of NHL.	IV
Bassig et al., 2019	Case-control study. Case and control groups were identified from the results of three prospective cohort studies. 167 NHL cases.	- Gilson 215 liquid handler - Chromatography isotope dilution high resolution mass spectrometer -912 Chemistry Analyzer (Hitachi, Tokyo, Japan)	It was determined that p0-DDE, one of OC pesticides, had the highest concentration in both NHL cases and controls. V-HCH and p0DDE concentrations in cases and controls showed great differences between individual cohorts. They were observed at very high levels in Shanghai compared to Singapore. A strong relationship was found between B-HCH levels and general NHL. No significant exposure-response relationship was observed between other OC pesticide levels and the risk of NHL. HCB concentrations were not associated with overall risk of NHL, except for lymphoid leukemia. However, high HCB levels were found to be associated with NHL among the cases diagnosed in both groups 7 years after blood collection.	IV
Ferri et al., 2017	Retrospective case-control study. 158 lymphoma cases including 30 HL cases and 128 NHL cases that were first diagnosed during the study period.	-World Health Organization (WHO) lymphoma classification (2008) - 40 ml blood sample for biological exposure parameters (serum polychlorinated biphenyls [PCB], aryl hydrocarbon receptors [AHR], lymphocytic oxidative) -Socio-demographic information questionnaire -CAREX database to evaluate occupational exposure to pesticides	No statistical significance was found between the risk of lymphoma and 22 chemical products. Increased risk was detected for all lymphomas in cases exposed to Captafol, exposed to Low Paraquat levels and Moderate radon levels.	IV
Koutros et al., 2019	Case-control study. 1690 NHL cases	-International Classification of Diseases for Oncology First Edition (ICDeOe1) to classify NHL -Socio-demographic information questionnaire - Questionnaire form for pesticide use	Significantly increased risk of NHL was found among malathion users. A statistically significant relationship was found between the duration of pesticide use and the risk of NHL. A weighted normalized (Z-score) one-unit change between pesticides increases the risk of NHL by 38%. A positive relationship was found between the use of OP and carbamate insecticides and the subtypes of lymphoma. Furthermore, a significant increased risk was also found in the use of carbonfuran and DLBCL.	IV
Klil-Drori et al., 2018	Hospital-based case-control study. 90 cases, 120 control.	- Gas chromatograph	It was found that DDE and HCB levels were not associated with B-NHL. However, PCB was found to be associated with B-NHL.	IV
Schinasi et al., 2015	Prospective cohort study. 822 NHL cases.	-InterLymph Consortium classification -World Health Organization Lymphoma classification - Questionnaire form for pesticide use	It was found that the risk of NHL was 24% higher in those who reported pesticide application. It was found that the risk of DLBCL was 49% in those who used pesticides by mixing and 72% in those who used pesticides intensively. This risk was high in young women. Women who use pesticides for domestic animals had 71% higher risk of plasma cell neoplasms. It was determined that the use of powder or spray in domestic animals increased the risk of follicular lymphoma by 62%.	IV

*This table was prepared by the author

In the study of Alavanja et al., information on tumor characteristics was obtained from state cancer records. The classification of NHL and its subtypes was examined according to the SEER coding scheme based on Pathology Working Group of the International Lymphoma Epidemiology Consortium classification. 1. Small B-cell lymphocytic lymphomas (SLL), chronic B-cell lymphocytic lymphomas (CLL), mantle-cell lymphomas (MCL); 2. Diffuse large B cell lymphomas; 3. Follicular lymphomas; 4. 'Other B-cell lymphomas' consisting of a diverse set of B-cell lymphomas; 5. Multiple myeloma; and 6. T-cell NHL and undefined cell type. First information on the use of 50 pesticide species was obtained from the questionnaire form that was filled out during cohort record. Three cumulative exposure measures were used to determine pesticide exposure: (i) lifetime days of pesticide use (namely, years of use of a particular pesticide and number of days used per year); (ii) usage intensity-based lifetime days (namely, product of exposure days and exposure intensity measure) and (iii) using each pesticide. Information on usage density

was derived from an exposure algorithm based on individual declaration (for instance, whether they mix pesticides, method of application, whether to repair equipment, or whether they use personal protective equipment) [19].

In the study of Bassig et al., samples conforming to standards were obtained using Gilson 215 liquid handler (Gilson Inc., Middleton, WI), and they were extracted by automated liquid-liquid extraction (LLE) using a liquid handler. The measurement of target analyses was performed using a chromatography isotope dilution high resolution mass spectrometer (GC-IDHRMS). Case-control pairs were analyzed sequentially in the sequential batch and laboratory workers were blinded according to the control status of the samples [25].

In the study of Ferri et al., 158 lymphoma cases that were first diagnosed during the study period were included, and each case was reviewed and classified using the World Health Organization (WHO) lymphoma classification. The control group was selected based on the same gender, same age class and the same the province of residence. Socio-demographic information was collected with a questionnaire form. CAREX database was used to evaluate occupational exposure to known and suspected carcinogenic pesticides [23].

In the study of Koutros et al., International Classification of Oncology (ICDeOe1) was used in the classification of NHL and its subtypes: follicular lymphoma (FL), di large B-cell lymphoma (DLBCL), small lymphocytic lymphoma (SLL) and "other". "Other" subtype histologies include all cases of FL or DLBCL or non-SLL or unknown. The cases and controls were matched by settlement (state/province) and age (±2 or 5 years). Other variables related to NHL risk factors such as demographic data, agricultural exposures (including use of pesticides) and lifestyle, medical and occupational history were obtained from the participants through questionnaire form [24].

In the study of Klil-Drori et al., serum blood samples were studied. The measurements of six organochlorine pesticides (DDT, DDE, b-hexachlorocyclohexane [b-HCH], α-HCH, hexachlorobenzene [HCB] and g-HCH [lindane]) were performed using gas chromatography combined with an electron capture detector [26].

In the study of Schinasi et al., Hodgkin Lymphoma (HL) neoplasms were categorized according to InterLymph Consortium recommendations and World Health Organization subtypes. The questionnaire form examining the use of pesticides at home or at work, form of use, mixing conditions of pesticides was used [6].

Results Obtained

In the study of Alavanja et al., NHL cases were detected in 523 cases, including 148 SLL / CLL / MCL, 117 diffuse large B cell lymphoma, 67 follicular lymphoma, 53 other B cell lymphoma (consisting of various B cell lymphoma sets) and 97 MM cases. It was found that the use of herbicides had a small but significant effect on the risk of some NHL subtypes, however, it did not affect the risk of NHL in general. Lindane was the only pesticide with a statistically significant increase for the risk of NHL. DDT indicated that there was a significant trend for the risk of NHL on the days of lifetime use. The relationship between the risk of follicular lymphoma and lindane was not statistically significant. Lifelong use of lindane was found to be associated with the risk of NHL [19].

In the study of Bassig et al., it was determined that p0-DDE, one of organochlorine (OC) pesticides, had the highest concentration in both NHL cases and controls. V-HCH and p0DDE concentrations in cases and controls showed great differences between individual cohorts. A strong relationship was found between B-HCH levels and general NHL. No significant exposure-response relationship was observed between other OC pesticide levels and the risk of NHL. HCB concentrations were not associated with overall risk of NHL, except for lymphoid leukemia. However, high HCB levels were found to be associated with NHL among the cases diagnosed in both groups 7 years after blood collection [25].

In the study of Ferri et al., no statistical significance was found between the risk of lymphoma and 22 chemical products. Increased risk was detected for all lymphomas in cases exposed to captafol, exposed to low paraquat levels and moderate radon levels [23].

In the study of Koutros et al., significantly increased risk of NHL was found among malathion users. A statistically significant relationship was found between the duration of pesticide use and the risk of NHL. A weighted normalized (Z-score) one-unit change between pesticides increases the risk of NHL by 38%. A positive relationship was found between the use of organophosphate (OP) and carbamate insecticides and the subtypes of lymphoma. Furthermore, a significant increased risk was also found in the use of carbonfuran and DLBCL [24].

In the study of Klil-Drori et al., it was found that DDE and HCB levels were not associated with B-NHL and that PCB increased the risk of B-NHL [26].

In the study of Schinasi et al., it was found that the risk of NHL was 24% higher in those who reported pesticide application. It was found that the risk of DLBCL was 49% in those who used pesticides by mixing and 72% in those who used pesticides intensively. This risk was high in young women. Women who use pesticides for domestic animals had 71% higher risk of plasma cell neoplasms. It was determined that the use of powder or spray in domestic animals increased the risk of follicular lymphoma by 62% [6].

DISCUSSION

DDT is one of the organochlorine pesticides that achieved success in the control of malaria and typhus during and after World War II [27]. It was used actively in pest control in the United States of America (USA) from the mid-1940s to the 1960s [28]. Although this product was banned for agricultural use around the world in 2009, it is still used in vector control in some countries [29]. Permethrin is one of the broad-spectrum synthetic pyrethroid pesticides commonly used in home and horticulture. Since it was found to be associated with liver tumors in animal experiments, it was classified as possible human carcinogen by The U.S. Environmental Protection Agency (EPA) [30]. Although terbufos, which is an organophosphate insecticide, was classified in the "non-carcinogenic group" by EPA [31], it was determined in the study of Alavanja et al. that the use of terbufos was associated with the risk of NHL and some subtypes [19]. Malathion was classified as "possible human carcinogen" by International Agency for Research on Cancer (IARC). While case-control studies carried out in different sample groups [32-34] indicated that there was a positive relationship between the use of malathion and the risk of NHL, as in the study of Koutros et al. [24] it was concluded in the study of Alavanja et al. that it was not associated [19]. These differences between the results may be due to time differences between exposure and disease development, differences in the use of pesticides, differences in sample groups examined, or differences in study types.

The carcinogenic mechanism of captafol is linked to interaction with thiol groups and cysteine that reduce defense against oxidative agents, lead to the formation of metabolites such as tetrahydrophthalimide, and lead to the formation of NS bonds with other biological substrates [35]. Moreover, it was reported that the risk of NHL was increased in the users of paraquat which is a herbicide commonly used in agriculture [36]. Acute exposure to paraquat may lead to fatal poisoning, and chronic exposure may pave the way for respiratory diseases and Parkinson's disease [37]. In the study of Ferri et al., the result that exposure to captafol and paraquat was associated with the risk of lymphoma supports the literature on carcinogenic mechanism [23].

In the literature, it was found that Lindane [27,34,38], DDT [9,19,39-41], terbufos [19], diazinon [33] and numerous organochlorine pesticides [42,43] were associated with the increased risk of NHL and its subtypes. It was reported that the use of pesticides induced oxidative stress by causing destruction in cell proliferation [44], triggered inflammatory response [45] and had an effect on genotoxicity. In some studies, it was indicated that pesticide exposure was associated with common chromosomal changes [46,47] Accordingly, it will be highly valuable to investigate potential biological mechanisms that directly affect the relationship between pesticide exposure and lymphoma.

Most epidemiological studies reflect the data of sample groups with male employees evaluating occupational exposure rather than household exposure. In a case-control study carried out with women working on the farm for 10 years or more, it was found that the NHL risk of women working on the farm was 2.12 times higher compared to those who did not work on the farm [48]. The risk of acute myeloid leukemia was also found to be higher in women living on the farm compared to women living in the city [49]. In the study of Schinasi et al., high risk of NHL and its subtypes among women living in farms supports the literature [6].

CONCLUSION

In six studies included in the review, it was demonstrated that pesticide use was associated with the risk of NHL and its subtypes. Although large-scale prospective cohort studies add important information at the level of evidence to the literature on this risk relationship, additional studies are needed on suspected professional factors. In addition to healthy lifestyle behaviors in the prevention of cancer, occupational applications and exposures should be evaluated if there are occupational cancers, and preventive health behaviors should be applied. At this point, workers should be informed about the use of personal protective equipment in agriculture. Healthcare professionals working with communities the main source of income is agriculture have significant roles in educating and informing the people.

DECLARATION OF CONFLICT OF INTEREST

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Original Article

Psychosocial triggers associated with major depressive episodes in women applying to psychiatric outpatient clinic

Psikiyatri polikliniğine başvuran major depresyon tanılı kadın hastalardaki potansiyel tetikleyiciler olarak psikososyal stresörler

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ABSTRACT

Aim: Factors such as personality traits, self-esteem, interpersonal relations and cognitive skills are considered among the risk factors of psychiatric disorders particularly for mood disorders. Presence of a single risk factor is not enough for the disease to emerge. The present study aimed to evaluate the presence of psychosocial triggering factors prior to the episodes of major depressive disorder (MDD) in female patients.

Materials and Methods: This retrospective study included a total of 62 female patients, who visited the psychiatry policlinic and have been diagnosed with MDD alone according to SCID-I. After the diagnostic evaluation of the patients, detailed clinical interview was conducted to assess the presence of triggering factors for depressive episode. All of the participants described triggering factors for major depressive disorder.

Results: Regarding the psychosocial factors as the potential triggers, 26 patients mentioned about the problem of communication and compliance with the spouse (42%), 10 mentioned about the presence of illness in the first-degree relatives (16%) and 10 mentioned about the conflict with the mother-in-law or other relatives (16%). When we collect "communication/compliance problem with the spouse" + "conflict with the mother-in-law/other family members" + "breaking up with the beloved one" + "husband's cheating on her" stressor groups as a "relationship conflict" group, the mean of BDI and BAI scores of "relationship conflict" group were highest among the all groups.

Conclusions: In the light of these outcomes, it can be concluded that particularly psychosocial factors associated with interpersonal relations play significant role as the triggering factors for depressive episodes in female patients. Among these factors, the problem of communication and compliance with the spouse is particularly striking.

Keywords: depression, female, psychosocial trigger

ÖZ

Amaç: Kişilik özellikleri, öz-saygı, kişilerarası ilişkiler ve bilişsel beceriler gibi faktörler, özellikle duygudurum bozuklukları başta olmak üzere psikiyatrik bozuklukların risk faktörleri arasında sayılmaktadır. Hastalığın ortaya çıkması için tek bir risk faktörünün varlığı yeterli değildir. Genetik yapının olumsuz çevresel faktörlerle etkileşimi de önemlidir. Bu çalışmada, kadın hastalarda major depresyon epizodlarından önce psikososyal tetikleyici faktörlerin varlığını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Psikiyatri polikliniğine başvuran ve SCID-1 ile major depresyon tanısı konulan toplam 62 kadın hasta retrospektif şekilde dizayn edilmiş olan çalışmaya alındı. Hastaların tanısal değerlendirmesinden sonra, depresif atak için tetikleyici faktörlerin varlığını değerlendirmek amacıyla ayrıntılı klinik görüşme yapıldı.

Bulgular: Potansiyel tetikleyiciler olarak psikososyal faktörlerle ilgili olarak, hastaların 26'sı eşi ile ilgili iletişim ve uyum hakkında (%42), 10'u birinci derece akrabalarda hastalık varlığından (%16), 10'u da kayınvalidesi ve veya başka akrabalarıyla olan anlaşmazlıktan bahsetmiş olup 8'i taşınmadan (%13), 6'sı sevgiliden ayrılmadan (%10) ve 2'si de eş aldatmasından bahsetmiştir (%3). "Eş ile iletişim / uyum sorunu", "kayınvalidesiyle / diğer aile üyeleriyle anlaşmazlık", "sevgilisinden ayrılmak" ve "eşi tarafından aldatılmak" stresörleri "ilişki çatışması" grubunda toplandığında bu grubun depresyon ve anksiyete skorlarının ortalaması tüm gruplar arasında en yüksek oranda bulunmuştur.

Sonuç: Bu bulgular ışığında, özellikle kadınlarda depresyon atakları için tetikleyici faktörler olarak kişilerarası ilişkilerle ilişkili psikososyal faktörlerin önemli rol oynadığı sonucuna varılabilir. Bu faktörler arasında eş ile iletişim ve uyum sorunu özellikle dikkat çekicidir.

Anahtar kelimeler: depresyon, kadın, psikososyal tetikleyici

INTRODUCTION

The relationship between major depressive disorder (MDD) and previous unfavorable psychosocial life events has been unveiled by many researchers [1-3]. Although a single factor is not enough for the disease to emerge, the interaction between genetic structure and unfavorable environmental factors exceeding a certain threshold and its timing are important. Approximately 70% of first depression attacks and 40% of recurrent episodes are triggered by a severe stressful life event [4]. In the literature, female gender, age over 40 years, unemployment, being single or divorced, genetic susceptibility, depressive personal trait, low education, unfavorable life events such as immigration etc., lack of close relationship, physical illness and treatment, and psychiatric disorders causing loss of skill have been propounded as the main risk factors for major depression. The intensity of the effect of these risk factors changes due to the type of depression. For example, while biological susceptibility plays more important role in those with severe depression, the role of environmental factors gains importance in those with mild depression [5]. It has been argued that severe life events are the most important trigger factor for depression. The studies which were conducted with population-based sample size, state that stress is reported 2.5 times more by MDD patients than the controls and that 80% of the patients have experienced serious stressful life events before the emergence of MDD [2]. Quality of social relationships, which is one of the psychosocial factors, is a major risk factor for major depression [6]. The relationship between depression and migration, which is another important factor for our country in recent times, has also been demonstrated in a meta-analysis study [7]. It is reported that loss and separation are the leading life events that precede MDD [8]. Moreover, it is thought that loss and separation might be associated rather with MDD than the other psychopathologies. There are a lot of points that may affect patients' susceptibility to depression in the face of stress. There is evidence that the patients with a history of depression are more vulnerable to episodesof depression in response to stressful life events. The patients with a history of depression are more likely to become depressed following a nonsevere event [9]. In addition, for those with several past episodes of depression, chronic stress appears to play a key role in triggering recurrences of depression [10]. The present study aimed to determine the psychosocial stress factors that may be the potential triggers in female MDD patients visiting the policlinic of a training and research hospital. The hypothesis of our study was that psychosocial factors associated with interpersonal relations play significant role as the triggering factors for depressive episodes in female patients.

MATERIALS AND METHODS

A total of 62 female patients, who consecutively visited Bakırköy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Education and Research Hospital, psychiatry policlinic between January and March 2017, who have been diagnosed with MDD based on the DSM-IV criteria, who were older than 18-year-old, and who have visited the psychiatry policlinic and been diagnosed with major depression for the first time, were enrolled into the study. The study was designed retrospectively. However, the treatment records were obtained from a depression follow-up program, which also covered their treatment schedule. Since the study was designed retrospectively, scientific suitability approval was obtained from the education supervisor of the No.1 psychiatry outpatient clinic of Bakırköy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Education and Research Hospital, where the patients were collected for the study. The patients had no co-morbidity other than major depression according to SCID-I criteria. The female patients, who have been diagnosed with first episode of major depressive disorder, completed the Structured Clinical Interview for DSM IV Axis-I Disorders (SCID-I), which was customized for the study, as well as socio-demographic data form, Beck Depression Inventory and Beck Anxiety Inventory, Clinic Global Impression Scale and Global Assessment Scale.

Study Inclusion Criteria

Being older than 18 years, volunteer to participate in the study, not having mental retardation, not having comorbidity other than major depression according to SCID-I, and the major depression's not being psychotic.

Study Exclusion Criteria

The patient with mental retardation, psychiatric disorder due to general medical condition and alcohol or substance abuse again the patient whose language and education level not sufficient to perform psychiatric interview were not included in the study.

A specialist clinician interviewed the patients and applied the scales to make the diagnosis and to determine the psychosocial stress factors. Within the interviewing period, the patients were questioned about the factors that were probably associated with the emergence of the symptoms of MDD and, if any, detailed anamnesis was taken. Psychosocial factors were classified under general topics including familial relations, health status of the subject or the relatives, economic problems, and moving/immigrating.

Sociodemografic Data Form

A data form that includes questions about clinical features, basic symptoms of the disease, past and current conditions of the patients' illnesses, and treatments applied during the past and hospitalization.

Structured Clinical Interview for DSM IV Axis I Disorders (SCID-I)

SCID-I is a structured clinical interview developed to make the diagnosis of psychiatric disorders in accordance with DSM IV Diagnostic Classification [11]. It is established for the use of specialists experienced in the field of psychiatry. During the interview, the interviewer can benefit from the other sources of knowledge in addition to the patient's answers. The validity and reliability study for Turkish population was done by Çorapçıoğlu and the colleagues [12].

Clinical Global Impression Scale

It is a scale evaluating in general the severity of any disease or the improvement of disease symptoms. The clinician rates the severity or improvement of the disease between 0 (not ill) and 7 (very severe) depending on his/her own overall experience concerning the disease in question [13].

Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI)

BDI is a 21-item scale evaluating the signs and symptoms of depression and scored as the sum of the answers. Each item is rated between 0 and 3; higher scores indicate severer disease. Total score is the sum of the scores and interpreted as following: 0 - 10: no depression, 11 - 17: mild depression, 18 - 23: moderate depression, ≥24: severe depression [14, 15]. BAI is a 21-item self-report scale, which is defined as the generalized symptoms of anxiety the subject experienced in the last week. The highest score of BAI is 63 (0 - 7: minimal anxiety, 8 - 15: mild anxiety, 16 - 25: moderate anxiety, 26 - 63: severe anxiety) [16,17].

Global Assessment Scale

The patient's lowest level of social, occupational and mental functionality is determined based on the patient's status in the last week. It is rated from 1 (lowest) to 100 (highest) with 0 representing inadequate information [18].

Statistical Analysis

The data were analyzed using the Statistical Program for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA). Normality of continuous data was determined by Shapiro-Wilk normality test. For continuous data with

Table 1. Sociodemographic characteristics of the patients diagnosed with major depression

	N=62	*%*
Marital Status		
Married	48	77.4
Single	12	19.4
Divorced	2	3.2
Child		
Yes	50	80.6
No	12	19.4
Living with		
Elementary family	52	83.9
Mother-in-law	10	16.1
Marriage		
Flirting	32	52.0
Arranged	30	48.0
Desire for marriage		
Voluntary	44	72.0
Involuntary	18	28.0
Domestic violence		
Yes	12	20.0
No	50	80.0

Table 2. Clinical features and scale scores of the patients diagnosed with major depression

	Mean	**Standard deviation**
Age, year	29.0	7.9
Duration of education (year)	8.1	3.2
Duration of marriage (year)	10.8	6.7
Clinical Global Impression (CGI)	4.3	0.7
Global Assessment Scale (GAS)	55	7.1
Beck Depression Inventory (BDI)	31.7	8.8
Beck Anxiety Inventory (BAI)	38.5	13.6

normal distribution, one-way analysis of variance (ANOVA) was used to compare means of more than two groups. Tukey's HSD test was applied as post-hoc, when one-way ANOVA test showed a significant difference between the groups. A p value of <0.05 was considered statistically significant.

RESULTS

The study population consisted of 48 married, 12 single and 2 divorced females, of whom 50 had children and 12 had none; 10 have been living with the mother-in-law, whereas the others have been living as elementary (nuclear) family; 32 married after flirting and 30 had their marriage arranged; 44 married voluntarily, whereas the others married involuntarily. Domestic violence was in question in 12 patients (**Table 1**).

In the married group, 10 have been living with the husband's family. The mean patient age was 29 ± 7.9 years, the mean duration of education was 8.1 ± 3.2 years, and the mean duration of marriage was 10.8 ± 6.7 years. The patients' mean BDI score was 31.7 ± 8.8 and the mean BAI score was 38.5 ± 13.6. The mean scores of clinical Global Impression Scale and Global assessment Scale were 4.3 ± 0.7 and 55 ± 7.1, respectively (**Table 2**).

Table 3. Psychosocial stressors as the potential trigger of major depression

	N	*%*
Communication/compliance problem with the spouse	26	42
Conflict with the mother-in-law/other family members	10	16
Health problem/illness of the relatives	10	16
Moving	8	13
Breaking up with the beloved one	6	10
Husband's cheating on her	2	3

All of the patients mentioned about triggering factors for depressive disorder. Of these patients, 26 pointed out the problem of communication and compliance with the husband (42%); 10 pointed out the presence of illness in the first-degree relatives (16%); 10 pointed out conflicts with mother-in-law or other family members (16%); 8 pointed out moving (13%); 6 pointed out break up with the beloved one (10%) and 2 pointed out their husbands' cheating on them (3%) as the potential psychosocial triggering factor (**Table 3**).

When we collect "communication/compliance problem with the spouse" + "conflict with the mother-in-law/other family members" + "breaking up with the beloved one" + "husband's cheating on her" stressor groups as a "relationship conflict" group, the mean age of the groups were 28 ± 7.60 years for "relationship conflict" group; 40 ± 10.80 years for "health problem" group and 22 ± 6.05 years for "moving/immigrating" group ($p<0.01$). Post-hoc pairwise comparisons revealed that age of "health problem of the relatives" group was significantly higher than age of "relationship conflict" group ($p<0.01$) and migration group ($p<0.01$). However, mean age of "relationship conflict" group was not significantly different than that of "moving/immigrating" group ($p=0.135$).

Duration of education were reported as 8.775 ± 3.44 years in "relationship conflict" group, 7.5 ± 2.99 years in "health problem of the relatives" group and 6 ± 2.36 years in "moving/immigrating" group. It was concluded that there is no significant difference in duration of education among groups ($p=0.07$).

Duration of marriage were 9.5 ± 5.81 years in "relationship conflict" group, 22.3 ± 13.87 years in "health problem of the relatives" group and 4.5 ± 2.76 years in migration group ($p<0.01$). Duration of marriage of "health problem of the relatives" group was significantly higher than age of "relationship conflict" group ($p<0.01$) and

Table 4. Comparison of clinical features and scale scores of the patients according to psychosocial stressors

	Relational Conflicts (n:44) Mean ± SD	Health Problems (n:10) Mean ± SD	Migration (n:8) Mean ± SD	p
CGI	4.775 ± 0.81	3.5 ± 0.55	3.2 ± 0.50	**<0.01**
GAS	56 ± 7.15	61 ± 7.92	45 ± 5.81	**<0.01**
BDI	34.05 ± 9.35	26 ± 7.32	28 ± 7.75	0.019
BAI	39.02 ± 13.81	36.4 ± 12.60	38.5 ± 13.58	0.86
Age	28 ± 7.60	40 ± 10.80	22 ± 6.05	**<0.01**
Education	8.775 ± 3.44	7.5 ± 2.99	6 ± 2.36	0.07
Marriage	9.5 ± 5.81	22.3 ± 13.87	4.5 ± 2.76	**<0.01**

One-way analysis of variance (ANOVA) was used to compare means of more than two groups.

***Relational Conflicts**: Communication/compliance problem with the spouse + Conflict with the mother-in-law/other family members + Breaking up with the beloved one + Husband's cheating on her*

"moving/immigrating" group (p<0.01). Duration of marriage of "relationship conflict" group was not significantly different than that of "moving/immigrating" group (p=0.193).

The mean of the CGI scores were 4.775 ± 0.81 in "relationship conflict" group, 3.5 ± 0.55 in "health problem of the relatives" group and 3.2 ± 0.50 in "moving/immigrating" group. CGI scores were significantly different among groups (p<0.01). Post-hoc pairwise comparisons revealed that CGI scores of "relationship conflict" group was significantly higher than those of "health problem of the relatives" (p<0.01) and "moving/immigrating" groups (p<0.01). However, CGI scores of "health problem" group was not significantly different than that of "moving/immigrating" group (p=0.673).

The mean of the GAS scores were reported as 56 ± 7.15 in "relationship conflict" group, 61 ± 7.92 in "health problem of the relatives" group and 45 ± 5.81 in "moving/immigrating" group. GAS scores were also significantly different among groups (p<0.01). GAS scores of "health problem" group was significantly higher than those of "relationship conflict" group (p<0.01) and "moving/immigration" groups (p<0.01). GAS scores of "relationship conflict" group was not significantly different than that of "moving/immigration" group (p=0.121).

The mean of the BDI scores were reported as 34.05 ± 9.35 in "relationship conflict" group, 26 ± 7.32 in "health problem of the relatives" group and 28 ± 7.75 in "moving/immigration" group. Depression levels were significantly different among groups (p<0.019). Post-hoc pairwise comparisons revealed that depression levels of "relationship conflict" group was significantly higher compared to "health problem of the relatives" group (p<0.032). Depression levels of "moving/immigration" group was not significantly different than those of "relational conflict" group (p=0.188) and "health problem of the relatives" group (p<0.884).

The mean of the BAI scores were 39.02 ± 13.81 in "relationship conflict" group, 36.4 ± 12.60 in "health problem of the relatives" group and 38.5 ± 13.58 in "moving/immigration" group. Anxiety levels were not significantly different among groups (p=0.86).

DISCUSSION

Before we started the study, we had hypothesized that among the possible potential risk factors the conflicts with close relatives are the most common concurrency with depression. Also, we had hypothesized that married females with children may have much more risk for depression about marriage problems. The present study actually identified that conflict with the spouse and his family (mother-in-law in particular) is the most possible potential psychosocial stress factor triggering the MDD. In addition, many patients stated that the husband's family makes contribution to this conflict with the spouse. In our study it was also found that depression levels of "relationship conflict" group was significantly higher compared to "health problem of the relatives" group (p<0.032). The mean of BDI and BAI scores of "relationship conflict" group were highest among the all groups. In addition, "relationship conflict" group presents more negative results in CGI scores, when we evaluate these together it appears compatible with previous studies that shows the effects of relational problems on depression [6]. The literature as well reveal that, overall health status of the females in conflicting families is unfavorably influenced, whereas the mental health of females is better in the families with close relationship where the emotions are clearly expressed [19]. In a study from Australia comprising 3820 subjects, depression and anxiety symptoms were found to be more common in the females with poor quality of relationship as compared to the females with good quality of relationship and to the single females [20]. Again, studies reported that subjects with high sociotropic values (need and dependency of an individual for having positive relations with other people) are more sensitive to

interpersonal relations than the autonomous subjects and that, conflicts in these areas would more strongly trigger the depression in sociotropic subjects [21]. The present study population is highly sociotropic (10 out of 48 married females have been living with the husband's family and many others have been residing closer) as compared to the western populations. This may explain why interpersonal conflict with the spouse and close relatives (mother-in-law) is the leading triggering factor for major depressive disorder in the present study while mourning and separation are the leading triggering factors in the western populations.

Of the study population, 48 were married, 12 were single and 2 were divorced. Again, 50 patients had children while 12 had none. Statistics confirm that mental diseases are less common in married subjects, which switch to relatively more routine and stable life, than the single subjects. The subjects do not only obtain sexual satisfaction and comfort in marriage but also gain numerous safety measures. Marriage largely impresses ability of interpersonal compliance and sense of responsibility upon the subject. The lack or deficiency of these necessities predisposes many mental problems particularly in females [22]. The literature comprises also the contradictory studies similar to the present study. These studies report that marriage has more negative impacts on women [5]. In the present study, the study population's consisting largely of married women (77.4%) exposes the importance of intra-marital conflicts in reactive depression. The probability of women with children, who are accounted for the majority of the study population (80.6%), not having enough support for child care due to the conflict with the husband can be addressed as the reason for high mean BAI scores and accordingly high BDI scores of the study population.

Again, it is seen that females diagnosed with major depressive disorder are composed largely of middle-aged females graduated from primary school. Depression can be seen at any age, but is more common in the middle ages particularly between 25 and 44 years [5], which is consistent with our findings suggesting that depression is more prevalent at middle ages. Literature review propounds that the risk of depression is higher in the subjects with the following characteristics: low education level and low income, unemployment, loss of the beloved one, financial difficulty, and low social level [23]. Again, a study conducted to determine whether high education level is a protective factor against depression and anxiety found significant relationship between low education level and anxiety and depression [24].

Opinions concerning that chronic stress and acute stress trigger MDD are controversial [3]. The majority of the researchers think that presence of chronic stress increases the risk of MDD triggered by acute stress (sensitivity), whereas limited number of researchers state just the opposite that chronic stress reduces (strengthen) the acute stress's triggering effect on MDD [25,26]. Some researchers, however, report that the effects of acute stress and chronic stress are not associated with each other and that they need to be evaluated separately. In the present study, we did not evaluate acute stress and chronic stress separately, but tried to identify the psychosocial factors that the patients considered associated with MDD. We observed that such a distinction is difficult to make and that chronic and acute factors determine each other and are engaged. For example, many patients that experience conflict with husband or mother-in-law for a long time present to the clinic with enhanced symptoms following an acute problem with these subjects. In fact, there is no consistency even between the efforts made to define chronic stress; i.e. "chronic" stands sometimes for the effects lasting for one month [27] but sometimes for the effects lasting for 12 months [25]. Accordingly, an acute stress for an author might be chronic for another. The present study does not allow us to evaluate whether chronic stress empowers or desensitizes the effect of acute stress.

Evaluation of psychosocial stress is significantly influenced by the person's subjective thoughts and explanation. For this reason, a factor identified as psychosocial stress, e.g. loss of a close relative, does not explain subjective processes. This poses methodological limitation and has the risk of overgeneralization. The fact that the same topic of psychosocial life has different mental outcomes on different people should be kept in mind during evaluation and treatment. Since the patients has been diagnosed with major depression for the first time and had no co-morbidity other than major depression according to SCID-I criteria, the sample size's being small. Again consisting only of female gender, absence of a control group, and the facts that chronic stress and acute stress have not been defined or evaluated separately, a measurement tool that would determine the intensity of the effect of psychosocial stress, assess the endogenous and subjective processes other than psychosocial risk factors and expose personality traits has not been used are the significant limitations of the present study.

Although the presence of psychosocial factors that are highly stressor has been determined before MDD both in the present study and in the earlier studies, it should be kept in

mind that there are many people not having depression despite the stressors they experience, which confirms that depression is associated not only with psychosocial factors but also the complex interaction between personal trait and many biological and genetic factors. Therefore, psychological, social and biological therapies need to be considered together in the treatment.

DECLARATION OF CONFLICT OF INTEREST

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Orijinal Makale

Algoloji kliniğine başvuran hastaların tanı ve tedavilerinin değerlendirilmesi

The evaluation of diagnosis and treatment of the patients who referred to the pain clinic

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ÖZ

Amaç: Bu çalışmadaki amacımız, hastanemiz ağrı polikliniğine 45 aylık sürede ağrı şikayeti ile başvuran hastaların demografik özellikleri, ağrı tipleri ve tedavilerini geriye dönük olarak değerlendirmektir.

Gereç ve Yöntemler: Çalışmamızda Temmuz 2015-Mart 2019 tarihleri arasında Sağlık Bilimleri Üniversitesi Samsun Eğitim ve Araştırma Hastanesi ağrı polikliniğine kronik ağrı şikayeti ile başvuran hastaların dosyaları incelendi. Hastaların demografik özellikleri, ağrı tipleri ve uygulanan tedaviler geriye dönük, kesitsel çalışma olarak değerlendirildi.

Bulgular: 45 aylık sürede polikliniğimize 25288 kronik ağrılı hastanın başvurduğu görüldü. Hastaların 16046'sı kadın (%63,5), 9242'si erkek (%36,5) olarak tespit edildi. En sık kanser dışı ağrı nedenleri (KDA); bel ağrısı, miyofasial ağrı ve nöropatik ağrı idi. Kanser ağrısı (KA) nedeni ile başvuran hasta sayısı 674 (%2,7) idi. Hastaların tamamına medikal tedavi ve 3635 (%14,4) hastaya ek olarak girişimsel ağrı tedavisi uygulandığı tespit edildi. En sık yapılan girişimsel ağrı tedavi yöntemleri; tetik nokta enjeksiyonu, eklem içi enjeksiyon uygulaması, transforaminal epidural enjeksiyon ve faset median sinir bloğu uygulaması olarak saptandı.

Sonuçlar: 45 aylık sürede algoloji kliniğimize yoğun bir hasta başvurusu olduğu ve hastaların %14,4'lük kısmına girişimsel ağrı tedavisi uygulandığı görülmüştür. Merkezimizin bu sonuçlarının kronik ağrı çalışmaları için önemli bir veri kaynağı olacağını düşünmekteyiz.

Anahtar kelimeler: ağrı, ağrı polikliniği, girişimsel ağrı tedavileri

ABSTRACT

Aim: The aim in this study is to evaluate retrospectively the patients who referred to the pain clinic in our hospital with pain in 45 months period with regards to pain types, demographic characteristics and treatment methods.

Material and Methods: In our study, we investigated the records of patients with chronic pain in Saglik Bilimleri University Samsun Training and Research Hospital pain clinic between July 2015-March 2019 in a cross-sectional study. Pain types, demographic characteristics and treatment methods were evaluated retrospectively.

Results: During 45 months period, it was showed that 25288 patients with chronic pain referred to the pain clinic. 16046 (63.5%) patients were female and 9242 (36.5%) patients were male. The most common causes of non-cancer pain were back pain, myofascial pain and neuropathic pain. The number of patients with cancer pain were 674 (2.7%). We observed that all of the patients had medical treatment and 3635 (14.4%) patients had both medical and interventional pain treatment. The most common interventional pain treatments methods were trigger point injection, joint injection, transforaminal epidural injection and facet median nerve block.

Conclusion: We have shown that it has been referred numerous patients in our clinic at 45 months period and interventional pain treatment has been administered to 14.4% of these patients. For this reason, we believed that these results will be an important data source for chronic pain studies.

Keywords: pain, pain clinic, interventional pain treatment

GİRİŞ

İnsanlık tarihi kadar eski olan ağrı kavramının günümüzdeki en geçerli tanımını Uluslararası Ağrı Araştırmaları Derneği (International Association for the Study of Pain= IASP) yapmıştır. IASP'nin tanımına göre ağrı; var olan veya olası doku hasarına eşlik eden veya bu hasar ile tanımlanabilen, hoşa gitmeyen duysal ve emosyonel deneyim olarak tanımlanmıştır [1]. Minimum 3 aydır devam eden ağrılar kronik ağrı olarak kabul edilmektedir [2]. Ağrı, objektif, subjektif, duyusal ve psikojenik komponentler içermektedir ve bu nedenle ağrıya verilen yanıt kişiden kişiye değişmekte, hatta aynı kişide bile farklı olabilmektedir [3].

Ağrının tedavisi için gerek medikal gerekse invaziv girişimler yapılmaktadır ve ağrı tedavisine çok fazla para harcanmaktadır [4]. Ağrı nedeniyle bireylerin günlük aktiviteleri kısıtlandığı gibi kronik ağrı çeken insanlarda psikososyal ve davranışsal bozukluklar gelişmekte ve bu insanlar hayata küsebilmektedir. Bu açılardan bakıldığında toplumsal bir sorun olan ağrı, sosyal ve ekonomik bir sorun olarak da kabul edilmelidir [5,6].

Bu çalışmada amacımız Temmuz 2015- Mart 2019 tarihleri arasında hastanemiz algoloji polikliniğine ağrı nedeni ile başvuran olgular incelenerek verdiğimiz hizmetlerin saptanması, uygulanan tedavilerin belirlenmesi, ayrıca ağrı polikliniğimize başvuran hasta popülasyonunun demografik özelliklerinin ve ağrı durumlarının, dünyada ve ülkemizde yapılmış diğer ağrı çalışmaları ile benzerliklerini ve farklılıklarını ortaya koymaktır.

GEREÇ VE YÖNTEMLER

Bu çalışma kesitsel çalışma olarak düzenlendi ve algoloji polikliniğine Temmuz 2015-Mart 2019 tarihleri arasında ağrı nedeni ile başvuran toplam 25288 hastanın dosyası geriye dönük olarak incelendi. Etik kurul izni (26.03.2019, TUEK 31-2019BADK/7-57) alındıktan sonra, algoloji kliniğine başvuran hastaların demografik özellikleri, ağrı tipleri ve tedavileri yöntemleri belirlendi. Elde edilen veriler kayıt altına alındı. Ağrı nedenleri temelde kanser ağrısı (KA) ve kanser dışı ağrı (KDA) olarak ayrıldı. KA ile başvuran hastaların kayıtları sağlıklı olmadığı ve eksiklikler olduğu için kanser tanılı hastaların kanser türleri değerlendirilemedi. Algoloji kliniğine başvuran tüm hastalar çalışmaya dahil edildi.

Çalışmaya alınan verilerin istatistiksel analizi "Statistical Package for Social Scienies (SPSS) for Windows 16.0" paket programı kullanılarak yapıldı. Veriler, sayı ve yüzde olarak ifade edildi. Grupların karşılaştırılmasında ki-kare testi kullanıldı. $P<0.05$ olan değerler anlamlı kabul edildi.

BULGULAR

Çalışmamızda değerlendirmeye alınan algoloji polikliniğine başvuran 25288 hastanın 205'i 18 yaş ve altı, 16827'si 19-64 yaş arası, 8256'sı 65 yaş ve üstü bulundu (**Tablo 1**). Hastaların 16046'sı (%63,5) kadın, 9242'si (%36,5) erkekti.

Tablo 1. Hastaların yaş gruplarına göre dağılımı

Yaş Grupları	Sayı	Yüzde (%)
18 yaş ve altı	205	0.8
19-64 yaş arası	16827	66,5
65 yaş ve üstü	8256	32,6

Tablo 2. Kanser olmayan hastaların dağılımları

Ağrı türü	Sayı (%)	Farmakolojik tedavi sayı (%)	İnvaziv+farmakolojik tedavi sayı (%)
Bel ağrısı	7383 (30)	6129 (83,0)	1254 (17)
Myofasial ağrı	3789 (15,4)	3279 (86,5)	510 (13,5)
Nöropatik ağrı	4122 (16,7)	3767 (91,4)	355 (8,6)
Boyun ağrısı	2223 (9,0)	1790 (80,5)	433 (19,5)
Baş ağrısı	786 (3,2)	532 (67,7)	254 (32,3)
Eklem ağrısı	2675 (10,9)	1991 (74,4)	684 (25,6)
Vasküler ağrı	654 (2,7)	606 (92,7)	48 (7,3)
Fibromyalji	2271 (9,2)	2271(100)	0
Diğer	711 (2,9)	661(93,0)	50(7,0)
TOPLAM	24614	21026 (85,4)	3588(14,6)

Kanser ağrısı (KA) nedeni ile başvuran hasta sayısı 674 (%2,7) idi. Kanser dışı ağrı (KDA) nedenleri arasında en sık bel ağrısı (%30), ikinci sıklıkla nöropatik ağrı (%16,7) ve üçüncü sıklıkla miyofasial ağrı (%15,4) tespit edildi. Tüm (kanser ve kanser olmayan) hastalara uygulanan tedaviler değerlendirildiğinde; 21653 hastaya (%85,6) farmakolojik, 3635 hastaya (%14,4) ise farmakolojik ve invaziv tedavi uygulandığı görüldü. Kanser dışı ağrılarda ise 21026 (%85,4) hastaya farmakolojik ve 3588 (%14,6) hastaya ise farmakolojik tedavi yanında invaziv tedavi uygulandığı belirlendi (**Tablo 2**). Eklem içi enjeksiyonların en çok diz eklemi (%61,4) ve omuz eklemine (%30,9) yapıldığı belirlendi.

Algoloji polikliniğine başvuruda bulunan hastalara yapılan invaziv girişimler değerlendirildiğinde en sık olarak tetik nokta enjeksiyonu, ikinci sıklıkta ise eklem içi enjeksiyonu uygulandığı gözlendi. Girişimsel ağrı tedavileri dağılımı **Tablo 3**'te verilmiştir.

Tablo 3. Girişimsel ağrı tedavileri dağılımı

Eklem içi enjeksiyon	815 (%22,4)
Tetik nokta enjeksiyonu	832 (%22,8)
Faset median sinir bloğu	453 (%12,5)
Gasser ganglion RFT	2 (%0,05)
Greater ve lesser oksipital sinir bloğu	127 (%3,5)
Periferik sinir bloğu	61 (%1,7)
Sfenopalatin bloğu	24 (%0,7)
Sfenopalatin RFT	6 (%0,2)
Splanknik blok	10 (%0,3)
Stellat ganglion bloğu	10 (%0,3)
Transforaminal epidural enjeksiyon	578 (%15,9)
İnterlaminer epidural enjeksiyon	85 (%2,3)
Nörolitik hipogastrik blok	2 (%0,05)
Nörolitik impar ganglion bloğu	22 (%0,6)
Nörolitik splanknik ganglion bloğu	11 (%0,3)
Faset sinir RFT	228 (%6,3)
Perkütan intradiskal RFT	10 (%0,3)
Dorsal root ganglion RFT	183 (%5,0)
Epiduroskopi	76 (2%,1)
Epidural port implantasyonu	1 (%0,03)
Epidural kateter uygulaması	35 (%1,0)
Spinal kord stimülasyonu	12 (%0,3)
Perkutan sempatik blok	52 (%1,4)
Toplam	3635

RFT: Radyofrekans termokoagülasyon

TARTIŞMA

Çalışmamızda hastaların cinsiyet dağılımında 25288 hastanın %63,5'i kadın %36,5'i ise erkek idi. Karaman ve ark.'nın [7] algoloji bölümüne başvuran hastaları değerlendirdikleri geriye dönük çalışmalarında kadın hastaların oranını %59,4, erkek hastaların oranını ise %40,6 olarak bulmuşlardır. Jonsdottir ve ark.'nın [2] kronik ağrının yaşam üzerine etkilerini inceledikleri çalışmada kronik ağrının her yaş grubu için kadınlarda daha fazla olduğu, yaşla beraber bu oranın da arttığını gözlemişlerdir. Yapılan çalışmalarda erkeklerin ağrı eşiğinin daha yüksek olduğu bildirilmiştir [2,8]. Yapılan bazı çalışmalarda ise doğumdan itibaren kadınların beyninde daha geniş anatomik ve fonksiyonel bağlantı olduğu için daha duyarlı olabilecekleri bildirilmiştir [9,10]. Bizim çalışmamızda da ağrı kliniğine başvuruda bulunan kadın hasta sayısı yüksekti. Bunun altında yatan nedenler arasında anatomik ve fonksiyonel farklılıkların yanı sıra kadınların ağrıyı daha kolay ifade edebilmeleri, ağrı eşiğinin düşük olması ve toplumsal özellikler olabileceğini düşünmekteyiz.

Bizim çalışmamızda en sık KDA nedeni bel ağrısı (%30), idi. İkinci sıklıkta nöropatik ağrı (%16,7) ve üçüncü sıklıkta miyofasial ağrı (%15,4) görüldü. Bu sonuç ülkemiz dışı çalışmalarla paralellik göstermese de ülkemizde yapılan çalışmalarla paralellik göstermektedir. Arıcı ve ark [11] iki yıllık ağrı polikliniği deneyimlerini paylaştığı çalışmada en sık ağrı yakınmaları, bel ağrısı (%31,2), miyofasyal ağrı (%26,9), nöropatik ağrı (%26,2) olarak bildirilmiştir. Ülkemizde yapılan diğer bir çalışmada ise en sık ağrı yakınmaları, miyofasyal ağrı (%22,6), nöropatik ağrı (%21,2), bel ağrısı (%15,7) ve baş ağrısı (%14,7) olarak bildirilmiştir [3]. Jackson ve ark.'nın [12] kronik ağrının epidemiyolojisi ile ilgili yaptıkları çalışmada sıklık sırasını baş ağrısı (%39), osteomusküler ağrı (%26) ve eklem ağrısı (%14) olarak

bildirmişlerdir. Ağrının iklim, sosyal ve ekonomik özelliklerden etkilendiği kanaatindeyiz.

Ağrı görülme sıklığı çok fazla olan ve etkilediği insanların yaşam kalitesini ciddi oranda etkileyen klinik bir durumdur [13]. Bu yüzden etkin tedavi edilmelidir. İnsanların ortalama yaşam süreleri uzamakta ve yaşla beraber ağrı şikayeti ile yapılan hastane başvuruları da artmaktadır. Bu amaçla ülkemizde ve dünyada ağrı poliklinikleri açılmıştır. Ağrı poliklinikleri, ağrı çeken hastaları multidisipliner yaklaşımla tedavi eden merkezlerdir. Ülkemizde ağrı 1990 yılından itibaren bilim dalı olarak kabul edilmektedir.

Ağrı rahatsız edici ve hoşa gitmeyen duygu olarak tanımlanır [1]. Yapılan birçok çalışmada insanların en sık doktora gitme nedeni olarak tespit edilmiştir [14,15,16]. Literatürde yaptığımız taramada ağrının toplumdaki oranı noktasında net bilgilere ulaşamadık ancak ağrının topluma göre oranının belirlenmesinde toplumun kültürel yapısı, eğitim düzeyi, gelişmişlik düzeyi ve sosyal yapısının önemli olduğu bildirilmiştir [16,17].

Ayaktan tedavi kliniğimize kabul edilen hastalardaki en yaygın ağrı sebebinin bel ağrısı olduğunu ve 1254 bel ağrılı hastaya girişimsel ağrı tedavisi uygulandığını gözlemledik.

Voigt ve ark. [18] yaptıkları derlemede baş ağrısının toplumda çok sık görüldüğünü bildirmişlerdir. Tedavi seçeneklerinde ise hastanın özellikleri ve ek sorunlarının önemini belirterek davranış modelli tedavi yaklaşımının önemine dikkat çekmişlerdir. Polikliniğimizde bel ağrısı ile gelen hastaların %17'sine, nöropatik ağrı ile gelen hastaların %8,6'sına, miyofasyal ağrı ile gelen hastaların %13,5'ine eklem ağrısı ile gelen hastaların %25,6'sına, boyun ağrısı ile gelen hastaların %19,5'ine, baş ağrısı ile gelen hastaların %32,3'üne ve vasküler ağrı ile gelen hastaların %7,3'üne medikal tedavi yanında invaziv tedavi uygulandığı gözlendi.

Cummings ve ark. [19] yaptıkları çalışmada miyofasial ağrıda tedavi şeçeneklerini inceledikleri çalışmalarında egzersiz, eğitim ve tetik nokta tedavilerini önermişlerdir. İlaç olarak antienflamatuarların da kullanılabileceğini belirtmişlerdir. Lavelle [20] ise myofasial ağrıda lokalizasyonu iyi yapılmış olan tetik nokta tedavisinin çok etkili olduğunu bildirmiştir. Biz miyofasial ağrı nedeni ile başvuran hastaların çoğunda egzersiz ve antienflamatuar tedaviyi tercih ettiğimizi tespit ettik.

Van Boxem ve ark. [21] yaptıkları derlemede radyofrekans ablasyon ve pulse radyofrekansın nöropatik ağrı tedavisinde çok etkin olduğunu bildirmişlerdir. Moisset ve ark. [22] nöropatik ağrı üzerine yaptıkları çalışmalarında tedavi şeçeneklerinde farmakolojik tedavi şeçenekleri olarak asetaminofen, NSAİİ, opioid tedavileri kullanılabileceği gibi tedaviye ek olarak veya alternatif olarak sinir blokları ve nöromodülasyon tekniklerinin önemini belirtmişlerdir. Biz de dosya incelememizde kliniğimize nöropatik ağrı ile başvuran 4122 hastanın 355'ine farmakolojik tedavinin yanısıra invaziv tedavi uygulamış olduğumuzu tespit ettik. İnvaziv tedavi olarak radyofrekans ablasyon, pulse radyofrekans ve sinir bloklarının kullanıldığını dosya incelememizde belirledik.

Tagliaferri ve ark. [23] kronik bel ağrısında manuel terapi, egzersiz tedavisi ve akupunkturu incelemiş ve tedaviler arasında ciddi bir fark gözlememişlerdir. Ayrıca kronik bel ağrısı ile geniş bir derleme yapan Urits ve ark. [24] kronik bel ağrısının tedavisinde multidisipliner yaklaşımın önemi üzerinde durmuş ve egzersiz ve medikal tedavinin eş güdümlü uygulanmasının önemini vurgulamıştır.

Yaptığımız dosya incelemesinde baş ağrısı ile başvuran 786 hastanın 254 (%32,3)'ünde farmakolojik tedaviye ek olarak invaziv tedaviye ihtiyaç duyduğumuzu belirledik. Vasküler ağrı görülme sıklığı literatürde %3 olarak belirtilmiştir [3]. Bizim çalışmamızda da bu oran %2,7 olarak tespit edilmiştir. Tedavi olarak farmakolojik tedavi ön plana çıkmıştır (%92,7).

SONUÇ

Çalışmamızda 45 aylık sürede polikliniğimize yoğun bir hasta başvurusu olduğu görüldü. Hastaların 16046'sı kadın (%63,5), 9242'si erkek (%36,5) olarak tespit edildi. En sık kanser dışı ağrı nedenleri (KDA); bel ağrısı, miyofasial ağrı ve nöropatik ağrı idi. Kanser ağrısı (KA) nedeni ile başvuran hasta sayısı 674 (%2,7) idi. Hastaların tamamına medikal tedavi ve 3635 (%14,4) hastaya ek olarak girişimsel ağrı tedavisi uygulandığı tespit edildi. En sık yapılan girişimsel ağrı tedavi yöntemleri; tetik nokta enjeksiyonu, eklem içi enjeksiyon uygulaması, transforaminal epidural enjeksiyon ve faset median sinir bloğu uygulaması olarak saptandı. Çalışmamızın limitasyonu kanser ağrısı olan hastalardaki kanser türlerinin belirlenmemiş olması ve başvuru yapan hastaların ağrı sürelerinin belirlenmemesidir. Ayrıca çalışmamızın prospektif olmaması, kesitsel olması, çok merkezli olmaması ve yaş dağılımlarının farklı olması diğer limitasyonlardır.

Sonuç olarak, hizmet kalitemizin saptanması, uyguladığımız tedavilerin tartışmaya açılması için kliniğimize başvuran hastaların klinik özellikleri ile ağrı çeşitliliklerinin ve tedavi yöntemlerinin değerlendirilmesi multidisipliner yaklaşım açısından aydınlatıcı olacaktır. Ağrı tedavisinde multidisipliner yaklaşımların ön plana çıkması ile tedavide daha iyi sonuçlar elde edileceği kanaatindeyiz. Merkezimizin

bu sonuçlarının kronik ağrı çalışmaları için önemli bir veri kaynağı olacağını düşünmekteyiz.

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Original Article

Etiological evaluation in 766 patients with pancytopenia; a single center experience

Pansitopenisi olan 766 hastada etyolojik değerlendirme; tek merkez deneyimi

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ABSTRACT

Aim: Pancytopenia is a clinical problem which has a wide differential diagnostic spectrum and may occur with various mechanisms. In this study we aimed to determine the most common etiologic causes in patients with pancytopenia.

Materials and Methods: The records of patients aged 18 years and older, who applied to the Health Sciences University Bakirkoy Dr. Sadi Konuk Training and Research Hospital between 2012 and 2017 and who were diagnosed with pancytopenia according to World Health Organization (WHO) criteria were retrospectively reviewed. Statistical Method: Mann-Whitney-U test was used for 2 groups and Kruskal-Wallis test was applied for 3 and more groups. Since no normal distribution was provided as a descriptive statistic, median and change interval values were given for continuous data.

Results: A total of 766 patients, 475 (62%) women and 291(38%) men, were included in the study. In these patients, non-hematologic causes were found in 77.7% and hematologic causes in 22.3% of patients with pancytopenia. Hematological etiologies were 72.2% benign and 27.8% malignant. Non-hematological causes were divided into groups as renal diseases (6.05%), rheumatological diseases (2.3%), infective diseases (10.7%), endocrinological diseases (3.8%), hypersplenism (14.4%), immunosuppressive drug use (17.4%), solid organ cancers (10.7%) and unidentified reasons (34.2%).

Conclusion: Pancytopenia should be evaluated carefully and the etiology should be detected quickly and corrected by appropriate treatment. It is an appropriate approach to exclude, firs the non-hematological causes (especially immunosuppressive drug use, hypersplenism, infection and solid organ cancers) and the benign causes of hematological reasons.

Keywords: pancytopenia, anemia, leukopenia, thrombocytopenia, malignancy

ÖZ

Amaç: Pansitopeni, çeşitli mekanizmalarla ortaya çıkabilen ve geniş bir ayırıcı tanı spektrumuna sahip klinik bir problemdir. Bu çalışmada pansitopenili hastalarda en sık görülen etiyolojik nedenleri belirlemeyi amaçladık.

Gereç ve Yöntem: Sağlık Bilimleri Üniversitesi Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi'ne 2012-2017 yılları arasında başvuran ve Dünya Sağlık Örgütü kriterlerine göre pansitopeni tanısı alan 18 yaş ve üstü hastaların kayıtları retrospektif olarak incelendi.

İstatistiksel Yöntem: İkili gruplara Mann-Whitney-U testi, 3 ve daha fazla grubun olduğu karşılaştırmalarda ise Kruskal-Wallis testi uygulandı. Tanımlayıcı bir istatistik olarak normal dağılım sağlanmadığından, sürekli veriler için ortanca ve değişim aralığı değerleri verildi. Bulgular: Çalışmaya 475 (%62) kadın ve 291 (%38) erkek olmak üzere toplam 766 hasta dahil edildi. Bu hastaların %77,7'sinde hematolojik olmayan nedenler, %22,3'ünde ise hematolojik nedenlerin pansitopeni etiyolojisinde rol oynadığı görüldü. Hematolojik etiyolojilerin %72,2'si benign, %27,8'i ise malign hastalıklardan oluşmaktaydı. Hematolojik olmayan nedenlerin ise; renal (%6,05), romatolojik hastalıklar (%2,3), enfektif hastalıklar (%10,7), endokrinolojik hastalıklar (%3,8), hipersplenizm (%14,4), immünsupresif ilaç kullanımı (%17,4), solid organ kanserleri (%10,7) ve tanımlanamayan nedenler (%34,2)'den oluştuğu görüldü.

Sonuç: Pansitopeni dikkatlice değerlendirilerek etiyolojisi hızlı bir şekilde tespit edilmeli ve uygun tedavi ile düzeltilmelidir. Öncelikle hematolojik olmayan nedenlerin (özellikle immünsupresif ilaç kullanımı, hipersplenizm, enfeksiyon ve solid organ kanserleri) ve hematolojik nedenlerden de benign hastalıkların dışlanması uygun bir yaklaşımdır.

Anahtar kelimeler: pansitopeni, anemi, lökopeni, trombositopeni, malignite

INTRODUCTION

The definition of pancytopenia adopted by WHO includes the combination of all here parameters: Hemoglobin (Hb) for non-pregnant women<12 g/dl and<13 g/dl for men, absolute neutrophile count<1800 /microl, platelet count<150000 /mm3 [1]. In healthy adults, hematopoiesis occurs in the bone marrow where mature blood cells migrate to other regions with the circulatory system. The balance between blood cell production, distribution in other organs, and ongoing cellular destruction determines the levels of circulating blood cells [2-5]. Pancytopenia may occur with various mechanisms. The etiologic classification consists of bone marrow infiltration (hematological malignancies, metastatic cancers, myelofibrosis and infectious diseases, tuberculosis, fungal infections, etc.), bone marrow aplasia (vitamin B12 or folate deficiency, aplastic anemia, infectious diseases such as HIV infection, viral hepatitis, parvovirus B19 infection and drugs) and blood cell destruction or sequestration (disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, ineffective erythropoiesis, myelodysplastic syndrome, megaloblastic disorders, hypersplenism). Although pancytopenia is a common clinical problem with a wide differential spectrum, there is not enough information about the incidence of causes except for a few studies [6-8]. In our study, the aim was to determine the most common etiologies in patients with pancytopenia and to contribute to the shortening of the transition period for appropriate treatment by making a rapid diagnosis.

MATERIALS AND METHODS

The records of patients, who were applied to our internal medicine outpatient clinics between 2012 - 2017 and diagnosed with pancytopenia according to WHO criteria were retrospectively analyzed. Gender, age, Hb, hematocrit (Hct), white blood cell count (WBC), platelet count, mean corpuscular volume (MCV), lactate dehydrogenase (LDH), vitamin B12, folate, serum iron, ferritin, thyroid stimulating hormone (TSH), free thyroxine (fT4), drug (immunosuppressive) use, presence of hepatomegaly and/or splenomegaly were recorded. The patients were divided into 2 groups according to hematological and non-hematological etiologies, which primarily led to pancytopenia. Hematologic etiology group was further divided into two groups as benign and malignant causes. The non-hematologic etiological group was further divided into subgroups as; infectious diseases, rheumatologic diseases, endocrinological diseases, renal diseases, hypersplenism, immune suppressive drug use, solid organ cancers and others (undetectable).

STATISTICAL METHOD

Normality tests were performed for each variable and Kolmogorov-Smirnov and Shapiro-Wilk tests were

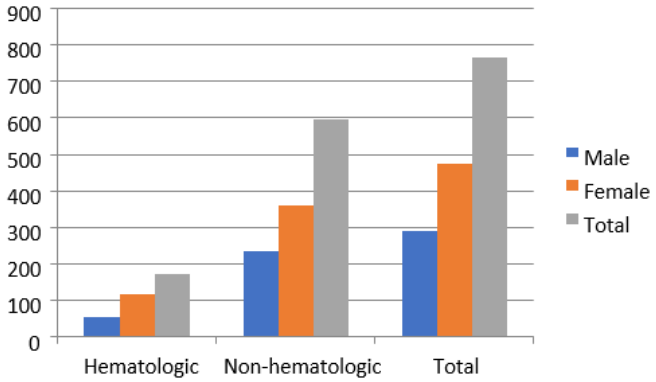

Figure 1. Gender distribution among groups

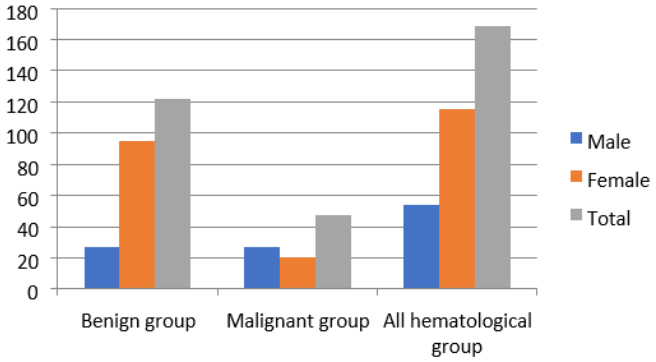

Figure 2. Gender distribution between hematological subgroups

performed. Since the variables were not normally distributed due to p <0.05, non-parametric methods were preferred in the analyzes. Mann-Whitney-U test was used for 2 groups and Kruskal-Wallis test was used for 3 and more groups. Since no normal distribution was provided as a descriptive statistic, median and change interval (max-min) values were given for continuous data. Frequency distribution tables for categorical data were interpreted. Data are presented as percentage and number. The analyzes were performed with SPSS 22.0 statistical analysis program and significance level was considered as p <0.05.

RESULTS

A total of 766 patients, 475 (62%) women and 291 (38%) men, were included. The mean age of men was 60.6 years, the mean age of women was 55.5 years, and the average age of all patients was 57.5 years. Non-hematological causes were found in 77.7% and hematological causes in 22.3% of patients with pancytopenia. Gender distribution among both groups is shown in **Figure 1**. Hematological etiologies were 72.2% benign and 27.8% malignant. Gender distribution in hematological subgroups is shown in **Figure 2**. Non-hematological causes were divided into groups as renal diseases (6.05%), rheumatological diseases (2.3%), infective diseases (10.7%), endocrinological diseases (3.8%), hypersplenism (14.4%), immunosuppressive drug use (17.4%), solid organ cancers (10.7%) and unidentified

Table 1. Non-hematological group gender–etiology distribution

Etiology	Male	Female	Total / %
Infectious causes	22	42	64 / 10.7
Rheumatological causes	0	14	14 / 2.3
Hypersplenism	33	53	86 / 14.4
Endocrinological causes	5	18	23 / 3.8
Immunosuppressive drug use	49	55	104 / 17.4
Renal causes	18	18	36 / 6.05
Solid organ cancers	38	26	64 / 10.7
Other reasons	71	133	204 / 34.2
Total	**236**	**359**	**595 / 100**

Table 2. Differences between hematological and non-hematological groups of variables, Mann-Whitney-U statistics

	Group	N	Average rank	Mann-Whitney-U statistics	p
Age	Hematologic	171	352.41	45556	**0.024***
	Non-hematologic	595	**392.44**		
Hb	Hematologic	171	373.93	49236	0.521
	Non-hematologic	595	386.25		
Hct	Hematologic	171	389.82	49791	0.671
	Non-hematologic	595	381.68		
WBC Count	Hematologic	171	372.79	49040	0.472
	Non-hematologic	595	386.58		
Platelet Count	Hematologic	171	384.25	50745	0.960
	Non-hematologic	595	383.29		
LDH	Hematologic	171	302.59	37036	**0.000***
	Non-hematologic	595	**406.75**		
MCV	Hematologic	171	369.50	48478	0.346
	Non-hematologic	595	387.52		
TSH	Hematologic	171	144.42	8183.5	0.319
	Non-hematologic	595	155.95		
fT4	Hematologic	171	124.73	5179.5	0.975
	Non-hematologic	595	125.07		
Serum iron	Hematologic	171	155.59	10917.5	**0.032***
	Non-hematologic	595	**176.03**		
Ferritin	Hematologic	171	137.38	9006.4	**0.000***
	Non-hematologic	595	**181.61**		
Folate	Hematologic	171	119.68	5863.5	0.853
	Non-hematologic	595	117.97		
Vitamin B12	Hematologic	171	140.60	9447.1	**0.000***
	Non-hematologic	595	**194.14**		

*p<0.05

Abbreviations: Hemoglobine, Hb; hematocrit, Hct; white blood cell, WBC; lactate dehydrogenase, LDH; mean corpuscular volume, MCV; thyroid stimulating hormone, TSH; free thyroxine, fT4.

reasons (34.2%). Gender and etiology distribution of non-hematological group is shown in **Table 1**. Differences between the hematological and non-hematological groups (**Table 2**) and benign and malignant groups from the hematological subgroups (**Table 3**) were shown in the tables below. Age (p=0.024), LDH (p=0.000), serum iron (p=0.032), ferritin (p=0.000) and vitamin B12 (p=0.000) levels were significantly higher in the non-hematological group. According to the comparison between hematological groups; Hb (p=0.000), Hct (p=0.000), WBC (p=0.000) and

Table 3. Differences between benign and malign hematological groups, Mann-Whitney-U test results

	Group	N	Average rank	Mann-Whitney-U statistics	p
Age	Benign	122	79.88	2242.5	**0.023***
	Malignant	47	**98.29**		
Hb	Benign	122	**93.73**	1802.0	**0.000***
	Malignant	47	62.34		
Hct	Benign	122	**93.43**	1839.0	**0.000***
	Malignant	47	63.13		
WBC Count	Benign	122	**93.23**	1862.5	**0.000***
	Malignant	47	63.63		
Platelet Count	Benign	122	**92.30**	1977.0	**0.002***
	Malignant	47	66.06		
LDH	Benign	122	81.65	2458.5	0.151
	Malignant	47	93.69		
MCV	Benign	122	81.36	2422.5	0.113
	Malignant	47	94.46		
TSH	Benign	122	39.47	1567.8	0.584
	Malignant	47	36.52		
fT4	Benign	122	24.29	1254.9	0.304
	Malignant	47	28.65		
Serum Iron	Benign	122	46.73	1796.3	**0.001***
	Malignant	47	**68.47**		
Ferritin	Benign	122	46.70	1952.2	**0.000***
	Malignant	47	**72.23**		
Folate	Benign	122	34.58	1162.1	0.378
	Malignant	47	39.38		
Vitamin B12	Benign	122	50.52	1836.3	**0.004***
	Malignant	47	**70.15**		

*p<0.05

Abbreviations: Hemoglobine, Hb; hematocrit, Hct; white blood cell, WBC; lactate dehydrogenase, LDH; mean corpuscular volume, MCV; thyroid stimulating hormone, TSH; free thyroxine, fT4.

Table 4. Evaluation of abdominal ultrasonography results

Abdominal Ultrasonography Report	Patients (n)
Hepatomegaly	55 (17.2%)
Splenomegaly	92 (28%)
Total	319 (100%)

platelet count (p=0.002) were significantly higher in benign hematological group. Serum iron (p=0.001), ferritin (p=0.000) and vitamin B12 (p=0.004) levels were significantly higher in the malignant hematological group. 55 (17.2%) out of 319 patients with abdominal ultrasonography had hepatomegaly and 92 (28.8%) had splenomegaly (**Table 4**).

DISCUSSION

Pancytopenia can be fatal if it cannot be diagnosed early [9]. Therefore, rapid detection of the underlying cause is extremely important in terms of coping with the disease and prognosis. It is important to investigate the most common pancytopenia etiologies and ones which may be less frequent but more serious, in the differential diagnosis.

In our study, we investigated whether we can predict the etiologies with hemogram and routine biochemistry results. As expected, in table 2, we observed significant differences between LDH, ferritin, serum iron and vitamin B12 among the hematological and non-hematological groups. In table 3, we obtained significantly lower Hb, Hct, WBC, platelet counts and higher serum iron, ferritin and vitamin B12 levels between malignant and bening hematological subgroups. These findings were indicative for our correct grouping.

In our study we found that the mean age of all patients was 57.5 and there was a female dominance with the percentage of 62**.** Gayathri BN et al. reported a mean age of 41 years and male gender as a dominant in a prospective study of 104 pancytopenia patients aged between 2 and 80 years in India. The difference in mean age was considered to be related only to the inclusion of the adult population in our study. Also, splenomegaly was more common than hepatomegaly in their study [10]. In our study abdominal ultrasound was performed less than half of the patients (319 patients) but consistently with this study splenomegaly was more common than hepatomegaly with the percentage of 28.8. M. Premkumar et al. found that the mean age was 32.8 and male gender was dominant in their study which evaluating the hematological etiology with 140 pancytopenia patients. As the etiological frequency; megaloblastic anemia (60.7%), infectious causes (16.4%), aplastic anemia (7.8%) and leukemia (9.2%) were detected [11]. Inconsistently with this study we found that the most common etiologic causes were non-hematological causes with the percentage of 77.7%. But similar to literature, we showed that benign causes (72.8%) were more frequently in the hematological etiology. In a study conducted by Imbert et al., with 213 adult pancytopenia patients in France, it was observed that malign hematological causes were more frequent and that was again not compatible with our study. According to this study, malignant myeloid disorders (acute myeloid leukemia, MDS and myelofibrosis) 42% and malignant lymphoid disorders 18% accounted for 60% of all hematological etiologies. The group containing the benign etiologies such as megaloblastic anemia was found to be 17% (8). It was thought that this difference could be related with adequate nutrition and socio-cultural level of the patient population. Hayat AS and at al. found that 72.94% of the patients were male and 27.05% were female in their study. In the etiological evaluation, they found that noncancerous causes were more frequent with a rate of 63.52% [12]. Yadav BS and at al. found the mean age of 35.15 ± 12.6 years and an equal female/male ratio in gender distribution, in their study with 58 pancytopenia patients

above the age of 18 [13]. In the study of Dubey TN and et al., which included 70 patients over 13 years of age, the male/female ratio was 1.4/1. In the etiological evaluation, megaloblastic anemia was in the first place with a rate of 41.4%. Aplastic anemia with the ratio of 22.9%, hypersplenism 15.7% and leukemic diseases 14.2% were also found in the etiology [14].

The shortcomings of our study were; it was retrospective and imaging and pathological examinations were not applied to all patients. We believe that the prospective studies with many more patients will shorten the algorithms applied to diagnose patients who apply with pancytopenia.

CONCLUSION

Pancytopenia should be evaluated carefully and the etiology should be detected quickly and corrected by appropriate treatment. In studies conducted, gender dominance is different for each study, so it is not true to say that pancytopenia is more common in male or female sex. According to our study, it is an appropriate approach to exclude, first the non hematological causes (especially immunosuppressive drug use, hypersplenism, infection and solid organ cancers, respectively) and the benign causes of hematological reasons. When family physicians encounter patient with pancytopenia, they should be calm and after diagnosis treat the benign causes. If there is no benign cause then they should refer the patients to advanced center immediately.

DECLARATION OF CONFLICT OF INTEREST

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Original Article

Comparison of subjective symptoms of autologous serum and dexpanthenol gels after pterygium surgery

Pterjium cerrahisi sonrası otolog serum ve dekspantenol jellerin subjektif semptomlarının karşılaştırılması

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ABSTRACT

Purpose: The aim of this study was to investigate the effect of autologous serum and dexpanthenol gel on subjective symptoms after pterygium surgery.

Methods: An evaluation was made of patients who underwent the same technique of pterygium surgery between June 2017 and December 2017. Patients were divided into 2 groups with autologous serum used postoperatively in Group 1 (n: 18) and 5% dexpanthenol gel in Group 2 (n: 12). Evaluation was made of both groups in respect of postoperative pain, stinging, irritation, redness and graft edema.

Results: There was no statistically significant difference between the groups in respect of pain, stinging and watering on the 1st, 3rd and 7th days. A statistically significant decrease in these complaints was observed on days 3 and 7 in the group using dexpanthenol. There was no statistically significant difference between the groups on days 1, 3 and 7in respect of redness and graft edema. In both groups, a statistically significant increase was determined in these findings on days 3 and 7.

Conclusion: After pterygium surgery, many agents increase the comfort of patients. Autologous serum is the most reliable and most investigated agent. Dexpanthenolmay be an alternative to anterior segment surgery in respect of patient comfort and wound healing.

Keywords: dexpanthenol, pterygium, autologous serum, verbal pain scale

ÖZ

Amaç: Bu çalışmanın amacı, pterjiyum cerrahisi sonrası otolog serum ve dekspantenol jelin subjektif semptomlar üzerindeki etkisini araştırmaktır.

Metod: Haziran 2017 ve Aralık 2017 tarihleri arasında aynı cerrah tarafından yapılan pterjiyum cerrahisi uygulanan hastaların değerlendirilmesi yapıldı. Hastalar 2 gruba ayrıldı. Grup 1'de (n: 18) ameliyat sonrası otolog serum kullananlar ve grup 2'de (n: 12) %5 dekspantenol jel kullanılar vardı. Her iki grupta da postoperatif ağrı, batma, tahriş, kızarıklık ve greft ödemi yönünden değerlendirme yapıldı.

Bulgular: Gruplar arasında 1., 3. ve 7. günlerde ağrı, batma ve tahriş açısından istatistiksel olarak anlamlı fark yoktu. Dekspantenol kullanan grupta 3 ve 7. günlerde 1. güne göre bu şikayetlerde istatistiksel olarak anlamlı bir azalma gözlendi. Gruplar arasında kızarıklık ve greft ödemi açısından 1., 3. ve 7. günlerde istatistiksel olarak anlamlı fark yoktu. Her iki grupta da, bu bulgularda 3. ve 7. günlerde 1. güne göre istatistiksel olarak anlamlı bir artış tespit edildi.

Sonuç: Pterjiyum cerrahisi sonrası birçok ajan hasta konforunu arttırmaktadır. Otolog serum en güvenilir ve en çok araştırılan ajandır. %5 Dexpanthenol jel, hastanın konforu ve yara iyileşmesi açısından ön segment cerrahisine alternatif olabilir.

Anahtar kelimeler: dexpanthenol, pterygium, otolog serum, sözel ağrı ölçeği

INTRODUCTION

Pterygium is a bulging fibrovascular tissue, usually observed in nasal bulb conjunctiva which protrudes from the interpalpebral space of the triangular shape onto the cornea. Pterygium may cause burning, stinging, redness, watering, itching and reduction in visual acuity. In the etiopathogenesis, there are hereditary factors, irritant chronic conjunctivitis, tear film changes, vitamin A deficiency, race, eye color, ultraviolet rays, chronic micro trauma of the eye, and infections. In addition, lifestyle and environment also have an effect (sandy, dusty, hot climate and exposure to the midday sun because of outdoor work) [1,2].

As the pterygium grows towards the center, surgery is often needed. Various forms of surgical treatment have been described and following almost all surgical treatments, patients may have various surgery-associated complaints (epithelial defect, sutures, etc.) during the healing process [3]. Various agents are used to reduce these complaints after surgery, the most widely used of which are artificial tears and autologous serum [4].

In recent years, several studies have shown that dexpanthenol, a panthenol-analogue, accelerates epithelial healing, as a precursor of co-enzymes that are a basic component of cellular metabolic processes [5]. The aim of the current study was to compare the effect of autologous serum and 5% dexpanthenol gel on postoperative patient comfort and the accelerating effect of the healing process.

MATERIALS AND METHODS

The study included 30 patients who were operated on by the same surgeon with a similar technique. None of the patients had any disease that would affect systemic and / or local wound healing. Approval for the study was granted by the Local Ethics Committee. In the study was adhered to the statement Helsinki. The surgical technique applied in all cases was pterygium resection with a crescent knife including the underlying Tenon's capsule, with insertion of autograft obtained from the upper bulbar conjunctiva, sutured by monofilament suture. The surgical suture was removed 7 days after surgery. The autologous serum was 50% tear diluted.

Patients were separated into two groups consecutively in this retrospective study. Written informed consents of the patients were obtained. Autologous serum was used in first operated cases (Group 1). Subsequently, % 5 Dexpanthenol gel (2 times a day) was used in second operated group (Group 2). Both groups were administered post-operative Loteprednol etobonate 0.5% (one drop 4 times a day), Polyvinyl alcohol single dose eye drops (one drop 4 times a day), and 0.3% tobramycin eye ointment (2 times a day). All patients attended follow-up examinations on days 1, 3 and 7 postoperatively.

Patients who underwent surgery were questioned in respect of pain, stinging, watering, redness and graft edema. They were asked to define the characteristics of the pain, differentiating between irritation and stinging and between constant and intermittent striking pain. These

questionnaires were completed by the patients' immediately after surgery and on postoperative days 1, 3 and 7. A Verbal Pain Scale (VPS) was used for pain; 0 (no pain VPS: 0), 1(mild pain VPS:1-3), 2 (moderate pain VPS:4-6), 3 (severe pain VPS:7-9) and 4 (unbearable pain VPS:10). The stinging sensation was graded as five categories; 0 (no stinging), 1 (slight stinging sensation), 2 (intermittent stinging sensation), 3 (severe stinging sensation), and 4 (unbearable stinging sensation so that the eyelids could not be opened). Complaints of irritation were rated as 0 (no irritation), 1 (intermittent irritation), 2 (more than 10 irritations per day), 3 (irritation to wiping with continuous wipes). Findings of redness and graft edema were classified as 0 (none), 1 (mild), and 2 (extreme).

Patients with pterygium and a history of corneal disease, eye trauma or previous intraocular surgery, contact lens wearers, evidence of current intraocular inflammation on slit lamp examination and eyes with recurrent pterygium were excluded from the study. The size of the pterygium was measured as 2.1-4mm from the limbus (horizontal length).

Statistical Analysis

All data were transferred to Excel and statistical analysis was performed using IBM SPSS for Windows version 22.0 software. Numerical variables were stated as mean ± standard deviation (SD) and qualitative variables as number (n) and percentage (%). When parametric test assumptions were met, the t-test was used in independent groups and the Mann Whitney U-test was used if there was no difference between the groups in terms of numerical variables. Evaluation of differences between the groups in terms of quality variables was examined using the Chi-square test. The Friedman test or the Cochran Q test was used to determine whether the severity of symptoms changed over time. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Group 1 comprised 4 (22.2%) male and 14 (77.8%) female patients with a mean age of 55.7± 10.4 years. Group 2 comprised 3 (25%) male and 9 (75%) female patients with a mean age of 49.3 ± 12.0 years (p=0.139, p=0.131). There was no statistically significant difference between the groups at days 1, 3, and 7 in respect of pain, stinging and irritation complaints (**Table 1**). In Group 2, a statistically significant decrease was determined in these complaints on days 3 and 7 (p=0.002, p0.001, p=0.002, respectively) (**Table 1**). There was no statistically significant difference between the groups on days 1, 3 and 7 in respect of redness (Group 1, p=0.006, Group 2, p=0.001) and graft edema (Group 1, p=0.001, Group 2, p= 0.001). In both groups, there was a statistically significant increase in these findings on days 3 and 7 **(Table 1**). No complication related to surgery and drugs developed in any patient.

Table 1. Distribution of Symptoms and Signs

Symptoms and Signs	Postoperative period	Group 1 (n=18)	Group 2 (n=12)	P Value between groups
Pain distribution	Day 1	0.89±0.90	1.17±0.72	0.249
	Day 3	0.89±0.58	0.67±0.49	0.415
	Day 7	0.50±0.71	0.67±0.49	0.368
	P value in-group	0.135	0.002*	n.a.
İrritation distribution	Day 1	0.89±0.58	1.33±0.49	0.095
	Day 3	0.89±0.32	0.67±0.49	0.184
	Day 7	0.89±0.32	0.67±0.49	0.184
	P value in-group	1.000	<0.001*	n.a.
Stinging distribution	Day 1	1.00±0.84	1.00±0.85	0.884
	Day 3	0.89±0.58	0.50±0.52	0.134
	Day 7	0.67±0.49	0.50±0.52	0.458
	P value in-group	0.449	0.002*	n.a.
Redness distribution	Day 1	0.28±0.46	0±0	0.066
	Day 3	0.78±0.43	0.67±0.49	0.678
	Day 7	0.67±0.49	0.83±0.39	0.419
	P value in-group	0.006*	<0.001*	n.a.
Graft Edema distribution	Day 1	0.06±0.24	0±0	1.000
	Day 3	0.89±0.58	1.00±0.00	0.632
	Day 7	0.83±0.62	1.00±0.00	0.465
	P value in-group	<0.001	<0.001	n.a.

***Pain distribution: 0** (VPS: 0), **1** (VPS:1-3), **2** (VPS:4-6), **3** (VPS:7-9), **4** (VPS:10), **Irritation distribution** : **0** (no irritation), **1** (intermittent irritation), **2** (more than 10 irritations per day), **3** (irritation to wiping with continuous wipes), **Stinging distribution** : **0** (no stinging), **1** (slight stinging sensation), **2** (intermittent stinging sensation), **3** (severe stinging sensation), **4** (unbearable stinging sensation so that the eyelids could not be opened), **Graft edema and Redness distribution**: **0** (none) , **1** (mild), and **2** (extreme).*

DISCUSSION

Pterygium starts with complaints such as burning, stinging, irritation, hyperemia and the feeling of a foreign body in the eye from time to time. After moderate conjunctival and subconjunctival edema, a fibrous tissue is formed as a result of a micro ulcer caused by repair and scarification mechanisms, starting from the conjunctiva and extending towards the cornea [3]. Pterygium is usually asymptomatic and may cause sensations of burning, stinging, foreign body and photophobia. Progression to the visual axis or deterioration of the tear film layer may cause secondary astigmatism and decreased vision. Due to mechanical irritation, pterygium may be irritated and cause severe pain, stinging, watering problems in patients [2,3].

Growth factors involved in the proliferation and differentiation of the corneal epithelium, such as vitamins and neuropeptides, are derived from the tears secreted from the lacrimal gland. They play an important role in wound healing [6]. Fox et al used autologous serum in Sjögren's syndrome for the first time in anterior segment eye disease [7]. A study by Kaya et al showed that autologous serum could be safely used in ocular surface problems due to various causes [8]. The mechanism of the healing effect of autologous serum is not yet fully understood, but growth factors and vitamins are thought to play a role. Most importantly, Epithelial Growth Factor is present in both serum and ophthalmic tears and has been found to be effective in the healing of traumatic epithelial abrasions [9]. Another substance that has been found to be effective in epithelization is fibronectin [10]. Serum concentration is an important factor in the efficacy of autologous serum and high concentrations of autologous serum have been found to be more effective [8].

Dexpanthenol (provitamin B5) occurs as a component of the analogous acid pantotene, which has an important role in the citric acid cycle of coenzymes [11]. It is a molecule necessary for proper structuring of the epithelial layer, which is an anti-inflammatory feature. In vitro experiments with dexpanthenol have demonstrated proliferation of human fibroblasts [12]. Raczynska et al. reported that using dexpanthenol gel in corneal and conjunctival injuries accelerated the wound healing process [13]. In a cohort study by Baumeister et al., post-PRK re-epithelialization and wound healing were observed to be faster in patients where dexpanthenol gel was used compared to those where it was not used [14].

In this study, the effects of autologous serum and dexpanthenol were investigated on wound healing and patient comfort in corneal and conjunctival wound healing. Patients in both groups were examined for complaints such as pain, stinging, irritation, redness and graft edema. The findings of the study suggested that each molecule is effective in patient comfort after anterior segment surgery. In the current study group using dexpanthenol there was found to be a statistically significant reduction in complaints of pain and irritation on days 3 and 7. Autologous serum may cause some problems in patient medication compliance due to weekly renewal and storage conditions. Therefore, dexpanthenol is a preferable agent because of the ease of patient accommodation and storage.

Limitations

Our study was performed in a relatively limited group. Our study should be supported by studies conducted with more patients. In our study, verbal scales were used for subjective symptoms. It was assumed that the patients gave accurate information. These are the main limitations of our study.

CONCLUSIONS

Many agents have been described to improve patient comfort after pterygium surgery. Of these, the most reliable and most investigated agent is autologous serum. The results of this study demonstrated that dexpanthenol is as effective and reliable a molecule after anterior segment surgery for patient comfort as autologous serum.

DECLARATION OF CONFLICT OF INTEREST

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Original Article

Comparison of ECG, laboratory and echocardiographic parameters in patients with acute myocarditis at acute attack and clinical remission

Akut atak ve klinik remisyonda akut miyokarditli hastalarda EKG, laboratuvar ve ekokardiyografik parametrelerin karşılaştırılması

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ABSTRACT

Aim: The pathogenesis of myocarditis, which has high morbidity and mortality in childhood and adolescence, has not been fully elucidated. The pathogenesis of acute myocarditis is a complex process in which multiple agents play a role. We aimed to compare ECG, laboratory and echocardiographic parameters of patients during acute exacerbation of myocarditis and clinical remission.

Material and Method: 144 patients (124 males, 20 females) with an acute myocarditis episode were included in the study (28 ± 5). These patients were called for control during the clinical remission period of 3-12 months. The ECG, laboratory and echocardiographic parameters of the patients were compared during acute exacerbation and clinical remission. QT and Tp-e ECG parameters were measured. In addition to routine biochemistry and hemogram parameters, troponin I, uric acid, CRP, sedimentation, TSH and cholesterol levels were measured. Left ventricular ejection fraction was measured as an echocardiographic parameter.

Results: When compared with the clinical remission Tp-e interval (p: 0.032), QT-max (p=0.014), QT-min (p=0.001), TSH (p<0.001), Trop (p<0.00), Urea (p=0.028), Alt (p=0.010), Ast (p<0.001), Wbc (p<0.001), Hb (p<0.001), Htc (p<0.001), Rdw (p<0.001), Plt (p<0.001), Mpv (p<0.001), Neu (p=0.003), Lym (p=0.013), Mon (p<0.001), Eo (p=0.003), Pdw (p<0.001), CRP (p=0.001), ESR (p<0.001), and HDL-C (p=0.002) were significantly changed in patients with acute attack myocarditis.

Conclusion: ECG parameters, inflammation markers, and HDL cholesterol levels were significantly improved in the clinical remission in addition to the left ventricular ejection fraction during acute exacerbation of the patients. LVEF, ECG parameters, inflammation markers, TSH and HDL cholesterol levels were thought to be important in terms of clinical course and pathogenesis of the disease.

Keywords: biochemical, ECG, echocardiography, myocarditis, remission

ÖZ

Amaç: Çocukluk ve ergenlikte yüksek morbidite ve mortaliteye sahip miyokardit patogenezi tam olarak aydınlatılamamıştır. Akut miyokardit patogenezi, çoklu ajanların rol oynadığı karmaşık bir süreçtir. Miyokarditin akut alevlenmesi ve klinik remisyon sırasında EKG, laboratuvar ve ekokardiyografik parametreleri karşılaştırmayı amaçladık.

Materyal ve Yöntem: Akut miyokardit atağı olan 144 hasta (124 erkek, 20 kadın) çalışmaya dahil edildi (28 ± 5). Bu hastalar 3-12 aylık klinik remisyon döneminde kontrol altına alındı. Akut alevlenme ve klinik remisyon sırasında hastaların EKG, laboratuvar ve ekokardiyografik parametreleri karşılaştırıldı. QT ve Tp-e gibi EKG parametreleri ölçüldü. Rutin biyokimya ve hemogram parametrelerine ek olarak troponin I, ürik asit, CRP, sedimantasyon, TSH ve kolesterol düzeyleri ölçüldü. Sol ventrikül ejeksiyon fraksiyonu ekokardiyografik parametre olarak ölçüldü.

Bulgular: Klinik remisyon ile karşılaştırıldığında, akut atak miyokarditli hastalarda Tp-e aralığı (p: 0,032), QT-max (p = 0,014), QT-min (p = 0,001), TSH (p <0,001), Trop (p <0,00), Üre (p = 0,028), Alt (p = 0,010), Ast (p <0,001), Wbc (p <0,001), Hb (p <0,001), Htc (p <0,001), Rdw (p <0,001), Plt (p <0,001), Mpv (p <0,001), Neu (p = 0,003), Lym (p = 0,013), Mon (p <0,001), Eo (p = 0,003), Pdw (p <0,001), CRP (p=0,001), ESR (p<0,001), and HDL-C (p=0,002) önemli ölçüde değişmiştir.

Sonuç: EKG parametreleri, inflamasyon belirteçleri ve HDL kolesterol düzeyleri, hastaların akut alevlenmesi sırasında sol ventrikül ejeksiyon fraksiyonuna ek olarak klinik remisyonda önemli ölçüde iyileşti. LVEF, EKG parametreleri, inflamasyon belirteçleri, TSH ve HDL kolesterol düzeylerinin hastalığın klinik seyri ve patogenezi açısından önemli olduğu düşünülmektedir.

Anahtar kelimeler: biyokimyasal, EKG, ekokardiyografi, miyokardit, remisyon

INTRODUCTION

Myocarditis is an inflammation of the myocardium, which is the heart muscle. Acute myocarditis is often caused by viral diseases, but less commonly it can be caused by non-infectious etiologies [1]. The incidence of myocarditis varies between 1% and 9% in postmortem examinations [2].

Its clinical presentation is very variable and can range from thin chest pain or fever to life-threatening congestive heart failure or even sudden cardiac death. While the classical myocarditis patient presents with a preceding viral illness followed by heart failure symptoms, clinical presentations range from mild chest pain with normal systolic function to cardiogenic shock and electrophysiological disturbances [3-5]. It is difficult to diagnose and treatment is usually supportive [6].

The pathogenesis of myocarditis, which has high morbidity and mortality, has not been fully elucidated. The pathogenesis of acute myocarditis is a complex process in which multiple agents play a role.

We aimed to compare ECG, laboratory and echocardiographic parameters of patients during acute exacerbation of myocarditis and clinical remission.

MATERIALS AND METHODS

This study was carried out cross-sectionally in the cardiology department of Kartal Koşuyolu Heart Diseases Training and Research Hospital between January 2015 and May 2016.

Our study consisted of 144 clinical acute myocarditis patients with a mean age of 28 (16-40) who had upper respiratory tract infection (etc.) were selected. The socio-economic level of the patients was compatible with the environment in which it lived and was not lower. These patients had a high Troponin-I level. Coronary angiography was performed and normal was detected. These patients were called for control during the clinical remission period (within 3-12 months). ECG, laboratory tests and echocardiography were performed for the patients who came to control.

The diagnosis of acute myocarditis was based on the inclusion of at least one of the following parameters.

1- Increase of cardiac damage biomarkers,
2- Electrocardiographic findings which are suggesting cardiac damage,
3- Abnormal cardiac function on echocardiography or cardiac magnetic resonance imaging [7].

Transthoracic echocardiography was performed in the left lateral decubitus position with a 2.5-3.5 MHz phase-array transducer probe (GE Vingmed, Horten, Norway Vingmed System 3). All echocardiographic parameters were measured off-line and the mean of 3 heart cavities was used. Left ventricular ejection fraction, diastolic and systolic end volumes were calculated by the Simpson modified method [8]. Venous blood samples were obtained from the antecubital ven for fasting routine laboratory tests. Routine biochemistry, hemogram, troponin-I, uric acid, CRP,

sedimentation, TSH and cholesterol levels were measured in our hospital's laboratory (Roche Diagnostics, Mannheim, Germany Hitachi 747).

EXCLUSION CRITERIA

The following diseases were excluded in the differential diagnosis of acute myocarditis:

1. Liver dysfunction,
2. Chronic lung disease,
3. Hemolytic disorders,
4. Malignities,
5. Concomitant inflammatory diseases (infections and autoimmune diseases),
6. Previous myocardial infarction,
7. Coronary artery disease

STATISTICAL ANALYSIS

Statistical analyzes were performed using the IBM-SPSS Statistics version 20 software (SPSS Inc., Chicago, Illinois). Clinical and laboratory data of patients were expressed as ± standard deviation and percentage (%). The paired simple test was used to evaluate the statistical significance of the difference between the groups. The results were accepted at p <0.05 significance level.

ETHICAL APPROVAL

All patients provided written informed consent. There is ethics committee approval from Kartal Koşuyolu Heart Disease Training and Research Hospital for the study. This study was published as an oral presentation at the14 th International Update in Cardiology and Cardiovascular Surgery (UCCVS) Congress (April 7, 2018).

RESULTS

When compared with the clinical remission Tp-e interval (76.8±0.27 to 72±0.23 msn, p= 0.032), QT-max (351.2±0.54 to 338.4±0.73 msn, p=0.014), QT-min (331.6±0.53 to 314.8±0.76 msn, p=0.001), TSH (1.88±0.46 to 1.17±0.12 ulU/mL, p<0.001), Trop (16.20±2.11 to 0.03±0.15 ng/mL, p<0.00), Urea(25.60±7.66 to 27.73±7.63 mg/dL, p=0.028), Alt (49.61±55.36 to 36.12±28.02 U/L, p=0.010), Ast (57.71±34.85 to 26.09±9.08 U/L, p<0.001), Wbc (9.69±3.04 to 7.68±2.15 10^3/µL, p<0.001), Hb (13.73±1.42 to 14.76±1.69 g/dL, p<0.001), Htc (40.72±4.25 to 44.30±4.63 %, p<0.001), Rdw (14.57±1.53 to 13.72±1.29 %, p<0.001), Plt (221.58±54.85 to 257.87±53.29 10^3/µL, p<0.001), Mpv (7.81±1.14 to 8.70±0.96 fL, p<0.001), Neu (7.42±5.76 to 4.63±1.69 10^3/µL, p=0.003), Lym (1.97±0.67 to 2.23±0.53 10^3/µL, p=0.013), Mon (0.95±0.38 to 0.59±0.20 10^3/µL, p<0.001), Eo (0.12±0.12 to 0.17±0.12 10^3/µL, p=0.003), Pdw (17.40±0.91 to 16.64±0.45 %, p<0.001), CRP (14.77±6.93 to 0.59±0.35 mg/dL, p=0.001), ESR (42.33±19.92 to 10.40±10.59 sn, p<0.001), and HDL-C (34.67±10.45 to 47.50±8.69 mg/dL, p=0.002) were significantly changed in patients with acute attack myocarditis (**Table 1** and **2**).

Table 1. ECG parameters

ECG parameters	Acute attack (n:144)	Clinical remission (n: 142)	P value
MEAN ±SD			
Tp-e, msn	76.8±0.27	72±0.23	0.032
QT, msn	339.6±0.52	329.6±0.74	0.051
QT-max, msn	351.2±0.54	338.4±0.73	0.014
QT-min, msn	331.6±0.53	314.8±0.76	0.001
QTc, msn	383.62±29.97	387.47±20.16	0.403

QT: QT time, QTc: QT time corrected, QT-max: QT maximum time, QT-min: QT minimum time, Tp-e: T wave peak and end.

Table 2. Biochemical parameters

Biochemical parameters	Acute attack (n:144)	Clinical remission (n: 142)	P value
MEAN±SD			
Pulse, beats/min	82.78±15.88	79.33±13.11	0.221
TSH, ulU/mL	1.88±0.46	1.17±0.12	<0.001
Uric acid, mg/dL	6.01±0.78	6.49±1.48	0.001
Trop, ng/mL	16.20±2.11	0.03±0.15	<0.001
Urea, mg/dL	25.60±7.66	27.73±7.63	0.028
Cr, mg/dL	0.78±0.16	0.77±0.13	0.647
Alt, U/L	49.61±55.36	36.12±28.02	0.010
Ast, U/L	57.71±34.85	26.09±9.08	0.000
Wbc: 10^3/µL	9.69±3.04	7.68±2.15	0.000
Hb, g/dL	13.73±1.42	14.76±1.69	0.000
Htc, %	40.72±4.25	44.30±4.63	0.000
Rdw, %	14.57±1.53	13.72±1.29	0.000
Plt, 10^3/µL	221.58±54.85	257.87±53.29	0.000
Mpv, fL	7.81±1.14	8.70±0.96	0.000
Neu, 10^3/µL	7.42±5.76	4.63±1.69	0.003
Lym, 10^3/µL	1.97±0.67	2.23±0.53	0.013
Mon, 10^3/µL	0.95±0.38	0.59±0.20	0.000
Eo, 10^3/µL	0.12±0.12	0.17±0.12	0.003
Pdw, %	17.40±0.91	16.64±0.45	0.000
CRP, mg/dL	14.77±6.93	0.59±0.35	0.001
ESR, sn	42.33±19.92	10.40±10.59	0.000
Glu, mg/dL	99.29±12.08	99.86±14.74	0.898
LDL-C, mg/dL	120.75±34.58	127.83±38.74	0.439
HDL-C, mg/dL	34.67±10.45	47.50±8.69	0.002
TRIG-C, mg/dL	142.33±57.59	180.58±82.74	0.198
TOTAL-C, mg/dL	184.08±50.03	211.83±46.70	0.067

ALT: Alanine Transaminase, AST: Aspartate Transaminase, Cr: Creatinine, CRP: C Reactive Protein, Eo: Eosinophyl, ESR: Erytrocyte Sedimentation Rate, HB: Hemoglobin, HDL-C: High Density Lipoprotein Cholesterol, Htc: Hematocrite, Glu: Glucose, LDL-C: Low Density Lipoprotein Cholesterol, Lym: Lymphocyte, Mon: Monocyte, MPV: Mean Platelet Volume, Neu: Neutrophil, PDW: Platelet Distibution Width, PLT: Platelet, RDW: Red cell distribution width, TRIG-C: Trigliseride Cholesterol, Total-C: Total Cholesterol, Trop: Troponine, TSH: Thyroid Stimulating Hormone, WBC: White Blood Cell.

ECHOCARDIOGRAPHIC FINDINGS (EF%)

In our study, the acute exacerbation of patients with acute myocarditis and the clinical remission LVEF after 3-12 months were 62.1% and 64.8%, respectively. No statistical analysis was performed.

DISCUSSION

In this study, we detected that ECG parameters (Tp-e, QT-max, QT-min), hemogram parameters (Wbc, Hb, Htc, Rdw, Plt, Mpv, Neu, Lym, Mon, Eo, Pdw), biochemical parameters (Tsh, Uric acid, Troponin, Alt, Ast, ESR, HDL-C) and echocardiographic parameters (EF) significantly found in acute attack myocarditis. As far as we know in the literature, although ECG, laboratory, and echo parameters were investigated in patients with myocarditis, no acute attack and clinical remission comparison studies have been performed.

Despite its rarity, myocarditis is a significant etiology of acute and chronic heart failure, often leading to dilated cardiomyopathy and the need for heart transplantation [9]. Also, myocarditis is one of the most important causes of sudden heart death in the young patient population [10]. Acute myocarditis is a major cause of morbidity and mortality.

An electrocardiogram (ECG) is routinely evaluated to assess electrical imbalance in myocarditis [11,12]. ECG abnormalities have been reported in 90% of acute myocarditis patients [13]. Myocarditis may cause sudden heart death in patients without structural heart disease. The most common reason for this is malignant ventricular arrhythmias. Tp-e ratio and Tp-e / QT ratio have been used as a new electrocardiographic marker in ventricular repolarization distribution [14,15]. Increased Tp-e interval and Tp-e / QT ratio are associated with malignant ventricular arrhythmias [16-18]. Prolongation of the QT interval has also been suggested as a risk factor for ventricular arrhythmia and death [19,20].

In our study, Tp-e, QT-max, and QT-min levels were found to be statistically significant in acute attack myocarditis compared to clinical remission. In the study conducted by Ucar et al. [21] found that the QT and Tp-e intervals were higher in acute myocarditis compared to the control group. 30 patients with myocarditis and 25 healthy age-matched control groups were included in the study of Güneş HM et al. [22] when compared with the control group, QT and Tp-e intervals, Tp-e/QT, and Tp-e/QTc ratios were significantly higher in patients with myocarditis.

As shown by our study, the troponin level, which was found to be higher in the acute attack myocarditis period, indicates myocardial damage.

Myocarditis is an inflammatory disease of the myocardium. The inflammation parameters (CRP, uric acid, sedimentation rate, leucocyte, etc.) were high in our study. Sharma et al. [23] showed that inflammatory biomarkers are associated with the severity of myocarditis (especially fulminant myocarditis). High CRP levels have been reported to be a risk factor for the development of fulminant myocarditis [24,25]. In a study by Gironès et al. [26] found that uric acid levels increased in myocarditis patients in 2014. During the acute attack of myocarditis, inflammatory markers such as CRP and erythrocyte sedimentation rate may increase [25].

In addition, TSH and HDL cholesterol levels were found to be statistically significant during the acute myocarditis attack in our study according to the period of remission. The low level of HDL cholesterol in the acute period may suggest a negative acute phase reactant. Low HDL cholesterol during an acute attack may play a role in the pathogenesis of the disease.

Echocardiography is a very vital tool in the evaluation of patients with acute myocarditis [27]. Echocardiography is a valuable test to evaluate the presence of ejection fraction (EF) and accompanying valve pathology. In our study, although EF was lower in acute attack myocarditis, it was not statistically significant.

Previous studies were organized as patients and control groups but in our study, comparisons were made during the acute episode and clinical remission of the same patient groups.

LIMITATIONS

The fact that our study is single-centered and not randomized and the number of patients is low are the main limiting factors.

In addition, myocarditis was diagnosed;

- Not conducting a molecular level study (eg PCR)
- No culture and serological testing
- No cardiac biopsy
- Cardiac MRI has not been performed.

This relationship needs to be supported by longer, more comprehensive and multicentred studies.

CONCLUSION

The incidence of myocarditis is approximately 10-22 / 100,000 people. Myocarditis is an inflammatory disease of

the myocardium. Timely diagnosis, prognosis and definitive treatment of myocarditis are important for the clinician. Despite advances in new diagnostic procedures, the diagnosis of acute myocarditis remains a major challenge.

In our study, Tp-e, QT-max, and QT-min were found to be significantly higher in patients with acute myocarditis than in clinical remission. There was no significant difference in QTc. The inflammation parameters (CRP, uric acid, sedimentation rate, leucocyte, etc.) were high in our study. In addition, TSH and HDL cholesterol levels were found to be statistically significant during the acute myocarditis attack in our study according to the period of remission.

In acute myocarditis, ECG changes, laboratory parameters, and echocardiography can be very useful in clinical practice to decide on appropriate treatment, length of hospital stay, and frequency of follow-up.

However, prospective studies with larger numbers of patients are needed to evaluate these parameters in myocarditis.

DECLARATION OF CONFLICT OF INTEREST

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Orijinal Makale

Çocuk romatoloji polikliğine bacak ağrısı nedeni ile başvuran hastaların değerlendirilmesi: Tek merkez deneyimi

Evaluation of patients presenting with leg pain to the pediatric rheumatology polyclinic: A single center experience

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ÖZ

Amaç: Bacak ağrısı çocukluk çağında sık görülen bir yakınma olup çocuk romatoloji polikliniklerine sık başvuru nedenlerinden birisidir. Bu çalışmada bacak ağrısı ile çocuk romatoloji polikliniğine başvuran olguların etiyolojilerinin araştırılması ve sık görülen nedenlerin ortaya konması amaçlanmıştır.

Gereç ve Yöntem: Ağustos 2018 ile Ağustos 2019 tarihleri arasında bacak ağrısı nedeniyle çocuk romatoloji polikliniğine başvuran 270 hasta çalışmaya dahil edildi. Hastaların dosyaları geriye dönük olarak incelendi. Hastaların başvuru yakınmaları, demografik, klinik ve laboratuvar verileri önceden hazırlanmış formlara kaydedildi.

Bulgular: Çalışmaya %63'ü (n=170) kız olmak üzere 270 hasta dahil edildi. Hastaların ortalama yaşı ve ortalama yakınma başlama yaşı sırasıyla 10,4 ± 4,8 ve 9,1 ± 3,2 yıl bulundu. Bacak ağrısının en sık sebebi 74 (%27,4) hasta ile hipermobilite sendromuydu. Daha sonra sırasıyla 41 (%15) hastaya büyüme ağrısı, 39 (%14,4) hastaya Osgood-Schlatter hastalığı, 32 (%11,8) hastaya post-enfeksiyöz artrit/artralji, 28 (%10,3) hastaya fibromiyalji, 20 (%7,4) hastaya juvenil idyopatik artrit tanısı konuldu. On (%3,7) hasta akut romatizmal ateş, 2 (%0,74) hasta akut lenfoblastik lösemi tanısı aldı. Yaş grupları değerlendirildiğinde özellikle fibromyalji tanısı alan hastaların hepsi adolesan kız çocuğuydu. Bacak ağrılarının %62,5'i çift taraflıydı**.** Hastaların %44'ünde gerçekten bacak ağrısı varken diğer hastalarda başvuru yakınması bacak ağrısı olmasına rağmen asıl gösterilen yer bacaklar değil diz ve ayak bilek eklemleriydi.

Sonuç: Çocukluk çağında bacak ağrısı sık karşılaşılan bir yakınma olup sıklıkla hipermobilite sendromu ve büyüme ağrısı gibi inflamatuvar olmayan nedenlere bağlı olarak görülebilmektedir. Çalışmamızda da bacak ağrısının en sık sebebi hipermobilite sendromuydu. Özellikle adolesan dönemde Osgood-Schlatter hastalığı ve fibromiyalji, çocukluk döneminde ise büyüme ağrısı ön planda düşünülmelidir. Bu benign hastalıkların yanında özellikle eklemde şişlik olduğunda juvenil idyopatik artrit ve akut romatizmal ateş gibi hastalıklar da akılda tutulmalıdır. Yine nadir görülen hastalıklardan lösemiler, avasküler nekroz, meniskopatiler de bacak ağrısı ile başvurabilir. Sonuçta çocuklarda bacak ağrısı önemsenmesi gereken bir yakınma olup hastalar iyi sorgulanmalı ve ayırıcı tanı iyi yapılmalıdır.

Anahtar kelimeler: bacak ağrısı, büyüme ağrısı, hipermobilite, artrit

ABSTRACT

Objective: Leg pain is a common complaint in childhood and is one of the most common causes of admission to pediatric rheumatology outpatient clinics. The aim of this study was to analyze the demographic data and etiology of patients presenting with leg pain and to reveal common causes.

Material and Methods: The files of patients who presented to our pediatric rheumatology outpatient department between August 2018 and August 2019 due to leg pain were retrospectively reviewed. Patient demographic, clinical, and laboratory data were obtained from the patients' files and hospital database. An information form that collected data on patient gender and current age, age at disease onset, age at diagnosis was completed for all patients.

Results: The study included 270 patients with a mean age of 10.4 ± 4.8 years, including 170 (63%) females and 100 (37%) males. The mean age of onset of complaints was 9.1 ± 3.2 years. The most common cause of leg pain was hypermobility syndrome with 74 (27.4%) patients. Respectively, 41 (15%) patients were diagnosed with growing pain, 39 (14,4%) patients with Osgood-Schlatter disease, 32 (11,8%) patients with post-infectious arthritis / arthralgia, 28 (10,3%) patients with fibromyalgia, 20 (7,4%) patients with juvenile idiopathic arthritis. Two patients had acute lymphoblastic leukemia and 10 patients had acute rheumatic fever. All patients with fibromyalgia were girls and adolescents. 62.5% of leg pain was bilateral. 44% of patients really had leg pain. Although the complaint of presentation in other patients was leg pain, it was not the legs but the localized knee and ankles.

Conclusion: Leg pain is a common complaint both in childhood and adolescence. Hypermobility syndrome was the most common cause in both periods. Osgood-Schlatter disease and fibromyalgia should be considered especially in adolescence and growing pain in childhood. In addition to these benign diseases, diseases such as juvenile idiopathic arthritis and acute rheumatic fever should be considered, especially when the joint is swollen. Leukemia's, avascular necrosis and meniscopathies may also present with leg pain. As a result, leg pain in children is a complaint that should be considered and patients should be questioned well and differential diagnosis should be made well.

Keywords: leg pain, growth pain, hypermobility, arthritis

GİRİŞ

Çocukluk çağında kas-iskelet sistemi ağrıları sık görülmekte olup özellikle bacak ağrısı çocuk romatoloji polikliniklerine en sık başvuru nedenlerinden birisidir**.** Bacak ağrısının ayırıcı tanısı oldukça geniştir; ancak olguların çoğunda nedenin kaynağı inflamatuvardan çok mekaniktir ve uzun dönemde sekellere neden olmayabilir [1, 2]. Bu inflamatuvar olmayan mekanik ağrıların romatolojik, enfeksiyon veya malignite gibi diğer kas-iskelet sistemi ağrısı yapan nedenlerden iyi ayırt edilmesi; erken teşhis, uygun tedavi ve uygun olmayan araştırmaların önlenmesi için esastır [3]. Büyüme ağrısı, hipermobilite sendromu, Osgood-Schlatter hastalığı, fibromiyalji, meniskopatiler, pes planus gibi inflamatuvar olmayan nedenlerle akut romatizmal ateş, juvenil idyopatik artrit, malign ve otoimmün hastalıklar gibi inflamatuvar nedenler bacak ağrısına neden olabilir.

Bacak ağrısı ile başvuran çocukta öykü çok önemlidir. Öykü alınırken ağrının yerleşimi, ağrının oluşum zamanı, süresi, niteliği, ağrının egzersiz ile ilişkisi, ağrıya eşlik eden sistemik bulgular ve travma dikkat edilmesi gereken noktalardandır. Yaş, cinsiyet, altta yatan hastalıklar gibi pek çok etken yol gösterici olmaktadır. Yapılacak fizik muayenede eşlik edebilecek ateş, döküntü, eklem bulguları, hepato-splenomegali, lenfadenomegali, kas gücü değerlendirilmesi ve yapısal iskelet anomalilerine dikkat edilmesi gerekir [4].

Büyüme ağrısı okul çağındaki çocukların %3-37'sini etkileyen, epizodik olarak görülen, genellikle bacaklarda (dizin arkası, uyluk ve baldırlarda), akşam veya geceleri ortaya çıkan, uykudan uyandırabilen, birkaç dakikadan birkaç saate kadar sürebilen ve nedeni bilinmeyen iyi huylu ağrı olarak tanımlanmaktadır [5, 6].

Hipermobilite herhangi bir sistemik romatizmal hastalık ile ilişki olmadan eklemlerin normalin üzerinde hareket genişliğine sahip olması ile karakterize klinik bir bulgudur [7, 8]. Eklem hipermobilitesine kemik, tendon, kas, ligaman, eklem ve omurgadan kaynaklanan kas iskelet sistemi semptomlarının eşlik etmesi durumu hipermobilite sendromu olarak bilinir [9, 10]. Bacak ağrısı ile başvuran hastalarda fizik muayenede hipermobilitenin değerlendirilmesi hastaların gereksiz tetkik ve tedavilere maruz kalmalarını önleyecektir.

Osgood-Schlatter hastalığı diz ağrısının en yaygın nedenlerinden biri olup özellikle aktif, hızlı büyüyen ve sportif çocuklarda görülmektedir. Tibial tüberkülün apofiziti olup patellar tendonun tekrarlayıcı traksiyonu sonucu gelişir [11, 12]. Radyografi tibial tüberkül apofizinin genişlemesini ve fragmantasyon varlığını gösterir. Ayrıca manyetik

rezonans görüntülemede kalsifikasyonlar, tendonda ve peritendinöz bölgede ödem varlığı gözlenebilir [11, 12].

Fibromiyalji, yaygın ağrı ve hassas noktalarla karakterize, uyku bozukluğu, sabah tutukluğu, yorgunluk, irritabl barsak gibi birçok semptomlar topluluğunun eşlik ettiği kronik ağrı hastalığıdır. Günümüzde fibromiyalji tanısı American College of Rheumatology 1990 kriterlerine göre konulmaktadır. Burada iki önemli nokta söz konusudur. En az 3 aydır devam eden yaygın ağrı olması ve 11 hassas nokta sayısı olmasıdır (18 noktadan 11'inde hassasiyet olması) [13, 14]

Bu çalışmada bacak ağrısı nedeni ile başvuran çocuklarda demografik verileri incelemek, ağrıların nedenlerini gözden geçirmek ve etiyolojilerini belirlemek amaçlanmıştır.

GEREÇ VE YÖNTEM

Ağustos 2018-Ağustos 2019 tarihleri arasında hastanemiz çocuk romatoloji polikliniğine bacak ağrısı ile başvuran 270 çocuk hastanın demografik ve klinik özellikleri, tetkik sonuçları ve tanılarına ait bilgiler poliklinik dosya kayıtlarından geriye dönük olarak elde edildi. Hastalar bacak ağrısı ayırıcı tanısına yönelik olarak öykü, fizik muayene ve laboratuvar tetkikleri yönünden incelendi. Tüm değerlendirmeler sonucunda Peterson kriterlerine göre büyüme ağrısı tanısı [15], Beighton kriterlerine göre hipermobilite sendromu tanısı [16], American College of Rheumatology 1990 kriterlerine göre fibromiyalji tanısı [14] kondu. Hastalar Grup 1: 0-10 yaş grubu çocukluk dönemi, Grup 2: 11 yaş ve üstü adolesan dönemi olarak ikiye ayrıldı.

Kas-iskelet sistemi veya bacak ağrısı yapabilecek herhangi bir kronik hastalığı veya ilaç kullanımı olan hastalar çalışmaya dahil edilmemiştir.

İstatistiksel yöntem olarak çalışmada kullanılan tüm istatistiksel hesaplamalar ve analizler için SPSS yazılım sürümü 20.0 (Statistical Packages for Social Sciences: SPSS Inc, Chicago, IL, ABD) kullanılmıştır. Demografik veriler ve tanı dağılımları deskriptif yöntemle analiz edilmiştir. Tanımlayıcı analizlerde, normal dağılıma uyan değişkenler için ortalama ± standart sapma kullanılmıştır.

BULGULAR

Çalışmaya %63'ü (n=170) kız olmak üzere 270 hasta dahil edildi. Hastaların ortalama yaşı ve ortalama yakınma başlama yaşı sırasıyla 10,4 ± 4,8 ve 9,1 ± 3,2 yıl bulundu. Bacak ağrısının en sık sebebi 74 (%27,4) hasta ile hipermobilite sendromuydu. Daha sonra sırasıyla 41 (%15) hastaya büyüme ağrısı, 39 (%14,4) hastaya Osgood-Schlatter hastalığı, 32 (%11,8) hastaya post-enfeksiyöz artrit/artralji, 28 (%10,3) hastaya fibromiyalji, 20 (%7,4) hastaya juvenil idyopatik artrit tanısı konuldu. On (%3,7) hasta akut romatizmal ateş, 2 (%0,74) hasta akut lenfoblastik lösemi tanısı aldı. İkişer hastada da aşil kısalığı, meniskopati ve kalça ekleminin avasküler nekrozu saptandı. Hastaların tanı dağılımları **Tablo 1**'de verilmiştir.

Tablo 1. Hastaların tanı dağılımı

Tanı	n (%)
Hipermobilite sendromu	74 (27,4)
Büyüme ağrısı	41 (15)
Osgood-Schlatter hastalığı	39 (14,4)
Post-enfeksiyöz artrit/artralji	32 (11,8)
Fibromiyalji	28 (10,3)
Juvenil idyopatik artrit	20 (7,4)
Pes planus	15 (5,5)
Akut romatizmal ateş	10 (3,7)
Aşil tendon kısalığı	2 (0,7)
Meniskopati	2 (0,7)
Akut lenfoblastik lösemi	2 (0,7)
Avasküler nekroz	2 (0,7)
Hashimato tiroiditi	1 (0,4)
Lumbal disk hernisi	1 (0,4)
Gluteal abse	1 (0,4)
Toplam	270 (100)

Grup 1'de 118 (%43,7) hasta varken grup 2'de 152 (%56,2) hasta vardı. Grup 1 ile grup 2'deki hastalar karşılaştırıldığında grup 2'de Osgood-Schlatter hastalığı ve fibromiyalji daha sık görülürken grup 1'de büyüme ağrısı ile hipermobilite sendromu daha sık görülmüştür. Tüm yaş grupları değerlendirildiğinde özellikle fibromyalji tanısı alan 28 hastanın hepsi adolesan kız çocuğuydu. Osgood-Schlatter hastalığı tanısı alan 39 hastanın 30'u erkekti. Bacak ağrılarının %62,5'i çift taraflıydı**.** Hastaların %44'ünde gerçekten bacak ağrısı varken diğer hastalarda başvuru yakınması bacak ağrısı olmasına rağmen asıl gösterilen yer bacaklar değil diz ve ayak bilek eklemleriydi.

TARTIŞMA

Bacak ağrısı çocukluk çağında sık görülen bir yakınma olup bu durum aileleri oldukça endişelendirir [17]. Ayırıcı tanısı inflamatuvar nedenlerden inflamatuvar olmayan nedenlere kadar oldukça geniştir.

Hipermobilite sendromu ilk kez 1967 yılında tanımlanmış, herhangi bir ikincil hastalık (konjenital sendrom veya konnektif doku hastalığı gibi) olmadan görülen eklemlerin normalin üzerinde hareket genişliğine sahip olması ile karakterize olan bir sendromdur. Yaygın kas-iskelet sistemi ağrısı yapabildiği iyi bilinmektedir. Prevelansı tahminen %7 ile %36 arasında değişmektedir [18]. Özellikle kızlarda ve yaş arttıkça daha fazla görülmektedir. [17,18]. Hipermobilite sendromu tanısında en sık Beighton kriterleri

kullanılmaktadır. Beighton tanı kriterleri hipermobilite sendromu tanısında kolay uygulanabilirliği ve eklemleri simetrik değerlendirmesi nedeniyle genel olarak kabul görmüştür [16]. Beighton skoru, beş manevranın uygulanması ile puanlanan ve toplam dokuz puan içeren kolay bir skorlama yöntemidir. Bu manevralardan dördü pozitifse hastada hipermobilitenin bulunduğu düşünülür [19, 20]. Hipermobil eklemlerde ağrının oluşmasında eklem instabilitesi, bozulmuş propriyosepsiyon ve buna bağlı mikro-travmalar veya otonom sinir sisteminde merkezi duyarlılık suçlanmaktadır [20]. Bizim çalışmamızda da literatürle uyumlu olarak çocuklarda bacak ağrısının en sık nedeni %27,4 ile hipermobilite sendromu olarak bulunmuştur.

Büyüme ağrısı 3-12 yaş arası çocukları etkileyen, genellikle bacaklarda (dizin arkası, uyluk ve baldırlarda), daha az sıklıkla bacaklara ek olarak kollarda da görülebilen, akşamları ve gece vakti ortaya çıkan, uykudan uyandırabilen, birkaç dakikadan birkaç saate kadar sürebilen ve nedeni bilinmeyen iyi huylu ağrılar olarak tanımlanmaktadır [21]. Büyüme ağrısı kemikte lokalize olmaz. Büyüme ağrısına sabah tutukluğu, topallama eşlik etmez. Çocuklar genellikle günlük aktivitelerinde sıkıntı yaşamazlar. İlk kez 1800'lü yıllarda tanımlanmış olup etiyolojisi halen bilinmemektedir [22]. Kas-iskelet sistemi anatomik bozuklukları ve D vitamini eksikliği en çok suçlanan nedenlerdendir [23, 24]. Vehapoglu ve ark. [24] 120 büyüme ağrısı olan çocuğun %61,6'sında 25-Hidroksi D vitamini düzeyinin düşük olduğunu, 3 ay D vitamini takviyesiyle ağrılarının düzeldiğini rapor etmişlerdir. Bununla birlikte, bu ilişkiyi netleştirmek için daha fazla araştırmaya ihtiyaç olduğu vurgulanmıştır [24]. Büyüme ağrısının tanısı klinik kriterlere dayanmakta olup aslında bir dışlama tanısıdır. Ağrının yerleşimi, sıklığı, zamanı, süresi, egzersizle ilişkisi ve eşlik eden sistemik semptomlar mutlaka sorgulanmalı ve iyi bir öykü alınmalıdır [25]. Tedavisinde aileler iyi bilgilendirilmeli, ağrıların kendi kendine sınırlı ve iyi huylu olduğu söylenmelidir. Analjezikler, pasif germe ve hipermobilitesi olan çocuklarda ortez; ağrı yönetimi için yardımcı olabilir [26]. Bizim çalışmamızda literatürle uyumlu olarak hastaların %15'inde büyüme ağrısı saptanmıştır. Bacak ağrısı ile başvuran çocuklarda bu tanı unutulmamalı ve hastalar buna göre değerlendirilmelidir.

Osgood-Schlatter hastalığı tuberositas tibianın traksiyon apofizitidir. Patellar tendon çekme kuvvetleri nedeniyle mikro avülsiyon kırığı oluşur. Tipik olarak büyüme çağındaki kızlarda 8-13 yaş, erkeklerde ise 10-15 yaşları arasında görülür [11, 12]. Diz ağrısının geç çocukluk ve erken ergenlik döneminde en sık görülen nedenlerinden birisidir. Özellikle aktif spor yapan çocuklarda daha fazla görülmektedir [12]. Genellikle kendi kendini sınırlayarak 1 yıl içinde kendiliğinden düzelir. İstirahat, basit analjezikler, birkaç hafta spordan kaçınma önerilir. Nadiren ortopedik girişim gerektirir. Yaklaşık %10'unda erişkin döneme geçebilir [11, 12]. Çalışmamızda da literatürle uyumlu olarak Osgood-Schlatter hastalığı saptanan 39 hastada ortopedik girişim ihtiyacı olmamıştır.

Sonuç olarak çocukluk çağında bacak ağrısı sık görülen bir yakınma olup, önemsenmesi gereken bir durumdur. İnflamatuvar olmayan nedenlerden romatolojik hastalıklara, enfeksiyonlara ve malignitelere kadar çok sayıda hastalık bu duruma neden olabilmektedir. Organik nedenler ekarte edildikten sonra büyüme ağrısı, hipermobilite sendromu ve Osgood-Schlatter gibi benign nedenlerin de tanıda akılda tutulması önemlidir. Çocuklarda bacak ağrısı önemsenmesi gereken bir yakınma olup hastalar iyi sorgulanmalı ve ayırıcı tanı iyi yapılmalıdır.

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Original Article

Investigation of genital hygiene behavior: An example of slum area

Genital hijyen davranışlarının belirlenmesi: Gecekondu bölgesi örneği

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ABSTRACT

Aim: This study was conducted to evaluate the genital hygiene behaviors of women living in a slum area.

Method: This descriptive research, which was conducted with women living in low socioeconomic level in Akıncılar and Suluca region of Adana. The population of the study was composed of approximately 420 women who living in Akıncılar and Suluca region. The sample was calculated by simple random sampling method and 146 women were included in the study. Data was collected using a Personal Information Form and Genital Hygiene Behaviors Inventory. The obtained data was analyzed using Mann-Whitney U, Kruskal-Wallis and Post-hoc test statistics.

Results: It was determined that the average age of the women was 31.25±10.42, 48.6% of them are illiterate, all of them married, not working and income perceptions are less than the income. It was determined that total median score of women from Genital Hygiene Behaviors Inventory are 46. It was found that the difference between Genital Hygiene Behaviors Inventory median scores of women according to educational status, educational status of spouses, perceptions of nutritional status, smoking status and frequency of changing daily pad were significant ($p<0.05$).

Conclusions: In this research, it was determined that Genital Hygiene Behaviors of women living in a slum area are insufficient.

Keywords: genital hygiene, women health, socioeconomic status

ÖZ

Amaç: Bu araştırma gecekondu bölgesinde yaşayan kadınların genital hijyen davranışlarının belirlenmesi amacıyla yapılmıştır.

Yöntem: Tanımlayıcı tipte bu araştırma, Adana'nın Akıncılar ve Suluca bölgesinde yaşayan sosyoekonomik düzeyi düşük kadınlar ile yürütülmüştür. Araştırmanın evrenini Akıncılar ve Suluca bölgesinde yaşayan yaklaşık 420 kadın oluşturmuştur. Örneklemi ise basit rastgele örneklem yöntemi ile hesaplanmış ve 146 kadın araştırmaya dâhil edilmiştir. Veriler; Kişisel Bilgi Formu ve Genital Hijyen Davranışları Envanteri kullanılarak toplanmıştır. Verilerin değerlendirilmesinde Mann Whitney U, Kruskal Wallis ve Post-hoc test istatistiği kullanılmıştır.

Bulgular: Kadınların yaş ortalamasının 31,25±10,42 olduğu, %48,6'sının okuryazar olmadığı, tamamının evli olduğu, çalışmadığı ve gelir durumu algılarının gelirlerinin giderlerinden az olduğu belirlenmiştir. Kadınların Genital Hijyen Davranışları Envanteri toplam puan ortanca değeri 46 olarak saptanmıştır. Kadınların eğitim durumları, eşlerinin eğitim durumları, beslenme durumu algıları, sigara içme durumları ve günlük ped değiştirme sıklığı değişkenlerine göre Genital Hijyen Davranışları Envanteri toplam ortanca değerleri arasında istatistiksel olarak anlamlı farklılık saptanmıştır ($p<0,05$).

Sonuç: Bu araştırmada gecekondu bölgesinde yaşayan kadınların genital hijyen davranışlarının yetersiz olduğu saptanmıştır.

Anahtar kelimeler: genital hijyen, kadın sağlığı, sosyoekonomik statü

INTRODUCTION

Genital infections are one of the health problems from which women have frequently suffered. Genital infections result from many reasons, among which the anatomical structure ranks first. Although the normal vaginal flora in the female reproductive system provides a natural protection mechanism, the risk of the genital infection does increase since the urethra, vagina and anus are juxtaposed [1,2]. In addition, many factors including more than one partner, inappropriate menstrual, toilet and post-coital hygiene habits, the wear of narrow and synthetic clothing, malnutrition, systemic diseases (diabetes), more than one birth, miscarriage and curettage, long and intense stress, long-term antibiotic and steroid use, vaginal douching, tampon use, poor environmental conditions caused by low socio-economic status, and lack of education contribute to the development of genital infections [1,3,4]. Ensuring genital hygiene is one of the most critical elements in the protection and maintenance of women's health and reproductive health.

Susceptibility to the genital infection can increase when great attention is not paid to genital hygiene. Serious complications occur when the infection is not treated [5]. These complications are low birth weight infants, fetal abortion and fetal death, congenital infections in the newborn, ectopic pregnancy, sepsis, cervical cancer, infertility and chronic pelvic pain [1,6]. Moreover, psychological and sexual problems, social isolation, fatigue and deterioration in the quality of life can be observed in women [7].

Gypsies in Turkey go on with their lives especially in rural areas [8]. It is known that half a million to 5 million Gypsy citizens reside in Turkey [9]. From the past to the present, the Gypsies have maintained their life along with many problems such as social exclusion, poverty, unemployment, housing, and the inability to access and benefit from basic rights and services [8].

Gypsies in Turkey, in general, have been living in the slum areas that are lack of sanitary conditions [10]. Early marriages, adolescent pregnancies, drug addiction, infant and child deaths, difficulties of nomadic life, insufficient hygiene conditions, malnutrition, unprotected sexual intercourse, unwillingness to use condoms, high incidence of infectious diseases, limited use of healthcare resources, lack of communication with health professionals and many negative behaviors affecting health are more common among Gypsies [11-13].

There are many studies examining genital hygiene behaviors in Turkey [5,14-20]. However, a limited number of studies investigating genital hygiene behaviors have been found especially in disadvantaged groups [2,4,21-23]. Midwives and nurses play very important roles in the protection, maintenance, and improvement of women's health. Therefore, identifying disadvantaged groups with especially low socioeconomic status and high environmental risk factors, assessing whether women in this

group are aware of the risk factors for the prevention of genital infections and determining whether they need education are the first actions to be taken in terms of maintaining preventive health services. Thus, this study was aimed to evaluate the genital hygiene practices of women living in slum areas.

MATERIAL AND METHODS

Type of research: This study was conducted in a descriptive manner to evaluate the genital hygiene behaviors of women living in a slum area.

Research site: This study was carried out with women living in Akıncılar and Suluca that are densely populated by Gypsies in the district Yüreğir of Adana.

Population and Sample of Study: When the population of the study is considered to consists of approximately 420 women living in Akıncılar and Suluca, a minimum of n = 146 women able to be included in the study was calculated by simple random sampling method whose population is known and 146 women were included in the study.

Inclusion Criteria: All women, who accepted to participate in the research and were Gypsies and married, were included in the study. Women with communication difficulties and mental disabilities were excluded from the study.

Data Collection Forms and Tools: The study data were gathered using a Personal Information Form and Genital Hygiene Behavior Inventory (GHBI).

1- Personal Information Form: This is a 22-item data collection form that is prepared by the researcher in accordance with the literature review and evaluates socio-demographic, obstetric and gynecological characteristics of women [2,5,7,21].

2- Genital Hygiene Behavior Inventory: GHBI was developed by Ege and Eryılmaz in 2005 [24]. The inventory consists of 27 questions regarding general hygiene, menstrual hygiene, toilet hygiene, and sexual hygiene. GHBI is a one-dimensional measurement tool specific to Turkish culture. The inventory is suitable for all sexually active women found in a group of ages from 15 to 49. Questions in GHBI were answered as "1-never", "2-sometimes", "3-often", "4-always. The negative items (17, 26 and 27) of the inventory were coded in reverse order to ensure compliance with the measurement. The lowest score from the inventory was 27 and the highest score was 108. The total score from the inventory gives the score of genital hygiene behavior. As the score increases, it is understood that genital hygiene behaviors reach the desired level. Cronbach's alpha coefficient of the scale was 0.86 [24].

Data Collection: The data were gathered by the researcher between May 10 to September 10, 2019. The researcher went to the relevant areas once a week on average to collect data. Data were collected through the face-to-face interview method in a suitable environment by protecting the privacy of women who meet the sampling criteria. Data collection was completed within approximately 5-10 minutes.

Data Evaluation: Coding and evaluation of the data were carried out in a computer environment. SPSS (Statistical Package of Social Science) 24.0 software was used to analyze the data. Frequency tables and descriptive statistics were employed for the analysis of the data. Kolmogorov-Smirnov test was used to test whether the data are normally distributed, and it was found that they did not exhibit a normal distribution. Mann-Whitney U test was used to compare two independent groups with measurement values while Kruskal-Wallis test was utilized to compare three or more independent groups with measurement values. The post-hoc test was used for further analysis. Results were evaluated at a 95% confidence interval. $p<0.05$ was considered statistically significant.

Ethical Declarations: The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee Decision (Date: 06.05.2019, Permission no: 2019/7/1) permission were obtained from Scientific Research and Publication Ethics Committee of Osmaniye Korkut Ata University. In addition, the objective of the study was explained to the participants and written approval was obtained from them via an informed consent form.

RESULTS

The mean age of the women was 31.25 ± 10.42 (min: 20 - max: 55). 48.6% of them were illiterate. All were married and were not working. Their incomes were lower than their expenditure. 53.4% of them had 3 or more children. 44.5% of them did not use any contraceptive methods. 46.6% of them had no normal vaginal discharge. 87.7% of them had vaginal douching after sexual intercourse. 76.1% of them changed pad four times or less a day at periods when menstruation was intensified. **Table 1** presents other findings related to the descriptive, obstetric and gynecological characteristics of women.

Table 1. Distribution of women according to descriptive, obstetric and gynecological characteristics

Descriptive characteristics	**X±SD**	**Min-Max**
Age average	31.25±8.78	20-55
Average number of pregnancies	3.56±2.2	0-18
Average number of children	2.72±1.3	0-9
Average number of curettages	0.74±1.0	0-7
Age average of menarche	12.65±1.2	10-17
Average of smoking per day	13.95±9.3	2-40
	n	**%**
Educational status		
Illiterate	71	48.6
Literate	6	4.1
Primary school	59	40.1
Secondary school	10	6.8
High school	0	0.0
Educational status of spouse		
Illiterate	39	26.7
Literate	9	6.2
Primary school	76	52.1
Secondary school	14	9.6
High school	8	5.5
Age		
20-29	63	43.2
30-39	53	36.3
40-49	24	16.4
50-59	6	4.1
Working condition		
No	146	100
Income perception		
Income less than expenditure	146	100
Nutritional status perception		
Good	26	17.8
Moderate	47	32.2
Poor	73	50.0
Number of pregnancies		
0-2	46	31.5
3 and over	100	68.5
Number of living children		
0-2	68	46.6
3 and over	78	53.4
Smoking status		
Yes	45	30.8
No	101	69.2
Contraception Methods		
OK	10	6.8
RIA	37	25.3
Condom	3	2.1
Withdrawal	14	9.6
Injection	9	6.2
Tube-ligation	7	4.8
No contraception	65	44.5
Menopause		
Yes	5	3.4
No	141	96.6
Discharge		
Normal, odorless, itchless	78	53.4
Anormal (malodorous/plentiful/itchy,cheesy)	68	46.6
Vaginal douching		
Yes	128	87.7
No	18	12.3
Presence of gynecological disease		
Yes	14	9.6
No	132	90.4
Frequency of changing pad (piece per day)		
0-4	111	76.1
5 and over	35	23.9

Table 2. Mean of Genital Hygiene Behavior Scale (GHBS)

Scale	**Score mean of GHBI**	**Median (Min-Max)**
		n=146
Total score of GHB	46.17±4.27	46 (36-58)

The total median GHBI value of women was found as 46 (min: 36 - max: 58), as shown in **Table 2**. Cronbach's alpha value of the scale was calculated as 0.658. When the findings comparing the GHBI scores according to the descriptive, obstetric and gynecological characteristics of women were examined, a statistically significant relationship was found between women's educational status and total median values of GHBI ($p<0.05$). Further analysis revealed that the difference results from the illiterate group ($p<0.05$; **Table 3**). There had been a statistically significant relationship between the education status of women's spouses and the total median values of GHBI ($p<0.05$). Further analysis showed that the difference is due to the group who finished high school education ($p<0.05$; **Table 3**). There existed a statistically significant relationship between the nutritional status of women's spouses and the total median values of GHBI [$p<0.05$). Further analysis demonstrated that the difference was caused by the group with a poor perception of nutritional status ($p<0.05$; **Table 3**). A statistically significant relationship was found between the total median values of GHBI according to the smoking status and daily frequency of pad change of women ($p<0.05$; **Table 3**).

DISCUSSION

This study was conducted with women living in Akıncılar and Suluca rural areas of Adana. The most important feature of these areas is that the socio-economic level is low and gypsies mostly live. It has been found that 48.6% of the gypsy women living in the study area were illiterate, all of them were not working, all of them had poor income perceptions and 50% of them had poor perceptions of nutritional status. Eskiocak et al. (2017) carried out a study on the health of the gypsies living in Edirne. They reported that being born as a gypsy constitutes a disadvantage in terms of healthily holding on to life and gypsies live a disadvantaged life in the fields of housing, nutrition, education, employment and social security [25]. In addition, it has been indicated that the research results carried out in Turkey and worldwide are similar to the scene in Edirne. These studies revealed that the unemployment rate is higher in gypsies, and gypsies are poorer than non-gypsies [25-27]. Kolukırık (2006) also reported that the biggest problems perceived by the gypsies were unemployment, poverty and lack of education [28]. Similarly, a study by Tanrıverdi (2014) reported that poverty and unemployment

Table 3. Comparison of GHBI scores by the descriptive, obstetric and gynecological characteristics of women

	Total median score of GHBI (min-max)	Test statistics
Educational status		
Illiterate	44(36-57)	
Literate	47.5(42-51)	
Primary school	47(39-56)	**X^2= 17.065**
Secondary school	49.5(47-58)	**p=0.002**
Educational status of spouse		
Illiterate	45(36-58)	
Literate	45(41-51)	
Primary school	46(38-57)	
Secondary school	48(41-51)	**X^2= 10.639**
High school	49.5(46-56)	**p=0.031**
Age		
20-29	47(36-58)	
30-39	46(39-55)	
40-49	47(39-57)	X^2= 0.787
50-59	41(38-46)	p=0.675
Nutritional status perception		
Good	49(44-54)	
Moderate	46(36-58)	**X^2= 15.779**
Poor	44(38-57)	**p=0.000**
Number of pregnancies		
0-2	46(36-58)	Z= -0.154
3 and over	46(38-57)	p=0.877
Number of living children		
0-2	46(36-58)	Z= -0.380
3 and over	46(39-56)	p=0.704
Smoking status		
Yes	44(36-57)	**Z=-2.278**
No	47(39-58)	**p=0.023**
Contraception Methods		
OK	45.5(42-50)	
RIA	45(39-57)	
Condom	47(44-48)	
Withdrawal	47(39-55)	
Injection	48(39-51)	
Tube-ligation	50(40-50)	X^2= 2.760
No contraception	46(36-58)	p=0.838
Menopause		
Yes	40(38-56)	Z=-1.926
No	46(36-58)	p=0.054
Discharge		
Normal, odorless, itchless	46(38-58)	Z=-0.659
Anormal (malodorous/plentiful/itchy,cheesy)	45(33-54)	p=0.510
Vaginal douching		
Yes	46(36-58)	Z=-0.904
No	47(41-53)	p=0.366
Presence of gynecological disease		
Yes	44.5(39-56)	Z=-0.213
No	46(36-58)	p=0.831
Frequency of changing pad (piece per day)		
0-4	45(36-57)	**Z= -3.888**
5 and over	48(41-58)	**p= 0.000**

Z-table value: Mann-Whitney U test, χ2-table value: Kruskal-Wallis H test

were the most commonly experienced problems [11]. Consistent with the literature, the disadvantages from which the gypsies suffered are overlapped with our research findings.

We found that 76.1% of gypsy women changed pad four times or less a day at intensive periods of menstruation. The low frequency of pad changing shows that women have insufficient knowledge about the maintenance of genital hygiene. In a study on the living conditions and genital hygiene practices of seasonal agricultural workers, Yağmur and Ergin (2017) found that only 12.2% of women changed pad 4 or more times per day during menstruation [4]. Karatay and Özvarış (2006) investigated the genital hygiene practices of women living in the slum area and found that 93.3% of women changed pad 4 or less per day [2]. Daşıkan et al. (2015) reported that 50.4% of women changed their pads or tampons 1-2 times per day [5]. Other studies also reported that the frequency of changing pad during menstruation was insufficient [14,23,29-31]. We established that 87.7% of the gypsy women applied vaginal douching after sexual intercourse. Vaginal douching, which destroys the normal flora of the vagina, poses a high risk for many female genital diseases and thus predispose women to vaginal infections, is often preferred by women in many countries of the world, especially in Muslim countries [18,32-34]. Pete et al. (2019) reported that women in Cameron used vaginal douching, which has been a cultural practice, and that 53.8% of them have inherited this tradition from their family [33]. Another study in Africa reported that they performed mostly vaginal douching since black women believed that the vagina contained germs [32]. Sunay et al. (2011) reported that women performing vaginal douching had a 3.9-fold higher risk of abnormal vaginal discharge than those who did not [34]. Cangöl and Tokuç (2013) reported that almost all of the women clean their vagina after sexual intercourse [15]. Other studies also indicated that vaginal douching was performed by women within the range of 51.4 to 87% [2, 5, 14, 18]. In line with these results, it is possible to say that some incorrect practices of genital hygiene have still continued to be done.

One of the important indicators of poor genital hygiene behavior is abnormal vaginal discharge. Several studies revealed that insufficient genital hygiene behaviors are one of the most important reasons for vaginal infection [20,31]. We found that 46.6% of the gypsy women had abnormal vaginal discharge (malodorous/abundant/itchy-cheesy). Yağmur and Ergin (2017) reported that approximately one-fifth of women working seasonally in agricultural activities had previously faced vaginal infection [4]. Karatay and Özvarış (2006) stated that 72.8% of the women living in the slum area experienced an abnormal discharge problem in

the past and 28.7% of them have still suffered from abnormal discharge problems [2]. Arslan Özkan and Kulakaç (2011) reported that 30.1% of women prisoners faced abnormal discharge problems [22]. In addition, Yılmaz and Kahraman (2019) found the rate of incidence of abnormal vaginal discharge as 62.7% [35]. Srivastava (2010) reported that 72.6% of women living in the rural areas of India developed one or more genital infections and that more than half of the participating women had poor menstrual hygiene practices [36]. All these results show us that women living in regions with especially low socio-economic level need more gynecological help and counseling.

In this study, the total median value of GHBI of women was found as 46 (min: 36 - max: 58) (**Table 2**). When the lowest score to be obtained from the scale is 27 and the highest score is 108, it can say that the total median values of GHBI of gypsy women are less than expected. This is a possible outcome in especially gypsies who are regarded as disadvantaged groups. When the relevant studies are examined, Ilgaz et al. (2015) found that the total score of GHBI was 72.1, and genital hygiene behaviors in women living in regions with low socioeconomic level were 5.5 times more negative than those living in regions with high socioeconomic level [21]. Arslan Özkan and Kulakaç (2011) found the mean GHBI of female prisoners to be 86.6 [22]. Karatay and Özvarış (2006) also reported that rural life entails a risk for genital hygiene behaviors. A study on Indian women revealed that genital infections were more common in rural areas than in urban those [37]. Research results show that rural life poses a risk for genital hygiene.

A statistically significant relationship was found between the total median values of GHBI of women according to their educational background ($p < 0.05$). Further analysis revealed that the difference was due to the illiterate group ($p < 0.05$; **Table 3**). In other words, a low level of education leads to a decrease in the total score of GHBI. The studies have already reported that the education level of gypsies is generally low [11,25,28]. Tanrıverdi et al. (2014) found that gypsies suffered badly from negativities such as unhealthy nutrition, adverse environmental conditions, inadequate use of secondary and tertiary health care services, poor hygiene and insufficiency in healthy lifestyle behaviors [11]. Koştu and Beydağ (2009) stated that the genital hygiene behaviors of women in high school and higher education level were better [14]. Daşıkan et al. (2015) found that women with the educational level of primary education and below experienced more complaints of genital discharge [5]. Yağmur and Ergin found vaginal infection to be mostly seen in the illiterate group [4]. A statistically significant relationship was found between the total median values of GHBI according to women's perceptions of nutritional status ($p < 0.05$). Further analysis showed the difference resulted from the group with a poor perception of nutritional status ($p < 0.05$; **Table 3**). Women with poor nutritional status perception had lower total median values of GHBI. Tanrıverdi et al. (2014) reported that gypsies could not eat properly due to economic deficiency in general [11]. Half of the women participating in our study were found to have poor perceptions of nutrition. We can say that these emergent outcomes are caused by low socioeconomic level.

Tanrıverdi et al. (2014) reported that smoking was widespread among gypsy women [11]. A statistically significant relationship was found between the total median values of GHBI according to the smoking status of women ($p < 0.05$; **Table 3**). Smoking women had lower total median values of GHBI. We can say that the general health outcomes of women who do not exhibit healthy lifestyle behaviors may be poor and their genital hygiene behaviors may also be more negative. There was a statistically significant relationship between the total median values of GHBI of women according to the frequency of daily pad change during the menstruation period ($p < 0.05$; **Table 3**). Women changing pad 5 or more times per day had a higher total median value of GHBI. Koştu and Beydağ (2009) found that women with more frequent pad change daily had a higher mean score of GHBI [14]. Yağmur and Ergin (2017) found that vaginal infections were highly seen in those with the insufficient frequency of daily pad changing [4]. Kahyaoğulu Süt (2016) reported that changing pad less than 4 during the intensive days of menstruation increases the incidence of a genital infection [17]. Our results show that women frequently changing pads during menstruation care more about genital hygiene behaviors.

CONCLUSIONS AND RECOMMENDATIONS

The results of this research suggest that women living in slum areas of the province Adana are poor genital hygiene behaviors and women's genital hygiene behavior is affected by educational level, nutritional status, smoking status, and frequency of changing pad daily. It has been found that women have educational requirements of genital hygiene behaviors.

In line with these results, the researcher prepared a training program involving the protection of genital infections and the proper application of genital hygiene practices for women living in the study area.

DECLARATION OF CONFLICT OF INTEREST

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Original Article

Long-term compliance to continuous positive airway pressure therapy in patients with severe sleep apnea syndrome

Şiddetli uyku apne sendromu olan hastalarda sürekli pozitif hava yolu basıncı tedavisine uzun süreli uyum

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ABSTRACT

Background and Aim: Compliance is the adherence of the patient to continuous positive airway pressure (CPAP) therapy after his/her decision to start treatment. The aim of this study is to evaluate the compliance to CPAP therapy in a large patient population and the results were presented after 5 years of follow-up period in order to emphasize long-term compliance with CPAP treatment in the light of the literature.

Materials and Methods: Patients who could not afford CPAP device or attend regular controls were excluded from the study and the remaining 174 patients were included in the study. At the end of 5 years, the patients were called back. A total of 110 patients met the eligibility criteria for the study110 patients (79 males, 31 females) whose charts were reviewed.

Results: Fifty of 110 study participants (45.5%) regularly used CPAP device for ≥4 hours and the remaining 60 (54.5%) patients did not use CPAP device regularly. At the end of 5 years, we found that 36.4% of the patients used the device 4 hours a night. AHI severity does not affect adherence to the device and compliance rates (χ^2=2.743; p=0.254).

Conclusion: The patients compliance rates with CPAP device was found concord with the literature. This study conveys greater importance than other relevant studies in the literature in that it encompasses a larger patient population followed up for a longer period.

Keywords: sleep apnea syndrome, positive airway pressure, compliance

ÖZ

Giriş ve Amaç: Kompliyans, hastanın tedaviye başlama kararından sonra sürekli pozitif havayolu basıncı (CPAP) tedavisine uymasıdır. Bu çalışmanın amacı, geniş bir hasta popülasyonunda CPAP tedavisine uyumu değerlendirmektir ve sonuçlar literatür ışığında CPAP tedavisine uzun vadeli uyumu vurgulamak amacıyla 5 yıllık takip süresinden sonra sunulmuştur.

Gereç ve Yöntem: CPAP cihazı alamayan veya düzenli kontrollere katılamayan hastalar çalışmaya alınmadı ve kalan 174 hasta çalışmaya dahil edildi. 5 yılın sonunda hastalar geri çağrıldı. Toplam 110 hasta, çizelgeleri gözden geçirilmiş 110 hasta (79 erkek, 31 kadın) için uygunluk kriterlerini karşılamıştır.

Bulgular: Çalışmaya katılan 110 kişiden 50'si (%45,5) düzenli olarak ≥4 saat CPAP cihazı kullanmış ve geri kalan 60 (%54,5) hasta düzenli olarak CPAP cihazı kullanmamıştır. 5 yılın sonunda hastaların %36,4'ünün cihazı gece 4 saat kullandığını tespit ettik. AHI şiddeti cihaza uyumu ve uyum oranlarını etkilemez ($\chi 2 = 2,743$; $p = 0,254$).

Sonuç: Hastaların CPAP cihazına uyum oranları literatürle uyumlu bulunmuştur. Bu çalışma, daha uzun süre takip edilen daha geniş bir hasta popülasyonunu kapsaması bakımından literatürdeki diğer ilgili çalışmalardan daha fazla önem taşımaktadır.

Anahtar kelimeler: uyku apne sendromu, pozitif hava yolu basıncı, kompliyans

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is an important health problem characterized by cessation of airflow within the upper respiratory tract, oxygen desaturation and interruption of sleep and may be associated with significant morbidity and mortality [1,2]. Continuous Positive Airway Pressure (CPAP) therapy which is based on the principle of maintaining patency of upper respiratory tract by external application of positive pressure on the upper respiratory tract during sleep is a "gold standard" treatment modality for respiratory system disorders occurring during sleep especially in patients with severe OSAS [3,4]. Since CPAP devices show their ameliorating effects only during their application, they haven't any completely curative effect. Therefore, the patient benefits from the treatment as long as he/she uses the device [5]. On this issue according to generally accepted principle, total application time of the device should last more than 70% of the duration of the patient's treatment and at least 4 hours a night [6]. Despite its benefits, compliance to CPAP is at a suboptimal level.

Compliance is the adherence of the patient to CPAP therapy after his/her decision to start treatment [7]. When we review the studies on compliance to CPAP treatment, based on the self-reports of the patients, compliance rates range between 65 and 90%, while control systems have revealed that 29-83 % of the patients are using their CPAP devices [8]. Detection of higher usage rates have been associated with feedback received only from the patients themselves [9]. Very few studies have evaluated long-term CPAP use objectively and still very scarce number of these studies have been performed with more than 50 patients. Only very few of the researchers have followed up their patients for more than one year [10,11].

In this study, compliance to CPAP therapy in our large patient population was evaluated and our results were presented after 5 years of follow-up period in order to emphasize long-term compliance with CPAP treatment in the light of the literature. This study conveys greater importance than other relevant studies in the literature in that it encompasses a larger patient population followed up for a longer period.

PATIENTS AND METHODS

Study design: The study was performed in the Ankara Diskapi Yildirim Beyazit Training and Research Hospital between 2008 and 2017. It is a prospective study. The patients who presented with snoring, excessive daytime sleepiness and apneic symptoms to our outpatient clinic were hospitalized overnight in the sleep laboratory and polysomnographic (PSG) examinations were conducted. Number of apneic, hypopneic episodes per hour was defined as apnea-hypopnea index (AHI). Based on AHI the patients were classified as mild (AHI=5-15), moderate (AHI=15-30) and severe OSAS (AHI>30). CPAP therapy was recommended for patients with moderate OSAS with risk factor(s) or severe OSAS. These patients were hospitalized for one more night and CPAP therapy was titrated. Patients who could not afford CPAP device or attend regular controls

Table 1. Descriptive analyses of the patients included in the study

Variables	*mean±SD (min-max) median (IQR) (min-max)*
Age	47.4±7.3 (28.0- 61.0)
Pressure (mmHg)	9.7±2.5 (5.0-15.1)
Compliance (h/day)	6.0 (2.0) (4.0- 7.0)
Apnea hypopnea index	45.6 (40.0) (12.4-122.3)
Oxygen desaturation index	39.9 (40.1) (1.7-133.4)
T90	30.4 (122.9) (0.0-386.0)
Median O_2 saturation	91.7 (5.1) (60.0-95.9)
Minimum O_2 saturation	77.0 (14.0) (48.0-89.0)
PaO_2	81.0±9.7 (57.5-103.9)
$PaCO_2$	36.0±3.5 (28.9-44.9)
sO_2	95.8 (1.9) (90.5-98.9)

T90 = % sleep time below $Sp0_2$

Table 2. Compliance according to gender

Gender	PAP compliance ≥4 hours	PAP compliance <4 hours	*p* Value	*p* Value
Male (n=79)	37/79	42/79	0.180	0.642
Female (n=31)	13/31	18/31	0.245	

Table 3. Compliance according to apnea hypopnea index

AHI	PAP compliance ≥4 hours	PAP compliance <4 hours	*p* Value	*p* Value
0-30	9 (18%)	19 (31.7%)	0.114	0.254
30-70	28 (56%)	29 (48.3%)	0.245	
>70	13 (26%)	12 (20%)	0.226	

AHI= Apnea hypopnea index

were excluded from the study. At the end of 5 years, the patients were called back. We could get in touch with patients whose phone numbers and/or addresses were unchanged. Stored data of the devices were examined to estimate total and daily compliance rates. Besides, arterial blood gas values of all patients were noted. Ethics committee approval was obtained for the study.

Statistical analysis: Data were analyzed using IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). A normal distribution of the univariate data was checked using Shapiro-Wilk test. Parametric tests were applied to data of normal distribution and non-parametric tests were applied to data of questionably normal distribution. Data are expressed as mean±SD or median (interquartile range), as appropriate. All differences associated with a chance probability of .05 or less were considered statistically significant.

RESULTS

Patients who could not afford CPAP device or attend regular controls were excluded from the study and the remaining 174 patients were included in the study. At the end of 5 years, the patients were called back. A total of 110 patients met the eligibility criteria for the study. Of the 110 patients (79 males, 31 females) whose charts were reviewed, the mean was 47.4±7.3 (range, 28 to 61) years. Individual data of the patients were presented in descriptive analyses (**Table 1**). Fifty of 110 study participants (45.5%) regularly used PAP device for ≥4 hours and the remaining 60 (54.5%) patients did not use PAP device regularly.

The patients used various brands of PAP devices (19 patients (38.0%) Goodknight 420E (Puritan Bennett/Tyco Healthcare; Pleasanton, CA), 13 patients (26.0%) Horizon LT plus (DeVilbiss/Sunrise Medical; Carlsbad, CA), six patients (12.0%) AutoTREND (Hoffrichter GmbH; Schwerin, Germany), two patients (4.0%) EvoCPAP (Evo804 comfortPAP, two patients (4.0%) SleepStyle™ 600 series (Fisher & Paykel Healthcare Limited, Auckland, New Zeland), two patients (4.0%) REMstar auto (Respironics; Murrysville, PA), two patients (4.0%) SOMNOsmart 2 (Weinmann GmbH; Hamburg, Germany), one patient (2.0%) Magellan (MAP; Munich, Germany), one patient (2.0%) Medical Industries (Sleepap; America), one patient (2.0%) Moritz BiPAP (ResMed; Germany). Positive airway pressure was delivered using APAP (14/50; 28.0%), BIPAP (4/50; 8.0%), BPAP (12/50;24.0%) and CPAP (20/50; 40.0%) devices. The compliance of CPAP users was 6.0±1.0 hr/d. Compliance with the device did not differ between male and female patients (p=0.642) (**Table 2**).

Besides the patients were divided into three groups according to their AHI values and compliance rates for each group were examined. The patients with AHI values of 0-30, 30-70 and ≥70 constituted Groups 1, 2 and 3, respectively. Accordingly, AHI severity does not affect adherence to the device and compliance rates (χ^2=2.743; p=0.254) (**Table 3**).

DISCUSSION

Compliance with the device used has an important role in the success of PAP therapy. Compliance is defined by the patient's adherence to PAP therapy, after he/she decided to start the therapy. After a night passed in sleep centers on PAP therapy, nearly 70% of the cases accept to continue their treatment at home. However, problems arising within the first week of therapy decrease PAP use and within the first months 10% of the patients discontinue PAP therapy [12]. Studies on compliance have not demonstrated any correlation between compliance and age, gender,

educational level, economical status and personality [13]. In our study, a statistically significant difference was not found between the compliance, gender and age of the patients.

Compliance to PAP therapy is evaluated with the duration of PAP usage. Application period of the PAP device is determined by either asking the patient or looking at the time counters on the monitor of the PAP devices. If only patients self-reports are taken into consideration then compliance rates ranges between 65 and 90 percent [8]. Compliance rates drop to 46 % when counter system is used [8]. Krieger et al. estimated long-term compliance using time counter of the CPAP device and after a nearly 8 month-follow-up period, more than 90 % acceptance rates were reported for 46 patients with OSAS [10]. This phenomenon was taken into account in our study and time counter systems of the devices were checked to obtain data that are more precise.

For a satisfactory compliance, investigators have various criteria. For a successful use of a PAP device, as a consensus, PAP device should be used during 70% of the required time period and at least 4 hours a night. Some investigators have reported that 4 hours of PAP use is required to ensure adequate oxyhemoglobin saturation [7], while others advocated PAP use for 6 nights a week and at least 6 hours a night [12,14,15].

In our study, 50 (45.5%) patients used PAP device and 60 (54.5%) patients did not use this device. At the end of 5 years, we found that 36.4% of the patients used the device 4 hours a night, which is in compliance with the literature. In our study, 20 (40.0%) patients used CPAP, while 30 (60.0%) patients did not use it. Any significant difference (i.e. between AHI values) between the severity of the disease in patients who used or did not use CPAP device was not found, while airway pressures in PAP users were significantly lower than non-users.

In our study, in order to determine if severity of OSAS affected compliance, the patients were divided into three groups according to AHI values and for each group compliance rates for each group were estimated. Accordingly, increased AHI does not affect adherence to the device use and compliance (χ^2=2.743; p=0.254).

In a study performed on 24 patients by Sanders *et al.*, long-term (10±8 months) compliance to CPAP therapy at home was analyzed and long-term compliance rate of 75 % was detected [16]. In a multicentered prospective European study, 75% of the cases were regular CPAP users [15]. According to the definition of regular usage in this study, during the 70% of the first 3 months of the treatment period, the patients used their PAP devices for 4 hours a night. In the same study, compliance rate in the USA was found to be 46 percent. This difference was said to stem probably from cultural diversities or different methods of patients' monitorization. Kribbs *et al.* followed up compliance of 35 patients by tracking monitor displays of CPAP devices. Even though 60 % of the patients reported CPAP use every night, in fact only 16 (46%) patients used CPAP device regularly for at least 4 hours during 70 % of the duration of their monitorization period [17]. Rauscher *et al.*, reported that after the first night on CPAP therapy, 47 of 65 (72%) patients accepted treatment at home. Age, gender, body weight, daytime PaO2 values did not differ between those accepted or rejected CPAP use [18]. However, in the study by Rolfe et al. during 78 months of the follow-up period, long-term CPAP use was reportedly accepted by 64% of the patients. In patients with excessive daytime sleepiness and severe hypoxemia, rate of acceptance is at its highest level. Hypoxemia has been indicated to be the best indicator of acceptance of CPAP [14]. In a study by Hoffstein *et al.* 105 (70.9%) out of 148 patients continued to use PAP device for a mean period of 17±11 months [9]. Majority (81%) of the cases perceived CPAP as an effective treatment and 83% of them reported a subjective improvement. The authors emphasized that compliance was not correlated with severity and side effects of the disease. They also indicated that rather awareness of symptomatic improvement by the patients and their desire to get well would increase compliance.

Hussain, S.F. et al. reported that obesity, excessive daytime sleepiness, witnessed apnea and improvement of daytime symptoms following use of CPAP were predictors of improved compliance. Use of antidepressants and CPAP induced sleep disturbances were predictors of poor compliance.

Lee et al. [20] reported that in southeast Asian population almost half of all patients with significant OSA rejected CPAP treatment upfront, but adherence among those who started CPAP is comparable to other reports. Challenges with CPAP acceptance as well as CPAP adherence need to be addressed to improve outcomes.

When all these studies are reviewed, the most effective factors on compliance to PAP use appear to be symptomatic improvement after CPAP use and excessive daytime sleepiness. The correlation between severity of sleep apnea and compliance is not a stable finding.

CONCLUSION

In this study, compliance with PAP device in our large patient population was evaluated after 5 years of follow-up period in order to emphasize long-term compliance with CPAP treatment. Our study conveys greater importance than other relevant studies in the literature in that it encompasses a larger patient population followed up for a longer period. Feedback provided from the stored data of the device, instead of the patients' self-reports yielded outcomes that are more objective and increased reliability of the study. We think that our study will shed light on future studies investigating the ways of increasing compliance of the OSAS patients to PAP therapy.

DECLARATION OF CONFLICT OF INTEREST

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Orijinal Makale

HbA1c düzeyi yüksek trigliserid düzeyinden etkilenir mi?

Is HbA1c level affected by high triglyceride levels?

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ÖZ

Giriş: Diyabetik hastalarda trigliserid yüksekliği, düşük dansiteli lipoprotein (LDL) kolesterolün artışı ve yüksek dansiteli lipoprotein (HDL) kolesterolün düşüklüğü ile karakterize aterojenik dislipidemi görülür. Lipoprotein anormallikleri diyabetli hastalarda görülen koroner arter hastalığı riskinin artmasını açıklamaktadır. Tip 2 diyabetli hastaların %30-60'ında dislipidemi olduğu tahmin edilmektedir. Glikolize hemoglobin (HbA1c) değerinin yüksek olması kötü glisemik kontrolün yanında komplikasyon riskinin artmış olabileceğini göstermekle birlikte ayrıca hastanın dislipidemi yönünden araştırılması ve uygun hastaların tedavi edilmesi açısından önemlidir. Bu çalışmamızda trigliserid değerinin yüksek HbA1c değerinden etkilenip etkilenmediğini, aralarında ilişki olup olmadığını tespit etmek için planladık.

Gereç ve Yöntemler: Temmuz 2017 ile Temmuz 2019 tarihleri arasında Diyarbakır Gazi Yaşargil Eğitim ve Araştırma Hastanesi Dâhiliye Polikliniği'ne başvuran diyabetes mellitus tanılı hastalar retrospektif olarak tarandı. Bu hastalar arasında HbA1c >6,5 ve trigliserid düzeyi 150-1000 mg/dl'nin arasında olanlar çalışmaya dahil edildi.

Bulgular: Hastalarımızın 2492'si kadın (%62), 1564'ü erkek (%38) idi. Hastalarımızın ortalama yaşı 53'tü (min-max; 18-65). HbA1c, trigliserid, cinsiyet, yaş ve glukoz arasında yapılan istatistiksel karşılaştırmada; HbA1c'nin trigliserid, yaş ve glukoz ile anlamlı farklılık gösterdiği (Sırasıyla; p değerleri: 0,000, 0,027, 0,000), cinsiyet ile istatistiksel olarak anlamlı fark olmadığı (p: 0,723), trigliseridin ise HbA1c, yaş, glukoz ve cinsiyet ile anlamlı farklılık gösterdiği görüldü (Sırasıyla; p değerleri: 0,000, 0,000, 0,000, 0,001).

Sonuçlar: HbA1c düzeyinin trigliseridin yükselmesinden etkilenmediği ve düşük sonuçlara neden olmadığı görüldü. Ayrıca yaş ile birlikte trigliserid, HbA1c ve glukoz düzeyinde düşüş olması ile HbA1c düzeyi artıkça trigliserid düzeyinde de artış izlenmesinin çalışmamızın en önemli verisi olduğunu düşünmekteyiz. Diyabetik hastanın glukoz regülâsyonunun sağlanamamasının lipid profilini olumsuz etkilediğini ortaya koyması açısından bu çalışmamızın değerli olduğunu düşünmekteyiz.

Anahtar kelimeler: HbA1c, glukoz, trigliserid, yaş

ABSTRACT

Aim: Diabetic patients have atherogenic dyslipidemia characterized by increased triglyceride, increased low-density lipoprotein (LDL) cholesterol, and low-density lipoprotein (HDL) cholesterol. Lipoprotein abnormalities explain the increased risk of coronary artery disease in patients with diabetes. It is estimated that 30-60% of patients with type 2 diabetes have dyslipidemia. The high HbA1c value indicates that the risk of complications may be increased in addition to poor glycemic control, but it is also important in terms of investigating the patient for dyslipidemia and treating appropriate patients. In this study, we planned to investigate whether HbA1c is affected by high triglyceride values and whether triglyceride elevation may indicate low HbA1c.

Material and Methods: In this study, Diabetic patients aged between 18-65 years with HbA1c > 6.5 who applied to Diyarbakır Gazi Yaşargil Training and Research Hospital Internal Medicine Clinic between July 2017 and July 2019 were included.

Results: In our study we found a negative relationship between the age of our patients and HbA1c, glucose and triglycerides. There was a linear correlation between HbA1c and triglyceride. In parallel with the rise of triglyceride, there was also an increase in HbA1c.As glucose and triglyceride increased, HbA1c also increased.

Conclusion: HbA1c level was not affected by elevated triglyceride and did not cause low results. We also think that the decrease in triglyceride, HbA1c and glucose levels with age and the increase in triglyceride level as HbA1c level increases are the most important data of our study. We think that this study is valuable in terms of demonstrating that failure of glucose regulation in diabetic patients adversely affects lipid profile.

Keywords: HbA1c, glucose, triglyceride, age

GİRİŞ

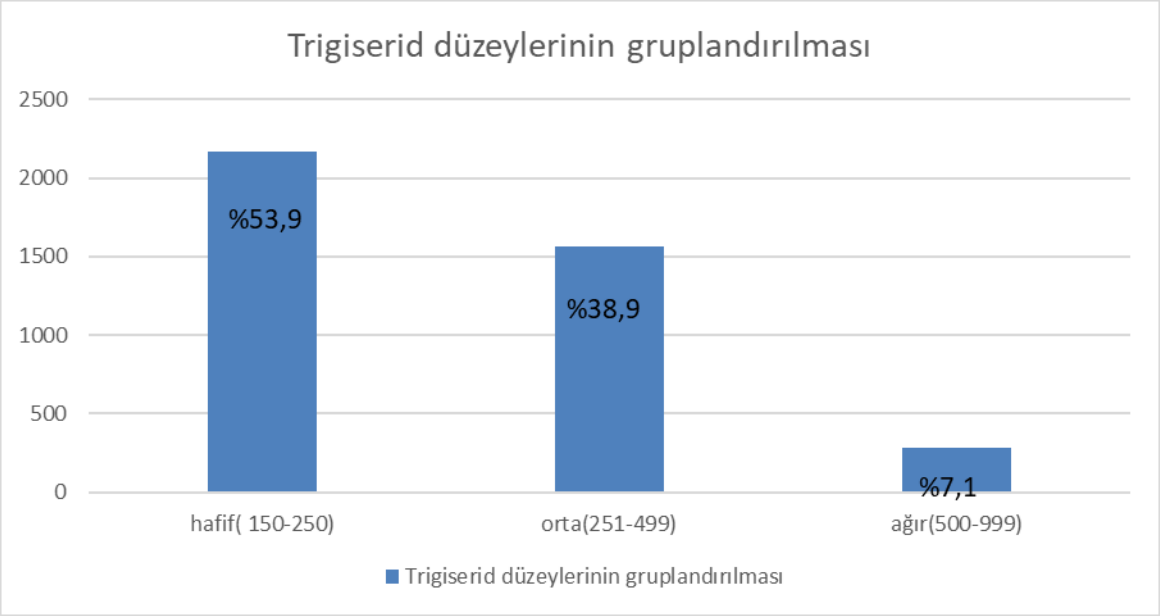
Diabetes mellitus (DM), insülinin etki etmediği veya insülinin eksikliği nedeniyle hücrelerin yağ, protein ve karbonhidrattan yeterince faydalanamadığı, devamlı tıbbi bakım gerektiren, en sık görülen kronik endokrin metabolizma hastalığıdır [1]. DM'nin dünyada ve ülkemizde sıklığı giderek artmaktadır [2]. Uluslararası Diyabet Federasyonu (IDF) 'ya göre, dünya genelinde 2019 yılında görülen 463 milyon diyabet hasta sayının 2045 yılına gelindiğinde 700 milyon diyabet hastasına ulaşması bekleniyor [3].

DM' de görülebilen komplikasyonlar; retinopati, nefropati ve nöropati gibi mikrovasküler ile koroner arter hastalığı, inme ve alt ekstremitelerin iskemisi gibi makrovasküler komplikasyonlardır. DM'li bireylerde normal popülâsyona göre mortalite artmaktadır. Mortalitenin artmasının esas nedeni makrovasküler komplikasyonlardır [4].

Diyabette trigliserid yüksekliği, düşük dansiteli lipoprotein (LDL) kolesterolün artışı ve yüksek dansiteli lipoprotein (HDL) kolesterolün düşüklüğü ile karakterize aterojenik dislipidemi görülür. Lipoprotein anormallikleri diyabetli hastalarda görülen koroner arter hastalığı riskinin artmasını açıklamaktadır. Tip 2 diyabetli hastaların %30-60'ında dislipidemi olduğu tahmin edilmektedir [5].

İnsülin direnci olan hastalarda, hormon duyarlı lipaz inhibisyonunda azalma olur ve adipoz dokudan karaciğere serbest yağ asidi geçişi artar. İnsülin karaciğerde lipoprotein lipaz (LpL) enzim aktivitesini düzenler ve apolipoprotein üretimini etkileyerek diyabetik dislipidemi gelişir [6,7]. Hipertrigliseridemi (HTG); Trigliserid düzeyinin 150 mg/dl fazla olması olarak tanımlanır. Trigliserid düzeyi hafif HTG (150-499 mg/dl), orta HTG (500-880 mg/dl) ve şiddetli HTG (>880 mg/dl) olarak sınıflandırılır [8]. HTG kardiyovasküler morbidite ve mortalitenin nedenlerinden biridir ve hipertrigliseridemi hastalarında pankreatit ve yağlı karaciğer hastalığı riskinde artış söz konusudur [9]. Diyabeti olmayanlara göre diyabetik hastalarda aterojenik lipid profili daha yüksek oranda görülür ve bundan dolayı dislipidemik diyabetiklerde kardiyovasküler mortalite oranı daha yüksektir. Lipid düzeylerinin diyabetik hastalarda hedeflenen değerlere düşürülmesi ile kardiyovasküler komplikasyonlar ve mortalitenin azaldığı gösterilmiştir [10].

Glikolize hemoglobin (HbA1c) diyabetik hastaların tanı ve tedavi takiplerinde rutinde kullanılan ortalama son 3 aylık glisemik düzeyi gösteren bir parametredir. Diyabetik komplikasyon gelişme riski açısından da fikir veren HbA1c'de bir birimlik artış dislipidemiden bağımsız olarak iskemik kalp hastalığı gelişme riskini yaklaşık %18 arttırır [11]. HbA1c değerinin yüksek olması kötü glisemik



Resim 1. Trigiserid düzeylerinin gruplandırılması

kontrolün yanında komplikasyon riskinin artmış olabileceği ve hastanın dislipidemi yönünden araştırılması ve uygun hastaların tedavi edilmesi açısından önemlidir. Bu çalışmamızda trigliserid değerinin yüksek HbA1c değerinden etkilenip etkilenmediğini, aralarında ilişki olup olmadığını tespit etmeyi amaçladık.

GEREÇ VE YÖNTEM

Bu çalışmamız Diyarbakır Gazi Yaşargil Eğitim ve Araştırma Hastanesi Dâhiliye Polikliniği'ne son 2 yılda (Temmuz 2017-Temmuz 2019) başvuran tüm tip 2 diyabet hastaları üzerinde yapıldı. Çalışmamız retrospektif olarak hastanemiz dâhiliye polikliniğine diyabet rutin kontrolleri için gelen ve 3 aylık periyodlarla bakılan rutin açlık glukoz, HbA1c ile trigliserid değerleri alınarak yapıldı. Çalışmaya 18-65 yaş arası HbA1c >6,5 olan diyabetik hastalardan trigliserid düzeyi 150-1000 mg/dl'nin arasında olanlar alındı. HbA1c düzeyi Arkray-Adams HA8180 cihazında HPLC yöntemiyle, glukoz düzeyleri heksodimeraz yöntemiyle ve trigliserid düzeyi kalorimetrim yöntem ile Roche Cobas C701 Brea cihazında çalışıldı.

Etik kurul onayı: Bu çalışmanın etik kurul onamı hastanemiz etik kurulunca 2019/329 sayı ile alınmıştır.

İstatistiksel Analiz: Çalışmada elde edilen sayısal veriler; aritmetik ortalama±standart sapma (SS), kategorik veriler; frekans (yüzde) olarak ifade edildi. İstatistiksel analizler SPSS 22,0 paket programı kullanılarak yapıldı. Normal dağılıma uygunluk Kolmogorov Smirnov testi ile değerlendirildi. Gruplar arasındaki farklılıklar gerektiğinde Kruskal Wallis testi ile araştırıldı. Gruplar arası korelâsyon değerlendirmeleri 'Spearman Testi' kullanılarak yapıldı. İstatistiksel anlamlılık için $p<0,05$ değeri kabul edildi.

Tablo 1. Hastalarımızın cinsiyet dağılımına göre Trigliserid, HbA1c, Glukoz ve Yaş ortalamaları

	Kadın (ort.)	SS	Erkek (ort.)	SS	Toplam	SS
Yaş	53	7,95	53	9,13	53	8,46
Trigliserid	236	123,4	247	154,3	240	136,4
HbA1c	8,8	2,21	8,9	2,17	8,9	2,2
Glukoz	192	105,5	197	102,7	194	104,4

Ort. Ortalama, SS: standart sapma

BULGULAR

Çalışmamıza alınan 4017 hastanın 2492'si kadın (%62), 1564'ü erkek (%38) ve ortalama yaşı 53'tü (min-max; 18-65). Hastalar Trigliserid düzeylerine göre üç gruba ayrıldı. Trigliserid düzeyi 150-250 mg/dl olanlar hafif, 251-499 mg/dl olanlar orta ve 500-999 mg/dl olanlar ise ağır HTG olarak gruplandırıldı. Hafif grupta 2167 kişi (%53,9), orta grupta 1564 kişi (%38,9) ve ağır grupta 286 (%7,1) kişi yer aldı (**Resim 1**).

Tüm hastalarımızın yaş ortalaması 53, TG ortalaması 240 mg/dl, HbA1c ortalaması %8,9 ve glukoz ortalaması 194 mg/dl olarak bulundu. Cinsiyetlere göre dağılım **Tablo 1**'de özetlendi.

Yaptığımız çalışmada hastalarımızın yaşı ile HbA1c, glukoz ve trigliserid arasında negatif bir ilişki görüldü. HbA1c ile trigliserid arasında ise doğrusal bir korelasyon olup trigliseridin yükselmesine paralel olarak HbA1c'de de yükselme olduğu görüldü. Glukoz ve trigliserid arttıkça HbA1c de artmaktaydı (**Tablo 2**).

Tablo 2. Tüm hastalarda HbA1c ve Trigliserid düzeylerinin diğer değişkenlerle korelâsyon analizi

	HbA1c		Trigliserid		Cinsiyet		Yaş		Glukoz	
	r	p	r	p	r	p	r	p	r	p
HbA1c	1,000		0,096	0,000	0,006	0,723	-0,035	0,027	0,689	0,000
Trigliserid	0,096	0,000	1,000		0,054	0,001	-0,077	0,000	0,119	0,000
Cinsyet	0,006	0,723	0,054	0,001	1,000		-0,083	0,000	0,0114	0,368
Yaş	-0,035	0,027	0,077	0,000	-0,083	0,000	1,000		-0,057	0,000
Glukoz	0,689	0,000	0,119	0,000	0,014	0,368	-0,057	0,000	1,000	

Tablo 3. Her grubun kendi içerindeki yaş ortalaması, glukoz düzeyi ve HbA1c düzeyleri

	Hafif (150-250 mg/dl)	Orta (251-499 mg/dl)	Ağır (500-999 mg/dl)
Yaş (Ortalama)	53	53	51
Glukoz (mg/dl)	182	204	231
HbA1c (%)	8,6	9,0	9,6

HbA1c, trigliserid, cinsiyet, yaş ve glukoz arasında yapılan istatistiksel karşılaştırmada; HbA1c'nin trigliserid, yaş ve glukoz ile anlamlı farklılık gösterdiği (Sırasıyla; p değerleri: 0,000, 0,027, 0,000), cinsiyet ile istatistiksel olarak anlamlı fark olmadığı (p: 0,723), Trigliseridin ise HbA1c, yaş, glukoz ve cinsiyet ile anlamlı farklılık gösterdiği görüldü. (Sırasıyla; p değerleri: 0,000, 0,000, 0,000, 0,001) (**Tablo 2**).

Pearson korelasyon analizine göre; HbA1c'nin glukoz ile beklendiği gibi güçlü derecede pozitif korelasyon gösterdiği (r=0,689), TG ile zayıf pozitif korelasyon (r=0,096) ve yaş ile zayıf negatif korelasyon(r=–0,035) gösterdiği saptanmıştır. (**Tablo 2**).

Hastaların trigliserid gruplarının yaş, glukoz ve HbA1c ile yapılan karşılaştırmalı incelemesinde her üç grupta da yaş ortalaması benzerdi. Glukoz ve HbA1c ise trigliserid düzeyi yükseldikçe paralel bir şekilde yükselmekteydi (**Tablo 3**).

TARTIŞMA

HbA1c değerinin yüksek olması kötü glisemik kontrolün yanında komplikasyon riskinin artmış olabileceği ve hastanın dislipidemi yönünden araştırılması ve uygun hastaların tedavi edilmesi açısından önemlidir. Çalışmamızda HbA1c değerinin yüksek trigliserid değerlerinden etkilenip etkilenmediğini araştırdık.

2007 yılında Khan HA ve ark. 1011 tip 2 diyabet hastasıyla yaptıkları çalışmada HbA1c düzeyi ile Trigliserid düzeyleri arasında pozitif korelasyon (p: 0,000, r: 0,153) ve HDL ile negatif korelasyon (p: 0,002, r: –0,128) gösterdiler; Trigliserid ile HbA1c arasındaki korelasyonun büyüklüğü (r: 0,153) glukoz ile olan korelasyonundan (r: 0,134) daha büyük olarak tespit etmişlerdi. Çalışmamızda trigliserid düzeyi ile HbA1c arasındaki pozitif korelasyon benzer olmakla birlikte, farklı olarak HbA1c düzeyi ile glikoz arasındaki korelasyonun (r: 0,689) büyüklüğü trigliseridle olan korelasyondan (r: 0,096) çok daha büyük görülmüştür [12]. Çalışmamızdaki hasta sayısı Khan ve ark.'lar yaptığı çalışmadaki hasta sayısının dört katı olduğu ve HbA1c'nin son üç aylık ortalama glukozu gösterdiği düşünüldüğünde çalışma sonuçlarımızın daha anlamlı olduğu kanaatindeyiz. Yine yapılan birçok çalışmada Trigliserid düzeyi ile HbA1c düzeyleri karşılaştırılmış ve anlamlı pozitif korelasyon saptanmıştır [13-15]. Bu çalışmalardan farklı olarak Yasemin Şefika Akdeniz ve ark. İstanbul Bakırköy Dr Sadi Konuk Eğitim Araştırma Hastanesi Endokrin Kliniğinde Ötiroid olan Tip 2 Diyabetli Hastalarda TSH ve HbA1c Düzeylerinin Trigliserid düzeyi üzerine etkisi incelenmiş ve trigliserid düzeylerine göre gruplandırdıkları grup 1 ve grup 2 hastalarda HbA1c ile trigliserid düzeyleri arasında pozitif korelasyon saptanmış. Trigliserid değerleri daha yüksek olan grup 3 ve 4 teki hastalarda ise trigliserid ve HbA1c düzeyleri arasında ilişki saptamamışlar [16]. Bizim çalışmamızda ise tüm HTG gruplarında pozitif korelasyon saptanmış ve trigliserid düzeyi yükseldikçe pozitif korelasyonun sürdüğü gözlemlenmiştir.

Deqiang Zheng ve ark. Çin'de yaptığı çalışmada yüksek trigliserit seviyelerinin, yetersiz glisemik kontrol ile güçlü bir şekilde ilişkili olduğu ortaya konmuş; dolayısıyla, trigliserit seviyelerinin baskılanmasıyla tip 2 diyabetes mellituslu hastalarda daha optimal glisemik kontrole ulaşabilinir sonucuna varmışlardır. Ancak insülin direnci ve insülin eksikliğinin serbest yağ asitlerinde artışa neden olarak artan yağ asitlerinin trigliserid üretimini stimüle ettiğini bu nedenle HTG'nin HgA1c düzeyi yüksekliğinin sebebi değil sonucu olduğu aşikardır [17,18].

Yaptığımız çalışmada hastalarımızın yaşı ile HbA1c, glukoz ve trigliserid arasında negatif korelasyon tespit edilmiştir (Sırasıyla; r değerleri: –0,035, –0,057, –0,077). Yaş artıkça HbA1c, glukoz ve Trigliserid düzeyinde azalış saptanmıştır. HbA1c ve trigliserid arasında ise doğrusal bir korelâsyon olduğu, trigliseridin yükselmesine paralel olarak HbA1c de yükselme olduğu görüldü (p:0,000, r: 0,096). Hastaların trigliserid gruplarının yaş, glukoz ve HbA1c ile yapılan karşılaştırmalı incelemesinde her üç grupta da yaş ortalaması benzerdi. Glukoz ve HbA1c düzeyi ise trigliserid

düzeyi yükseldikçe paralel bir şekilde yükselmekteydi. Her üç grupta da HbA1c düzeyinin trigliserid düzeyiyle pozitif korele olduğu görüldü. Ayrıca yaş ile birlikte trigliserid, HbA1c ve glukoz düzeyinde düşüş olması ve HbA1c düzeyi artıkça trigliserid düzeyinin artmış olmasının çalışmamızın en önemli verisi olduğunu düşünmekteyiz. Diyabetik hastanın glukoz regülasyonunun sağlanamamasının lipid profilini olumsuz etkilediğini ortaya koyması açısından bu çalışmamızın değerli olduğunu düşünmekteyiz. Bu çalışmanın bulguları, HbA1c'nin uzun süreli glisemik kontrolün yararlı bir biyobelirteci olduğu gibi aynı zamanda trigliserid düzeyinin iyi bir öngörücüsü olduğunu açıkça göstermektedir.

Çalışmamızın retrospektif olması en önemli kısıtlayıcı nedendi. Hasta sayısının daha kapsamlı olduğu, trigliserid düzeylerinin yanında antitrigliserid ilaç kullanımının olup olmadığı, vücut kütle indekslerinin olduğu prospektif çalışmaların yapılması ile daha doğru sonuçlara varılabileceği kanaatindeyiz.

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Original Article

A mathematical modelling for the COVID-19 pandemic in Iran

İran'daki COVID-19 pandemisi için matematiksel bir modelleme

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ABSTRACT

The novel coronavirus which is known as SARS-CoV-2 or COVID-19 emerged in China with the first clinical case in December 2019, and afterwards, it has turned into a global problem very fast. Iran is a crowder Middle Eastern country with a population of 82531700. Until 31.03.2020, the number of cases in Iran reached 44605, and 2898 patients lost their lives. This study aimed to simulate the progression of the COVID-19 pandemic in Iran with modified mathematical modelling established based on the information that the time-dependent change (spreading rate) in the number P of the individuals who has caught a contagious disease is proportional to the multiplication of the numbers of those who have caught the disease and those who have not. If the precautions are increased a little bit, as its reflection on the progression of the disease would be "exponential", it seems possible for the number of cases to decrease down to around 120 thousand and for the deaths to be around 8 thousand or even lower. According to our modified mathematical modelling results, in order to change the course of the pandemic in Iran, effective individual and public precautions should definitely be taken urgently. The most effective individual precautions may be listed as paying maximal attention to hygiene, having a natural and healthy diet, increasing mobility and exercise and paying attention to social isolation.

Keywords: COVID-19, mathematical modelling, pandemic, precautions, public health

ÖZ

SARS-CoV-2 veya COVID-19 olarak bilinen yeni koronavirüs, Çin'de Aralık 2019'daki ilk klinik vaka ile ortaya çıktı ve daha sonra çok hızlı bir şekilde küresel bir soruna dönüştü. İran, nüfusu 82531700 olan bir kalabalık Ortadoğu ülkesidir. 31.03.2020 tarihine kadar İran'daki vaka sayısı 44605'e ulaştı ve 2898 hasta hayatını kaybetti. Bu çalışmada, genel anlamda bulaşıcı hastalığa yakalanmış bireylerin P sayısının zamana göre değişim (yayılma) hızı; hastalığa yakalanmış olanların sayısı ile yakalanmamış olanların sayısının çarpımı ile orantılı olması bilgisinden yola çıkarak oluşturulan yeni bir modifiye özgün matematiksel modelleme üzerinden COVID-19 pandemisinin İran'daki gidişatının simüle edilmesi amaçlandı. Önlemler biraz artarsa, hastalığın ilerlemesi üzerine yansıması "üstsel" olacağı için, vaka sayısının 120 bine düşmesi ve ölümlerin 8 bin civarında olması bile mümkün görünmektedir. Modifiye matematiksel modelleme sonuçlarımıza göre, İran'daki pandeminin seyrini değiştirmek için etkili bir şekilde bireysel ve kamusal önlemler mutlaka acilen alınmalıdır. En etkili bireysel önlemler hijyene azami önem vermek, doğal ve sağlıklı beslenmek, hareketliliği ve egzersizi arttırmak ve sosyal izolasyona dikkat etmek olarak sıralanabilir.

Anahtar kelimeler: COVID-19, matematiksel modelleme, pandemi, önlemler, halk sağlığı

INTRODUCTION

The novel coronavirus which is known as SARS-CoV-2 or COVID-19 emerged in China with the first clinical case in December 2019, and afterwards, it has turned into a global problem very fast. COVID-19 starts with upper respiratory tract infection symptoms and may progress towards lower respiratory tract infections and respiratory distress. It may create a life-threatening situation as a result of viral pneumonia progressing with diffuse lung involvement. One of the countries in the world where it has progressed most rapidly is Iran [1-3]. In Iran, the first COVID-19 case was seen on 19.02.2020. Iran is a crowder Middle Eastern country with a population of 82531700. Until 31.03.2020, the number of cases in Iran reached 44605, and 2898 patients lost their lives. COVID-19 infection, which is spread very fast, has reached pandemic conditions in Iran, as in the entire world [4]. The diagnosis of COVID-19 is made at molecular medicine laboratories with the method of reverse transcription-polymerase chain reaction. The fight against the pandemic has got easier with the help of RT-PCR analysis. However, in the diagnosis of the disease, while molecular analyses are important, clinical findings should definitely be considered. Additionally, classical viral infection findings may be seen with biochemical analyses, and radiological imaging may be useful in diagnosis [5]. Due to the rapid progression of the COVID-19 pandemic in Iran and the high numbers of infected and deceased cases, it is important to know about the progression of the disease in the near future. It is important to use scientific modelling to know about the number of cases in the near future and how much these potential numbers could be reduced with the universal precautions that could be taken. This study aimed to simulate the progression of the COVID-19 pandemic in Iran with novel, modified mathematical modelling established based on the information that the time-dependent change (spreading rate) in the number P of the individuals who has caught a contagious disease is proportional to the multiplication of the numbers of those who have caught the disease and those who have not.

METHOD

It is known that the spreading rate of a contagious disease emerging in a region with a population M is proportional to the multiplication of the numbers of those who have caught the disease and those who have not [6]. Where λ is the proportional constant, this situation is expressed in the mathematical language with the following differential equation:

$$\frac{dP}{dt} = \lambda P(M - P) \qquad (1)$$

Additionally, the model given by (1) in the literature was developed by Cakir and Savas in a way to simulate the COVID-19 pandemic trend in Turkey (7).

In this study, it was modified as "**the spreading rate of the disease $\left(\frac{dP}{dt}\right)$ is directly proportional to the multiplication of the numbers of those who have caught the disease and those who have not and inversely proportional to the time variable**" and analyzed specifically for the "COVID-19 pandemic in Iran". Accordingly, the mathematical model representing the progression of the disease in Iran was established in the form of:

$$\begin{cases} \dfrac{dP}{dt} = \dfrac{63r}{100t^{0.37}}P(M-P) & (2) \\ P(0) = P_0 & (3) \\ P(t_1) = P_1 & (4) \end{cases}$$

The meanings assigned to the variables and parameters used in the model are shown below.

t: time variable (in days),

$P(t)$: number of patients at time *t*,

$\frac{dP}{dt}$: derivative expressing the spreading rate of the disease,

λ: a parameter containing all factors that affect the change in spreading based on time.

In addition to this, let us express the initial number of patients by $P(0) = P_0$ (at time $t = 0$), the number of patients at a later time by $P(t_1) = P_1$ (at time $t = t_1$), and the highest possible number of patients as M.

In difference to the model (1) in the literature whose right-hand side uses a proportionality constant λ, in our study, we used a function on the right-hand side explicitly including the variable *t* as $\lambda(t) = \frac{63r}{100t^{0.37}}$. This choice of ours allowed us to establish a mathematical model that allows us to reach more realistic data in the form of a (2)-(4) initial value problem (IVP). Here, r is a positive proportionality constant.

Now, let us solve the (2)-(4) initial value problem. For this, let us first take the differential equation (2) in type of separation of variables.

$$\frac{dP}{dt} = \frac{63r}{100t^{0.37}}P(M-P) \Rightarrow \frac{dP}{P(M-P)} = \frac{63r}{100t^{0.37}}dt$$

$$\Rightarrow \frac{P}{(M-P)} = ce^{Mrt^{0.63}} \quad (5)$$

$$\Rightarrow P(t) = \frac{Mc}{\left(e^{-Mr\,t^{0.63}} + c\right)}$$

Using the initial condition $P(0) = P_0$ in (5),

$$P(0) = P_0 = \frac{Mc}{(e^0 + c)} \Rightarrow c = \frac{P_0}{M - P_0}. \quad (6)$$

Additionally, if the condition (4) is used to determine the parameter r corresponding to the rate of spreading, it is seen that,

$$P(t_1) = P_1 = \frac{Mc}{e^{-Mr\,t_1^{0.63}} + c} \Rightarrow e^{-Mr\,t_1^{0.63}} + c = \frac{Mc}{P_1}$$

$$\Rightarrow -Mr = t_1^{-0.63} ln\left(\frac{P_0\,(M-P_1)}{P_1\,(M-P_0)}\right). \quad (7)$$

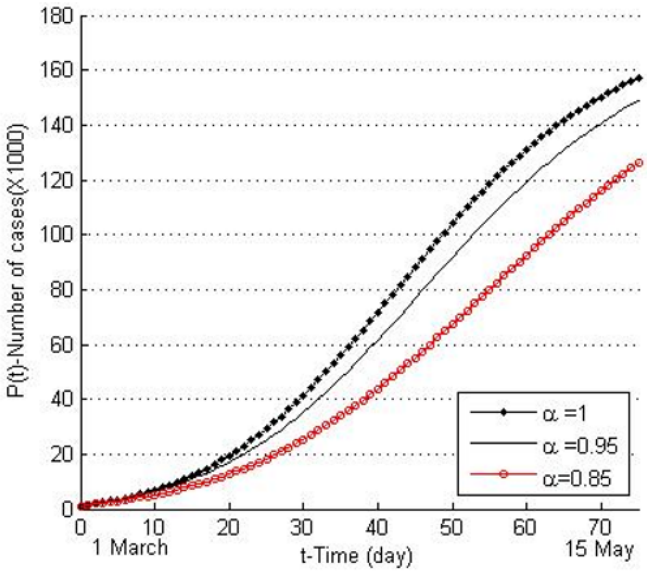

Figure 1. Changing in the number of cases between 1 March - 15 May 2020

Putting the expressions (6) and (7) in the formula (5), the solution of the (2)-(4) IVP is obtained as

$$P(t) = \frac{Mc}{\left(c + e^{-k\,t^{0.63}}\right)}. \quad (8)$$

Here, $k = \frac{1}{t_1^{0.63}} ln\left(\frac{P_1\,(M-P_0)}{P_0\,(M-P_1)}\right)$, and it is a positive constant.

RESULTS

The behavior of the analytical function (8) we obtained as the theoretical solution of the (2)-(4) IVP represents the change in the number of patients in the period of 1 March - 15 May. To analyze this change in more detail and more tangibly, the information that the actual number of patients on 1 March 2020 ($t = 0$ −onset) was $P(0) = P_0 = 978$ individuals, and the actual number of patients on 31 March 2020 (taking $t_1 = 31$) was $P(t_1) = P(31) = P_1 = 44605$.

In the case that the potential number of patients that could catch the disease is $M = 180000$, we may see the changing trend in the number of cases in a future 45-day period in **Figure 1**.

Based on the ratios of the cases and deaths reached by the day 31 March, the Corona-related death numbers expected for the one and a half months in the future are shown in **Figure 2**.

In the case that current practices continue ($\alpha = 1$), it is expected for the number of cases to reach 160 thousand in mid-May, while the number of deaths is expected to exceed 10 thousand.

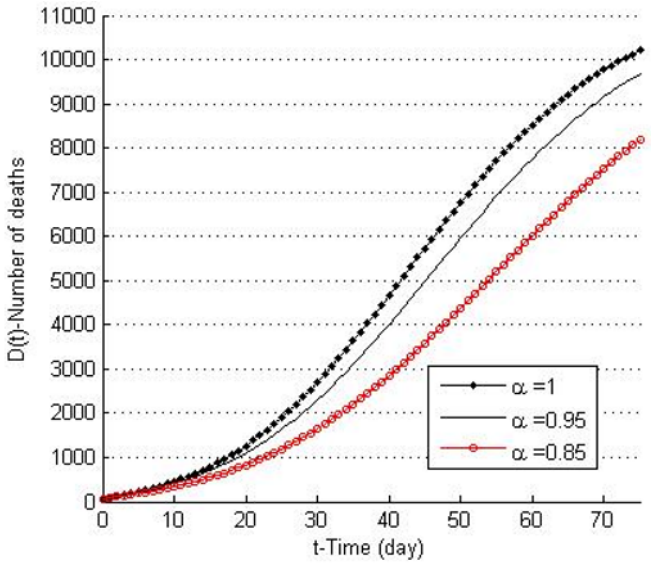

Figure 2. Changing in the number of deaths between 1 March - 15 May 2020

If the precautions are increased a little bit, as its reflection on the progression of the disease would be "exponential", it seems possible for the number of cases to decrease down to around 120 thousand and for the deaths to be around 8 thousand or even lower. We are obtaining these inferences with the help of an *α* control parameter that expresses the exponential reflections of precautions which we added to the solution of the mathematical model we established.

In contrast, in the case of alleviating existing practices or the public not taking the situation seriously, it is clear that these numbers will go up even further.

DISCUSSION

According to our mathematical modelling results, if serious precautions are not taken, it is projected that approximately 120000 new cases will emerge in Iran, and the number of the deceased may exceed 10 thousand in the next 40 days. For this reason, with the help of taking public and individual precautions in Iran within a scientific framework and strict implementations of these, a significant reduction may be achieved. The amount of increase of the COVID-19 pandemic has an "exponential" change. This is why precautions to be taken will be very effective in reducing the spreading rate of the disease. According to the analysis results on our modified mathematical model that we are presenting in this study, even a small increase in the precautions will create a large difference in terms of patient numbers and the number of patients who will lose their lives. If serious rates of effective precautions are not taken, the course of the pandemic in Iran may display a very fast change in the negative direction. For these reasons, every individual or social precaution to be taken in Iran will be very significant in terms of controlling the COVID-19 pandemic and overcoming it with fewer losses. Our previous mathematical modelling results reflecting the situation in Turkey showed numerical differences, while they had similarities to Iran in terms of behaviors towards precautions. As in Turkey, with a small amount of effective precautions, it will be possible to highly reduce the number of cases in Iran. Our research results numerically demonstrate this situation (7).

CONCLUSION

According to our modified mathematical modelling results, in order to change the course of the pandemic in Iran, effective individual and public precautions should definitely be taken urgently. The most effective individual precautions may be listed as paying maximal attention to hygiene, having a natural and healthy diet, increasing mobility and exercise and paying attention to social isolation. Being confined at home for social isolation may lead to a more sedentary life and an unhealthy diet. This situation weakens the immune system. We should be mobile within the home and regularly do simple exercises. Additionally, efforts should be spent to eat healthy. This way, the spreading rate of the disease will decrease, and as the immune system is strengthened, the mortality rate of patients diagnosed with COVID-19 will decrease. It should be noted that smoking is a fact that increases the risk factor related with COVID-19. Vitamin and antioxidant supplements are thought to be beneficial in prophylaxis and treatment. Additionally, in the public sense, it is necessary to make official regulations towards social isolation, diagnose suspicious cases by applying molecular tests fast, isolate patients and protect especially the elderly more.

DECLARATION OF CONFLICT OF INTEREST

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Original Article

Frequency of personality types based on enneagram in a Turkish sample: A web-based cross-sectional study

Türkçe bir örneklemde enneagrama dayalı kişilik tiplerinin sıklığı: Web tabanlı kesitsel bir çalışma

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ABSTRACT

Objectives: Although the Enneagram is known for hundreds of years, research in this area is scarce. The purpose of this study was to analyze the frequency of personality types of a Turkish-speaking sample and compare the rates of different personalities with demographic data.

Methods: The Tastan Personality Types Inventory, an instrument based on Enneagram, was hosted at Google Forms and made available via the university's academic web page. Online responses were collected between 08.04.2015 and 22.8.2019. Participants of the study were Turkish speaking people aged adolescents and adults.

Results: Results for 1646 participants were analyzed. The mean (±SD) age was 29.48±11.03 years. The most commonly encountered main personality type was number 2, "the helper," (n=335, 20.4%), while number 8, "the challenger" was the most frequently encountered personality wing (284, 17.3%). The frequency of type 8 personality was decreasing with increasing age, while the reverse was true for type 3 personality (χ^2=130.623, p<0.001). While the type 1 personality was more common among males (n=51 (9.5%) vs. n=63 (5.7%)), the type 4 was almost twice common among females (n=48 (8.9% vs. n=183 (16.5%)) (χ^2=28.835, p<0.001). Also, the probability of type 1 personality was increasing as the level of education increased (χ^2=67.316, p<0.001).

Conclusion: There are differences in the personality types of the studied population concerning demographic variables. These findings imply that personality is not a lifelong constant entity, but it can change with age and education. Further studies should investigate the relationship of the Enneagram personality types with certain disease entities in defined populations.

Keywords: personality, personality assessment, psychometrics

ÖZ

Amaç: Enneagram yüzlerce yıldır bilinmesine rağmen, bu alandaki araştırmalar azdır. Bu çalışmanın amacı Türkçe konuşan bir örneklemin kişilik tiplerinin sıklığını analiz etmek ve farklı kişiliklerin oranlarını demografik verilerle karşılaştırmaktır.

Yöntem: Enneagram'a dayalı bir araç olan Taştan Kişilik Tipleri Envanteri Google Formlar'da barındırıldı ve üniversitenin akademik web sayfası üzerinden kullanıma sunuldu. Çevrimiçi yanıtlar 08.04.2015 ve 22.8.2019 tarihleri arasında toplanmıştır. Çalışmanın katılımcıları Türkçe konuşan ergenler ve yetişkinlerdir.

Bulgular: Bu araştırmada 1646 katılımcının verileri analiz edildi. Ortalama (± SD) yaş 29,48 ± 11,03 yıl idi. En sık karşılaşılan ana kişilik tipi 2 numaralı "yardımcı" (n = 335, %20,4), 8 numaralı "meydan okuyucu" ise en sık karşılaşılan kişilik kanadıdır (284, %17,3). Tip 8 kişilik sıklığı artan yaşla birlikte azalırken, tip 3 kişilik için tersi doğruydu (χ^2 = 130,623, p <0,001). Tip 1 kişilik erkeklerde daha yaygın iken (n = 51 (%9,5) ve n = 63 (%5,7)), tip 4 kadınlarda neredeyse iki kat fazlaydı (n = 48 (%8,9'a karşılık n = 183 (%16,5)) (χ^2 = 28,835, p <0,001) Ayrıca, eğitim düzeyi arttıkça tip 1 kişilik olasılığı da artmaktadır (χ^2 = 67,316, p <0,001).

Sonuç: İncelenen nüfusun kişilik tiplerinde demografik değişkenler açısından farklılıklar vardır. Bu bulgular kişilik tipinin beşikten mezara kadar aynı olmadığını, eğitim ve yaşla değişebileceğini düşündürmektedir. Enneagram kişilik tiplerinin tanımlanmış popülasyonlardaki belirli hastalıklarla ilişkisi araştırmalıdır.

Anahtar kelimeler: kişilik, kişilik değerlendirmesi, psikometri

INTRODUCTION

Background and Rationale

Knowing the personality traits has advantages for the person as well as the people in contact [1]. It will not only help to facilitate communication and establish a favorable dialogue between people, but can also aid professionals in psychology, medicine [2], arts, business, and education. Some have suggested the use of personality traits in personnel recruitment, sales, and marketing [3]. Personality traits have been hypothesized to be clinically useful for diagnosis, client conceptualization, treatment planning, as well as for predicting treatment outcomes, potential strengths, and barriers to treatment [4].

Standardized psychometric tests of adult personality and psychopathology such as the Minnesota Multiphasic Personality Inventory [5], the Five-Factor Model [6], Zuckerman-Kuhlman Personality Questionnaire [7], Temperament and Character Inventory [8], and Kupfer Detre Scale [9], were utilized by health professionals as part of their assessment procedures. Although the Enneagram principles are known in Europe since the 1920s [10], its use has not become widespread, partly due to missing appropriate measurement scales [11].

The Enneagram of Personality is a concept categorizing using nine interconnected personality types [12]. It was suggested that the Enneagram can serve as a tool for understanding the ideas and behaviors of others as well as improving relationships with family, friends, and co-workers [13]. The Enneagram proposes explanations of why a person acts in a certain way and recommends directions for individual growth [3].

Although the Enneagram is known since ancient times [14], the assessment of an individual requires experience and time. Hence, it was not widely employed as a psychometric measurement tool. However, there are recent efforts to develop scales measuring temperament based on the Enneagram [11,15].

Objectives

The purpose of this study was to analyze the frequency of personality types of a Turkish-speaking sample and compare the frequencies of different personalities with demographic data.

METHODS

Study Design

The study was conducted in a descriptive, cross-sectional design between 08.04.2015 and 22.8.2019. Study reporting was done following the STROBE guidelines [16]. This study has been approved by the Ataturk University Faculty of Medicine Clinical Research Ethics Committee (No: B.30.2.ATA.0.01.00/168-Date:10.24.2016).

Table 1. Internal consistency of the inventory and its subscales

Component	Number of items	Cronbach's alpha
1	5	0.631
2	4	0.379
3	6	0.811
4	5	0.809
5	5	0.676
6	4	0.618
7	4	0.835
8	6	0.740
9	5	0.810
Total	44	0.866

Setting

The Tastan Personality Types Inventory (TPTI) [11] was hosted at Google Forms (https://docs.google.com/forms/d/e/1FAIpQLSeN90dTISi43Bjh4GRX7zDc01cow4hcpTrn0Ao2Eab7E4rm5g/viewform) and made available via the university's academic web page http://aile.atauni.edu.tr. Responses were collected online. A note on the purpose of data collection was included in the form.

Variables

The primary outcome variable of the study was the leading personality type, as defined by the TPTI [11]. Additionally, demographic questions included were age, sex, educational status, occupation, and city of residence.

The TPTI uses 44 questions to identify the leading personality and one personality wing based on the Enneagram theory [14]. Scoring of the TPTI is made by a 7-point Likert scale, ranging from 0 (Strongly No) to 6 (Strongly Yes). All items of the inventory are positively scored. The mean scores of the nine components and a total score by adding all component scores were calculated. The Cronbach's alpha internal consistency score for all 44 items, and the nine dimensions are given in **Table 1**.

Bias

Since the questionnaire was self-applied, one can assume an anonymous atmosphere. However, interference by third persons during data entry cannot be precluded. Nevertheless, we performed detailed post-hoc data checking and debugging to minimize bias.

Participants

Participants of this study are Turkish speaking people who randomly or with some advice accessed the data collection tool on the World Wide Web. Responses for the years 2015, 2016, 2017, 2018, and 2019 were 699, 788, 136, 333, and 549, respectively (Total 2505 entries). Records with matching age, sex, and e-mails (n=526; 21.0%) were accepted as repeated entries, of which all except the last entry were deleted. Also, records with duplicating scores for all domains (n=32; 1.6%) were considered as entries by the same person and removed.

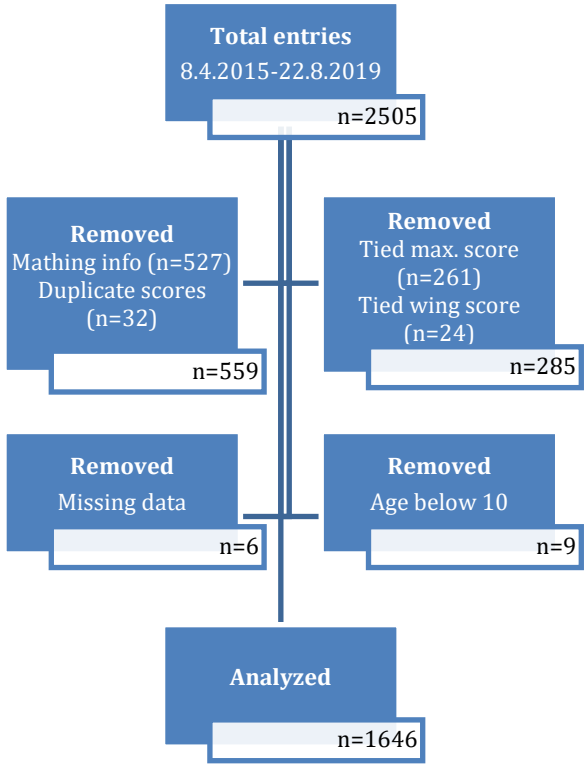

Figure 1. Study flow diagram

The automatic scoring algorithm could not decide on the primary personality type for 261 participants, who had tied maximum scores. These and additional 24 participants with tied wing scores could not be categorized by the computer and thus, removed. Lastly, 9 participants below 10 years and 7 participants with missing data (age, sex) were excluded, ending up with 1646 participants for analysis (**Figure 1**).

Study Size

The sample size of the population was calculated based on the primary outcome "Main personality type." To compare the nine personality types between two groups using Chi-Square with an effect size of 0.14 (low), an alpha error of 0.05, and a power of 0.99, a total sample size of 1602 participants is required [17].

Statistical Methods

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 software (SPSS Inc., Chicago, IL, USA). The results were presented as frequencies, percentages, means, and standard deviations (SD). The Kolmogorov-Smirnov test was performed to test if the

Table 2. Demographic characteristics of the participants

		n	%
Sex	**Female**	**1107**	**67.3**
	Male	**539**	**32.7**
Occupation	White collar employee with bachelor degree	428	26.0
	Teacher	225	13.7
	Government officer	221	13.4
	Blue collar worker and housewives	187	11.4
	Student	553	33.6
	Unemployed	32	1.9
Education	Primary school	46	2.8
	Secondary school	114	6.9
	High school	195	11.8
	University	1022	62.1
	Masters	179	10.9
	PhD	90	5.5
Geographical Area	Mediterranean	90	8.3
	East Anatolia	129	11.9
	Aegean	177	16.3
	South-East Anatolia	213	19.6
	Central Anatolia	184	16.9
	Marmara	220	20.3
	Black sea	59	5.4
	Outside Turkey	14	1.3

Table 3. Distributions of the primary personality types

			TPTI Score of the primary personality	
Personality type	Frequency	Percent	Mean	SD
1-The perfectionist	114	6.9	4.97	0.75
2-The helper	335	20.4	5.17	0.69
3-The achiever	204	12.4	5.21	0.66
4-The romantic	231	14.0	5.30	0.65
5-The observer	136	8.3	5.22	0.68
6-The loyalist	47	2.9	5.19	0.66
7-The adventurer	247	15.0	5.44	0.60
8-The challenger	95	5.8	5.18	0.73
9-The peacemaker	237	14.4	5.27	0.62
Total	1646	100.0		

numerical variables were normally distributed. The independent samples t-test and one-way ANOVA with post hoc Tukey test were used to compare numerical data. The Chi-Square test was used to compare categorical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Participants

Results for 1646 participants were analyzed. The mean (±SD) age was 29.48±11.03 years (min. 10, max. 72). More women took part in the study than men. Also, university students comprised a significant portion of the sample. Responses came from all seven geographical regions of Turkey and even a few from outside Turkey (**Table 2**).

Table 4. Distribution of the personality wings

			TPTI Score of the wing personality	
	Frequency	Percent	Mean	SD
1	289	17.6	3.96	0.89
2	224	13.6	4.33	0.76
3	289	17.6	4.30	0.89
4	170	10.3	4.22	0.97
5	182	11.1	4.20	0.93
6	69	4.2	3.78	0.98
7	79	4.8	4.06	1.07
8	284	17.3	4.00	1.00
9	60	3.6	3.99	0.98
Total	1646	100.0		

Descriptive Data

The most commonly encountered primary personality type was number 2, "the helper," while number 8, "the challenger" was the most frequently encountered personality wing (**Tables 3** and **4**).

Outcome Data

Frequencies of the primary personality types showed significant differences concerning different demographic features. As examples of some remarkable findings, the rate of type 8 personality was decreasing with increasing age, while the reverse was true for type 3 personality. The type 2 personality was predominantly stronger both among males and females. However, while the type 1 personality was more common among males, the type 4 was almost twice common among females. Also, the probability of type 1 personality was increasing as the level of education increased. On the other hand, the occupation was related to the type of personality too. While all participants had more type 2 personalities, this trait was highest among the unemployed (**Table 5**).

The mean TPTI scores concerning the main personality types were different. Participants with type 5 personality had significantly higher mean scores compared to the types 1 (Tukey p 0.010) and 6 (Tukey p 0.040). Participants with type 5 personality had the highest scores, while people with type 6 personality had the lowest scores (**Figure 2**).

DISCUSSION

Key Results

This study demonstrated that the most commonly encountered leading personality type in the studied

Table 5. Differences in the main personality types

	Main Personality Type																			
	1		2		3		4		5		6		7		8		9			
	n	%	n	%	n	%	n	%	n	%	n	%	N	%	n	%	n	%	χ^2	*p*
Age groups (years)																			130.623	**<0.001**
19 and below	22	7.2	72	23.7	17	5.6	52	17.1	19	6.3	9	3.0	55	18.1	30	9.9	28	9.2		
20-29	42	6.6	121	19.1	49	7.7	103	16.2	72	11.4	18	2.8	105	16.6	42	6.6	82	12.9		
30-39	25	6.9	74	20.4	65	17.9	44	12.1	24	6.6	15	4.1	42	11.6	13	3.6	61	16.8		
40-49	21	7.9	46	17.2	54	20.2	23	8.6	16	6.0	4	1.5	37	13.9	9	3.4	57	21.3		
50 and above	4	5.1	22	28.2	19	24.4	9	11.5	5	6.4	1	1.3	8	10.3	1	1.3	9	11.5		
Sex																			28.835	**<0.001**
Female	63	5.7	237	21.4	134	12.1	183	16.5	84	7.6	31	2.8	158	14.3	59	5.3	158	14.3		
Male	51	9.5	98	18.2	70	13.0	48	8.9	52	9.6	16	3.0	89	16.5	36	6.7	79	14.7		
Education																			67.316	**<0.001**
Secondary sch. or below	4	2.5	40	25.0	24	15.0	22	13.8	8	5.0	6	3.8	29	18.1	6	3.8	21	13.1		
High school	12	6.2	38	19.5	27	13.8	24	12.3	17	8.7	3	1.5	33	16.9	18	9.2	23	11.8		
University	68	6.7	210	20.5	97	9.5	161	15.8	91	8.9	32	3.1	153	15.0	59	5.8	151	14.8		
Masters	18	10.1	31	17.3	37	20.7	19	10.6	15	8.4	2	1.1	22	12.3	9	5.0	26	14.5		
PhD	12	13.3	16	17.8	19	21.1	5	5.6	5	5.6	4	4.4	10	11.1	3	3.3	16	17.8		
Occupation																			104.874	**<0.001**
White collar with bachelor	38	8.9	88	20.6	65	15.2	56	13.1	28	6.5	14	3.3	51	11.9	24	5.6	64	15.0		
Teacher	14	6.2	37	16.4	30	13.3	33	14.7	18	8.0	8	3.6	36	16.0	11	4.9	38	16.9		
Government officer	13	5.9	37	16.7	39	17.6	24	10.9	19	8.6	4	1.8	40	18.1	14	6.3	31	14.0		
Blue collar and housewives	10	5.3	34	18.2	34	18.2	24	12.8	14	7.5	4	2.1	19	10.2	1	0.5	47	25.1		
Student	37	6.7	129	23.3	35	6.3	85	15.4	55	9.9	17	3.1	97	17.5	43	7.8	55	9.9		
Unemployed	2	6.3	10	31.3	1	3.1	9	28.1	2	6.3	0	0.0	4	12.5	2	6.3	2	6.3		

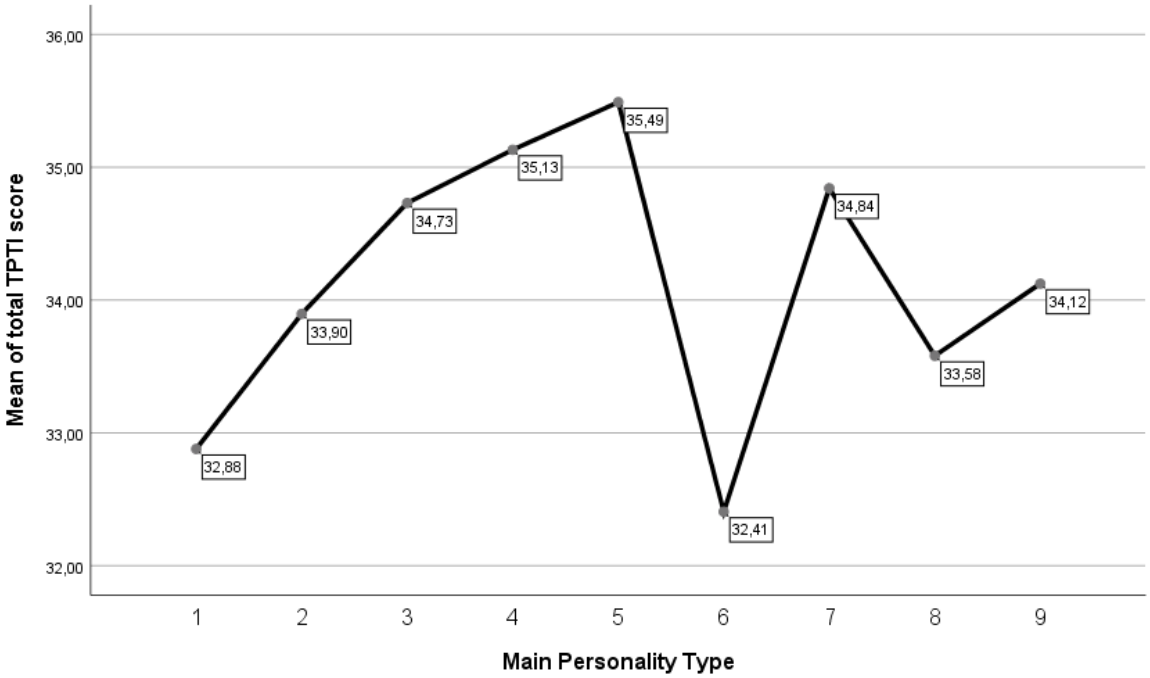

Figure 2. Mean TPTI scores of participants with different main personality types

population was number 2, "the helper," while number 8, "the challenger" was the most frequently encountered personality wing. On the other hand, the occupation was related to the type of personality too. Type 2 personality was strongest among the unemployed. The frequency of type 8 personality was decreasing with increasing age, while the reverse was true for type 3 personality. On the other hand, while the type 1 personality was more common among males, the type 4 was almost twice common among females. Also, the probability of type 1 personality was increasing as the level of education increased.

Interpretation

The Enneagram assigns one primary temperament type and a wing personality to each individual. While number one "the perfectionist" personality type believes in the correctness of moral values, the number two "the helper" believes in his/her importance, number three "the achiever" strives for perfectness, number four "the romantic" gives importance to own freedom, number five "the observer" trusts in the power of knowledge, number six "the loyalist" emphasizes the trust provided by the people, number seven "the adventurer" gives importance to materiality, number eight "the challenger" counts for power, and number nine is called "the peacemaker" [3,14]. However, the personality of a person is a combination of all nine types [18].

The approach based on the personality type can be an advantage for healthcare providers, who recognize that each individual is different. Furthermore, the doctor's personality type preferences are often very different from those of the patients [19]. The Enneagram was used to predict healthy lifestyle changes. Researchers have investigated the relationship between Enneagram personality types and perceived risk of heart disease and readiness to lifestyle modification [20]. The achiever personality can have an increased willingness to lifestyle modification, while a reverse relationship was found between the challenger personality and readiness to lifestyle modification. It may be deducted that the Enneagram personality types may be used to check any kind of willingness to change.

In our study, the most commonly encountered primary personality type was number 2, "the helper," while number 8, "the challenger" was the most frequently encountered personality wing. As to the original study during the scale development, the most prevailing personality among the participants was found as personality number nine, the peacemaker [11]. Other researchers [12,21] consistently identified the number nine-personality type is the most frequent personality type. However, the populations studied in all the given studies consisted of university students, which make us postulate that there are trans-country similarities in the personality distributions but with variability between the different groups in the same country.

As remarkable findings, the frequency of type 8 personality in our study was decreasing with increasing age, while the reverse was true for type 3 personality. Although there is no available literature to interpret this finding, we considered it as an indicator that the personality traits are changing with age. The challenger side of a person may get rasped over time, while they may become more understandable and ready to help others as they get older, and, thus, wiser.

On the other hand, while the type 1 personality was more common among males, the type 4 was almost twice common among females. This finding might be related to the gender identities in the Turkish population [22]. Also, the probability of type 1 personality was increasing as the level of education increased. The type 1 personality was explained as "…are conscientious and ethical, with a strong sense of right and wrong. They are teachers, crusaders, and advocates for change: always striving to improve things, but afraid of making a mistake..." [23]. From this perspective, it might be expectable that education induces some change in the personality.

One study on medical students compared the Jefferson Scale of Empathy scores in different Enneagram personality groups [18]. It was revealed that type 2 and 6 students showed the two highest empathy scores, while the empathy score of type 3 students was the lowest. Also, it was demonstrated that an Enneagram group counseling program is effective in establishing positive self-identification in nursing college students [12]. Although we found some differences in the personality types concerning the occupational groups with strikingly high proportions of type 2 personalities among the unemployed, this finding requires additional elaboration due to the relatively low number of participants in this group.

According to the Enneagram, the nine personality types can be further sub-categorized into different groups called the hornevian groups, and the harmonic groups [24]. In the current era of knowledge, increasingly, more responsibilities are transferred to the individuals concerning their own health. Thus, instruments such as the Enneagram scales may become reliable frameworks for understanding differences with patients, families, and co-workers [25].

Study Limitations

A significant limitation of this study is the relatively ill-defined study population. Turkish speaking participants from anywhere could participate in the study. However, we achieved a high sample size that could collect responses coming from all seven geographical regions of Turkey. Also, due to the nature of data collection, the participants must have a certain level of computer literacy. Thus, the study cannot claim generalizability to the Turkish population but can give a strong idea about the general distribution of the Enneagram personality types in Turkey. Also, the

measurement tool used [11] had high sensitivity and specificity, which can be considered as a strength of the study.

Conclusion

Our research indicates that the number 2 personality is the most frequent personality type among the studied Turkish-speaking population. Further studies should investigate the relationship of the Enneagram personality types with certain disease entities in specific communities using the main personality types, hornevian groups, and harmonic groups.

DECLARATION OF CONFLICT OF INTEREST

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Original Article

Non-alcoholic fatty liver disease in patients with familial hypercholesterolemia

Ailevi hiperkolesterolemisi olan kişilerde non-alkolik yağlı karaciğer hastalığı

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ABSTRACT

Aim: The liver plays a crucial role in the synthesis and catabolism of cholesterol. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the developed world and commonly associated with metabolic comorbidities such as diabetes mellitus, hypertension, dyslipidemia, and obesity. The aim of this study was to investigate the frequency of NAFLD in Familial Hypercholesterolemia (FH).

Material and Method: Between 2017 and 2018, individuals with FH who had been referred to the Department of Endocrinology at Erzurum Regional Training and Research Hospital were admitted to this single center case-control study. Total 30 individuals (17 female and 13 male) who have FH were compared to a control group included 39 participants (30 female and 9 male). The two groups were thought to be well matched in terms of sample size and gender distribution. Family history was registered. Diagnosis is made by blood tests and ultrasound imaging of liver.

Results: The two groups showed no significant differences in terms of age and gender. NAFLD was seen at 12 of 39 individuals in the control group. It was seen at 16 of 30 persons in the FH group ($p = 0.058$). Total cholesterol (mg / dl) (333.27 ± 58.46) (219.23 ± 82.84) ($p = 0.000$), LDL (mg / dl) (249.93 ± 45.43) (127.11 ± 46.52) ($p = 0.000$) and CRP (mg / L) (3.37 ± 4.16) (1.43 ± 1.96) ($p = 0.014$) levels were significantly different between the FH and control groups respectively.

Conclusion: There isn't a significant difference between control and FH groups in terms of NAFLD. The absence of NAFLD on ultrasonography, should not reduce the severity and importance of FH, and the treatments should be made to prevent complications such as atherosclerosis.

Keywords: hypercholesterolemia, non-alcoholic fatty liver disease, ultrasonography

ÖZ

Amaç: Karaciğer, kolesterol sentezinde ve katabolizmasında çok önemli rol oynar. Non-alkolik yağlı karaciğer hastalığı (NAYKH), gelişmiş ülkelerde kronik karaciğer hastalığının en sık sebebidir ve sıklıkla diabetes mellitus, hipertansiyon, dislipidemi ve obezite gibi metabolik hastalıklarla komorbidite gösterir. Bu çalışmanın amacı Ailevi Hiperkolesterolemide (AH) NAYKH görülme sıklığını araştırmaktır.

Gereç ve Yöntemler: 2017-2018 yılları arasında Erzurum Bölge Eğitim ve Araştırma Hastanesi Endokrinoloji Polikliniğine başvurmuş olan AH'li kişiler tek merkezli bu vaka kontrol çalışmasına alındı. AH'li toplam 30 kişi (17 Kadın 13 erkek), 39 kişiden oluşan (30 kadın, 9 erkek) kontrol grubu ile karşılaştırıldı. İki grup sayı ve cinsiyet yönünden denkti. Aile öyküsü kaydedildi. Tanı kan tetkikleri ve karaciğer ultrasonografisi ile kondu.

Bulgular: İki grup arasında yaş ve cinsiyet açısından anlamlı fark görülmedi. NAYKH, kontrol grubundaki 39 kişiden 12'sinde saptanırken, AH grubunda 30 kişiden 16'sında görüldü (p = 0,058). AH ve kontrol gruplarının sırasıyla toplam kolesterol (333,27 ± 58,46) (219,23 ± 82,84) (mg / dl) (p = 0,000), LDL (249,93 ± 45,43) (127,11 ± 46,52) (mg / dl) (p = 0,000) ve CRP (3,37 ± 4,16) (1,43 ± 1,96) (mg / L) (p = 0,014) düzeyleri arasında anlamlı fark bulundu.

Sonuçlar: AH ve kontrol grupları arasında NAYKH açısından anlamlı bir fark yoktur. Ultrasonografide NAYKH saptanmaması, AH'ye yaklaşımdaki ciddiyeti azaltmamalıdır.

Anahtar kelimeler: hiperkolesterolemi, non alkolik yağlı karaciğer hastalığı, ultrasonografi

INTRODUCTION

Lipoproteins are essential for transport of cholesterol, triglycerides, and fat soluble vitamins through body fluids to and from tissues. Disorders of lipoprotein metabolism are called as dyslipidemias. If the levels of LDL are very high, it is likely genetic.

Familial hypercholesterolemia (FH) is a common and serious autosomal dominant disorder that leads to aggressive and premature atherosclerosis, although there is not a unique gene involved. The diagnosis is performed using lipid phenotype, physical stigmata, for example, tendon xanthomas and familial history of hyperlipidemia. FH is one of the most frequently occurring Mendelian disorders, representing about 1 in 500 individuals. More than 1600 different mutations have been reported in association with FH. As a consequence of a mutation in the LDL-receptor gene, impaired transport of LDL into the cells results in a reduced rate of clearance of LDL from the circulation and causes hypercholesterolemia [1].

NAFLD is the leading cause of chronic liver disease in USA, affecting nearly a third of the US population [2]. It is estimated that around 64 million people in USA have NAFLD, with annual direct medical costs of about US $ 103 billion (US $ 1613 per patient) [3]. NAFLD may be considered the hepatic event in the metabolic syndrome and is therefore linked with common metabolic syndrome risk factors such as obesity, insulin resistance, hypertension, and dyslipidemia [4]. FH is characterized by elevated plasma levels of LDL (usually 200-400 mg / dL) in the absence of hypertriglyceridemia [5]. Disease recognition is usually based on detection of hypercholesterolemia on routine screening. Elevated levels of cholesterol lead to tendinous xanthomas and coronary, cerebral, and peripheral vascular atherosclerosis at an early age. Untreated FH is associated with an increased risk of cardiovascular disease. A familial history of hyperlipidemia and / or premature coronary disease is supportive of the diagnosis. Diagnosis is usually made on clinical grounds.

Approximately 70% of the plasma LDL is cleared by the liver. In this process the first step involves binding of LDL to cell surface receptors.

NAFLD is the most common acquired metabolic disorder and affects 3-12% of western population. NAFLD is strongly associated with overweight / obesity and insulin resistance. NAFLD is found to increase the risk for hepatocellular carcinoma. Over the past 15 years, NAFLD is the most common cause of elevated liver enzymes found in the population [6]. Ethnicity affects the prevalence of NAFLD. In pathogenesis, insulin resistance and hepatocellular oxidative injury takes place. Individuals with insulin resistance and metabolic syndrome, the visceral adipose tissue increases and becomes dysfunctional. Adiponectin production reduces, and inflammatory cytokines production increases. Fat laden cells are easily damaged by oxidative stress causing apoptosis. There isn't any specific blood test for NAFLD. Subjects with NAFLD are usually asymptomatic.

The term "Nonalcoholic steatohepatitis" (NASH) is preferred to use for histologic features of hepatocyte injury [7]. The majority of hepatocellular lipids are stored as triglycerides, but free fatty acids, cholesterol, and phospholipids, may contribute. In NASH triglyceride accumulation and inflammation coexists. Pathologic steatosis is defined as involving more than 5% of hepatocytes. NASH involves liver lipid accumulation (steatosis) combined with hepatic inflammation. Individuals with simple steatosis are generally asymptomatic. Abdominal ultrasound imaging may reveal fat accumulation in the liver. Serum ALT AST are elevated in about 90% with NASH. Liver biopsy is the most reliable diagnostic tool.

The prevalence of NAFLD in the general population is increasing, but only a small proportion will develop NASH. Estimates in the United States are that only 2% - 3% of all adults have NASH, compared with an estimation of 20% of Americans with NALFD [8].

Pathogenesis of NAFLD: When hepatocyte mechanisms for triglyceride synthesis such lipid uptake and lipogenesis overwhelm mechanisms for triglyceride disposal such degradative metabolism and lipoprotein export lead to accumulation of fat within hepatocytes. There isn't any specific blood test for NAFLD. Subjects with NAFLD are usually asymptomatic.

Diagnosis of NAFLD is made when abnormal liver aminotransferases or features of fatty liver are noted during an evaluation performed for other reasons. Obesity and other features of metabolic syndrome such as hypertriglyceridemia, low levels of HDL, hyperglycemia, and hypertension are present in most patients.

The aim of this study was to investigate the frequency of NAFLD in FH.

MATERIAL AND METHODS

Between 2017 and 2018, individuals with FH who had been referred to the Department of Endocrinology at Erzurum Regional Training and Research Hospital were admitted to this case-control study. Total 30 individuals (17 female and 13 male) who have FH were compared to a control group included 39 participants (30 female and 9 male). The mean age was 49.16 ± 11.63 in the study group and 45.97 ± 8.073 in the control group. The two groups were thought to be well matched in terms of sample size and gender distribution. A careful social, medical and family history obtained. Family history of cardiovascular disease (first-degree relatives: males younger than 55 years, females younger than 60 years) was also registered. Diagnosis was made by blood tests and ultrasound imaging of liver.

Biochemical and hormone analysis. Fasting blood samples were collected in gel tubes that did not include anticoagulants to measure blood glucose, cholesterol, C-reactive protein (CRP), thyroid stimulating hormone (TSH), free T3 (FT3), free T4 (FT4), thyroid peroxidase immune body (anti-TPO), anti-thyroglobulin immune body (anti-TG), and liver and renal function. An additional blood sample was collected in an EDTA tube and used to measure the hemogram. All the blood samples were collected after 12 h overnight fasting and centrifuged at 1800 × g for 15 min before analyzing.

Biochemical parameters were measured colorimetrically using Abbott original reagents in an Abbott Architect c8000 autoanalyzer. Plasma lipid and lipoprotein levels were measured after a 12-h overnight fast. The total cholesterol and triglyceride levels in the plasma were measured enzymatically. After precipitation of apoB containing lipoproteins, HDL was measured. LDL was estimated by using following equation:

LDL = total cholesterol - (TG / 5) - HDL

Hypothyroidism, nephrotic syndrome, obstructive liver disease, viral hepatitis, excessive alcohol consumption, drug-induced or congenital liver diseases, surgical procedures (gastric by pass, extensive small bowel resection, jejunoileal by pass), autoimmune diseases, pregnancy, inborn errors of metabolism, medications associated with hepatic steatosis excluded.

Clinical Research approval was received for this study from the Local Ethics Committee of Erzurum Regional Training and Research Hospital. World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects were applied in this study.

A hepatic USG examination was performed by the radiologists. NAFLD was defined as an increase at the liver echogenicity and graded from 1 to 3. The normal liver parenchyma has a homogeneous echogenicity equal to the renal cortex and spleen.

Grade 1: Increased diffuse echogenicity,

Grade 2: The portal vein branches and diaphragm echogenicity were partly obscured by the increased parenchyma echogenicity.

Table 1. Total cholesterol (mg / dl), LDL (mg / dl) and CRP (mg / L) levels were significantly different between the familial hypercholesterolemia (FH) and control groups

	FH (mean ± SD)	Control (mean ± SD)	p-values
Total cholesterol	333.27 ± 58.46	219.23 ± 82.84	0.000
LDL	249.93 ± 45.43	127.11 ± 46.52	0.000
CRP	3.37 ± 4.16	1.43 ± 1.96	0.014

FH: familial hypercholesterolemia

Table 2. The ultrasound imaging of liver of the familial hypercholesterolemia (FH) and control groups (p = 0.058)

	FH	Control
NAFLD	16	12
Normal liver ultrasound	23	27

NAFLD: Non-alcoholic fatty liver disease.

Grade 3: The diaphragmatic outline was not visualized, and the posterior segments of the liver were poorly assessed [9].

STATISTICAL ANALYSIS

We performed all statistical analyses using SPSS for Windows, version 17.0. Unless otherwise stated, results were expressed as mean ± SD. We used the Mann-Whitney U test or independent sample t test between two subject groups, and used the Pearson correlation test or Spearman correlation test, as appropriate. A p value less than 0.05 was considered statistically significant.

Informed consent statement: All involved persons (subjects or legally authorized representative) gave their informed consent prior to study inclusion.

Conflict-of-interest statement: There isn't any conflict-of-interest statement.

Data sharing statement: Presented data are anonymized and risk of identification is low.

RESULTS

Serum AST, ALT, and creatinine levels of FH group were not higher than control group, but total cholesterol (mg / dl) (333.27 ± 58.46) (219,23 ± 82,84) (p = 0.000), LDL (mg / dl) (249,93 ± 45,43) (127,11 ± 46,52) (p = 0.000) and CRP (mg / L) (3,37 ± 4,16) (1,43 ± 1,96) (p = 0.014) levels were significantly different between the FH and control groups respectively (**Table 1**).

The ultrasound imaging of liver of the two groups were similar. NAFLD was seen at 12 of 39 individuals in the control group. It was seen at 16 of 30 persons in the FH group (p = 0,058) (**Table 2**).

DISCUSSION

This is the first study to evaluate NAFLD in patients with FH.

Fatty liver frequency was not found different among FH and control groups. High serum triglyceride levels and low serum HDL levels are seen at about 50% of patients with NAFLD [10].

In this study CRP concentrations (mg / L) in FH (3.37 ± 4.16) were significantly high from control group (1.43 ± 1.96) (p = 0.014). CRP concentrations in patients with FH were found significantly higher than control group in numerous studies [11,12]. CRP levels were associated with the presence of cardiovascular disease in FH patients [13]. Systemic inflammation induced by hypercholesterolemia may facilitates the progression to steatohepatitis.

In this study, triglyceride and HDL levels weren't significantly different between groups. Overproduction of VLDL (very-low-density lipoprotein) particles is an important cause of familial combined hyperlipidemia and it is driven by the amount of hepatic fat [14]. Increased VLDL and relatively normal levels of LDL secretion takes place in the hepatic steatosis at insulin resistance [15]. NAFLD patients exhibited significantly reduced HDL compared to the control subjects [16].

Sun et al. observed a significant association between LDL level and prevalence of NAFLD in 5689 subjects who had undergone liver ultrasonography. They have demonstrated that increased levels of LDL within the normal range have an independently relationship with an elevated risk of NAFLD [17]. Unlike this study, our study includes only the individuals who have FH.

In a study, statistically significant high levels of serum triglyceride, LDL and HDL were found in the cases with NAFLD compared to the control group [18]. But in our study, there wasn't a significant difference at TG and HDL levels of the groups.

In the Multi-Ethnic Study of Atherosclerosis, LDL concentrations have generally been reported to be at normal levels in the setting of NAFLD [19].

It was shown that high cholesterol / high fat diets in some animal models caused steatosis in the liver and lesions of the aorta [20,21]. But that animals have lipid metabolism different from that of humans.

In this study, FH group didn't show any important difference from control group in the terms of NAFLD.

The limitation of this study is that the sample size is small.

CONCLUSION

There isn't a significant difference between FH and control groups in the terms of NAFLD. The absence of NAFLD on ultrasonography, should not reduce the severity and importance of FH, and the treatments should be made to prevent complications such as atherosclerosis.

DECLARATION OF CONFLICT OF INTEREST

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Orijinal Makale

İnterlökin-6 düzeyinin epileptik nöbet ile ilişkisi

The relationship between interleukin-6 and epileptic seizure

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ÖZ

Amaç: Epileptik nöbet geçiren hastalarda interlökin-6 (IL-6) düzeyinin nöbet türü, etiyolojisi ile infeksiyon parametreleri olan ateş, lökosit ve c-reaktif protein (CRP) ile ilişkisinin incelenmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya 24 kişiden oluşan hasta grubu ve 24 kişiden oluşan kontrol grubu olmak üzere toplam 48 kişi dahil edildi. Hastaların IL-6, ateş, lökosit ve CRP değerleri ölçülerek kaydedildi. Hastalar nöbet türüne ve etiyolojisine göre sınıflandırıldı. IL-6 düzeylerindeki yüksekliğin, infeksiyon parametreleri, nöbet türü ve etiyolojisiyle olan ilişkisi değerlendirildi.

Bulgular: IL-6 düzeyi nöbet hastalarında kontrol grubuna göre yüksek bulundu. Epilepsi hastalarında IL-6 düzeylerindeki yükselmenin ateş, lökosit ve CRP düzeylerindeki yükselme ile arasında korelasyon bulunmadı. Hastalar nöbet türüne göre değerlendirildi. Hasta grubu ve kontrol grubunun IL-6 düzeyleri karşılaştırıldığında kontrol grubu ile parsiyel nöbet geçiren hastalarla arasında anlamlı fark bulunmazken (p=0,270), primer jeneralize, sekonder jeneralize ve jeneralize status ile arasında anlamlı fark belirlendi (sırasıyla p=0,012, p=0,011, p=0,040). Nöbet etiyolojisi ile IL-6 düzeyleri arasında ilişki saptanmadı.

Sonuç: Epileptik nöbet geçiren hastalarda IL-6 düzeyi diğer infeksiyöz parametrelerden ve etiyolojiden bağımsız olarak yüksek saptanabilmektedir. IL-6 düzeyi, primer jeneralize, sekonder jeneralize nöbetlerde ve jeneralize statusta, parsiyel nöbetlere göre anlamlı olarak yüksek bulunabilir.

Anahtar kelimeler: epilepsi, interlökin-6, epileptogenez, infeksiyon

ABSTRACT

Aim: The aim of this study was to evaluate the relationship between interleukin-6 (IL-6) levels and the type of the seizure, etiology of the seizure and the infection parameters which were fever, leukocyte count and c-reactive protein (CRP) in epileptic patients.

Material and Methods: A total of 48 people were included in the study, containing a patient group of 24 and a control group of 24. IL-6, fever, leukocyte and CRP levels were measured and recorded. The patients were categorized according to the type and etiology of the seizures. The relationship between IL-6 levels and infection parameters, type and etiology of seizures were evaluated.

Results: IL-6 levels were significantly higher in epileptic patients than that of the control group. There were no correlations between IL-6 levels and fever, leukocyte and CRP. The patients were evaluated according to the seizure type. There was no significant relationship between IL-6 levels of control group and IL-6 levels of patients with partial epileptic seizures (p=0.270). However, there was significant relationship between IL-6 levels of the control group and that of patients with primary generalized, secondary generalized seizures and generalized status epilepticus (p=0.012, p=0.011 and p=0.040, respectively). Epilepsy etiology was not associated with levels of IL-6.

Conclusion: High levels of IL-6 after epileptic seizures might be detected independent from infection parameters and epilepsy etiology. IL-6 levels might be higher in patients with primary generalized, secondary generalized seizures and generalized status epilepticus than that of patients with partial seizures.

Keywords: epilepsy, interleukin-6, epileptogenesis, infection

GİRİŞ

Epilepsi, serebral nöronların bir kısmının veya tamamının senkronize bir şekilde anormal elektriksel deşarjı sonucu oluşan ve patofizyolojisi halen tam olarak anlaşılamamış bir hastalıktır. Son yıllarda epilepsi ile immün sistem arasında kompleks bir ilişki olduğuna dair çok sayıda çalışma bulunmaktadır. Sitokin ekspresyonu ve immün hücrelerdeki anormallikler epilepsili hastalarda ve hayvan modellerinde gösterilmiştir. Nöronal eksitabilitede ve epileptogenezde immün sistemin önemli rolü olabileceği üzerine kanıtlar birikmektedir. Epilepsi hayvan modellerinin çoğunda nöbetlerin glial aktivasyona ve pro-inflamatuar sitokinlerden interlökin-1 beta (IL-1 β), tümör nekroz faktörü alfa (TNF-a) ve interlökin-6 (IL-6) düzeylerinde artışa neden olduğu bulunmuştur. Çalışmalar, IL-1-β ve IL reseptör antagonisti (IL-RA) sistemlerinin epileptik aktiviteyi etkileyebileceğini ve nöronal eksitabiliteye katkıda bulunabileceğini göstermiştir [1-3]. Antiepileptik ilaçların da sitokin seviyelerini etkileyebileceği belirtilmektedir [4].

Çalışmalar, özellikle IL-6 üzerine yoğunlaşmaktadır. IL-6, B lenfositlerin çoğalması ve farklılaşması, immmunglobulin yapımı, ateş ve akut faz proteinlerinin yapımında rol alan proinflamatuar özellikte bir sitokindir. Nöbet sonrasında ölçülen yüksek IL-6 düzeylerinin nöronal eksitasyon nedenli olabileceği düşünülmektedir. Bununla beraber, IL-6 düzeyinin normale dönmesinin iki haftayı bulması nöbetle birlikte subakut inflamatuar bir sürecin de devreye giriyor olabileceğini gösterebilir. IL-6 düzeyindeki yüksekliğin nöbetin türü ile ilgili olabileceğini gösteren çalışmalar varsa da bununla ilişkisiz olduğunu gösteren çalışmalar da mevcuttur [3,5-7].

Bu çalışmada epileptik nöbet geçiren hastalarda IL-6 düzeyinin nöbet türü, etiyolojisi ve infeksiyon göstergeleri olan ateş, lökosit ve c-reaktif protein (CRP) düzeyleri ile ilişkisinin incelenmesi amaçlanmıştır.

GEREÇ VE YÖNTEM

Tek merkezli ve prospektif olarak planlanan bu çalışma için Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi Etik Kurulu'na başvurularak 05.02.2012 tarih ve 127 sayı ile etik kurul onayı alındı. Mayıs 2012-Mayıs 2013 tarihleri arasında acil servise epileptik nöbet ile başvuran veya serviste yatarken epileptik nöbet geçiren tüm hastalar çalışmaya alınma kriterleri çerçevesinde değerlendirildi. Bu kriterler 18 yaşın üstünde olmak, 24 saat içinde epileptik nöbet geçirmek ve nöbet sonrası bilincin açık olması olarak belirlenmişti. Dışlama kriterleri ise epileptik nöbet tanısından şüphelenmeye neden olan öykü, travmatik bir nedene bağlı olarak nöbet geçirmek, aktif bir infeksiyon geçirmek, malignite ve hastanın genel durumunu bozan ve başvurusunda nöbetten daha öncelikli olarak tedavi

Tablo 1. Kontrol ve hasta grubunun demografik özellikleri, hasta grubunun klinik ve laboratuar özellikleri

	N	%	Ortalama yaş±SS(min.-max.)
Kontrol grubu	24		47,8±12,67(30-76)
Kadın	10	41,6	
Erkek	14	58,4	
Hasta grubu	24		48,17±21,7(17-84)
Kadın	10	41,67	
Erkek	14	58,33	
Nöbet türü			
Primer jeneralize nöbet	17	70,8	
Sekonder jeneralize nöbet	3	12,6	
Parsiyel nöbet	2	8,3	
Jeneralize status	2	8,3	
Nöbet etiyolojisi			
İdiyopatik	16	66,7	
Semptomatik	8	33,3	
Lezyon lokalizasyonu			
Sağ	2	25	
Sol	6	75	
Ateş			
Normal	18	75	
Yüksek	6	25	
CRP			
Normal	14	58,33	
Yüksek	10	41,67	
Lökosit			
Normal	11	45,83	
Yüksek	13	54,17	
Antiepileptik ilaç kullanımı			
Var	7	29,17	
Yok	17	70,83	

n: sayı SS: standart sapma min.: minimum max.:maksimum

edilmesi gereken her türlü tıbbi durum idi. En az 6 ay önce serebrovasküler olay geçirmiş ve sonrasında epileptik nöbet geçiren hastalar da çalışmaya dahil edildi. Böylece 10'u kadın, 14'ü erkek toplam 24 hasta çalışmaya alındı. Kontrol grubu da hasta grubunun yaş ve cinsiyet durumu göz önünde bulundurularak herhangi bir hastalığı olmayan 10 kadın ve 14 erkek olmak üzere toplam 24 kişiden oluşturuldu.

Tüm hastaların IL-6, CRP, lökosit, ateş, akciğer grafisi ve tam idrar sonuçları kaydedildi. Epileptik nöbetin türü ve etiyolojisi değerlendirilerek kaydedildi. Nöbet türü, Uluslararası Epilepsi İle Savaş Derneği (ILAE) sınıflamasına (1981) göre primer jeneralize nöbet, sekonder jeneralize nöbet, parsiyel (basit ve kompleks)nöbet ve jeneralize status olarak 4 gruba ayrıldı. Hasta ve kontrol grubundan üç adet heparinli tüpe alınan kanlar 4000 devirde 10 dakika santrifüj edildikten sonra elde edilen plazmalar merkez biyokimya laboratuarında -80º C'de dipfrizde saklandı ve yeterli hasta ve kontrol sayısına ulaşıldıktan sonra IL-6 düzeyleri ölçüldü. Ateş düzeyi için normalin üst sınırı 37 ºC alınarak değerlendirildi. CRP düzeyi için normalin üst sınırı 5 mg/l olarak belirlendi. Lökosit düzeyi için normalin üst sınırı 10000 K/mL olarak belirlendi. Ölçülebilir en düşük IL-6 değeri 2 pg/mL idi. "Intraassay coefficient variation" %4,5±4,7 idi. Laboratuar analiz yöntemleri olarak CRP düzeyi için Roche firmasının C502 cihazı ile turbidimetrik yöntem kullanılarak, lökosit için Beckman firmasının LH780 cihazı ile hematoloji analizüri yöntemi kullanılarak, tam idrar tahlili için Dirui firmasının FV200 ve H800 cihazları kulanılarak, IL-6 düzeyi için Siemens firmasının Immulite 2000 cihazı ile sandviç yöntemi kullanılarak ölçüldü.

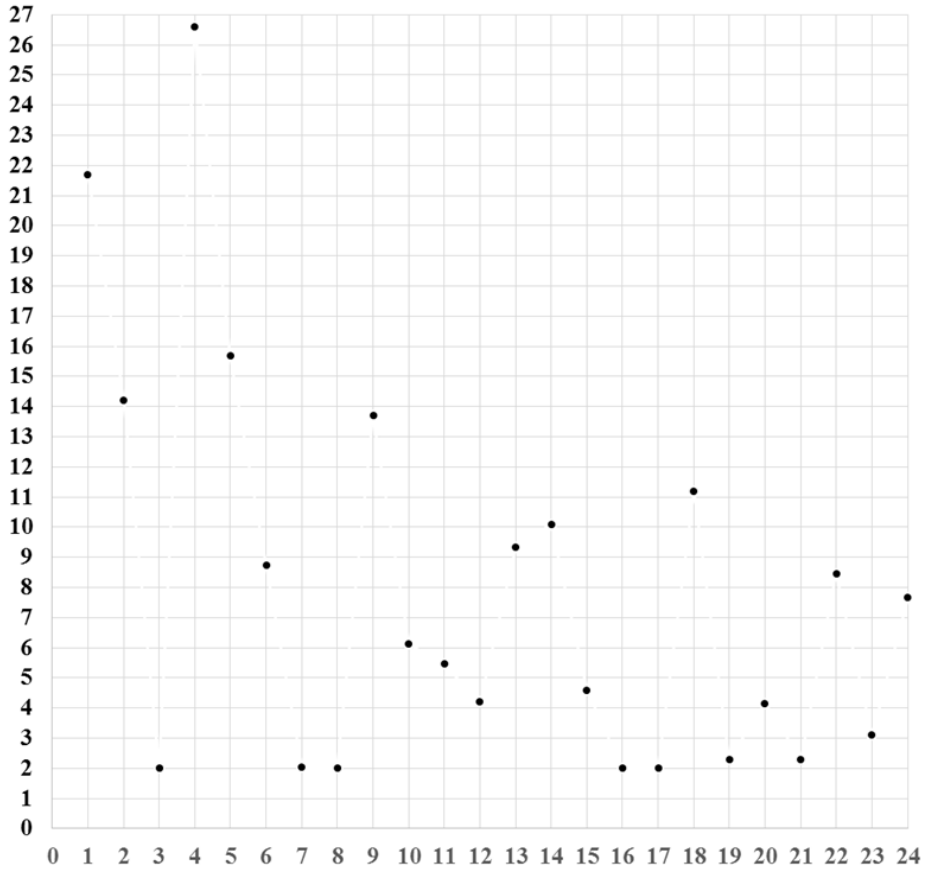
İstatistiksel Analiz

Verilerin analizi "SPSS for Windows 20.0" paket programıyla yapıldı. Verilerin tanımlanmasında sayı, yüzde, ortalama±standart sapma değerleri kullanıldı. Değişkenler arasındaki ilişkilerin değerlendirilmesinde Spearman korelasyon testi kullanıldı. Normal dağılımı olmayan veriler için Mann-Whitney U test ve Kruskal-Wallis test kullanıldı. $P<0,05$ düzeyi istatistik olarak anlamlı kabul edildi. Gruplar arasında yapılan post hoc analizler için Bonferroni düzeltmesi yapıldı.

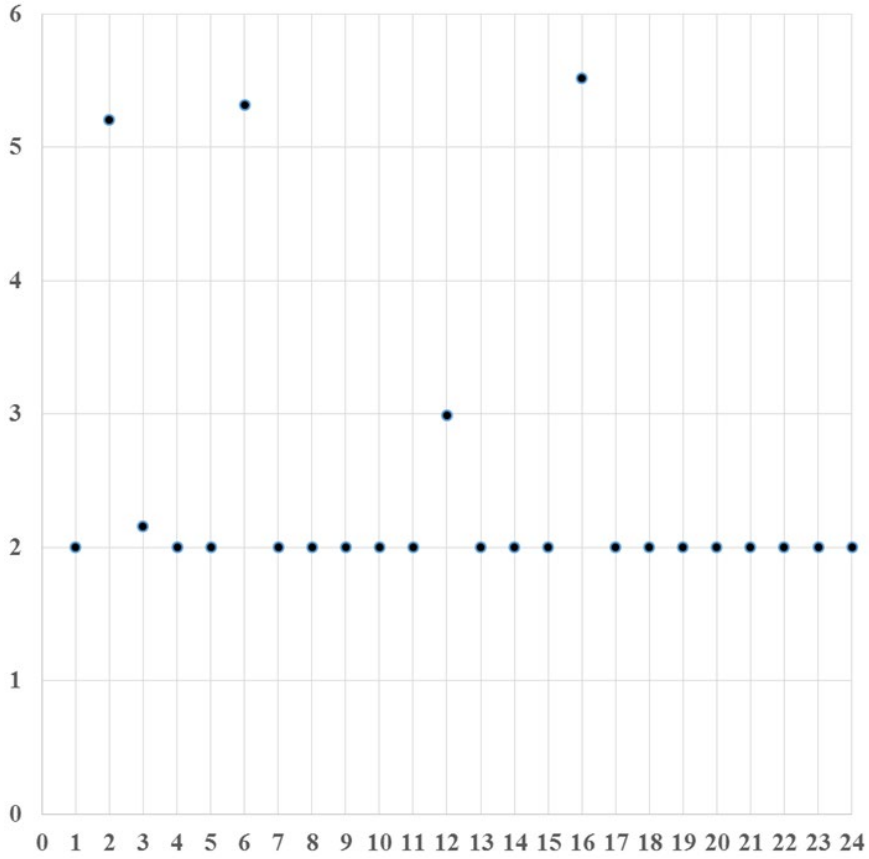
BULGULAR

Çalışmaya alınan hastaların demografik özellikleri **Tablo 1**'de özetlenmiştir. Hastaların yaşı 17-84 arasında olup ortalama yaş 48,17±21,7 idi. Kontrol grubunun yaşı ise 30-76 yıl arası olarak belirlendi (ortalama 47,8±12,67). Hastaların 17'sinde primer jeneralize nöbet, 3'ünde sekonder jeneralize nöbet, 2'sinde parsiyel nöbet, 2'sinde jeneralize status saptandı. Yirmi dört hastanın 16'sında idiyopatik nedenli nöbet saptanırken 8'inde vasküler lezyon mevcuttu. Vasküler lezyonlu hastaların 2'sinde lezyon sağ hemisferde iken 6'sında sol hemisferdeydi. On sekiz hastada ateş, 11 hastada lökosit, 14 hastada CRP değerleri normal olarak saptandı. İki hasta karbamazepin, 2 hasta levetirasetam kullanırken 2 hastada ikili, 1 hastada üçlü antiepileptik ilaç kullanımı mevcuttu. On yedi hasta tedavi altında değildi.

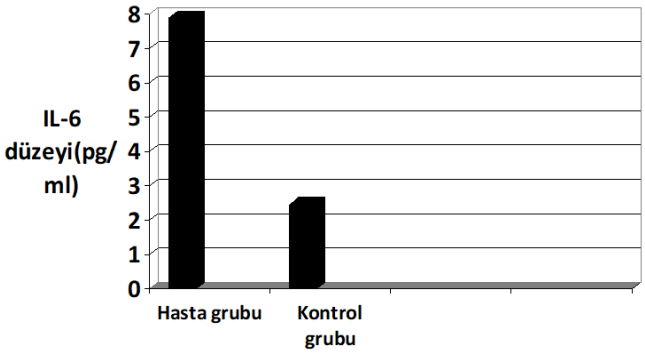
Hasta ve kontrol grubunun IL-6 düzeyleri klinik ve laboratuar özelliklerine göre değerlendirildi (**Tablo 2** ve **Tablo 3**). Yirmi dört hastanın IL-6 değeri 2-26,6 pg/mL arasındaydı (ortalama 7,9±6,59) (**Grafik 1**). Yirmi dört sağlıklı gönüllünün IL-6 değeri ise 2,0-5,52 pg/mL arasındaydı (ortalama 2,47±1,13) (**Grafik 2**). Hasta grubunun IL-6 düzeyi ile kontrol



Grafik 1. Hasta grubunda IL-6 düzeylerinin dağılımı



Grafik 2. Kontrol grubunda IL-6 düzeylerinin dağılımı

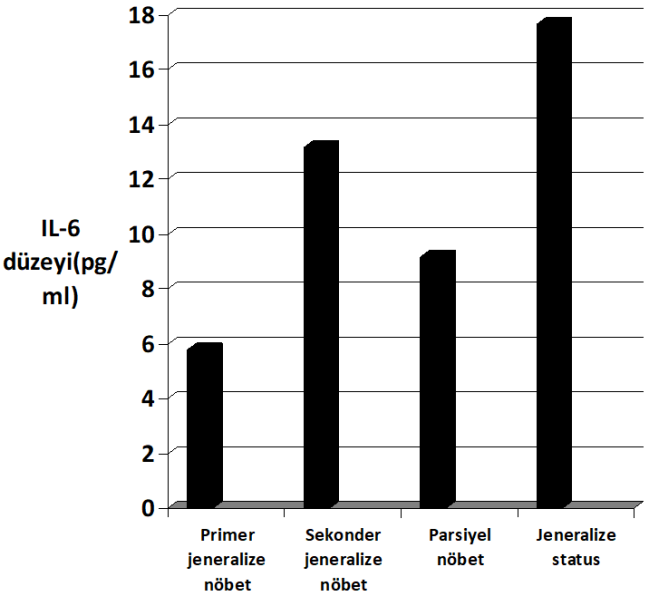


Resim 1. Hasta ve kontrol gruplarının ortalama IL-6 düzeyleri

Tablo 2. Hasta grubunun nöbet türüne ve etiyolojisine göre kontrol grubu ile karşılaştırılması

	IL6 (Ortalama±SS)	IL-6 (min.-max.)	p
Kontrol gurubu	2,47±1,13	2-5,52	
Hasta grubu	7,9±6,59	2-26,6	0,000
Nöbet türü			0,000
Primer jeneralize nöbet	5,79±4,34	2-15,7	0,012*
Sekonder jeneralize nöbet	13.16±7,5	7,67-21,7	0,011*
Parsiyel nöbet	9,17±7,1	4,15-14,2	0,270*
Jeneralize status	17,67±12,62	8,75-26,6	0,040*
Nöbet etiyolojisi			0,000
İdiyopatik	6,92±6,86	2-26,6	0,002*
Semptomatik	9,86±5,94	2-21,7	0,000*

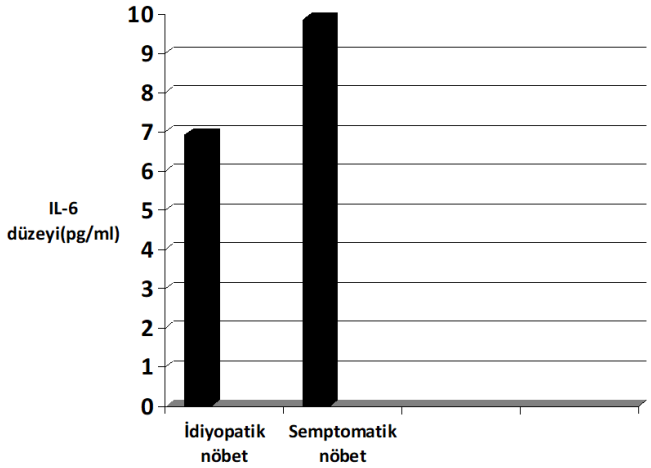
Min: minimum max:maksimum *:Bonferroni düzeltmesi uygulandı.



Resim 2. Hasta grubunda nöbet türlerine göre IL-6 düzeyleri

grubunun IL-6 düzeyi arasında ileri derecede anlamlı fark saptandı (p<0,001) (**Resim 1**).

Primer jeneralize nöbet geçiren 17 hastanın IL-6 düzeyi 2,0-15,7 pg/mL (ortalama 5,79±4,34), sekonder jeneralize nöbet geçiren 3 hastanın IL-6 düzeyi 7,67-21,7 pg/mL (ortalama



Resim 3. Hasta grubunda etiyolojiye göre IL-6 düzeyleri

13,16±7,5), parsiyel nöbet geçiren 2 hastanın IL-6 düzeyi 4,15 pg/mL ve 14,2 pg/mL (ortalama 9,17±7,1), jeneralize status geçiren 2 hastanın IL-6 düzeyi 8,75 pg/mL ve 26,6 pg/mL (ortalama 17,67±12,62) olarak ölçüldü (**Tablo 2**, **Resim 2**). Nöbet türlerine göre sınıflandırılmış olan hasta gruplarının IL-6 düzeyleri kontrol grubu ile karşılaştırıldı. Yapılan istatistiksel değerlendirmede gruplar arasında anlamlılık belirlendi (p<0,001). Nöbet türlerine göre ayrılmış hasta grupları ile kontrol grubunun IL-6 düzeyleri karşılaştırıldığında ise kontrol grubunun parsiyel nöbet geçiren hastalarla arasında anlamlı fark bulunmazken (p=0,270), primer jeneralize nöbet, sekonder jeneralize nöbet ve jeneralize status ile aralarında anlamlı fark saptandı(primer jeneralize nöbet için p=0,012, sekonder jeneralize nöbet için p=0,011, jeneralize status için p=0,040).

Hastalar nöbet etiyolojisine göre ayrılarak kontrol grubu ile karşılaştırıldı. İdiyopatik nöbet geçiren hasta grubunda IL-6 düzeyi 6,92±6,86 pg/ml iken semptomatik nöbet geçiren hasta grubunda IL-6 düzeyi 9,86±5,94 pg/ml olarak bulundu (**Tablo 2**, **Resim 3**). IL-6 düzeyi gerek idiyopatik gerek semptomatik nöbetli hastalarda kontrol grubuna göre anlamlı olarak yüksekti (idiyopatik nöbet için p=0,002, semptomatik nöbet için p<0,001). İdiyopatik ve semptomatik nöbetli hasta grupları birbiri ile karşılaştırıldığında ise anlamlı fark bulunmadı (p=0,754).

Hastaların IL-6 düzeyleri ile ateş, lökosit ve CRP düzeylerindeki yükselmenin birbiriyle ilişkisi değerlendirildiğinde IL-6'nın ateş, lökosit ve CRP ile korelasyonu anlamlı bulunmadı (ateş için p=0,698, lökosit için p=0,099, CRP için p=0,691). Hastaların cinsiyetleri, yaşı ve antiepileptik ilaç kullanımı ile IL-6 düzeyleri arasında anlamlı ilişki yoktu (cinsiyet için p=0,769, yaş için p=0,101, antiepileptik ilaç kullanımı için p=0,373). Lezyon lokalizasyonu ile IL-6 düzeyi arasında anlamlı ilişki saptanmadı (p=0,739). Bulgular **Tablo 3**'te özetlenmiştir.

Tablo 3. Hasta grubunun IL-6 düzeyinin klinik özelliklere göre karşılaştırılması

	IL-6 (Ortalama±SS)	IL-6 (min.-max.)	p
Lezyon lokalizasyonu			0,739
Sağ	10,93±4,61	7,64-14-2	
Sol	9,51±6,67	2-21,7	
İlaç kullanımı			0,373
Var	11,04±9,57	2-26,6	
Yok	6,61±4,70	2-15,7	
Ateş			0,698
Normal	7,49±5,48	2-21,7	
Yüksek	9,1±9,78	2-26,6	
CRP			0,691
Normal	6,91±5,16	2-15,7	
Yüksek	9,29±8,3	2-26,6	
Lökosit			0,099
Normal	5,46±4,37	2-14,2	
Yüksek	9,97±7,57	2-26,6	
Cinsiyet			0,769
Kadın	7,78±6,08	2,03-21,7	
Erkek	8,7±7,04	2-26,6	
Yaş	48 ±21,7	2-26,6	0,101

Min: minimum max:maksimum SS:Standart sapma

Hastaların tam idrar tahlili ve akciğer grafilerinde patoloji saptanmadı.

TARTIŞMA

Çalışmamızda kontrol grubunda IL-6 değerleri 2,0-5,52 pg/ml olarak (ortalama 2,47±1,13) belirlenirken, hasta grubunda ise IL-6 değerleri 2-26,6 pg/mL pg/mL arasındaydı (ortalama 7,9±6,59). Gerek kontrol grubunda gerek hasta grubunda IL-6 değerlerinin daha önce yapılan çalışmalarla benzer aralıkta olduğu görüldü [3,5].

Hasta grubu ile kontrol grubunun IL-6 değerlerinin ortalaması arasında anlamlı fark saptandı. Literatürdeki çalışmalar gözden geçirildiğinde epilepsi ile sitokinler arasındaki ilişkiyi inceleyen, yakın yıllarda yapılan iki çalışmada da serum IL-6 düzeylerinin yüksek bulunduğu görülmektedir [1,2]. Epileptik nöbet geçiren hastaların beyin omurilik sıvısı (BOS) ve serum IL-6 düzeylerinin incelenmesi ile BOS'ta bulunan değerlerin daha yüksek olduğu saptanmıştır [8]. Febril nöbet geçiren çocuklarda yapılan bir çalışmada ise IL-1 ve IL-6 düzeyleri değerlendirilmiş ve bu iki sitokinde de artış belirlenmiştir [9].

Hastaların lökosit, CRP ve ateş düzeylerindeki yükselmenin IL-6 düzeyindeki yükselmeyle ilişkisi incelendiğinde her üç parametrenin de IL-6 düzeyi ile anlamlı korelasyon göstermediği saptandı. Bu durumda epileptik nöbette IL-6'nın bu infeksiyon parametrelerinden bağımsız olarak yükselebildiği sonucuna varıldı. Bu konuda literatürde yer alan çalışma sayısı kısıtlı olmakla beraber Peltola ve ark.nın çalışmasında plazma IL-6 düzeylerindeki yükselmenin diğer infeksiyon parametreleriyle arasındaki ilişki incelendiğinde CRP düzeylerindeki yükselme ile arasında anlamlı korelasyon belirlenmiş ancak haptoglobinle korelasyon saptanmamıştır. Bu bulgular ışığında epileptik nöbetlerin IL-6 gibi sitokinlerin üretimini provoke ettiği ve bunun akut faz reaksiyonunu tetiklediği, bu nedenle akut nöbet geçiren hastalardaki infeksiyon belirteçlerinin artışının infeksiyon lehine yorumlanmaması gerektiği ifade edilmiştir [10].

Çalışmamızdaki hastaların IL-6 değerleri nöbet türü göz önünde bulundurularak değerlendirildi. Kontrol grubu ile hasta grubu karşılaştırıldığında IL-6 düzeyleri parsiyel nöbet geçiren hasta grubu hariç tüm nöbet türlerinde kontrol grubuna göre istatistiksel olarak anlamlı fark olacak şekilde yüksekti. Bu fark en yüksek oranda sekonder jeneralize nöbette iken ikinci olarak primer jeneralize ve son olarak jeneralize status türündeydi. Epileptik nöbet sonrası meydana gelen IL-6 yüksekliğinin nöbet türüyle olan ilişkisi yoğun olarak incelenen konulardan biridir. Bir çalışmada nöbet sonrası 3. ve 6. saatlerde bakılan IL-6 düzeyinin tonik-klonik nöbet geçiren hastalarda parsiyel nöbet geçiren hastalara göre daha yüksek olduğu belirtilmiştir [11]. Bir başka çalışmada sekonder jeneralize nöbet geçiren hastalarda kompleks parsiyel nöbet geçiren hastalara oranla IL-6 seviyesindeki artışın daha fazla olması nedeniyle IL-6 yüksekliğinin nöbet aktivitesinin yaygınlığıyla ilişkisinin olabileceği ifade edilmiştir [3]. Parsiyel nöbet geçiren hastaların temporal ve ekstratemporal kaynaklı nöbetli hastalar olarak ayrılıp değerlendirildiği bir çalışmada IL-6 yüksekliği sadece temporal lob epilepsili hastalarda gözlenerek bu sonucun temporal lobun eksitatör aktiviteye daha duyarlı olması şeklinde yorumlanmıştır [4]. Uludağ ve ark. ise jeneralize, sekonder jeneralize ve kompleks parsiyel nöbet geçiren hasta gruplarında IL-6 düzeylerini yüksek bulmuş ancak gruplar arasında anlamlı fark olmadığını belirtmişlerdir [5]. Hasta sayısının 1218 olduğu bir çalışmada interiktal dönemdeki hastalar temporal lob kaynaklı epilepsi, ekstratemporal lob kaynaklı epilepsi ve idiyopatik jeneralize epilepsi olarak üç gruba ayrılarak BOS'ta sitokin düzeylerine bakılmış ve IL-6 düzeyinde gruplar arasında anlamlı fark saptanmamış, bununla beraber IL-6 düzeyinin nöbet şiddetiyle koreleasyonu bulunmuştur [12]. Epilepside inflamatuar mediatörlerin rolünün değerlendirildiği bir meta analizde ise tek nöbet türünde veya sadece beyin hasarı durumunda yükselen sitokinlerin aksine IL-6'nın farklı

nöbet etiyolojisi ve türlerinde yüksek saptanan sitokinlerden biri olduğu sonucuna varılmıştır [13].

Çalışmamızda idiyopatik ve semptomatik nöbet geçiren her iki hasta grubunda da IL-6 düzeyi kontrol grubuna göre yüksek bulundu. İki hasta grubu arasında ise istatistiksel fark saptanmadı. Bu durum epileptik nöbetlerdeki IL-6 düzeyinde artışın nöbet etiyolojisinden bağımsız olabileceğini düşündürmektedir. Sitokinlerin epilepsideki rolünü gösteren çalışmaların çoğu idiyopatik epilepsili hastalarda yapılmış olmakla beraber az sayıda semptomatik epilepsi hastası ile de yapılmış çalışma mevcuttur. Çoklu antiepileptik ilaç kullanan mental retardasyonlu hastalarda yapılan bir çalışmada da IL-6 yüksekliği saptanmıştır [14]. Epilepsisi olan hastalarda akut nöbetten bağımsız olarak IL-6 düzeyinin araştırıldığı bir çalışmada ise tuberoz skleroz ve kortikal displazisi olan hastaların IL-6 düzeyinin kontrol hastalarına oranla anlamlı şekilde yüksek olduğu belirlenerek immunohistokimyasal analizlerde IL-6 ve IL-6 reseptörlerinin kaynağının kortekstеki hasarlı hücreler olduğu tespit edilmiş ve tuberoz skleroz ve kortikal displazili hastalarda IL-6'nın önemli rolü olabileceği öne sürülmüştür [15].

Hasta grubumuzdaki IL-6 artışının antiepileptik ilaç kullanımıyla ve semptomatik epilepsili hastalardaki lezyon lokalizasyonuyla anlamlı ilişkisi saptanmadı. Bu sonuç yakın yıllarda yapılmış geniş hasta gruplu çalışmalarda elde edilmiş sonuçlarla uyumlu olmakla birlikte bu etkenlerin IL-6 düzeyini etkilemediğini düşünmek için erken olduğu da ifade edilmiştir [2,4].

Bütün bu çalışmalardan epilepsi ile IL-6 artışı arasında bir ilişki bulunduğu ancak bu ilişkinin mekanizmasını anlamaya yönelik çalışmaların devam etmekte olduğu anlaşılmaktadır. Bu zamana kadar yapılmış araştırmalarda IL-6 artışı gerek idiyopatik gerekse semptomatik epilepsili hastalarda ve her nöbet türünde gözlenmiştir. Bizim çalışmamızda sistemik veya santral infeksiyonu olan hasta olmadığından epileptik nöbetle meydana gelen IL-6 yüksekliğinin infeksiyonla ilişkisi incelenemedi. İnfeksiyon parametreleri olan ateş, lökosit ve CRP düzeylerinin IL-6 ile korelasyonu saptanmadı.

ÇALIŞMANIN KISITLILIKLARI

Çalışma ile ilgili en önemli kısıtlılık hasta sayısının az olması, lökosit, CRP ve ateş dışındaki infeksiyon parametrelerine bakılamamış olması, yeterli sayıda hastaya ulaşılamadığından kontrol IL-6 düzeylerinin ölçülememiş olması ve patogenezin değerlendirememiş olması olarak düşünülebilir. Ayrıca çalışma 2017 yılından önce planlandığı için nöbet türleri 2017 yılında ILAE tarafından yayınlanan güncel sınıflandırmaya göre belirlenmemiştir [16].

SONUÇ

Sonuç olarak, çalışmamızda hasta grubumuzda IL-6'nın epileptik nöbet etiyolojisinden, ateş, lökosit ve CRP düzeylerinden, antiepileptik ilaç kullanımından ve lezyon lokalizasyonundan bağımsız olarak yükseldiği, bu yüksekliğin nöbet türü ile ilişkili olabileceği saptandı. Bu sonuçlar epileptik nöbetin incelenen tüm diğer etkenlerden bağımsız olarak IL-6 artışına neden olabileceğini, IL-6 değerindeki yüksekliğin epileptik nöbetin bir sonucu ve/veya epileptogenez sürecinin bir parçası olabileceğini düşündürmektedir. Çalışmanın nöbet türü, nedeni, hasta sayısı açısından daha geniş bir grupla yapılması ile bulunacak sonuçların epileptogenez mekanizmasını anlamaya ve gelecekte yapılacak epileptogenezi önleme amaçlı tedavi yöntemlerindeki gelişmelere katkıda bulunabileceğine inanıyoruz.

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Orijinal Makale

9 ay-4 yaş çocuklarda anne sütü alım süresinin ve beslenme alışkanlıklarının primer malnütrisyon gelişimi üzerine etkileri

The effects of breastfeeding time and feeding habits on primary malnutrition development in 9 months-4 years old children

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ÖZ

Giriş-Amaç: İlk 1000 günlük periyotta bebek beslenmesi paterni çocuğun büyüme ve gelişiminde önemli bir etkiye sahiptir. Anne sütü kullanım süresi ile beslenme alışkanlıklarının malnütrisyon gelişimi üzerindeki etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Çocuk Gastroenteroloji ve Genel Pediatri polikliniklerine ardışık başvuran 9 ay-5 yaş aralığındaki 250 primer malnütrisyonlu ve 250 malnütrisyonsuz hastalara anne sütü alım sürelerini ve beslenme alışkanlıklarını sorgulayan bir anket formu doldurtuldu.

Bulgular: Çalışmaya katılan malnütrisyonlu hastaların yaş ortalaması 19,77±9,90 ay, malnütrisyonu olmayan hastaların ise 20,584±10,971 ay idi. Yaş ve cinsiyet açısından iki grup arasında istatiksel olarak anlamlı fark yoktu (sırasıyla P=0,385, P=0,140). Sadece anne sütü alma süresi ile toplam anne sütü alma süresi malnütrisyonlu hasta grubunda anlamlı olarak daha düşük idi (sırasıyla P=<0,001, P=0,001). Malnütrisyon gelişimi için sadece anne sütü ile beslenme süresinin minumum kesim noktasını ≤ 4,5 ay bulduk (duyarlığı %72, özgüllüğü %54 P=0,001). Aynı zamanda malnütrisyonlu grupta bebek beslenmesine babanın anlamlı olarak daha az iştirak ettiğini gördük (P=<0,001). İki yaş üzerinde olan çocuklarda kendi kendini beslemesine izin verilmeme oranının malnütrisyonlu grupta daha yüksek olduğunu gördük (P=<0,001). Parmak besinlere geçme yaşının malnütrisyonlu grupta daha yüksek olduğunu gördük (P=0,002). Öğününü bitirme süresinin malnütrisyonlu grupta daha uzun olduğunu gördük (P<0,001). Malnütrisyonlu grupta yaşına uygun olmayan besleme sıklığının daha fazla olduğunu gördük (P<0,001).

Sonuç: Çalışmamız anne sütü alım süresi ve beslenme alışkanlıklarının malnütrisyon gelişimine etki ettiğini göstermektedir.

Anahtar kelimeler: anne sütü, beslenme alışkanlıkları, çocuk, yetersiz beslenme

ABSTRACT

Objective: Infant feeding pattern in the first 1000 days period has significant effect on the growth and development of child. We aimed to investigate the effects of breastfeeding duration and feeding habits on malnutrition.

Material and Methods: Patients who were consecutively admitted to the pediatric gastroenterology and pediatric outpatient clinics were included in the study. 250 patients with primary malnutrition and 250 patients without malnutrition were asked to complete questionnaire questioning breast milk intake times and feeding habits.

Results: The mean age of the patients with malnutrition was 19.77 ± 9.90 months and 20.584 ± 10.971 months for patients without malnutrition. There was no statistically significant difference between the two groups in terms of age and sex **(P = 0.385, P = 0.140, respectively)**. Only breastfeeding time and total breastfeeding time were significantly lower in malnourished patients (P = <0.001, P = 0.001, respectively). For malnutrition development, we found the minimum cut-off point of breastfeeding time to be ≤ 4.5 months (sensitivity 72%, specificity 54% P = 0.001). We also found that the father was significantly less involved in feeding the baby in the malnutrition group (P = <0.001). We found that the rate of non-self-feeding was higher in malnourished group in children over two years of age (P = <0.001). We found that the age of transition to finger food was higher in the malnutrition group (P = 0.002). We found that the duration of the meal was longer in malnutrition group (P <0.001).

Conclusion: Our study shows that the duration of breastfeeding and feeding habits affect malnutrition development.

Keywords: breast milk, feeding habits, child, malnutrition

GİRİŞ

Malnütrisyon, tüm dünyada çocuklar arasında hala büyük bir halk sağlığı sorunu olmaya devam etmektedir. Küresel olarak her beş yaş atındaki çocukların üçte biri yetersiz beslenmektedir [1]. Birleşmiş Milletler Çocuklara Yardım Fonu (UNİCEF), 2018'de beş yaş altı 155 milyon çocuğun bodur, 52 milyon çocuğun ise aşırı zayıf olduğunu bildirmiştir [2].

İlk 1000 günlük periyotta bebeğin beslenme şekli çocuğun büyüme ve gelişiminde önemli bir etkiye sahiptir [3]. Büyüme ve gelişmenin hızlı olduğu bu dönemde en önemli besin kaynağı hiç şüphesiz anne sütüdür. Anne sütü (AS) besinsel içerik ve kalori açısından biyolojik yararlılığı yüksek ve sindirimi kolay bir besindir. Anne ve bebek için başta beslenme olmak üzere sosyal, ekonomik, gelişimsel ve psikolojik yönden birçok yararı gösterilmiştir [4]. Dünya sağlık örgütü (WHO), UNİCEF, Amerikan Pediatri Akademisi (AAP) bebeklerin 0-6 ay sadece AS ile beslenmelerini, altıncı ayda tamamlayıcı beslenmeye geçilmesini ve emzirmeye iki yıl devam edilmesini önermektedir. Sağlık Bakanlığı Türkiye Halk Sağlığı Kurumu AS ile beslenen küçük çocukların beslenmesiyle ilgili alışkanlıkların bu dönemde kazandırılması ve annelerin bu konuda bilinçlendirilmesini önermektedir [5]. Bazı çalışmalar AS ile beslenen bebeklerde yaşamın ilk aylarında büyümelerinin daha hızlı olduğunu belirtirken, bazı çalışmalar da beslenme zamanı ebeveyn davranışlarının büyüme üzerine etkili olabileceğini belirtmektedir [4,6,7].

Bu nedenle çalışmamızda AS kullanım süresi ile beslenme alışkanlıklarının malnütrisyon gelişimi üzerindeki etkisini araştırmayı amaçladık.

GEREÇ VE YÖNTEMLER

Çocuk Gastroenteroloji polikliniğine Ekim 2018 – Mayıs 2019 tarihleri arasında ardışık gelen 9 ay-4 yaş arası primer malnütrisyon (PM) tanılı 250 pediatrik hasta ile aynı yaş grubunda malnütrisyonu olmayan 250 kontrol hastasının ebeveynlerine AS alım sürelerini ve beslenme alışkanlıklarını sorgulayan bir anket formu doldurtuldu.

Örneklem büyüklüğü ve kontrol grubu sayıları daha önce yapılmış benzer çalışmalar baz alınarak belirlendi [8]. Çalışma sonrası G*Power 3.1.9.2 ile 0.05 anlam seviyesinde, gruplardaki AS kullanımları esas alınarak post hoc analiz yaptığımızda her grupta 250 hasta sayısı bulunmasının çalışmamızda %85,1 etki gücüne sahip olduğunu gördük.

Hiçbir hastada malnütrisyona sebep olacak organik bir sebep yok idi. Bu çalışmaya katılan hastaların hepsi Türk vatandaşı idi.

Çalışma Helsinki İlkeler Deklerasyonuna uygun olarak yapıldı. Çalışma öncesi ailelerden bilgilendirilmiş onam alındı. (Necip Fazıl Şehir Hastanesi ve Sütçü İmam

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Beslenme Durumunun Değerlendirilmesi

Çalışmaya katılan iki yaşından küçük çocuklar düz bir zeminde, sırt üstü yatar pozisyonda ikinci bir kişinin yardımı ile baş ve dizler sabitlenerek infantometre yardımı ile ölçüldü. İki yaş üzeri çocuklar ise en yakın milimetreye kalibre edilmiş dikey portatif bir stadyometre kullanılarak çorap ve ayakkabı olmadan ölçüldü. Ağırlık, bir kilogramın en yakın ondalık kesirine kadar dijital elektronik tartı ölçeği kullanılarak hafif kıyafetlerle ölçüldü. Dünya Sağlık Örgütü (WHO) verileri kullanılarak, ağırlık Z skoru, boy Z skoru, boy-kilo Z skoru, vücut kitle indeksi (VKİ) Z skoru, yaşa ve cinsiyete göre hesaplandı. Vücut ağırlığı, boy, VKİ parametrelerinin herhangi birinde Z skoru -2'nin altında olan hastalar yetersiz beslenmiş olarak kabul edildi. Kötü beslenmenin ciddiyeti aşağıdaki gibi sınıflandırılmıştır [9]:

Orta düzeyde düşük kilo (Zayıflık): Yaşa göre kilo Z skoru ≥−3 SDS ile <−2 SDS arasında

Şiddetli düzeyde düşük kilo (Şiddetli zayıflık): Yaşa göre kilo Z skoru <−3 SDS

Normal: Yaşa göre kilo Z skoru >−2 SDS

Orta düzeyde bodurluk: Yaşa göre boy Z skoru ≥−3 SDS ile <−2 SDS arasında

Şiddetli düzeyde bodurluk: Yaşa göre boy Z skoru ≥ −3 SDS

Normal: Yaşa göre boy Z skoru > −2 SDS

Çalışmaya Dahil Edilme Kriterleri

Çalışmaya alınan malnütrisyonlu hastalarda sekonder malnütrisyona sebep olabilecek Prematürite, intrauterin gelişme geriliği, tekrarlayan idrar yolu enfeksiyonu, kronik böbrek yetmezliği, tekrarlayan alt solunum yolu enfeksiyonu, kistik fibrozis, konjenital kalp hastalıkları, kalp yetmezliği, serebral palsi, çöliyak hastalığı, inflamatuar bağırsak hastalığı, sendromik (Down send, Turner Send gibi) hastalıklar gibi klinik bilgi, semptom ve/veya bulgu yoktu. Şüphelenilen hastalar tetkik edildi. Sekonder malnutrisyon tespit edilen hastalar çalışmaya dahil edilmedi.

Değerlendirme Anketi

Çocuğun doğum sonrası aldığı ilk gıdanın ne olduğu, ne zamana kadar sadece AS aldığı, toplam kaç ay AS kullandığı, ek gıdaya ne zaman geçildiği, beslenme ortamı, sizce baba çocuk beslenmesine yardım ediyor mu? Çocuğun aldığı gıdaların kıvamı, miktarı, kaç saat ara ile beslenmeye zorlandığı, kaşık kullanmaya ne zaman izin verildiği, parmak besinlere ne zaman geçildiği, beslenme sırasında televizyon, tablet vb. kullanılıp kullanılmadığı, beslenmenin ne kadar sürdüğü ile ilgili soruları içeren anket formu hazırlandı. Bu anket beslenme hemşiresi gözetiminde ebeveynlerle bire bir 15-30 dakikalık görüşmelerle dolduruldu.

Benzer şekilde çocuğun beslenme sıklığı; anneye anketten önceki 24 saat içinde çocuğun kaç kez beslendiği soruldu. Öğünlerde katı, yarı katı veya yumuşak yiyeceklerden hangilerini alabildiği sorgulandı. Buna göre, 9-24 aylık emzirilen çocuklar için üç ya da daha fazla kez ve 9-24 aylık emzirilmeyen çocuklar için beş ve daha fazla ana öğün ile beslenmeleri minimum beslenme sıklığı olarak kabul edildi [10].

Anket en az bir Çocuk Gastroenteroloji uzmanı veya bir Pediatri uzmanı tarafından değerlendirildi. Ankette yaşa göre besleme hataları tespit edilen ebeveynlere beslenme eğitimi verildi.

İstatiksel Analizler

Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago) 22 paket programı kullanılarak yapıldı. Değişkenler ortalama ± standart sapma, sayı (n) ve yüzde (%) olarak gösterildi. Sayısal değişkenlerin normal dağılım gösterip göstermediği Kolmogrov Smirnov testi ile incelendi. Normal dağılım gösteren parametreler için Student's t-testi veya tek yönlü varyans analizi (ANOVA), normal dağılım göstermeyen parametreler için Mann Whitney U-testi veya Kruskal Wallis testi kullanıldı. İstatistiksel önemlilik testi olarak ki-kare testi, Student's t-testi veya Mann Whitney U-testi kullanıldı. Bir bağımlı değişkenin birbirinden bağımsız ikiden fazla grup arasındaki aritmetik ortalamasını ve buna göre anlamlı bir farklılığın olup olmadığını ortaya koymak için one way ANOVA testi uygulandı. Bir bağımlı değişken ile bir ya da daha fazla bağımsız değişken arasındaki ilişkiyi göstermek için lojistik regresyon analizi yapıldı. P değeri <0,05 saptanan değerler istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Malnütrisyonu olmayan hasta grubunda yaş ortalaması 20,58±10,97 ay, Malnütrisyonu olan grupta ise 19,77±9,90 ay idi. Yaşa göre iki grup arasında anlamlı bir fark yoktu (p=0,385). Malnütrisyonu olmayan grupta 131 (%52,6) erkek, malnütrisyonlu grupta ise 135 (%54) kız hasta vardı. Cinsiyet açısından gruplar arasında anlamlı bir fark yoktu (p=0,140) (**Tablo 1** ve **2**).

Tablo 1. Beslenme şekli ve alışkanlıklarına göre gruplar arasındaki farklılıkların değerlendirilmesi

		Malnütrisyon yok	Malnütrisyon var	P
		N-%	N-%	
Cinsiyet	Kız	118-47,4	135-54	0,140
	Erkek	131-52,6	115-46	
Doğum sonrası ilk gıda	Anne sütü	227-90,8	218-87,2	0,192
	Mama ve/veya diğer gıdalar	23-9,2	32-12,8	
Çocuğun beslenme ortamı	Aile ile birlikte sofrada	216-86,4	206-82,4	0,218
	Anne ile ayrı ortamda	34-13,6	44-17,6	
Sizce baba çocuk beslenmesine katılıyor mu?	Hayır	215-86	244-97,6	<0,001
	Evet	35-14	6-2,4	
Bir yaş üzerindeki hastalarda sadece blenderden geçirilmiş veya yumuşak kıvamlı gıdalarla beslenen çocuk sayısı	Yok	158-85,9	114-66,3	<0,001
	Var	26-14,1	58-33,7	
Bir yaş üzerinde parmak besinlerle beslenebilme yetisi kazanamamış çocuk sayısı	Yok	247-98,8	232-92,8	0,002
	Var	3-1,2	18-7,2	
İki yaş üzerinde kendi kendini besleme yetisi kazanamamış çocuk sayısı	Yok	244-97,6	202-80,8	<0,001
	Var	6-2,4	48-19,2	
İki yaş üzerinde tabak, kaşık kullanma yetisi kazanamamış çocuk sayısı	Yok	216-86,4	208-83,2	0,319
	Var	34-13,6	42-16,8	
Yaşına göre sık besleme	Yok	224-89,6	193-77,2	<0,001
	Var	26-10,4	57-22,8	
Öğünlerde sıklıkla televizyon, tablet ve telefon kullanır mısınız?	Hayır	202-80,8	194-77,6	0,378
	Evet	48-19,2	56-22,4	
Öğünü bitirme süresi 45 dakikayı geçiyor mu?	Hayır	245-98	226-90,4	<0,001
	Evet	5-2	24-9,6	

Crosstabs- Chi-square test

Primer malnütrisyonu olan hastaların 181'i (%72,4) orta düzeyde düşük kilolu, 57'si (%22,8) aşırı düşük kilolu idi.

Hastalar doğum sonrası aldıkları ilk gıdaya göre değerlendirildiğinde malnütrisyonu olmayan grupta 227 (%90,8) AS, 23 (%9,2) mama, şekerli su, inek sütü gibi gıdalar verilmiş idi. Malnütrisyonlu grupta ise 218 (%87,2) hasta AS alırken 32 (%12,8) hasta mama veya diğer gıdalar verilmişti. Doğum sonrası verilen ilk gıdaya göre iki grup arasında anlamlı bir fark yoktu (p=0,192) (**Tablo 1**).

İki grup arasında sadece altı ay AS alma oranlarına baktığımızda malnütrisyonlu hastaların 67'sinin (%26,8), malnütrisyonu olmayan hastaların ise 114'ünün (%45,6) altı ay sadece AS ile beslendiğini tespit ettik. Bu durum iki grup arasında anlamlı olarak farklı idi (p<0,001). Tüm hastalara göre değerlendirdiğimizde ise 181 çocuğun (%36,2) altı ay sadece AS ile beslendiğini tespit ettik.

Hastaların beslenme ortamı ile ilgili olarak iki grup arasında anlamlı bir fark yoktu (p=0,218). Anneye ''sizce baba çocuk beslenmesine yardım ediyor mu?'' sorusu soruldu. Malnütrisyonlu grupta 244 (%97,6) anne hayır derken 6 (%2,4) anne babanın aktif olarak çocuğun beslenmesine yardım ettiğini belirtti. Malnütrisyonu olmayan grupta ise 216 (%86) anne hayır derken, 35 (%14) anne babanın aktif olarak çocuğun beslenmesine yardım ettiğini belirtti. Malnütrisyonu olmayan grupta babaların istatiksel olarak daha yüksek oranda bebek beslenmesine iştirak ettiğini tespit ettik (P<0,001).

Bir yaş üzerinde olan hastalar yedikleri besinlerin kıvamına göre değerlendirildiğinde, malnütrisyonu olmayan grupta 26 (%14,1) hasta, malnütrisyonlu hasta grubunda ise 58 (%33,7) hastanın sadece blenderden geçirilmiş yumuşak kıvamlı gıdalar ile beslenmekteydi. Bu durum iki grup arasında istatiksel olarak farklı idi (p<0,001).

Parmak besinlere geçme yaşına bakıldığında bir yaş üzerinde hala parmak besinlerle beslenme becerisi kazanmamış hasta sayısı malnütrisyonlu grupta 18 (%7,2) iken malnütrisyonu olmayan grupta üç (%1,2) idi. Bu oranının malnütrisyonu olan grupta daha fazla olduğunu gördük (p<0,001) (**Tablo 1**).

İki yaş üzeri hastaların kendi kendilerini besleme yetilerine göre bakıldığında malnütrisyonu olmayan grupta altı (%2,4) hastanın, malnütrisyonlu grupta ise 48 (%19,2) hastanın hala kendi kendini besleme yetisi kazanamadığını tespit ettik. Bu

Tablo 2. Anne sütü kullanım süreleri ile malnütrisyon arasındaki ilişkinin değerlendirilmesi

	Malnütrisyon yok (250)	Malnütrisyon var (250)	P
Kaç ay sadece anne sütü aldı	4,98±1,81	4,38±2,03	0,001
Ek gıdaya kaçıncı ayda geçti	4,98±1,81	4,94±2,58	0,849
Anne sütü kaçıncı ayda kesildi	12,02±7,43	9,09±5,43	0,001

İndependent Samples T test

Tablo 3. Malnütrisyon gelişimi için anne sütü kullanım sürelerin en iyi kesim noktasının belirlenmesi ve risk analizi

Değişkenler	Malnütrisyon için en iyi kesim noktası	Duyarlılık	Özgünlük	AUC (%95 C.I.)	AUC için P değeri
Sadece anne sütü ile beslenme süresi	≤4,5	0,720	0,540	0,588(0,538-0,637)	0,001
Anne sütü ile toplam beslenme süresi	≤11,5	0,512	0,308	0,605(0,555-0,655)	<0,001

İstatiksel analiz: ROC Curve analise

AUC: ROC eğrisi altında kalan alan

Risk Faktörleri	OR	%95 güven aralığı	P	Risk
Sadece anne sütü ile beslenme süresi ≤4,5	2,190	1,511-3,176	<0,001	Var
Anne sütü ile toplam beslenme süresi <12	2,357	1,636-3,397	<0,001	Var

İstatiksel analiz: Logistic Regression Analysis

OR: Olasılık oranı

durum iki grup arasında anlamlı olarak farklıydı (p<0,001) (**Tablo 1**).

İki yaş üzerinde tabak kaşık kullanma becerisi kazanamamış hasta sayısı malnütrisyonlu grupta 42 (%16-8), malnütrisyonu olmayan grupta ise 34 (%13,6) idi. Bu durum iki grup arasında farklı değildi (p=0,319) (**Tablo 1**).

Hastalar yaşa göre beslenme sıklığı değerlendirildiğinde malnütrisyonlu grupta 57 (%22,4) hastanın, malnütrisyonu olmayan grupta ise 26 (%10,4) hastanın yaşına göre sık beslenmeye çalışıldığı tespit edildi. Bu durum malnütrisyonlu grupta anlamlı olarak daha yüksek idi (p<0,001) (**Tablo 1**).

Beslenme sırasında televizyon, tablet, telefon görsellerini kullanarak beslenen hasta sayısı malnütrisyonlu grupta 56 (%22,4), malnütrisyonu olmayan grupta ise 48 (%19,2) idi. Bu durum iki grup arasında anlamlı olarak farklı değildi (p=0,378).

Beslenme süresine göre değerlendirildiğinde, beslenme süresinin 45 dakikayı geçtiğini söyleyen ebeveyn sayısı malnütrisyonlu grupta 24 (%9,6), malnütrisyonu olmayan grupta ise 5 (%2) idi. Malnütrisyonu olan grupta bu oran anlamlı olarak daha yüksek idi (p<0,001).

Hastalar AS alım süresine göre değerlendirildiğinde, malnütrisyonu olan grupta sadece AS alım süresinin 4,38±2,03 ay olduğunu, malnütrisyonu olmayan grupta ise 4,98±1,81 ay olduğunu gördük. Malnütrisyonu olan grupta sadece AS kullanım süresinin anlamlı olarak daha düşük olduğunu gördük (p=0,001). Benzer olarak AS ile beslenme toplam süresinin malnütrisyonu olan grupta (9,09±5,43ay), malnütrisyonu olmayan grupa (12,02±7,43ay) göre anlamlı olarak daha düşük tespit ettik (p=0,001). Ek gıdaya geçiş zamanları açısından iki grup arasında anlamlı fark yoktu (p=0,849) (**Tablo 2**).

Malnütrisyon gelişimi açısından AS kullanım sürelerinin en iyi kesim noktası ROC cure analizi ile belirlendi. Buna göre sadece AS ile beslenme süresi ≤ 4,5 ay ise %72 sensitivite, %54 spesifite, area under the curve (AUC): 0,588(0,538-0,637) (p=0,001) ile malnütrisyon gelişme olasılığını ön gördük. Malnütrisyon gelişimi açısından AS ile toplam beslenme süresinin en iyi kesim noktası ise ≤ 11,5 ay sensitivite %51,2 spesitivite %30,8 AUC: 0,605(0,555-0,655) (p<0,001) idi (**Tablo 3**).

Hastaların malnütrisyon gelişimi için risk faktörlerini lineer regression analizi ile değerlendirdiğimizde; eğer sadece AS ile beslenme süresi ≤ 4,5 ay ise malnütrisyon gelişme riskinin 2,19 kat artırdığını (p<0,001), AS ile toplam beslenme süresinin ≤ 12 ay olması ise malnütrisyon gelişim riskini 2,36 kat artırdığını (p<0,001) tespit ettik (**Tablo 3**).

TARTIŞMA

Bebeklik dönemindeki beslenme şeklinin büyüme ve gelişme üzerine önemli etkileri vardır. Anne sütü özellikle ilk 1000 günde bebeğin biyolojik ve psikolojik gereksinimlerini karşılayan önemli bir besin kaynağıdır [4,11,12]. Bu dönemde ebeveynlerin çocuklarını besleme şekilleri çocukta beslenme alışkanlıklarını geliştirir. Bu fikirlerden yola çıkarak yaptığımız bu çalışmada malnütrisyonu olan grubun %12,8'i, malnütrisyonu olmayan grubun ise %9,2'si doğum sonrası

ilk beslenme olarak AS dışında gıdaları (mama, su, şekerli su, inek sütü) tercih etmişti. Elazığ 'da 1997 yılında yapılan benzer bir çalışmada doğum sonrası kadınların %30,8'inin bebeklerine AS'den önce şekerli su verdiği belirtilmiştir [13]. Bu annelerin dörtte biri kolostromu pis ve zararlı bulduğunu belirtmiştir [13]. Çalışmamızda bu durum azalmış görünmektedir. Bu azalma günümüzde eğitimsel ve kültürel iyileşmenin bir göstergesi olabilir.

Düşük gelirli ve orta gelirli ülkelerde, altı aylıktan küçük bebeklerin sadece %37'si yalnızca AS ile beslenmektedir. Birkaç istisna dışında, yüksek gelirli ülkelerde emzirme süresi daha kısadır [14]. Ülkemizde emzirme yaygın olmasına rağmen, bebeklerde sadece AS ile beslenme Türkiye Nüfus ve Sağlık Araştırması (TNSA) 2008'de %42 iken, 2013'te ise %30'a düşmüştür. Dolayısıyla sadece AS ile beslenme önerildiği gibi yaygın değildir [15]. Biz de çalışmamızda ilk altı ay sadece AS ile beslenme oranının malnütrisyonlu grupta malnütrisyonlu olamayan gruba göre anlamlı düşük olduğunu gördük (sırasıyla %26,8'e, %45,6) (p<0,001). Tüm hastalara göre değerlendirdiğimizde ise literatür ile uyumlu olarak 181 çocuğun (%36,2) altı ay sadece AS ile beslendiğini tespit ettik.

Hiç AS almayan veya erken aylarda AS kesilen bebeklerde malnütrisyonun daha sık görüldüğü bildirilmiştir [8,16]. Bazı çalışmalarda ise ilk altı ay sadece AS alanlarda almayanlara göre yaşamın ilk aylarında büyümelerinin daha fazla olduğu tespit edilmiştir [6,17,18]. Bizim çalışmamız da bu çalışmaları destekler niteliktedir. Malnütrisyonu olan hasta grubunda sadece AS ile beslenme süresini ve AS'nden kesilme süresini malnütrisyonu olmayan gruba göre anlamlı düşük bulduk (p<0,001).

Yine başka bir çalışmada 24 aydan fazla süre AS alanlarda 24 aydan daha kısa süre AS alanlara oranla düşük kilolu olma olasılığının 2,6 kat daha fazla olduğu bildirilmiştir [1]. Biz de çalışmamızda sadece AS kullanım süresi ≤ 4,5 ay ise malnütrisyon gelişme riskinin 2,19 kat artığını (p=0,001), toplam AS kullanım süresinin <12 ay ise malnütrisyon gelişme riskinin 2,357 kat artığını (p<0,001) gösterdik.

Ebeveynlerin beslenme zamanı tutumları yaşamın ilk 24 ayında bebeğin öğrenme sürecinde gıda beğenisinin gelişmesine ve kendi kendine beslenme becerisini kazanmasını şekillendirir. Elde edilen bu becerilerinin sonraki yeme davranışını, büyümesini ve kilo durumunu etkileyebildiği çeşitli çalışmalarda gösterilmiştir [7,19,22]. Bu nedenle beslenme zamanında ebeveynlerin hangi davranışlarının çocukların kilo ve beslenme alışkanlıklarını olumlu hangilerinin olumsuz etkilediğini belirlenmesi gerekmektedir. Parmak gıdalarıyla beslenme (8-12 ay) ve kendi kendine beslenme eğitimi (12-18 ay) iki yaş altında başlamaktadır [23]. Ancak bebeğin bu süreçte öğrenme yetisinin gelişmesi elinde olmayan çevresel faktörler nedeniyle gecikebilmektedir. Gelişim basamaklarına uygun olarak parmak besinlerle, kaşıkla ve kendi kendine beslenme dönemi olan 6 ay – 3 yaş arasında çocukların özellikle ebeveynlerin zorlamasına bağlı besin reddi geliştirdiği vurgulanmaktadır. Ayrıca iki yaş civarındaki çocukların beslenirken çevreyi kirletmesi, oyalanarak beslenmesi beslenme zamanını uzatmaktadır. Bu da ebeveynleri kaygılandırarak aşırı kısıtlayıcı hale getirebilmektedir. Tüm bu durumlar çocuğun öğrenme yetilerini geciktirmektedir [24]. Bu nedenle hangi çocuğun ne zaman bu yetilere sahip olabileceği çevresel faktörlere bağımlıdır ve kesin bir yaş sınırı koymak zor olsa da ebeveyn ve bebek etkileşiminin uyumlu olduğu bir ailede en geç iki yaşında bir çocuğun kendi kendini besleyebilmesi ve bir yaşından sonra parmak besinlerle beslenme becerisi kazanması beklenmektedir. Bu yaşa ulaşmasına rağmen hala bu yetilerin geliştirilmesine izin verilmemesi aslında bir besleme davranış bozukluğudur. Bildiğimiz kadarıyla malnütrisyonlu hastalarda ebeveyn tutumunu değerlendiren ayrıntılı bir çalışma yoktur.

Bizim çalışmamızda beslenme ortamı, iki yaş üzerinde kaşık, tabak kullanma yetisi kazanan çocuk sayısı, beslenme sırasında televizyon, tablet vb. görsellerin izletilme oranları ile ilgili iki grup arasında anlamlı bir fark yoktu. Ancak çocuğun beslenmesine babanın iştirak etmesi malnütrisyonu olmayan grupta daha yüksekti (p<0,001). İki yaş üzerinde kendi kendini besleme ve bir yaş üzerinde parmak besinlerle beslenme yetisini kazanmamış çocuk sayısının malnütrisyonu olan grupta daha fazla olduğunu gördük (sırasıyla p<0,001, p=0,002).

Çocuklar normalde 7-8. aylarda pütürlü gıdalarla beslenmeye başlar, 12. ayda çiğnenebilen katı gıdaları tüketebilir hale gelir. Bu dönemlerde beslenme sırasında kusma, boğulayazma gibi talihsizlikler yaşanır ise ebeveynler tedirginlikten tüm gıdaları blenderdan geçirerek beslemeyi tercih edebilir. Bu durum katı gıdaları yutma becerisinin gecikmesine ve gelişme geriliğine sebep olabilir. Ebeveynler ek gıda ile besleme dönemlerinde bebeği besleyebilmek için öğün aralarında sık besin ısrarları çocukta besin reddine neden olabilir [23,24]. Çalışmamızda malnütrisyonlu grupta ebeveynlerin çocuklarını yaşına göre daha sık beslemeye çalıştıklarını ve bir yaş üzerinde sadece blenderdan geçirilmiş yumuşak kıvamlı gıda tüketiminin daha sık olduğunu gösterdik (sırasıyla p<0,001, p<0,001). Aynı zamanda malnütrisyonu olan grupta 45 dakikayı geçen beslenme süresinin daha sık görüldüğünü tespit ettik (p<0,001). Bu tespitlerimiz malnütrisyonlu hastalarda

beslenme içeriğinin yanında besleme şeklinin ve ebeveyn besleme davranışlarının da dikkate alınması gerektiğini göstermektedir.

Çalışmamızın eksik yönleri; çalışmaya katılan hastaların sosyo-ekonomik durumları, ebeveynlerin yaşları, eğitim durumları, gebelikte annenin beslenme durumu, kaç kilo aldığı, vitamin takviyesi alıp almadığı, doğum öncesi ve sonrası annelerin beslenme eğitimi alıp almadığı gibi sosyo-demografik özelliklerin sorgulanmamış olmasıdır. Ayrıca, geçmişte gerçekleşen olaylarla ilgili sorulara cevap vermede bir hatırlama yanlılığı olabilir.

Sonuç olarak, çalışmamız AS alım süresin ve beslenme alışkanlıklarının malnütrisyon gelişimi üzerinde etkilerinin olduğunu göstermektedir. Bu nedenle doğum öncesi ve sonrasında ebeveynlere uzmanlarca bebek beslenmesinin öğretilmesi ve desteklenmesinin önemli olduğunu düşünmekteyiz.

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Original Article

The possible protective effects of curcumin in the case of benzo(a)pyrene administration on rat sperm motility and morphology

Benzo(a)piren uygulaması durumunda kurkuminin sıçan sperm motilitesi ve morfolojisi üzerine olası koruyucu etkileri

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ABSTRACT

Background: In this study, our aim is to investigate the possible protective effects of curcumin on potential damage caused by benzo(a)pyrene (BaP) on rat sperm motility and morphology.

Methods: 36 Wistar Albino male rats were divided into six groups: Group 1, Control; Group 2, Corn oil (BaP dissolver); Group 3, DMSO (Curcumin dissolver); Group 4, BaP; Group 5, Curcumin; Group 6, BaP+Curcumin. By the end of the six week oral administration period, left caudal epididymis and ductus deferens tissues were placed in Pure Sperm Wash (Nidacon) solution (at 37°C) and dissected. Sperms were counted and stained. Measurements of the perinuclear ring of the manchette and the posterior portion of the nucleus were performed. All of the parameters were evaluated statistically.

Results: BaP administration caused a decrease in the number of total sperms and total motile sperms, while increasing abnormalities in tail, acrosome and cytoplasmic droplet particularly. Abnormalities did not approach the control group by curcumin administration in expected rates, but the percentage reduced. The number of total and motile sperms increased by curcumin. All parameters were statistically supported.

Conclusions: In conclusion, curcumin is one of the antioxidant that could be used potentially to inhibit the effects of Benzo(a)pyrene, but is ineffective in preventing all abnormalities.

Keywords: benzo(a)pyrene, curcumin, rat, sperm, morphology

ÖZ

Amaç: Çalışmada, sıçan sperm hareketliliği ve morfolojisi üzerinde benzo(a)pyrene (BaP) uygulamasının neden olduğu potansiyel hasarlar üzerinde kurkuminin olası koruyucu etkilerinin incelenmesi amaçlanmıştır.

Yöntemler: 36 adet Wistar albino sıçan altı gruba ayrılmıştır: Grup 1, Kontrol; Grup 2, Mısır Yağı (BaP) çözücüsü; Grup 3, DMSO (kurkumin çözücüsü); Grup 4, BaP; Grup 5, Kurkumin; Grup 6, BaP+Kurkumin. Altı haftalık oral uygulama sonrasında deneklerin sol kaudal epididimis ve duktus deferens dokuları Pure Sperm Wash (Nidacon) solüsyonuna alınarak (37°C) diseke edilerek sperm elde edildi. Spermler sayıldı ve boyandı. Manşetin perinükleer halkası ve nukleusun posterior parçası arası mesafe ölçülerek kaydedildi. Tüm veriler istatistiksel olarak analiz edildi.

Bulgular: BaP uygulaması sıçanlarda total sperm sayısı ile total hareketli sperm sayısında azalmaya; kuyruk ve akrozom anomalisi ile sitoplazmik droplet oranında ise artışa sebep olmuştur. Görülen anomalilerin kurkumin uygulaması ile beklenen oranlarda ve kontrol grubuna yaklaşacak şekilde düzelmediği ancak görülen anomali yüzdesinin azaldığı tespit edildi. Total sperm ve total hareketli sperm sayısının ise kurkumin uygulaması ile arttığı görüldü. Tüm veriler istatistiksel olarak da desteklendi.

Sonuç: Sonuç olarak kurkuminin bir antioksidan olarak, benzo(a)pyrene uygulamasının yol açtığı hasarlar üzerinde azalmaya yol açtığı ancak anomaliler üzerinde tamamen koruyucu olamadığı kanısına varıldı.

Anahtar kelimeler: benzo(a)pyrene, kurkumin, sıçan, sperm, morfoloji

INTRODUCTION

Environmental toxicants, especially hormonally active xenobiotics, have been identified as adversely affecting reproductive health in recent years [1,2]. Polycyclic aromatic hydrocarbons (PAHs) are a group of important vocational and environmental pollutants [3], formed during incomplete combustion of organic materials [4]. They have been found in air, water, food, and others [4]. PAHs become a significant environmental problem for humans and animals by affecting their health [5]. According to animal experiments, PAHs damage ovarian follicles, decrease the weights of reproductive organs, and cause infertility and abnormal fetal development [6], as well as being associated with the induction of paternally transmitted germ line mutations [7].

Benzo(a)pyrene (BaP) is a well-acknowledged member of the PAH group, and is released into the environment as a result of industrial emissions, forest fires, the manufacture of products such as tar, coke and aluminum, vehicle exhaust, oil spills from tankers, coal burning, wood fires and cigarette smoke [8]. It is known that BaP is a Group 1 carcinogen and has a toxic effect on reproduction according to animal models [8,9]. BaP exposure also shows its effects on male reproductive health [10,11], and causes inhibition of spermatogenesis, decreased sperm production and motility, sperm cell apoptosis besides disrupting hormone profiles, such as reduced plasma testosterone and changing Leydig cell steroidogenesis [1,2]. Moreover, BaP induces oxidative stress, DNA damage and apoptosis in testicular tissue [1], and also inhibits the rate of DNA synthesis in spermatogenic cells among experimental animals through induction of oxidative stress [12]. In addition, it has been found that inhibition of DNA synthesis and other detrimental effects were prevented by treatment of animals with free radical scavengers [13].

Curcumin is one free radical scavenger [14] and a natural phytochemical derived from *Curcuma longa*; also known as turmeric [15]. According to a number of studies, curcumin is a potential therapeutic for many diseases, because of its anticarcinogenic, antioxidant, reno-protective, cardioprotective, neuroprotective [16], antimicrobial, immunomodulatory, anti-inflammatory properties and also it is effective on anti-Alzheimer's activities [17]. It shows these activities as strong antioxidant capacities that protect against oxidative damage in lipids, proteins, and DNA [18]. It has shown no toxicity *in vitro* in several cell culture systems, and *in vivo* in animal models and Phase I human clinical trials [16]. Additionally, the safety, tolerability, and non-toxicity of curcumin in high doses are well established by such human clinical trials [19]. In addition, it has been reported that curcumin protects the male reproductive tract against the damaging effects of oxidative stress [20]. According to the results of several studies, it is believed that curcumin may prevent peroxidative alteration in sperm and the testicular membrane which leads to the improvement of sperm

motility and a decrease in sperm defects against various stressful conditions and reproductive damage [21]. Curcumin affects sperm functions as motility/capacitation and acrosome reaction/fertilization [17].

Therefore, the aim of this study is to investigate the possible protective effects of curcumin, as an antioxidant, on potential damage caused by benzo(a)pyrene (BaP), which is an important environmental pollution factor, on rat sperm motility and morphology.

METHODS

Chemicals

BaP and Curcumin were purchased from Sigma Chemical Co. (St Louis, MO, USA) and BaP was dissolved in corn oil by heating to obtain suitable concentrations for use. Curcumin was dissolved in DMSO (Sigma/Aldrich Chemical Co.). Fresh solutions were prepared daily and were stored in conical tubes at room temperature in darkness.

Animals

A total of thirty six Wistar albino male rats (Gazi University Medical School Experimental Animal Breeding and Experimental Research Center, Ankara, Turkey) were used in this research. Rats weighing 250 - 300 g were housed in clean, sterile, polypropylene cages under standard vivarium conditions (12 - hour light / dark cycle) with access to water and standard chow (Korkutelim Yem Ltd., Antalya, TURKEY) composing of 14% fat, 12% water, 25% protein, 7% cellulose, 8% total ash, 2% inorganic ash, 1% NaCl, 1-1.8% calcium, 0.9% phosphore, 0.5-0.8% sodium, 1% lysine, and 0.3% methionine with adequate mineral and vitamin levels for the animals. The animals were housed one per cage in an air-conditioned animal room at 22 ± 3°C and 55 ± 10% humidity. The animal experiments were premeditated and executed in accordance with ethical norms approved by Institutional Animal Ethics Committee Guidelines. The animals were acclimatized to laboratory conditions for seven days prior to the start of the experiments.

Curcumin Preparation

0.6 g curcumin was dissolved in 15 ml DMSO and applied to the animals by gavage in 100 ml / kg / days dosage.

BaP Preparation

0.06 g BaP was dissolved in 15 ml corn oil and applied to the animals by gavage in 10 ml / kg / days dosage.

Experimental Design

The rats were separated into six groups: Group 1, Control; Group 2, Corn oil (BaP dissolver 1ml / kg / days); Group 3, DMSO (Curcumin dissolver 1ml / kg / days); Group 4, BaP (10 ml / kg / days); Group 5, Curcumin (100 ml / kg / days); and Group 6, BaP + Curcumin (10 ml / kg / days + 100 ml / kg / days). They were applied by gavage at the same time every day for six weeks. At the end of the experiment, left caudal epididymis and ductus deferens tissues were collected under ketamine (45 mg / kg) and Xylazine (5 mg / kg) anesthesia.

Preparation of the Sperms

Left caudal epididymis and ductus deferens tissues were removed into Pure Sperm Wash (Nidacon) (at 37°C) solution and dissected. Sperms were counted using a Makler Counting Chamber for spermiogram and stained with Spermac Stain (FertiPro) (Lot: FP12S05, Ref. No: SPS050) for morphological analysis. Perinuclear ring of the manchette and posterior portion of the nucleus measurements were performed. All of the parameters were evaluated statistically.

Spermac Stain

A thin feathered-edge smear of fresh, undiluted, and liquified semen sample was dried in air for five minutes. After this, the sample was fixed in formaldehyde solution for five minutes and washed in distilled water for 7 x 1 minutes. It was stained for two minutes in Stain A. When introducing the slide into the stain solution, the slide was slowly dipped seven times (about one dip per second) in and out of the stain. After that the sample was washed in distilled water for 7 x 2 minutes. The same procedure was performed for Stain B and C. At the end of the staining procedure, the sample was observed under a Photo-light microscope (DM4000B Image Analyze System, Leica, Germany) and a Leica DFC280 plus camera (1000x) using oil immersion.

Acrosome = dark green, nucleus = stained red, equatorial region = pale green, midpiece and tail = green.

Statistical Analyses

All of the parameters were analyzed using the Statistical Data Package for Social Sciences (SPSS) version of the 19.0 Software (SPSS Inc., Chicago, IL) program. All data was presented as Mean ± Standard Deviation (SD). The differences between the groups were analyzed by Levene statistic test, Duncan statistic test and ANOVA tests.

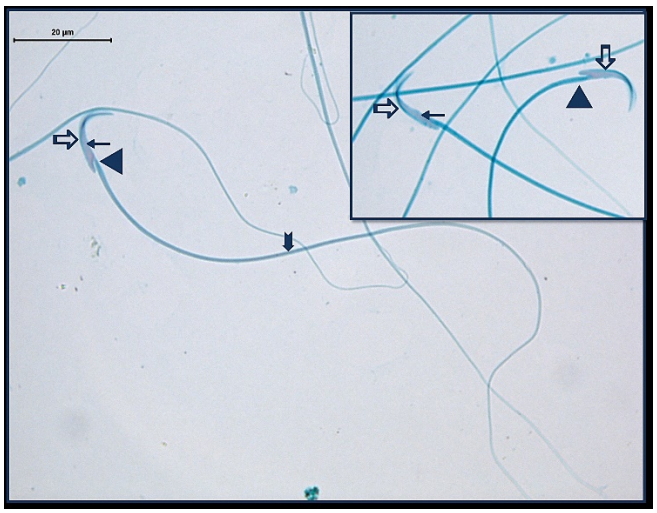


Figure 1. Normal sperms structure. Nucleus (→), acrosome (⇨), neck (▶) and tail (➡) (Spermac x1000)

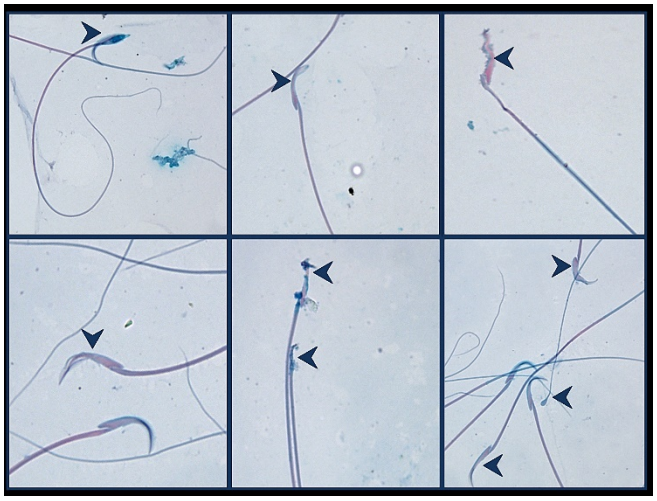


Figure 2. Sperms with head-structure abnormalities (➤) (Spermac x1000)

RESULTS

Spermac Stain Results

After sperm-smears were stained by Spermac stain, normal-structure sperms were seen with hook-shaped heads, convex-located acrosomes, central-located nuclei, normal neck structures and tails get thinner forward last pieces (**Figure 1**). Some sperms exhibited abnormalities at different rates for different groups. These abnormalities are classified as head, neck, acrosome, tail and cytoplasmic droplet. Different abnormal shapes of the hook-shaped head structures were seen as abnormal heads of sperms, and pinhead sperms were also revealed from place to place (**Figure 2**). The neck abnormalities were found mostly as bending or as thickening of the neck (**Figure 3**). Rupturing of the distal part, and bending or thinning of the middle part in some segments were seen by examination of tail abnormalities (**Figure 4**). The acrosome abnormalities were

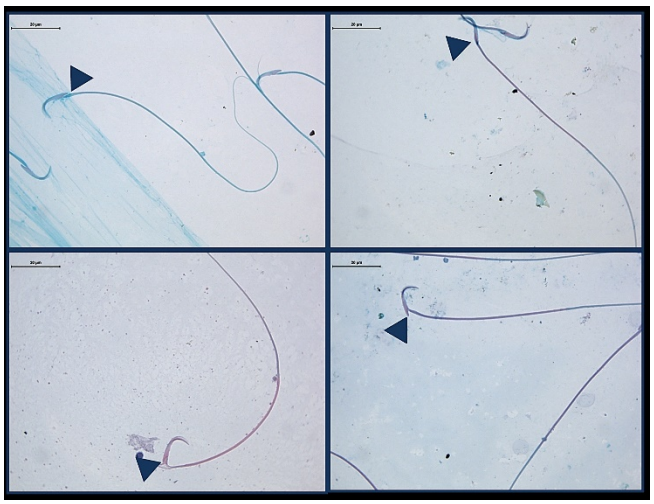


Figure 3. Sperms with neck-structure abnormalities. Neck (▶) (Spermac x1000)

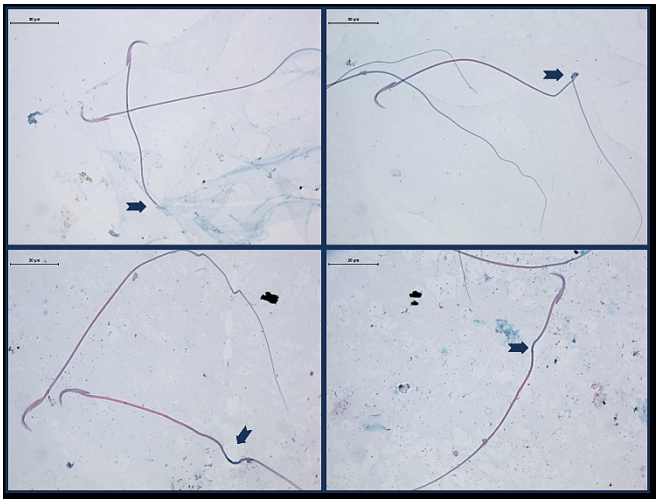


Figure 4. Sperms with tail-structure abnormalities. Tail (➡) (Spermac x1000)

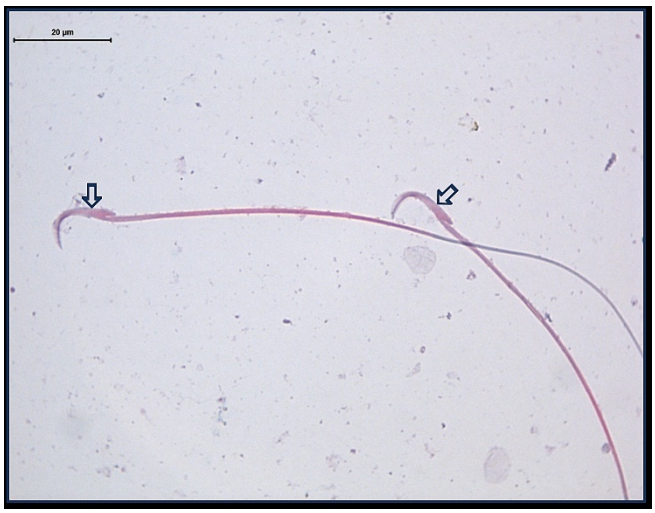


Figure 5. Sperms with acrosome abnormalities. Acrosome (⇨) (Spermac x1000)

usually observed in the form of a complete elimination of the acrosome, while some of the acrosome showed weak structure in the away region of the neck in sperms (**Figure 5**). In some sperms, cytoplasmic droplets were seen

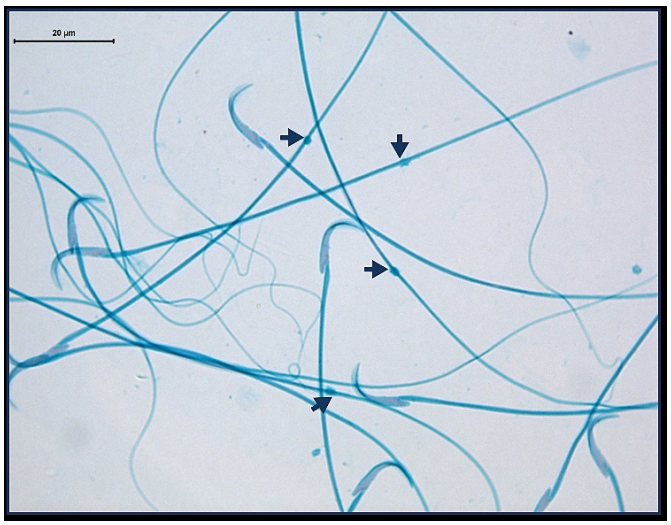


Figure 6. Sperms with cytoplasmic droplet (➔) (Spermac x1000)

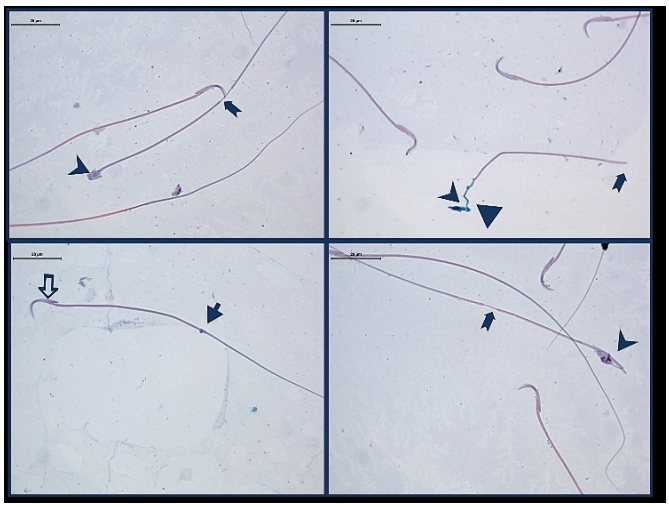
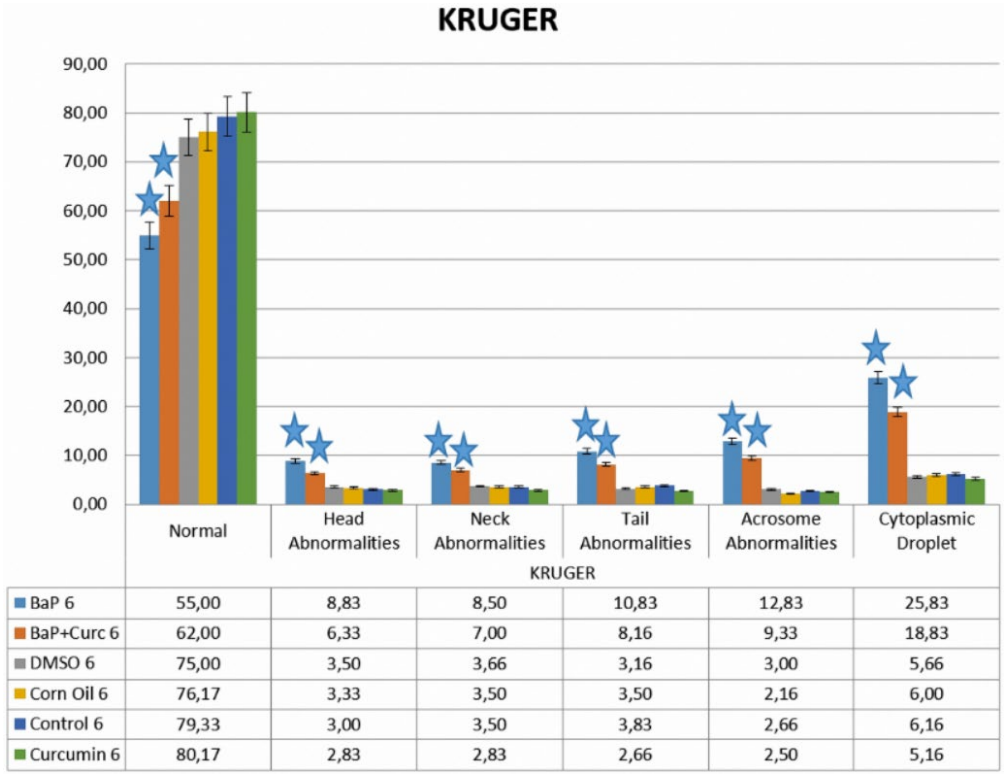


Figure 7. Sperms with multiple abnormalities. Head (➤), acrosome (⇨), neck (▶), tail (➡) and cytoplasmic droplet (➔) (Spermac x1000)



KRUGER	Normal	Head Abnormalities	Neck Abnormalities	Tail Abnormalities	Acrosome Abnormalities	Cytoplasmic Droplet
BaP 6	55,00	8,83	8,50	10,83	12,83	25,83
BaP+Curc 6	62,00	6,33	7,00	8,16	9,33	18,83
DMSO 6	75,00	3,50	3,66	3,16	3,00	5,66
Corn Oil 6	76,17	3,33	3,50	3,50	2,16	6,00
Control 6	79,33	3,00	3,50	3,83	2,66	6,16
Curcumin 6	80,17	2,83	2,83	2,66	2,50	5,16

Graphic 1. The descriptive statistics with the error bars of normal and abnormal sperm numbers between the groups

in different parts of the tail (**Figure 6**). In some areas, some sperms were seen with multiple abnormalities (**Figure 7**).

By statistical evaluation according to groups it was concluded that the number of normal sperms decreased by BaP administration. In addition, the number of normal sperms were similar in the control, corn oil, DMSO and curcumin administration groups. Head, neck, tail and acrosome abnormalities increased by BaP administration and it was noted that acrosome abnormalities and cytoplasmic droplets were the most commonly seen abnormalities by BaP administration through the sperms. In the BaP+Curcumin administration group it was observed that the number of normal sperms increased while the number of sperms with abnormalities decreased (**Graphic 1**).

ARC Measurement Results

By statistical evaluation of the perinuclear ring of the manchette and the posterior portion of the nucleus measurement (ARC) it was observed that the angular distance increased by BaP administration. The angular rate

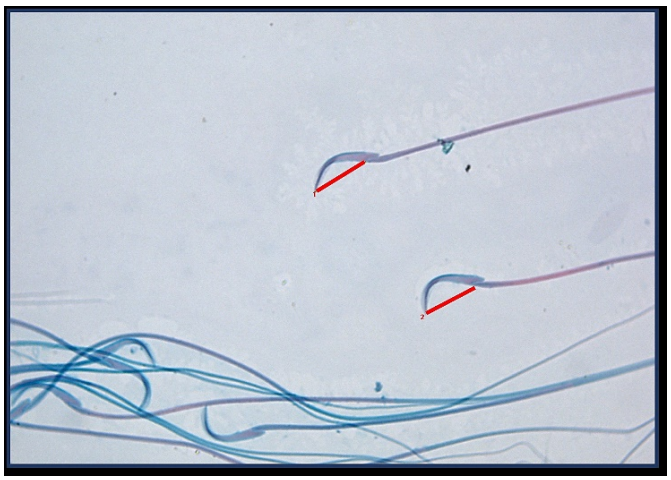
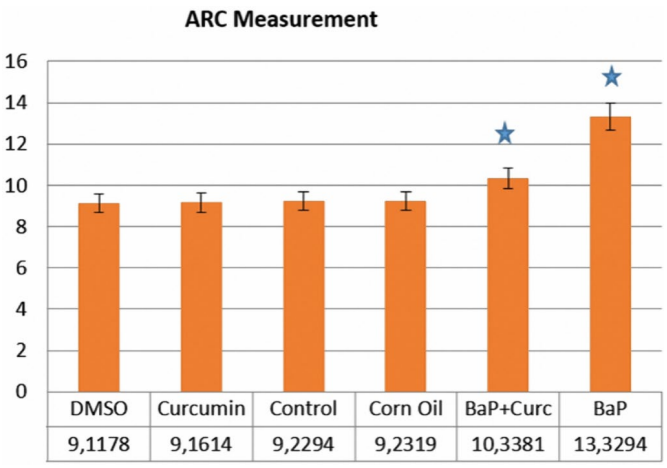
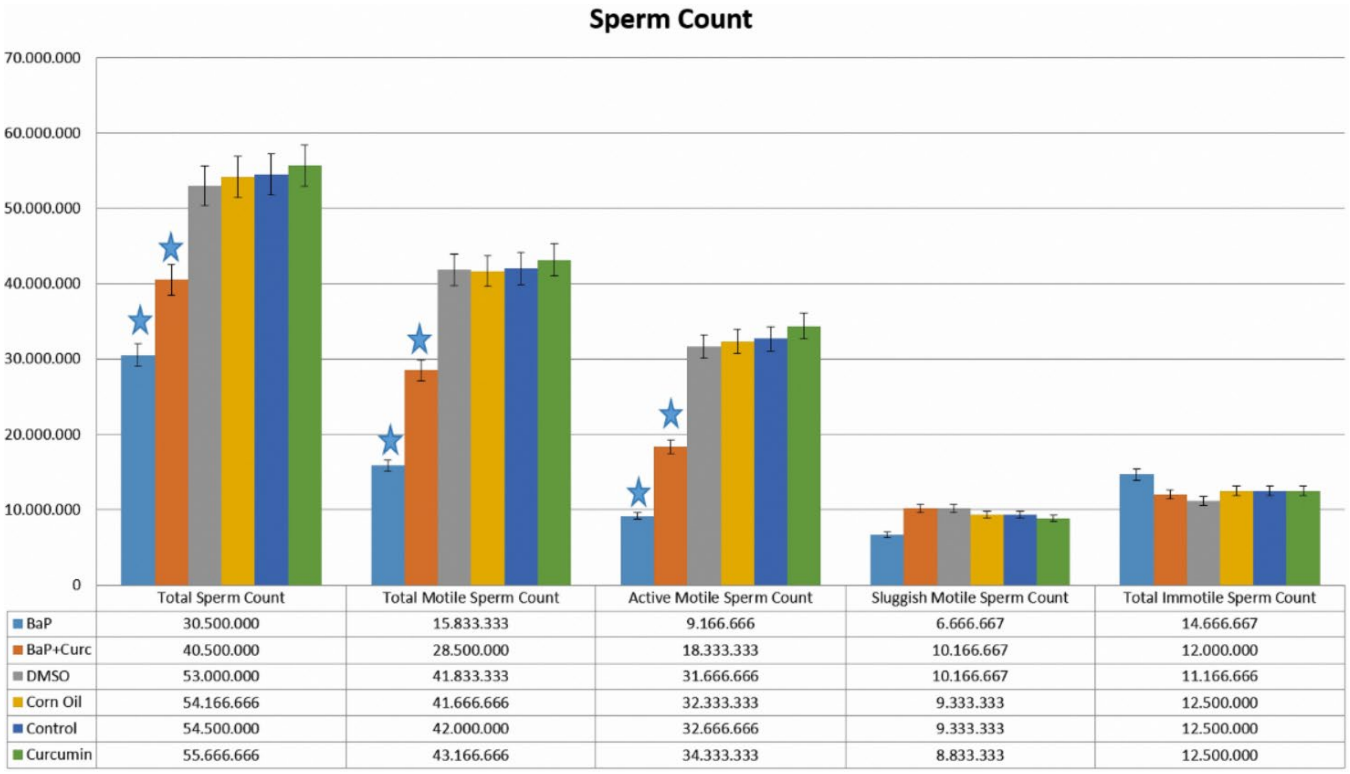


Figure 8. Perinuclear ring of the manchette and the posterior portion of the nucleus (ARC) measurement



Graphic 2. The descriptive statistics with the error bars of perinuclear ring of the manchette and the posterior portion of the nucleus (ARC) measurement between the groups



	Total Sperm Count	Total Motile Sperm Count	Active Motile Sperm Count	Sluggish Motile Sperm Count	Total Immotile Sperm Count
BaP	30.500.000	15.833.333	9.166.666	6.666.667	14.666.667
BaP+Curc	40.500.000	28.500.000	18.333.333	10.166.667	12.000.000
DMSO	53.000.000	41.833.333	31.666.666	10.166.667	11.166.666
Corn Oil	54.166.666	41.666.666	32.333.333	9.333.333	12.500.000
Control	54.500.000	42.000.000	32.666.666	9.333.333	12.500.000
Curcumin	55.666.666	43.166.666	34.333.333	8.833.333	12.500.000

Graphic 3. The descriptive statistics with the error bars of spermiogram results between the groups

was similar in the control, corn oil, DMSO and curcumin groups. In the BaP + Curcumin group it was established that curcumin brought the rate of sperms closer to the control group ($p < 0.05$) (**Figure 8** and **Graphic 2**).

Spermiogram Results

The number of total sperms, total motile sperms, active motile sperms, sluggish motile sperms and total immotile sperms were counted for all groups and all subjects using a Makler Counting Chamber with the variables being analyzed statistically. According to the data obtained, the total number of sperms, total motile sperm and active motile sperm decreased by BaP administration. In the control, corn oil, DMSO and curcumin groups, no significiant difference was observed statistically. In the BaP + Curcumin administration group, the total number of sperms, total motile sperm and active motile sperm increased (**Graphic 3**).

DISCUSSION

The present study is designed to determine the possible adverse effects of BaP and the possible protective effects of curcumin as an antioxidant on male fertility after direct exposure through rats. To determine the effects of BaP and

also curcumin on reproduction, we focus on morphological examinations of sperm and spermiogram.

BaP induced testicular malformation, decreased sperm motility with 10 mg / kg (high dose) oral administrations over six weeks, so Mohamed et al. conclude that exposure to BaP at high doses decreases the fertilization potential through mice in subsequent generations and has an adverse effect on sperm function and fertility [10]. Similarly, Reddy et al. found in their study that 100 µg / kg BaP administration causes testicular and epididymal toxicity, endangers male reproduction by affecting spermatogenesis, and steroidogenesis, by inducing oxidative toxicity in testis and epididymis, and by reducing fertility efficiency through rats [22]. Another study in this field also shows that long-term exposure to low concentrations of BaP might disrupt testosterone production in Leydig cells *via* an alteration of steroidogenic proteins and also decrease epididymal sperm quality by disturbing testosterone levels *via* Leydig cells [11]. Banerjee et al. investigated the effects of five mg / kg BaP for 60 days through rats and found that BaP exposure decreases the epididymal sperm count and motility, diminishes serum testosterone level and induces apoptosis in testis. Researchers also examined the protective effects of 50 mg / kg resveratrol as an antioxidant against these destructions, and came to the conclusion that resveratrol could be a new hope as a potential protector of reproductive health against BaP [1].

Supporting the literature, the number of normal sperms decreased by BaP administration according to our study, with head, neck, tail and acrosome abnormalities increasing through BaP administration, and it was determined that acrosome abnormalities and the cytoplasmic droplets are the most commonly noted abnormalities with BaP administration. In addition, it was seen that the number of total sperm, total motile sperm and active motile sperm decreases with BaP administration.

Dose-response modelling was studied by O'Brien et al. administering BaP in different doses (from 12.5 to 100 mg / kg / day) for 28 days by gavage to male mice. After this, they collected germ cells from the cauda epididymis and seminiferous tubules. As a result, they demonstrated that oral exposure to BaP causes spermatogonial stem cell mutations, in different phases (post-spermatogonia, dividing spermatogonia, and spermatogonial stem cells) of spermatogenesis [23]. Another study also demonstrated that BaP exposure during fetal development increases mutation in the soma and sperm of adult mice [24].

The transformation of spermatids into functional sperm is extremely important during mammalian spermiogenesis involving the shaping and condensation of the nucleus and the formation of the acrosome and tail [25]. Additionally, microtubules are critical components of cells. Control of microtubule length, number, and movement is essential for many cellular processes, so mutation is associated with defects in microtubule structures involved in the division of immature sperm cells, in structures that shape the sperm head and the sperm tail which is essential for sperm movement in the female reproductive tract. Nucleation of microtubules in the manchette is thought to arise in the perinuclear ring region of the spermatid head, so while examining head abnormalities through mutants, abnormal manchette structure or function is important. For instance, elongating spermatids display several abnormalities, including perinuclear rings [26]. In line with this, fractionated manchette perinuclear rings of various diameters have been demonstrated [25], so the distance between the perinuclear ring of the manchette and the posterior portion of the nucleus is important for the determination of deformation in the nucleus [26].

The distance between the perinuclear ring of the manchette and the posterior portion of the nucleus (ARC) is measured in our study and it can be seen that the angular distance increases with BaP administration, and that curcumin brings closer the rate of sperms to the control group.

Curcumin, used for thousands of years in natural medicine, is now considered to be a potentially therapeutic drug in clinical practice. Until now, few studies have been published on the possible protective or therapeutic effects of curcumin on fertility [21,27]. The action of curcumin on semen quality parameters as an antioxidant in different toxic condition was investigated by Glombik et al. who found that the anti-inflammatory and anti-oxidant effects of curcumin were dependent on its concentration. In summary, curcumin has a protective effect against any toxic condition of the male reproductive system, but high concentrations also have a cytotoxic on male reproductive cells *in vitro* [15].

According to examinations based on semen parameters in toxic or destructive conditions, such as varicocele [14] and cyclophosphamide [28] models, it has been determined that curcumin administration can decrease NO levels and improve sperm parameters [14], amplify sperm count, motility and viability, especially when used with zinc and can reverse adverse effects of arsenite on sperm parameters [28].

The number of normal sperms increased while the number of sperms with abnormalities decreased with Curcumin

administration against BaP according to our study. Additionally, the number of total sperm, total motile sperm and active motile sperm increased in the BaP + Curcumin administration group.

Unlike other studies, Naz found in his research that curcumin causes intracellular acidification and membrane hyperpolarization thereby inhibiting sperm forward motility through healthy and fertile men when sperm samples were incubated at various concentrations (50 - 400 μM) of curcumin [16].

Soleimanzadeh and Saberivand examined the antioxidant properties of curcumin against oxidative stress in the cryopreservation process. It is known that cryopreservation induces reactive oxygen species generation and is responsible for sperm damage. According to this study, when sperm samples are supplemented with 2.5 mM curcumin in a freezing process, it can be concluded that curcumin addition during freezing results in positive effects on sperm parameters after thawing through adult rats [29]. Similarly, Zhang et al. Showed that curcumin can significiantly improve sperm motility against oxidative damage induced by the H_2O_2 of leucocytospermic patients [30].

Although there are few studies that describe the relationship between BaP, curcumin and male reproduction, a study published in 2016 shows that curcumin modulated MAPKs and p53 prevents oxidative stress, regulates the expression of pro and anti apoptotic proteins so protecting male germ cells from BaP induced apoptosis, especially when used with resveratrol by creating a synergistical effect. In addition, it was determined in this study that 50 mg curcumin and resveratrol prevents germ cell apoptosis in BaP administrations, but increasing the dose does not show any further improvement in their functions [2].

CONCLUSION

Taken together, curcumin is one of the antioxidant that could be used potentially to inhibit the detrimental effects of benzo(a)pyrene on semen parameters, but it is not sufficient to prevent all abnormalities.

This is the first study based on the effects of curcumin applications on semen parameters of rats in BaP administration, so we are of the opinion that future studies should be based on using combined antioxidants with curcumin which can provide more descriptive results regarding this research.

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DECLARATION OF CONFLICT OF INTEREST

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Original Article

The severity of intrahepatic cholestasis of pregnancy can shorten the first stage of labor in multiparous women induced by prostaglandin E2

Gebelik intrahepatik kolestazının şiddeti, prostaglandin E2 ile indüklenen multipar kadınlarda doğumun ilk aşamasını kısaltabilir

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ABSTRACT

Aim: To determine the relationship between increased serum bile acid concentrations and the first stage of labor in multiparous women induced by vaginal prostaglandin E2 (PGE2) with intrahepatic cholestasis of pregnancy (ICP).

Material and Methods: In this retrospective case-control study 283 multiparous women with ICP and 283 healthy multiparous pregnant women were admitted for induction of delivery, were inserted PGE2 (10 mg dinoprostone) vaginally. The groups with mild, moderate and severe ICP were compared with control group in terms of the time from beginning of PGE2 vaginal insertion to active phase of labor, the time from beginning of PGE2 vaginal insertion to complete dilatation of cervix and fetal outcomes.

Results: The time from beginning of PGE2 insertion to active phase in the mild, moderate and severe ICP groups were shorter than in the non-ICP group; 3.19±0.32, 7.26±0.34, 8.71±0.35 hours, respectively ($p<0.01$). The time from beginning of PGE2 insertion to complete dilatation of cervix in the groups with mild, moderate and severe ICP were shorter than in non-ICP group; 3.03 ± 0.45; 10.33 ± 0.62; 14.44 ± 0.53, respectively ($p<0.01$). There was no difference between the groups in terms of fetal outcomes except fetal weight and the presence of meconium ($p<0.01$).

Conclusion: Increased bile acid concentrations in multiparous pregnant women induced by vaginal PGE2 with mild, moderate and severe ICP are associated with shorter duration of cervical ripening and labor induction time to delivery. The study concluded that multiparous women with ICP can deliver faster as the severity of cholestasis increases.

Keywords: bile acid, duration of labor, intrahepatic cholestasis of pregnancy, prostaglandin E2, severity of cholestasis

ÖZ

Amaç: Vajinal prostaglandin E2 (PGE2) ile indüklenen multipar kadınlarda gebeliğin intrahepatik kolestazına (ICP) bağlı artan serum safra asit konsantrasyonları ile doğumun ilk evresi arasındaki ilişkiyi belirlemek.

Gereç ve Yöntemler: Bu retrospektif vaka-kontrol çalışmasında 283 ICP'li ve 283 sağlıklı multipar gebe doğum indüksiyonu için kabul edildi, vajinal olarak PGE2 (10 mg dinoproston) yerleştirildi. Hafif, orta ve şiddetli ICP'li gruplar, PGE2'nin vajinal yerleştirilmesinin başlangıcından doğumun aktif evresine kadar geçen süreler, PGE2'nin vajinal yerleştirilmesinin başlangıcından serviksin tamamen dilatasyonuna kadar geçen süreler ve fetal sonuçlar açısından kontrol grubu ile karşılaştırıldı.

Bulgular: Hafif, orta ve şiddetli ICP gruplarında PGE2'nin yerleştirilmesinin başlangıcından aktif evreye kadar geçen süre ICP olmayan gruptakine göre daha kısaydı; sırasıyla, 3,19±0,32, 7,26±0,34, 8,71±0,35 saat (p <0,01). Hafif, orta ve şiddetli ICP gruplarında PGE2'nin yerleştirilmesinin başlangıcından serviksin tamamen dilatasyonuna kadar geçen süre ICP olmayan gruptakine göre daha kısaydı; sırasıyla, 3,03±0,45, 10,33±0,62, 14,44±0,53 saat (p <0,01). Gruplar arasında fetal ağırlık ve mekonyum varlığı dışında fetal sonuçlar açısından fark yoktu (p <0,01).

Sonuç: Hafif, orta ve şiddetli ICP'de vajinal PGE2 ile indüklenen multipar gebe kadınlarda artan safra asidi konsantrasyonları, daha kısa servikal olgunlaşma süresi ve daha kısa doğum indüksiyon süresi ile ilişkilidir. Bu çalışma, ICP'li multipar gebelerin kolestazın şiddeti arttıkça daha hızlı doğum yapabilecekleri sonucuna vardı.

Anahtar kelimeler: doğum süresi, gebeliğin intrahepatik kolestazı, kolestazın şiddeti, prostaglandin E2, safra asidi

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder characterized by an increase in serum bile concentrations (≥10 mmol/L) in the third trimester with itching, and recovers rapidly during the postnatal period, but may recur in subsequent pregnancies [1]. It occurs with an incidence of 0.3-5.6% of all pregnancies [2]. Although genetic, endocrine, and environmental factors have been implicated in the etiology, the underlying pathophysiology has not yet been elucidated [3].

ICP may result in maternal complications (preeclampsia, gestational diabetes mellitus, and postpartum hemorrhage) and fetal complications (prematurity, meconium staining, fetal distress, and sudden intrauterine death) [4]. In 1.2% of pregnancies, women who still have ICP after the 37th gestational week may experience sudden intrauterine fetal loss and the risk increases proportionally as the gestational week and bile acid concentrations increase [5]. Serum bile acid concentrations >40 μmol/L are associated with increased adverse pregnancy outcomes [6]. The bile acids are known to be cardio-myotoxic and may result in sudden intrauterine fetal loss due to either fetal cardiac arrhythmias or restriction of placental chorionic veins through a vasoconstrictive effect [7]. In addition, bile acids increase fetal bowel movements and may cause amniotic staining with meconium [8].

Vaginal delivery at 37 weeks gestation is recommended to prevent maternal and fetal morbidities and term stillbirth; however, there is still no consensus on the mode and timing of delivery [9]. According to a study, the most appropriate time for delivery to prevent fetal death without increasing the risk of fetal prematurity was the 36th gestational week [10]. Some pregnant women with ICP experience premature spontaneous delivery [11]. Increased bile acid levels induces myometrial contractility by increasing the susceptibility of endogenous oxytocin [12]. Preterm birth is more common in pregnant women with ICP, but increased serum bile acid concentrations does not change the duration of spontaneous deliveries [13]. We hypothesized that the severity of ICP might augment cervical ripening and shorten the first stage of labor via the vaginal route in multiparous women induced by vaginal prostaglandin E2 (PGE2) for starting labor.

The aim of this study was to show how increased severity of ICP affected the time from beginning of PGE2 vaginal insertion to active phase of labor, the time from beginning of PGE2 vaginal insertion to complete dilatation of cervix, the need for oxytocin induction, and neonatal outcomes in multiparous women induced by vaginal PGE2 with ICP.

MATERIALS AND METHODS

A total of 780 multiparous women who had delivered vaginally were enrolled in this retrospective case control study conducted between 2010 and 2018 in Maternity

Hospital, Samsun, Turkey. Four hundred ninety-seven ICP files were pulled from the hospital archive and 122 files were excluded firstly, due to having cesarean delivery. As well as 92 files were excluded due to spontaneous deliveries. The remaining 123 multiparous women with mild ICP, 101 multiparous women with moderate ICP, 59 multiparous women with severe ICP who were hospitalized for delivery at 36-37 weeks' gestation through the use of vaginal PGE2 were included in the study. Two hundred and eighty-three healthy multiparous pregnant women with oligohydramnios in 36-37 weeks' gestation who were admitted for induction of delivery by vaginal PGE2, were included in the control group for comparisons. Pregnant women with preeclampsia, gestational diabetes mellitus, chronic diseases such as hypothyroidism, multiple pregnancies, polyhydramnios, presentation anomalies, fetal anomalies, and previous cesarean section were excluded from both groups. Ethics committee approval was obtained (TUEK 191-2018 GOKAEK/13-100).

ICP was defined as a clinical condition in pregnancy with serum bile acid concentrations 10 μmol/L and above, accompanied by pruritus. Serum bile acid concentrations in pregnant women with ICP were grouped as mild (10-19.9 μmol/L), moderate (20-39.9 μmol/L), and severe ICP (40 μmol/L and above) [14]. Each pregnant woman with ICP started oral administration of urso-deoxycholic acid (UDCA) (10-15 mg/kg/day), and their bile acid concentrations were measured weekly as well as undergoing Doppler ultrasonography and non-stress tests (NST) [15].

In Samsun Maternity hospital, all women with ICP were delivered by induction of labor at 36-37 weeks' gestation according to the severity of the disease. Additionally, the decision for delivery was made immediately in patients with a serum bile acid concentration of ≥100 μmol/L, in utero fetal death due to ICP before the 37th gestational week in previous pregnancy, deteriorated clinical and laboratory findings despite drug treatment in the 36th-37th gestational weeks after fetal pulmonary maturation.

Prostaglandin E2 (Propess®, Ferring, Italy) (10 mg dinoprostone) was placed in the posterior vaginal fornix to ensure cervical maturation, withdrawn when cervical dilatation reached 4 cm and the effacement reached 60%. Thus, uterine contractions reaching 200 Montevideo units per 20-minute period were achieved spontaneously. Twenty units oxytocin (Synpitan®, Deva, Turkey) was administered to the patients with reduced contraction frequency or potency during their follow-up. Continuous external fetal monitoring and hourly maternal blood pressure follow-up were performed. Cesarean section was performed for indications such as fetal distress or labor arrest.

First stage of labor is the time from onset of labor to complete cervical dilation and it consists of a latent phase (gradual cervical change) and an active phase (rapid cervical change) [16]. The time to active phase which indicates successful labour induction, was calculated as the time from the beginning of PGE2 vaginal insertion to active phase of labor. The time to total cervical dilatation which was accepted as first stage of labor, was calculated as the time from the beginning of PGE2 vaginal insertion to total cervical dilatation.

Demographic information including age, gravidity, parity, abortion, gestational week for delivery; laboratory values including bile acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin concentrations; and data on the time from beginning of PGE2 vaginal insertion to active phase of labor, the time from beginning of PGE2 vaginal insertion to complete dilatation of cervix, need for induction were collected from the hospital's archive records for both groups. We also collected data on fetal weight, 5th Apgar score, umbilical cord arterial pH values, need for intubation, and the presence of meconium in amnion fluid.

Pregnancy weeks were calculated according to the last menstrual period. First trimester ultrasound recordings used for those who did not know their last menstrual period. According to the data we inspected retrospectively, fasting serum bile acid concentrations had been evaluated using, a Cobas 6000-C501 analyzer (Roche, Indianapolis, IN, USA), and AST, ALT, and total bilirubin levels had been evaluated using an AU5800 clinical chemistry analyzer (Beckman Coulter, Brea, CA, USA).

Statistical analysis: The study data were statistically analyzed using IBM SPSS Statistics 21.0 (IBM Corp. Armonk, NY). Descriptive data were expressed in means ± standard deviations and median (minimum-maximum). Oneway ANOVA Test and Kruskal Wallis Test were used to compare three or more groups. Bonferroni Test was used as a subgroup analysis to find out which group caused the significant difference. Chi-square test was used for the analysis of categorical variables. P value < 0.05 was considered statistically significant. For subgroup analysis P value < 0.008 was considered statistically significant.

RESULTS

A total of 566 women met criteria for inclusion in this study, 283 in the control group and 283 in the ICP case group. The

Table 1. Evaluation of demographic characteristics, pregnancy induction characteristics and laboratory results of pregnant women according to severity of ICP

	Control (n=283)	Mild (n=123)	Moderate (n=101)	Severe (n=59)	P value
Age (year)	26.40±4.59	27.67±5.15	26.90±4.90	26.02±3.54	0.051
Gravidity	3 (2-6)	3 (1-5)	3 (2-5)	3 (2-6)	0.052
Parity	1 (1-3)	1 (1-3)	1 (1-4)	1 (1-4)	0.467
Abortion	0 (0-4)	1 (0-2)	1 (0-2)	0 (0-2)	0.071
Gestational week	36.90±0.29	36.90±0.29	36.84±0.36	36.81±0.39	0.186
Bile acid (µmol/L)	0[a]	16.29±2.72[b]	31.17±6.33[c]	73.82±39.47[d]	<0.001*
AST (IU/L)	22.57±8.99[a]	42.95±19.57[b]	66.51±48.29[c]	107.03±65.82[d]	<0.001*
ALT (IU/L)	21.92±9.00[a]	41.83±19.86[b]	70.20±59.70[c]	106.42±69.99[d]	<0.001*
Total bilurubin (mg/dL)	1.08±0.32[a]	1.10±0.15[b]	1.08±0.22[ac]	1.19±0.22[bd]	0.034*

ICP=intrahepatic cholestasis of pregnancy, AST=aspartate aminotransferase, ALT=alanine aminotransferase. a-d: There is no difference between groups labeled under the same letter. Data presented as mean±standard deviation and median (minimum-maximum).

Table 2. Evaluation of labor and neonatal characteristics of pregnant women according to severity of ICP

	Control (n=283)	Mild (n=123)	Moderate (n=101)	Severe (n=59)	P value
Time to active phase (h)	17.12±3.81[a]	13.93±2.50[b]	9.86±2.54[c]	8.41±2.05[cd]	<0.001*
Time to complete dilatation of cervix (h)	28.33±5.42[a]	25.29±3.51[b]	17.99±5.43[c]	13.88±3.24[d]	<0.001*
Induction	216 (76.3%)[a]	72 (58.5%)[b]	43 (42.6%)[c]	16 (27.1%)[d]	<0.001*
Fetal weight (gr)	3019.28±135.68[a]	2793.01±174.53[b]	2728.71±166.90[bc]	2623.73±176.90[d]	<0.001*
Fetal pH	7.32±0.09	7.34±0.09	7.33±0.12	7.31±0.12	0.200
Intubation	26 (9.2%)	10 (8.1%)	14 (13.9%)	11 (18.6%)	0.092
Meconium	21 (7.4%)[a]	10 (8.1%)[ab]	22 (21.8%)[c]	15(25.4%)[cd]	<0.001*

ICP=intrahepatic cholestasis of pregnancy. One-Way ANOVA and Chi-square were used for comparisons of parameters. a-d: There is no difference between groups labeled under the same letter. Data presented as mean±standard deviation and n (%)

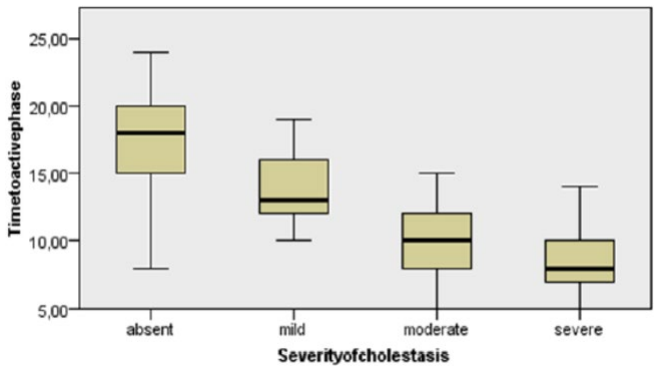

Figure 1. The time from beginning of PGE2 vaginal insertion to active phase of labor according to severity of ICP groups

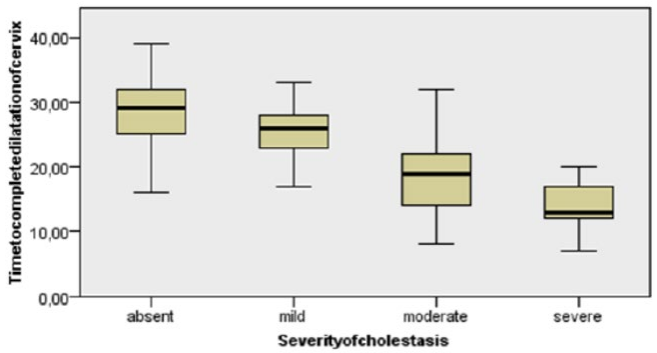

Figure 2. The time from beginning of PGE2 vaginal insertion to complete dilatation of cervix according to severity of ICP groups

Bile acid concentrations of the patients with ICP ranged from 10.3 µmol/L to 281 µmol/L. In the ICP case group, 123 met criteria for mild ICP (43%), 101 moderate (36%), and 59 severe (21%). The evaluation of demographic characteristics and laboratory results of pregnant women with and without ICP is presented in **Table 1**.

The evaluation of labor and neonatal characteristics of pregnant women with and without ICP is presented in **Table 2**.

The time from beginning of PGE2 vaginal insertion to active phase in the mild, moderate and severe ICP groups were shorter than in the non-ICP group, respectively 3.19±0.32, 7.26±0.34, 8.71±0.35 hours (p<0.001) (**Figure 1**). The time from beginning of PGE2 vaginal insertion to complete dilatation of cervix in the groups with mild, moderate and severe ICP were shorter than in non-ICP group, respectively 3,03 ± 0,45; 10,33 ± 0,62; 14,44 ± 0,53 (p<0.001) (**Figure 2**). The need for induction in the groups was decreased with increased levels of ICP (p<0.001). There was no difference between the groups in terms of fetal outcomes except fetal weight and the presence of meconium (p<0.001). The presence of meconium in amnion in the groups was correlated with increased levels of ICP (p<0.001).

DISCUSSION

This is the first evaluation to compare the first stage of labor in multiparous women induced by vaginal PGE2 with mild, moderate, severe ICP, and no ICP. It was observed that as the bile acid concentration increased, the effect of vaginal PGE2 was augmented and the need for induction was reduced. Thus, the time from beginning of vaginal PGE2 insertion to active phase of labor and the time from beginning of vaginal PGE2 insertion to complete dilatation of cervix were reduced.

In clinical practice, spontaneous and iatrogenic preterm deliveries occur as the bile acid concentration increases in pregnant women with ICP, and negative fetal consequences may be experienced [17]. There is still no consensus on the gestational week for delivery of pregnancy with ICP due to the need for NICU, which may be associated with premature birth, and the risk of stillbirth because of late birth decision. Even though women with ICP use UDCA regularly to decrease bile acid concentrations, albeit rare, they may still experience stillbirths, when birth decision is taken after the 37th gestational week [18]. In particular, if the serum bile acid concentration exceeds 100 µmol/L, the birth decision may be taken as early as the 34th gestational week [15]. In our ICP groups the mean gestational week for induction by vaginal PGE2 were 36^{th}.

Increased serum bile acid concentrations in women with ICP is known to cause spontaneous preterm birth by increasing myometrial activity and oxytocin sensitivity [19]. In this study, based on the hypothesis that pregnant women with ICP delivered faster than those without ICP, it was predicted that bile acids would accelerate cervical maturation, and this would naturally accelerate the stages of labor. The PGE2, which was placed in the posterior fornix of vagina for inducing labor in pregnant women with ICP, provided faster cervical augmentation and regular uterine contractions. In patients with ICP, cervical ripening was more than seven hours faster than in those without ICP. It was observed that the cervical maturation of patients with a serum bile acid concentration >20 µmol/L was completed in 10 hours. In the literature, there are no studies that examined the effects of bile acids on cervical maturation. This is the first study on increased serum bile acids augmenting cervical maturation.

Bile acids increases the sensitivity of oxytocin in myometrial cells, and even colic acid produced myometrial contractions by increasing mRNA and protein levels at oxytocin receptor in vitro [12]. The mean time from beginning of vaginal PGE2 insertion to complete dilatation of cervix in women with ICP was ten hours shorter than in women without ICP. In the ICP group, as the serum bile acid concentration increased, the mean time from beginning of vaginal PGE2 insertion to total cervical dilatation decreased dramatically. In fact, those with a serum bile acid concentration ≥40 µmol/L had active birth pain after as little as five hours on average. When the time from beginning of vaginal PGE2 insertion to active phase of labor was shortened, the time from beginning of vaginal PGE2 insertion to complete dilatation of cervix was also shortened. Therefore, as the serum bile acid concentrations increased, the time from beginning of vaginal PGE2 insertion to complete dilatation of cervix was shortened. The mean time from beginning of vaginal PGE2 insertion to complete dilatation of cervix fell below 18 hours in women with a serum bile acid concentration ≥20 µmol/L.

Serum bile acid concentrations over 40 µmol/L as high-risk pregnancy with ICP; no difference is observed in modes of delivery of pregnancies that are terminated at the 37th gestational week [20]. In a retrospective study, there was no increase in intervention delivery or cesarean delivery rates in women with ICP [21]. Also, no difference was observed in terms of the first and second stage of the delivery periods of pregnant women with ICP compared with the control group. It was found that the rate of emergency cesarean sections in women with and without ICP whose deliveries began spontaneously were similar [22]. However, pregnant women with ICP whose labor was induced by oxytocin, required emergency cesarean sections less frequently. It was reported that bile acids, which increase uterine contractility, reduce the delivery duration and the need for emergency cesarean section by removing the possible fetal distress [22]. The need for urgent cesarean section was detected as 24.5% in multiparous pregnant women with ICP who had vaginal delivery previously, in our study. A serum bile acid concentration of ≥10 µmol/L accelerates the delivery period and reduces the risk of fetal distress and the need for emergency cesarean section.

Meconium staining is more frequent in infants with a maternal bile acid concentration ≥40 µmol/L [23]. Although severe ICP allows delivery without creating fetal distress by shortening the delivery duration, high concentrations of bile acids affect fetal colonic activity directly in the early weeks of pregnancy, resulting in the presence of meconium in amnion fluid [24]. A possible correlation of amnion staining with meconium was detected for a bile acid concentration ≥20 µmol/L in the present study.

Retrospective nature and comparing ICP patients with oligohydroamnios pregnancy patients are major flaws in this study. Failure to prevent fetal deaths despite close fetal

examination using ultrasound and cardiotactography prevents obstetricians from performing prospective studies in ICP. Currently, there is no guideline describing the optimal time to initiate delivery in ICP. It is generally emphasized in these guidelines that the decision to give birth can be made according to the clinical presentation of pregnant women and fetal well-being [25].

In conclusion, pregnant women with ICP and serum bile acid concentrations of 10 μmol/L and above did not generally have negative maternal and fetal outcomes in delivery at the 36th gestational week. PGE2 affected cervical ripening faster as serum bile acid concentrations increased. Thus, deliveries started faster and the first stage of labor were shortened in women with ICP, induced by vaginal PGE2.

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DECLARATION OF CONFLICT OF INTEREST

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Olgu Sunumu

Sürekli ayaktan periton diyalizi uygulanan bir hastada mortal seyreden polimikrobiyal peritonit

Polymicrobial peritonitis case in a patient who underwent continuous ambulatory peritoneal dialysis result with exitus

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ÖZ

Peritonit, sürekli ayaktan periton diyalizi uygulanan hastalarda sık görülen bir komplikasyondur ve vakaların çoğunluğunda genellikle tek bir etkene bağlı olarak gelişir. Bununla birlikte, hastaların yaklaşık %1-4'ünde polimikrobiyal peritonit gelişmektedir. Bu hastaların çoğunda gram negatif bir etken ile birlikte mantarlar, nadiren de birden fazla gram pozitif patojen rapor edilmektedir. Polimikrobiyal peritonit gelişen olgularda intraabdominal odak araştırılması önerilmektedir. Bu yazıda 29 yaşında 7 senedir kronik böbrek hastalığı olan ve son bir senedir sürekli ayaktan periton diyalizi uygulanan periton kültüründe *Serratia fonticola, Enteroccus faeicum ve Criptococcus laurenti* üreyen ve mortal seyreden bir hasta sunuldu.

Anahtar kelimeler: Polimikrobiyal peritonit, *Serratia fonticola, Enteroccus faeicum, Cryptococcus laurenti*

ABSTRACT

Peritonitis is a common complication in patients undergoing continuous ambulatory peritoneal dialysis. Majority of cases are usually due to a single agent. Besides, polymicrobial peritonitis develops in approximately 1-4% of patients. A gram-negative pathogen with another bacteria or fungus and rarely more than one gram- positive pathogen are responsible for this polymicrobial peritonitis. It is recommended to investigate intraabdominal focus in patients with polymicrobial peritonitis. In this article, we present a 29-year-old patient with chronic renal disease for 7 years who underwent continuous ambulatory peritoneal dialysis for the last 1 year and had polymicrobial peritonitis due to *Serratia fonticola, Enterococcus faecium and Cryptococcus laurenti* and resulted with exitus.

Keywords: Polymicrobial peritonitis, *Serratia fonticola, Enteroccus faeicum, Cryptococcus laurenti*

GİRİŞ

Peritonit, sürekli ayaktan periton diyalizi (SAPD) uygulanan hastalarda sık görülen bir komplikasyondur ve genellikle intraluminal kontaminasyona bağlı olarak gelişmektedir. Nadiren barsaktan bulaş şeklinde, hematojen yolla ya da vajenden yayılım ile de gelişebilir. İntraluminal kontaminasyonda daha çok *Staphylococcus epidermidis* gibi cilt flora üyesi olan koagülaz negatif stafilokoklar ile enfeksiyon görülürken visseral organlar yoluyla bulaşta gram negatif monomikrobiyal ya da polimikrobiyal enfeksiyon gelişebilir. Fungal peritonit ise çok nadir olmakla birlikte sıklıkla Candida türlerine bağlı olarak gelişir, nadiren de diğer funguslar etken olabilir. Fungal peritonitte kaynak intraabdominal organlar olabileceği gibi dış ortamdan kontaminasyon sonucu da gelişebilir. Özellikle, polimikrobiyal peritonit etkenleri içerisinde yer aldığı durumlarda , fungal peritonit yüksek mortalite ve tedavi yanıtsızlığı ile ilişkilidir [1]. Bu yazıda, periton sıvı kültüründe gram negatif, gram pozitif bakteri ile fungus üreyen ve barsak perforasyonu sonucunda exitusla sonuçlanan 27 yaşında bir erkek hastada gelişen polimikrobiyal peritonit sunuldu.

OLGU

Yirmi dokuz yaşında 7 yıldır kronik böbrek hastalığı (KBH) olan, son bir senedir sürekli ayaktan periton diyalizi (SAPD) tedavisi uygulanan erkek hasta düşme, karın ağrısı, gaita inkontinansı şikayetleri ile acil servise başvurdu. Hastanın özgeçmişinde; kardiyak tamponad, Metilentetrahidrofolat redüktaz (MTHFR) gen mutasyonu, retinal arter trombozu, böbrek taşı ve iskemik serebrovasküler olay öyküsü mevcuttu. Fizik muayenede; ateş 38,2^{o}C, kan basıncı 90/40 mmHg, nabız: 90/dakika idi. Genel durum kötü, bilinç uykuya meyilli, oryantasyonu ve kooperasyonu kısıtlı idi. Ense sertliği, Kernig, Brudzinski bulguları negatifti. Karın muayenesinde palpasyonda yaygın hassasiyet mevcuttu. Periton kateteri çıkış yerinde kızarıklık ve akıntı yoktu. Diğer sistem muayeneleri normaldi. Laboratuvar incelemesinde; hemoglobin 10,8 gr/dL (13,5-18 gr/dL), lökosit 4300 /mm^3 (4000-10500. 10^6/mm^3), trombosit 172.000 /L (150000-450000. 10^6/L) idi. Serum kreatinin 10,1 mg/dL (<1.2 mg/dL), Na: 130 mmol/L (135-150 mmol/L) idi. Diğer biyokimyasal testleri normaldi. Eritrosit sedimantasyon hızı 57 mm/saat (0-20 mm/saat) , C-reaktif protein 536 mg/L (≤ 5mg/L), prokalsitonin 81 µg/L (<0,5 µg/L) saptandı. Periton sıvısı hücre incelemesinde; 9600 /mm^3 lökosit görüldü, Gram boyası ve metilen mavisi ile mikroskopik incelemede %100 polimorfonüklear lökosit (PNL) görüldü, mikroorganizma görülmedi. Akciğer grafisinde mediasten geniş saptandı, infiltrasyon görülmedi. Beyin bilgisayarlı tomografi (BT) görüntüleme normal olarak raporlandı. Abdomen BT'de çekumda çıkan kolon çevresinde serbest sıvı izlenmiş olup çekum duvarı kalın ve hafif ödemli görüldü, sağ alt kadranda perihepatik ve perisplenik alanda minimal serbest sıvı izlendi. Elektroensefalogramda orta derecede frekans yavaşlaması ile karekterize zemin aktivitesi düzensizliği izlendi. Hastadan periton sıvısı kültürü ve kan kültürü alındıktan sonra ampirik olarak intraperitoneal sefazolin ve intraperitoneal gentamisin ve intravenöz (i.v.) oarak piperasilin-tazobactam tedavisi başlandı. Tedavinin 3. gününde hastanın periton sıvısı kültüründe *Serratia fonticola* (meropenem, imipenem, ertapenem, kolistin, tigesiklin duyarlı) üremesi oldu. Etken VITEK-2 otomatize identifikasyon ve antimikrobiyal duyarlılık sistemi (Biomerioux, Fransa) ile tanımlandı. Hastanın mevcut tedavileri kesilip intravenöz meropenem ve intraperitoneal imipenem tedavisi başlandı. Karbapenem tedavisinin 1. gününde hastanın prokalsitonini 81 µg/L'den 29 µg/L' e, CRP düzeyi ise 536 mg/L'den 134 mg/L'ye geriledi. Tedavinin 2. gününde periton sıvısının hafif bulanık görünümde idi, kontrol periton hücre sayımı 16.160/mm^3 lökosit ve Gram boyamasında gram pozitif kok görülmesi üzerine, periton sıvısı kültürü için örnek alındıktan sonra hastanın mevcut karbapenem tedavisine intravenöz vankomisin ve intraperitoneal vankomisin tedavisi eklendi. Hastada vankomisin kan düzeyi bakılamadı. Hastaya uygulanan antimikrobiyal tedaviler **Tablo 1**'da özetlendi.

Karbapenem tedavisnin 3., vankomisin tedavisinin 1. gününde hastanın periton kateterinde gaita partikülü görülmesi üzerine kateteri çekildi ve kateter ucu kültürü gönderildi. Çekilen acil abdomen BT' de barsak perforasyonu ile uyumlu görünüm saptandı. Çekilen acil abdomen BT'de barsak perforasyonu ile uyumlu görünüm saptandı. Hasta acil operasyona alındı. Operasyonda batının kirli olduğu görüldü, yaklaşık 200 cc gaita ile karışık seropürülan mai aspire edildi, tüm batın ince ve kalın barsak diffüz fibrinle örtülü olduğu görüldü, çıkan kolonun nekroze ve bu alandan perfore olduğu görüldü, sağ hemikolektomi ve uç ileoostomi açıldı. Hasta postoperatif vazopresöre rağmen hipotansif seyretti ve exitus kabul edildi. Hastanın exitus olduktan 2 gün sonra sonuçlanan periton sıvısı kültüründe *Cryptococcus laurenti* ve *Enterococcus faecium* üremesi rapor edildi. Etkenler VITEK-2 otomatizde identifikasyon ve antimikrobiyal duyarlılık sistemi (Biomerioux, Fransa) ile tanımlandı. Hasta exitus olduğu için doğrulama testi yapılmadı.

Tablo 1. Hastanın günlere göre tedavi detayları ve laboratuvar bulguları

Tedavi günleri / **Değişkenler**	**1. gün**	**3.gün**	**4.gün**	**Tedavi Sonunda**
İntraperitoneal (IP*) uygulanan tedavi	Yükleme tedavisi: Sefazolin 1 gr + gentamisin 16 mg İdame tedavisi: 4X250 mg/ gün sefazolin + 4 X8 mg/gün gentamisin	Yükleme tedavisi: İmipenem 500 mg İdame tedavisi: 4 X100 mg/gün imipenem	Yükleme tedavisi: vankomisin 2 gr İdame tedavisi: 4 X50 mg/gün vankomisin (İP imipenem tedavisi ile kombine şekilde)	
İntravenöz (IV**) uygulanan tedavi (intraperitoenal tedavi ile eş zamanlı)	3 X4,5 gr/gün piperasilin-tazobactam	2 X250 mg/gün meropenem	1 gr vankomisin/ 4 günde (IV meropenem tedavisi ile kombine şekilde)	
Periton hücre sayımı	9600 lökosit/mm^3	1620 lökosit/ mm^3	16160 lökosit/ mm^3	
Kültür sonucu		Serratia fonticola (1. gün alınan ve 3. gün sonuçlanan kültür)	Enterococcus faecium (3. gün alınan 4.gün sonuçlanan kültür)	Enterococcus faecium ve Cryptococcus laurenti (4. gün alınan ve exitus sonrası sonuçlanan kültür)
Prokalsitonin	81 µg/L	29 µg/L	Çalışılmadı	
CRP	536 mg/L	134 mg/L	373 mg/L	

İP*: İntraperitoneal ,
IV**: intravenöz

TARTIŞMA

Polimikrobiyal etkenlere bağlı peritonitler yüksek mortalite ile ilişkilidir. Peritonit barsak perforasyonu kaynaklı intraabdominal kontaminasyon sonucu gelişebileceği gibi aşırı derece inflamasyon ve barsak invazyonunu takiben gelişen perforasyon sonucu da gelişebilir. Sunduğumuz olguda ilk abdomen BT görüntülemede perforasyon saptanmaması ve alınan ilk kültürde sadece *Serratia fonticola* (*S. fonticola*) üremesi nedeni ile peritonitin odağının intraabdominal sızıntı olabileceği düşünüldü. Ancak hasta exitus olduktan sonra üreyen mikroorganizmalardan birinin *Criptococcus laurenti* gibi çevresel bulaşa neden olabilen bir etken olması nedeniyle kateterin dışardan kontamine olabileceği düşünüldü. Kültürde öncesinde *S. fonticola,* hasta exitus olduktan sonra ise *Criptococcus laurenti* ve *Enterococcus faecium*'un birlikte rapor edilmesi nedeniyle hastadaki peritonit polimikrobiyal olarak değerlendirildi.

S. fonticola su, toprak ve kuş dışkısından izole edilen bir mikroorganizma olup, son yıllarda insanlarda enfeksiyon etkeni olarak da bildirilmektedir [2-5]. Klinik izolatlardan elde edilen *S. fonticola* suşlarına ilişkin yapılan bir derlemede, 17 hasta değerlendirilmiş, 11 hastanın genitoüriner örneklerinde polimikrobiyal üremelere eşlik ettiği rapor edilmiştir. Literatürde *S. fonticola'*ya bağlı enfeksiyon gelişen toplam 6 olgu bildirilmiştir. Bu olgular sırası ile; trafik kazası sonrası protez konulan ve sonrasında uyluğunda apse ve bakteremi gelişen hasta, bisiklet kazası sonrası septik artrit gelişen bir hasta, polimikrobiyal deri yumuşak doku enfeksiyonu gelişen iki olgu, ishal gelişen immünsüprese bir hasta ve ürosepsis gelişen bir hasta şeklinde bildirilmiştir (5). Olguların çoğunda, travma ilişkili bir cilt kontaminasyonu takiben gelişen enfeksiyon mevcuttur. Sunduğumuz olguda da öncesinde düşme anamnezi mevcuttu. Önemli bir nozokomiyal etken olan enterokok türleri gastrointestinal florada bulunur. Enterokoklara bağlı olarak gelişen peritonit olgularının yaklaşık olarak yarısında başka etkenlerin de olduğu bildirilmiştir [6]. Bu nedenle, periton kültüründe enterokoklar izole edildiğinde; gastrointestinal flora elemanı olmaları nedeniyle intraabdominal odak açısından görüntüleme gerekebilir. Sunduğumuz olguda periton sıvısında enterokok üremesi hastada gelişen barsak perforasyonu ile ilişkilendirilmiştir.

Cryptococcus laurentii, neoformans dışı kriptokoklardan biridir ve nadiren enfeksiyona neden olur. Otomatize sistemler ile yanlış tanımlanabilir ve doğrulama testi gerekmektedir. Olgumuzda etken VITEK-2 ile tanımlanmış ve doğrulaması yapılamamıştır. Bununla birlikte; özellikle immünsüprese hastalarda fungemi, diyare, menenjit ve cilt enfeksiyonu gibi çeşitli enfeksiyonlara da neden olabildiği bildirilmektedir [7-10]. *Crytococcus neoformans* dışındaki kriptokok enfeksiyonları için bozulmuş hücresel immün yanıt ve invaziv alet varlığı risk faktörleridir. Sunduğumuz olguda hem periton sıvı kültüründe ve hem periton kateter ucu kültüründe üremiş olması, geniş spektrumlu antibiyotiğe rağmen tedaviye yanıt alınamamış olması, olguda invaziv alet (periton diyaliz kateteri) bulunması bu mikroorganizmanın doğrulama testinin yapılmamış olmasına karşın etken olabileceğini düşündürmüştür.

Literatürde *Cryptococcus laurentii*'nin peritonit etkeni olarak bildirildiği üç olgu mevcuttur [11-13].

Literatürde, *Cryptococcus laurentii'*ye bağlı peritonit bildirilen üç olguda da immünsüpresif tedavi öyküsü bildirilmemiş ve olguların üçünde de periton kültüründen

sadece *Cryptococcus laurentii* izole edildiği rapor edilmiştir. Bu olgularda etkenin bulaş yolu üzerine yorum yapılmamakla birlikte; bir olguda önceki bakteriyel peritonitlere yönelik antibiyotik kullanımının fungal peritonit için risk oluşturabileceği bildirilmiştir. Bir olguya amfoterisin B, bir olguya vorikonazol tedavisi uygunlanmış ve bu iki olgu da başarı ile tedavi edilmiştir. Üçüncü olguda ise tedavinin detaylarına ulaşılamamıştır.

Travma sonrası *Cryptococcus laurentii*'ye bağlı peritonit olgusu bildirilmemiştir.

Sunduğumuz olgu *Cryptococcus laurentii'* nin eşlik ettiği polimikrobiyal bir peritonit olgusu olması ve mortal seyretmesi nedeniyle literatürde bildirilen *Cryptococcus laurentii'*ye bağlı fungal peritonit olgularından farklıdır.Literatür tarandığı kadarı ile literatürde travmaya bağlı olarak *Cryptococcus laurentii'*ye bağlı fungal peritonit gelişen olgu bildirilmemiştir.

Polimikrobiyal peritonit olgusu olarak sunduğumuz hastada, barsak perforasyonu gelişmiş ve sonrasında hastada exitus gelişmiştir. Hastada kültür sonucu hasta öldükten sonra rapor edildiğinden periton sıvısında üreyen *Enterococcus faecium* ve *Cryptococcus laurentii'*ye yönelik tedaviler başlanamamıştır.

Sonuç olarak; sunduğumuz olguda olduğu gibi monomikrobiyal üreme saptanmasına rağmen uygun antimikrobiyal tedaviye yanıt alınamayan hastalarda, peritonitin polimikrobiyal etkenlere bağlı olabileceği akılda tutulmalı ve diğer olası etkenleri de kapsayacak şekilde tedavi protokolünde değişiklik yapılmalıdır.

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Orijinal Makale

Üniversite öğrencilerinde belirsizliğe tahammülsüzlük, endişe ve bilişsel sınav kaygısı ilişkisi

Uncertainty intolerance, worry, and cognitive test anxiety in university students

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ÖZ

Amaç: Bu çalışmada üniversite öğrencilerinin belirsizliğe tahammülsüzlük, endişe ve bilişsel sınav kaygısı düzeylerinin birbirleriyle olan ilişkisi araştırılmış ve mevcut demografik farklılıklar test edilmiştir.

Metot: Çalışmamıza Üsküdar Üniversitesindeki 174 lisans ve yüksek lisans öğrencisi dahil edilmiştir. Çalışmada verilerin toplanmasında Belirsizliğe Tahammülsüzlük Ölçeği (BTÖ), Bilişsel Sınav Kaygısı Ölçeği (BSKÖ) ve Penn State Endişe Ölçeği (PSEÖ) kullanılmıştır. Verilerin değerlendirilmesinde bağımsız örneklem t-testi, ANOVA ve korelasyon analizi gibi yöntemlerden yararlanılmıştır.

Bulgular: Elde edilen bulgulara göre sınav kaygısı, belirsizliğe tahammülsüzlük ve endişe arasında güçlü ve pozitif yönlü bir korelasyonun varlığı gösterilmiştir. Kız öğrencilerin belirsizliğe tahammülsüzlük ve sınav kaygısı düzeyleri erkek öğrencilere göre daha yüksek bulunmuştur. Bunun yanı sıra öğrencilerin belirsizliğe tahammülsüzlükleri, yaş ve gelirlerine göre anlamlı bir şekilde farklılık göstermemektedir.

Tartışma: Belirsizliğe tahammülsüzlüğün endişeye yol açtığı gösterilmiştir. Belirsizlik intoleransı patolojik endişenin tutarlı bir gösterge olduğu bilinmektedir. Bu bilgilerin ışığında ve çalışmamızın verilerinin değerlendirilmesi doğrultusunda çalışmamızda belirsizliğe tahammülsüzlüğün ve endişenin test anksiyetesine yol açtığı düşünülmüştür. Kadınlarda ve yüksek başarı sıralaması olan öğrencilerde belirsizliğe tahammülsüzlüğün yüksek saptanması onların yetiştirilmelerine, toplumsal rollerine ve rol modellerine bağlı olabilir.

Anahtar kelimeler: belirsizliğe tahammülsüzlük, sınav kaygısı, endişe

ABSTRACT

Objective: The purpose of our research is to determine the relations between; intolerance of uncertainty, worry and test anxiety into a non-clinical sample.

Methods: Our research consists of 174 students studying Bachelor's and Master's degrees in various departments of the Üsküdar University. Intolerance of uncertainty scale, cognitive test anxiety scale, and Penn State worry scale have used for collecting data. İnter-scale relations were examined by correlation and regression analysis methods. For scores obtained from scales compared to socio-demographic data statistical techniques have been used such as independent sample t-test and ANOVA.

Results: According to the findings, there is a strong and positive correlation between test anxiety, intolerance of uncertainty and worry. Female students' uncertainty intolerance and test anxiety levels were higher than the male students. On the other hand, in terms of variables such as age, income and shelter preferences, the students' exam anxiety did not differ significantly.

Conclusions: The researches show that the higher intolerance of uncertainty which is a cognitive vulnerability, leads to higher levels of both worry and anxiety. In addition, intolerance of uncertainty has known as a consistent indicator of pathological worry. In light of this information, in our research, it is found that high intolerance of uncertainty and worry caused the test anxiety. The reason why both female students and students with higher success rankings are more intolerant of uncertainty may be related to their upbringing and their role in society and role models.

Keywords: intolerance to uncertainty, test anxiety, worry

GİRİŞ

Günümüzde üniversite öğrencileri, bir yandan akademik başarılara odaklanırken diğer yandan da kendilerini hem eğitim hem de diğer sosyal açılardan etkileyen psikolojik meselelerle mücadele etmektedirler. Gerek teorik çerçeve gerekse ilgili literatür eğitim hayatının ve dolayısıyla akademik başarının depresyon, kaygı ve stres gibi toplumlarda oldukça yaygın olan mental problemlerden aşırı düzeyde etkilendiğini göstermiştir. Söz konusu yaygın mental hastalıkların yanı sıra öğrencileri negatif yönde etkileyen ve geleceğe tereddütlü bakmalarına yol açan bir diğer önemli husus "Belirsizliğe Tahammülsüzlük" (BT) ya da diğer adıyla "Belirsizlik İntoleransı"dır.

Belirsizliğe Tahammülsüzlük en basit olarak belirsizliğe olumsuz tepkiler olarak tanımlanmaktadır [1]. Tanımlar araştırmacıya bağlı olarak bir noktaya kadar değişse de kısaca bir kişinin belirsizliğe dair negatif düşünce ve beklentiler geliştirdiği bilişsel bir durumdur [2]. Bu çalışmanın ana odağı, üniversite öğrencilerinin belirsizliğe tahammülsüzlük, endişe ve bilişsel sınav kaygısı düzeylerinin birbirleriyle olan ilişkisini araştırmak ve olası demografik farklılıkları karşılaştırmaktır.

Çalışmamızın birincil amacı üniversite öğrencilerinin belirsizliğe tahammülsüzlük, bilişsel sınav kaygısı ve endişe düzeyleri arasındaki ilişkiyi saptamaktır. Sekonder amacımız ise üniversite öğrencilerinin belirsizliğe tahammülsüzlük, bilişsel sınav kaygısı ve endişe düzeylerinin sosyodemografik değişkenlere göre farklılıklarını göstermektir.

Üniversite öğrencilerinin yaşadıkları sınav stresi literatürde birçok değişkenle açıklanmaya çalışılmıştır. Carleton et al., belirsizliğe tahammülsüzlüğün öğrencilerin akademik performanslarını oldukça etkilediğini belirtmiştir [1]. Literatürde bazı psikolojik bozukluklar belirsizliğe tahammülsüzlük ile ilişkilendirilmiştir. Örneğin McEvoy ve Mahoney, Genelleştirilmiş Anksiyete Bozukluğunun yüksek olduğu vakalarda belirsizliğe tahammülsüzlüğün ve gelecek odaklı endişenin de yüksek olduğunu saptamıştır [3]. Bunun yanında Carleton ve arkadaşları depresyon, sosyal fobi ve panik bozukluğu gibi çeşitli duygusal bozuklukların tedavisini takiben belirsizliğe tahammülsüzlükte de iyileşmelerin sağlandığını ortaya koymuşlardır [1].

Bahsedildiği gibi belirsizliğe tahammülsüzlük, endişe ve sınav kaygısı, öğrenciler için oldukça önemli problemlerdendir. Üniversite öğrencileri için, geleceklerini inşa ettikleri bu önemli evrede söz konusu problemlerle başa çıkmak hayati öneme sahiptir ve bu çalışmada bilişsel sınav kaygısı ve endişenin belirsizlik ve belirsizliğe tahammülsüzlükten ne derecede etkilendiğine odaklanılmıştır.

GEREÇ VE YÖNTEMLER

2018-2019 eğitim yılının ilk döneminde Üsküdar Üniversitesi'nin farklı bölümlerinde öğrenim gören 173 öğrenciye uygulanan ölçekler kullanılmıştır. Çalışmanın örneklemini Üsküdar Üniversitesi'nin çeşitli bölümlerinde öğrenim gören, lisans ve yüksek lisans öğrencileri oluşturmaktadır. Anketlerde cinsiyet, sınıf ve yaş gibi ana demografik verilerdeki dağılım olabildiğince homojen tutulmuştur.

Çalışmamızın etik kurulu belgesi T.C. Üsküdar Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu Başkanlığı'nın 25/09/2018 tarihli 10 no.lu toplantısında alınmıştır. Çalışmamız Helsinki İlkeler Deklarasyonuna uyularak gerçekleştirilmiştir.

Veri Toplama Araçları

Belirsizliğe Tahammülsüzlük Ölçeği: Orijinali 27 maddeden oluşan bu ölçeğin, İngilizce versiyonunun iç tutarlılığı 0,94, güvenilirliği 0,74 olarak bulunurken, Sarı ve Dağ tarafından uyarlanan Türkçe versiyonunun iç tutarlılığı 0,91, güvenilirliği 0,78 olarak hesaplanmıştır [4]. Bu ölçeğin klinik olmayan örneklemde yüksek ve düşük endişe düzeyindeki kişileri ayırt edebildiği, bu nedenle ölçek geçerliliğinin yeterli olduğu vurgulanmaktadır. Bu ölçek dört faktörden oluşmaktadır: Türkçe versiyonu için Sarı ve Dağ dört ana faktör yapısı tespit etmişlerdir [4]. Bunlar: 1) 'Belirsizlik üzücü ve stres vericidir', 2) 'Belirsizlik eyleme geçmeyi engeller', 3) 'Belirsiz olaylar olumsuzdur ve kaçınılması gerekir', 4) 'Belirsizlik adil değildir'. 5'li Likert tipi yapıya sahip olan ölçeğin cevapları 1: 'beni hiç tanımlamıyor' ve 5: 'beni tam olarak tanımlıyor' şeklindedir. Türkçe versiyonunda 21. madde silinmiştir ve 26 maddelik bir ölçek elde edilmiştir.

Bilişsel Sınav Kaygısı Ölçeği: Bozkurt ve ark. tarafından geçerlilik-güvenilirlik çalışmaları yapılarak Türkçeye uyarlanan bu ölçeğin orijinali Cassady ve Johnson tarafından geliştirilmiştir. Ölçeğin orijinali 25 maddeden oluşurken Bozkurt vd. (2017) tarafından geliştirilen Türkçe versiyonunda 22. ve 24. Maddeler kullanılmamıştır ve dolayısıyla 23 maddelik bir ölçek elde edilmiştir. 4'lü Likert tipi yapıya sahip ölçekte cevaplar 1: beni hiç tanımlamıyor ve 4: beni tamamiyle tanımlıyor şeklindedir [5].

Penn State Endişe Ölçeği: Meyer et al. tarafından geliştirilen PSEÖ, bir konunun aşırı veya kontrol edilemeyen endişe seviyelerine doğru ölçülmesini amaçlayan 16 maddelik bir öz bildirim anketidir[6]. Ölçek 5'li Likert tipidir ve 1: Benim için hiçbir zaman doğru değil ve 5: benim için her zaman doğru şeklindedir. Ölçeğin Türkçe geçerlilik-güvenilirlik çalışmaları 2008 yılında tarafından yapılmıştır [7].

Veri Analiz Yöntemleri

Bu çalışmada ölçeklerden elde edilen skorlar cinsiyet, yaş, lise türü, sınıf, başarı sırası, anne-baba eğitim seviyesi, gelir durumu ve barınma türü gibi sosyo-demografik veriler doğrultusunda karşılaştırılmış, bu amaçla da bağımsız örneklem t-testi ve ANOVA gibi tekniklerden yararlanılmıştır. Normallik ve varyans eşitliği gibi ön varsayımlar ihlal edilmediğinden parametrik olmayan testlere ihtiyaç duyulmamıştır. Bunun yanı sıra ölçekler arası ilişkiler Pearson korelasyon ve regresyon analizi yöntemleri ile incelenmiştir. Tip-I Hata Değeri α=0,05 olarak belirlenmiştir.

BULGULAR

Demografik Verilerin Yayılımı

Bu bölümde çalışmada kullanılan demografik değişkenlere ait temel istatistikler frekans tablolarıyla verilmiştir.

Örneklemde yer alan kız öğrencilerin oranı %52,6 iken erkek öğrencilerin oranı %47,4'tür; ankete katılan öğrencilerin cinsiyet dağılımının birbirine yakın olmasına özen gösterilmiştir. Analizlerde çok fazla grup kullanmamak amacıyla yaşlar iki yıl olacak şekilde gruplar halinde toplanmıştır. Örneklemin çoğunluğunu 18-21 yaş grubunda yer alan öğrenciler oluşturmaktadır. 22 ve üzeri yaşta bulunan öğrencilerin oranı yaklaşık %31'dir. Ankette 10.000 ve altı ile 10.001 ve 20.000 arası iki ayrı grup iken birleştirilerek 20.000 ve altı şeklinde tek bir grup elde edilmiştir. Buna göre örneklemdeki öğrencilerin yaklaşık %35'i sıralamada 50 bin ile 100 bin arasındadır. Toplam 30 öğrenci ise sınavda ilk 100 bine girememiştir (**Tablo 1**).

Korelasyon ve Regresyon Analizleri

Üç ana ölçeğin (sınav kaygısı, endişe ve belirsizliğe tahammülsüzlüğün birbirleriyle olan ilişkileri incelenmiştir. İlk olarak öğrencilerin sınav kaygılarının genel endişe ve belirsizliğe tahammülsüzlük durumlarından ne derecede etkilendiğinin görülmesi amacıyla En Küçük Kareler Yöntemi (EKK) yardımıyla çoklu doğrusal regresyon analizi uygulanmıştır. Burada değişkenler arasındaki çoklu doğrusallık gibi olası problemler göz ardı edilmiştir. **Tablo 2**, sınav kaygısının (SK) bağımlı değişken, endişe (PSE) ve belirsizliğe tahammülsüzlüğün (BT) ise bağımsız değişkenler (açıklayıcı değişken) olarak kullanıldığı regresyon sonuçlarını içermektedir.

Burada sınav kaygısı değişkeni şu şekilde formülize edilebilir:

$$SK = 11{,}791 + 0{,}432PSE + 0{,}361BT$$

Tablo 1. 173 üniversite öğrencisinin demografik özelliklerine ilişkin istatistikler. Kategorik değişkenler frekans dağılımı ve yüzdelik şeklinde sunulmuştur

		Frekans	Yüzde
Cinsiyet	Kadın	91	%52,6
	Erkek	82	%47,4
Yaş	18-19	50	%28,9
	20-21	55	%31,8
	22-23	28	%16,2
	24-25	40	%23,1
Lise Türü	Devlet	109	%63
	Özel	64	%37
Sınıf	1	49	%28,3
	2	26	%15,0
	3	41	%23,7
	4	33	%19,1
	Lisansüstü	24	%13,9
Başarı Sırası	20000 ve altı	47	%27,2
	20001-50000	35	%20,2
	50001-100000	61	%35,3
	100001 ve üstü	30	%17,3
Aylık Gelir	2000 TL ve altı	83	%48,0
	2001-5000 TL	72	%41,6
	5001 TL ve üzeri	18	%10,4

Modelin genel anlamlılığı için F değeri 52,248'dir ve bu değer sınav kaygısının PSE ve BT ile istatistiksel olarak anlamlı bir şekilde açılanabildiğini gösterir (p<0,05). Açıklayıcı değişkenler PSE ve BT'nin bireysel anlamlılık testleri için p<0,001 olarak hesaplandığından her iki değişken de ayrı ayrı sınav kaygısını açıklamada istatistiksel olarak anlamlı değişkenlerdir. Modelin belirlilik katsayısı (R^2) ise PSE (endişe) ve BT'nin (belirsizliğe tahammülsüzlük) sınav kaygısındaki toplam varyansın yaklaşık %38'inin açıklayabildiklerini göstermektedir (**Tablo 2**).

Daha önce literatürde de belirtildiği gibi üç ana ölçeğin birbirleriyle pozitif yönlü bir ilişkisi vardır. **Tablo 3**'te yer alan çapraz korelasyon analizleri literatürle uyumludur. Sınav kaygısı ile Penn State Endişe Ölçeği ile ölçülen genel endişe seviyesi arasındaki Pearson korelasyon katsayısı(r) 0,416 iken belirsizliğe tahammülsüzlük ile arasındaki r ise 0,552'dir. Belirsizliğe tahammülsüzlük ile endişe arasındaki r ise 0,274'tür (**Tablo 3**).

Belirsizliğe Tahammülsüzlüğün Demografik Özelliklere Göre Karşılaştırılması

Belirsizliğe tahammülsüzlük toplam puanı ve bu ölçeğin alt gruplarına ait değerlerin, cinsiyete göre farklılık gösterip göstermediği **Tablo 4**'teki sonuçlara göre yorumlamıştır. Ana ölçek olan BT toplam değeri için kadın öğrencilerin ortalaması 82,46 iken erkek öğrencilerde bu değer 71,32'dir. BTÖ puanı, ne kadar yüksek olursa belirsizliğe tahammülsüzlük o kadar yüksektir. Dolayısıyla kız öğrencilerin hem BT toplam puanında hem de BT'nin alt ölçeklerinde erkeklere göre daha yüksek puana sahip oldukları, bir başka ifadeyle belirsiz durumlara karşı daha tahammülsüz oldukları görülmektedir. BT'ye ait tüm ölçeklerde p-değeri 0,05'ten küçük olduğundan dolayı fark istatistiksel olarak anlamlıdır (**Tablo 4**).

BT'nin yaş gruplarına göre farklılaşıp farklılaşmadığı test edilmiştir. Levene testi istatistiği için p değerleri 0,05'ten büyüktür ve varyans homojenliği varsayımı parametrik test olan ANOVA için sağlanmıştır. Fakat "BT puanları yaş gruplarına göre farklılaşmaz" hipotezi hem toplam BT puanı, hem de alt ölçekler için %5 anlamlılık seviyesinde reddedilememiştir. Dolayısıyla üniversite öğrencilerinin belirsizliğe tahammülsüzlük puanları yaş gruplarına göre istatistiksel olarak anlamlı farklılaşmamaktadır (**Tablo 5**).

BT ve alt ölçeklerinin ortalamalarına bakıldığında, sıralaması yüksek olan öğrencilerin BT puanları da yüksektir. Örneğin üniversite giriş sınavı sıralaması 20.000 ve altı seviye olan öğrencilerin BT toplam puan ortalamaları 88,72 iken sıralamada 100.000 üzerinde yer alan öğrencilerin ortalamaları 67,20'dir. Bu da göstermektedir ki daha başarılı öğrenciler belirsizliği daha çok olumsuz olarak görmektedir. BT toplam puanı ve alt ölçekler için yapılan tüm testlerde p-değeri 0,05'ten küçüktür. Dolayısıyla belirsizliğe

Tablo 2. Sınav kaygısının belirsizliğe tahammülsüzlük ve endişe ile ilişkisi

Değişkenler	Beta	Std. Hata	t	p	Model R^2	Model F	Model p
Sabit Terim	11,791	5,274	2,235	0,027	0,381	52,248	0,000
ENDİŞE	0,432	0,095	4,558	0,000			
BELİRSİZLİĞE TAHAMMÜLSÜZLÜK	0,361	0,048	7,549	0,000			

Tablo 3. Ölçekler arası korelasyon analizi. r: Pearson korelasyon katsayısı, p: p değeri, **p<0,001

Ölçekler	İstatistik	SK	PSE	BT
SINAV KAYGISI (SK)	r	1	0,416**	0,552**
	p		<0,001	<0,001
ENDİŞE (PSE)	r	0,416**	1	0,274**
	p	<0,001		<0,001
BELİRSİZLİĞE TAHAMMÜLSÜZLÜK (BT)	r	0,552**	0,274**	1
	p	<0,001	<0,001	

Tablo 4. Belirsizliğe Tahammülsüzlük ile cinsiyet için bağımsız örneklem t-testi sonuçları, n: örneklem sayısı, ort.: aritmetik ortalama, S: standart sapma, t: t değeri, p: p değeri

BELİRSİZLİĞE TAHAMMÜLSÜZLÜK		n	Ort.	S	t	p	Levene p
Belirsizlik stres verici ve üzücüdür	Kadın	91	28,77	7,289	2,872	0,005	0,339
	Erkek	82	25,68	6,789			
Belirsizlik ile ilgili olumsuzluk benlik değerlendirmeleri	Kadın	91	24,77	6,997	3,859	0,000	0,060
	Erkek	82	20,88	6,181			
Geleceği bilmemek rahatsız edicidir	Kadın	91	12,91	3,617	3,779	0,000	0,739
	Erkek	82	10,84	3,578			
Belirsizlik eyleme geçmememi engelliyor	Kadın	91	16,01	4,391	3,237	0,001	0,373
	Erkek	82	13,91	4,095			
BELİRSİZLİĞE TAHAMMÜLSÜZLÜK	Kadın	91	82,46	20,950	3,704	0,000	0,096
	Erkek	82	71,32	18,342			

Tablo 5. Belirsizliğe tahammülsüzlük ölçeği puanlarının ortalamalarının öğrencilerin yaş, üniversite giriş sınavı başarı sıralamaları ve gelir düzeyleri ile değişip değişmediğine dair yapılan ANOVA sonuçları, n: örneklem sayısı, Ort.: aritmetik ortalama, S: standart sapma, F: F değeri, p: p değeri

Değişken	Değerler	n	Ort.	S	F	p	Levene P
Yaş	18-19	50	77,70	20,634	1,435	0,235	0,378
	20-21	55	73,45	21,832			
	22-23	28	76,43	18,932			
	24-25	40	82,18	18,975			
	Total	173	77,18	20,475			
Başarı Sırası	20000 ve altı	47	88,72	22,046	11,899	0,000	0,110
	20001-50000	35	81,66	21,228			
	50001-100000	61	70,62	14,097			
	100001 ve üstü	30	67,20	18,505			
	Total	173	77,18	20,475			
Gelir	2000 TL ve altı	83	75,00	20,472	0,962	0,384	0,708
	2001-5000 TL	72	78,82	20,731			
	5001 TL ve üzeri	18	80,67	19,439			
	Total	173	77,18	20,475			

tahammülsüzlük öğrencilerin başarı sıralamasına göre istatistiksel olarak anlamlı farklılık göstermektedir (**Tablo 5**).

Tablo 5'te ayrıca belirsizliğe tahammülsüzlük ölçeği puanlarının ortalamalarının öğrencilerin gelir durumları ile değişip değişmediği incelenmiştir. BT ve alt ölçekleri için p değerleri 0,05'ten yüksek olduğundan %5 seviye söz konusu farklılıklar anlamlı bulunamamıştır (**Tablo 5**).

TARTIŞMA

Bu çalışma, klinik olmayan bir örneklemde, belirsizliğe tahammülsüzlük, endişe ve sınav kaygısı arasındaki ilişkiyi incelemektedir. Burada en önemli amaç, üniversite öğrencilerinin belirsizliğe tahammülsüzlük düzeylerinin ve genel endişe durumlarının sınav kaygısı üzerinde anlamlı bir etkiye sahip olup olmadığını belirlemektir. Belirsizlik intoleransı özünde, düşük ihtimaline rağmen olumsuz bir olayın gerçekleşmesinin tamamen imkânsız olmadığı gerçeğini kabul etmenin zorluğu olarak tanımlanabilir. Belirsizliğe tahammülsüzlüğe dair literatür çoğunlukla kaygı ve depresyon ile ilişkisi üzerinde durmuştur [1]. Belirsizliğe tahammülsüzlük yapısının erken gelişimi, olumsuz bir olay ihtimalinin aşırı tahmin edilmesine, istenmeyen durumlarda kişisel ve duygusal uyarılmanın abartılmasına, olumsuz durumlar karşısında artan uyarılma düzeylerinin sürdürülmesine ve negatif durumlar için daha yüksek tahammül eşiklerinin oluşumuna neden olmaktadır [8]. Tüm bu göstergeler daha yüksek BT'nin daha yüksek endişe ve kaygı düzeylerine neden olan bir bilişsel savunmasızlığa neden olduğunu göstermektedir.

Belirsizliğe tahammülsüzlüğün kaygıyla çok güçlü bir şekilde bağlantılı olacağına dair teorik bir bakış açısı hiç şaşırtıcı değildir. Potansiyel bir tehdidin sonucu olarak karşılaşılan tehdidin büyüklüğü veya bu tehdidin üstesinden gelme konusundaki belirsizlik kaygıya yol açacaktır. Carleton ayrıca belirsizlikten kaynaklanan endişenin evrensel olduğunu, çünkü tüm insanların bir durumla başa çıkma becerilerinde belirsizlik yaşayabileceğini ve tüm insanların potansiyel olarak gelecekteki istenmeyen olayları deneyimleme riskiyle karşı karşıya kalacaklarını ileri sürmektedir [1].

Belirsizliğe tahammülsüzlük yapısının erken gelişimi, olumsuz bir olay ihtimalinin aşırı tahmin edilmesine, istenmeyen durumlarda kişisel ve duygusal uyarılmanın abartılmasına, olumsuz durumlar karşısında artan uyarılma düzeylerinin sürdürülmesine ve negatif durumlar için daha

yüksek tahammül eşiklerinin oluşumuna neden olmaktadır [9]. Tüm bu göstergeler daha yüksek BT'nin daha yüksek endişe ve kaygı düzeylerine neden olan bir bilişsel savunmasızlığa neden olduğunu göstermektedir. Bu çalışmalar, yüksek düzeyde BT varlığının önemli bir varoluşsal paradoksun göstergelerinden olduğunu ortaya koymaktadır. Çünkü insanlar kendilerini olumsuz bir sonuç ihtimaline karşı korumaya çalıştıklarında bir yandan da kaygı artışına neden olarak tahammül eşiklerini düşürürler.

Sınav kaygısı, bir performansa dayalı akademik kaygı biçimi olarak, dünyada özellikle öğrencileri ve akademik toplulukları etkileyen bir gerçekliktir. Şaşırtıcı olmayan bir şekilde, öğrenciler sınavlar ve diğer değerlendirme ölçütlerindeki performanslarından endişe ederler. BT ve endişe, sınav kaygısının ortaya çıkmasında ve büyümesinde önemli bir rol oynayan iki bağlanmış yapıdır. Araştırmalar, BT'nin patolojik endişenin tutarlı bir göstergesi olduğunu ortaya koymuştur [10,11]. Eğer bir kişi belirsizliği kabul edilemez buluyorsa, onunla yüz yüze geldiğinde aşırı endişelenebilir.

Üniversite öğrencilerinin belirsizliğe tahammülsüzlükleri üniversite sınavı başarı sıralamalarına göre anlamlı bir şekilde farklılık gösterir. Daha yüksek başarı sıralamasına sahip öğrencilerin belirsizliğe tahammülsüzlük değerleri de yüksektir. Bu ilişkinin araştırılmaya değer olduğu düşünülmüştür.

Bu çalışmada Bİ yapısını klinik olmayan bir popülasyona uygulayarak literatüre ilgili noktada katkı sağlanmıştır. Klinik olmayan örneklemde bilişsel sınav kaygısı ve stres boyutlarıyla BT'yi anlamak ve yordamak, stres ve belirsizliğe tahammülsüzlüğün sınav kaygısını hangi yönlerde etkilediğini açıklamaya olanak tanımıştır. Sınav kaygısı, klinik olmayan örneklerde bulunabilecek yaygın bir anksiyete türüdür. Bir sınava dair olumsuz bir sonuç olasılığı, her öğrenci için büyük bir kaygı kaynağı olabilir. Bu noktada test kaygısı ile Bİ arasındaki bir bağlantı, sınavdan alınacak olumsuz bir sonuç olasılığını tolere edememe ölçüsüdür. Bu nedenle bu çalışma, BT yapısının klinik olmayan bir kaygı durumu içinde verimli bir şekilde incelenmesini sağlamıştır.

Çalışma bu yönüyle literatüre önemli bir katkı yapmaktadır zira üniversite öğrencileri özelinde bu üç ölçek ile bir araştırmaya Türkiye'deki literatürde rastlanmamıştır.

Kadın öğrencilerde belirsizliğe tahammülsüzlüğün yüksek olması rol modeller, toplumsal roller ve yetiştirilme tarzıyla açıklanabilir. Belirsizliğe tahammülsüzlük, endişe ve sınav kaygısı bazı demografik özelliklere göre farklılık gösterirken gelir durumu gibi doğrudan ilgili olabileceği düşünülen bir kısım değişkenlerin öğrencilerin bu özelliklerini etkilemediği ilginçtir ve ileri araştırmaya değer olduğu düşünülmüştür. Sınav kaygısı, belirsizliğe tahammülsüzlük ve endişe arasında güçlü ve pozitif yönlü bir korelasyonun varlığı saptanmıştır. Bir başka ifadeyle, yüksek belirsizliğe tahammülsüzlük ve/veya endişenin, yüksek sınav kaygısına sebep olduğu sonucuna ulaşılmıştır.

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Original Article

Prognostic significance of body mass index and diabetes in patients with malignant glioma

Malign gliom hastalarında vücut kitle indeksi ve diyabetin prognostik önemi

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ABSTRACT

Aim: We aimed to determine whether there is a relationship between body mass index (BMI) and diabetes (DM) before treatment and survival with this study.

Material and Methods: The results of patients who received radiotherapy between 2010 - 2018 were evaluated with this retrospective study. BMI was categorized into 3 groups: normal (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2), obese (≥30 kg/m2). Presence of diabetes was evaluated by considering oral antidiabetic use and file information before treatment. Patient, treatment and tumor characteristics were evaluated with descriptive statistics. Kaplan-Meirer, log-rank and cox-regression analyzes were performed. P <0.05 was considered statistically significant.

Results: The results of 174 cases were evaluated. Diabetes was present in 22 patients (12.6%). In univariate analyzes, being over the age of 65 (p <0.001), Karnofsky performance score (KPS) below 80 (p <0.001), diabetes (p = 0.017), having grad 4 pathology (p <0.001), performing subtotal excision / biopsy (p <0.001), hypofractioned / whole brain radiotherapy (p <0.001), and not receiving adjuvant chemotherapy (CT) (p <0.001) had a negative effect on overall survival (OS). In multivariate analyzes, being over 65 years old, having grad 4 pathology, performing subtotal excision / biopsy and not taking adjuvant CT were found to be effective on OS. Median overall survival in diabetics was 9.65 months and 17.74 months in non-diabetics (p = 0.017). No statistically significant relationship was found between BMI and OS.

Conclusion: Pre-existing diabetes in malignant glioma patients is a risk factor for poor outcomes. It is important to control diabetes and related conditions.

Keywords: malign glioma, diabetes, body mass index, prognosis

ÖZ

Amaç: Bu çalışma ile tedavi öncesi vücut kitle indeksi (VKI) ve diyabet ile sağ kalım arasında bir ilişki olup olmadığını belirlemeyi amaçladık.

Gereç ve Yöntemler: Bu retrospektif çalışma ile 2010-2018 tarihleri arasında radyoterapi (RT) uygulanmış hastaların sonuçları değerlendirildi. VKI, 3 gruba kategorize edildi: normal (18,5-24,9 kg/m^2), aşırı kilolu (25-29,9 kg/m^2), obez (≥30 kg/m^2). Diyabet varlığı, hastaların tedavi öncesi oral antidiyabetik kulanımı ve dosya bilgileri göz önüne alınarak değerlendirildi. Hasta, tedavi ve tümör karakteristikleri tanımlayıcı istatistikler ile değerlendirildi. Kaplan-Meirer, log-rank ve çoklu analizlerde cox-regresyon analizleri yapıldı. P<0,05 istatistiki anlamlı olarak kabul edildi.

Bulgular: 174 olgunun sonuçları değerlendirildi. Diyabet hastaların 22'sinde (%12,6) mevcuttu. Tek değişkenli analizlerde, 65 yaş üstünde olmak (p<0,001), Karnofsky performans skorunun (KPS) 80'in altında olması (p<0,001), diyabet olması (p=0,017), grad 4 patolojiye sahip olmak (p<0,001), subtotal eksizyon/biopsi yapılması (p<0,001), hipofraksiyone/tüm beyin radyoterapisi uygulanması (p<0,001) ve adjuvan kemoterapi (KT) almamak (p<0,001) genel sağ kalım üzerinde olumsuz etkili idi. Çok değişkenli analizlerde ise, 65 yaş üstü olmak, grad 4 patolojiye sahip olmak, subtotal eksizyon/biopsi yapılması ve adjuvan KT almamak genel sağ kalım (GS) üzerine etkili olarak bulundu. Diyabetiklerde medyan genel sağkalım 9,65 ay iken diyabetik olmayanlarda 17,74 ay idi (p=0,017). VKI ile GS arasında istatistiki anlamlı bir ilişki gösterilemedi.

Sonuç: Önceden var olan diyabet kötü sonuçlar açısından bir risk faktörüdür. Diyabet ve ilişkili durumların kontrol altında olması önemlidir.

Anahtar kelimeler: malign glioma, diyabet, vücut kitle indeksi, prognoz

INTRODUCTION

Malignant gliomas account for about half of all brain tumors in adults [1]. The World Health Organization (WHO) classifies grad 3 (anaplastic gliomas) and grad 4 (glioblastoma) gliomas as malign gliomas [1]. Currently the standard treatment applied to high grade glioma involves a maximally-safe resection, concurrent radiotherapy (RT) and temozolamide treatment followed by adjuvant temozolamide [2]. Despite all treatments, survival is very low in malignant gliomas. 5-year survival is 18% for WHO grad 3 tumors and <5% for glioblastomas (GBM) [3]. In addition to known bad prognostic factors such as age, O-6 methylguanine DNA methyltransferase (MGMT) status, Karnofsky performance score (KPS), it is important to identify prognostic factors before treatment [4].

Obesity and diabetes (DM) are among the most important health problems in the world [5]. Cancer incidence is expected to increase due to increased risk factors such as obesity, DM and lifestyle [6,7]. While 9.3% of the global adult population is diabetes in the world [8], this rate was found to be 9-15.7% in studies conducted with glioma patients [3,9,10]. World health organization defines obesity as body mass index (BMI) ≥30kg / m^2 and overweight as BMI≥25 kg / m^2 [5]. The prevalence of obesity in the Turkey was reported to be 28.5% [11]. In studies on gliomas, the frequency of obesity was found between 20-30 [3,9,12]. Increased BMI has been associated with various types of cancer: colorectal cancers, breast, endometrium, ovarian, kidney, pancreas, esophageal cancers [13,14]. It was stated that DM and high BMI contributed to 5.7% of all incidental cancer cases in 2012 in a study conducted in 2018 [10]. There is evidence that DM is associated with endometrium, bladder, pancreas, liver, colorectal and breast cancer [3,9,15]. The underlying cause of the relationship between BMI, DM and cancer is hyperglycemia, hyperinsulinemia, chronic inflammation, and irregularity in sex hormone activity [10]. However, the relationship between malignant gliomas and high BMI and DM is contradictory in studies. Therefore, with this study, we aimed to determine the relationship between malignant gliomas and DM, high BMI.

MATERIAL AND METHODS

With this study, the results of 174 patients who received radiotherapy in our clinic between January 2010 and December 2018 were retrospectively analyzed. The study included grade 3-4 glioma patients according to WHO criteria, over the age of 18, whose diagnosis was confirmed by histopathologically, weight, height and DM story can be reached. Type 1 diabetes patients were not excluded from the study. Ethics committee approval was obtained before starting the study. Due to the nature of the study, informed

consent forms were not obtained from the patients. Patient data and treatment characteristics were obtained from medical records and hospital system.

Body mass index was calculated according to the kg / m2 formula, considering weight and height measurements before treatment. It was categorized into 3 groups: normal weight (18.5-24.9 kg / m^2), overweight (25-29.9 kg / m^2), obese (≥30 kg / m^2).

The presence of diabetes was defined by considering disease history, antidiabetic use, blood glucose levels at least 6 months before the operation.

Groups were categorized as gross total excision (GTR) and subtotal excision/biopsy considering the resection width operation notes and Magnetic Resonance Imaging (MR) images taken after surgery.

Radiotherapy

All patients were treated with 3D conformal radiotherapy. Conventional radiotherapy was considered as a 1.8-2 Gy fraction dose and 50 Gy and above dose. 30-42.5 Gy RT was applied in 10-16 fractions in hypofraction and whole brain radiotherapy. RT was started within 5-6 week after the operation. MRI was performed in each patient before RT. CT simulation was performed in supine position for planning purposes. By fixing with a thermoplastic mask, a tomography of 3-5 mm section thickness was taken. Computed tomography (CT) images were fused with preop and postop MR images. Gross tumor volume (GTV) was defined as the volume and operation bed enhanced by MR image. This volume was created by giving the clinical target volume (CTV) with a margin of 1.5-2 cm and the planned tumor volume (PTV) with a margin of 0.5 cm to CTV. All brain RT was applied with 3D conformal radiotherapy, hypofractionated or conventional treatments were applied with intensity-adjusted RT (IMRT). All patients were treated with eclipse planning system.

Chemotherapy

Simultaneously, 75 mg / m^2 / day temozolomide treatment was applied 7 days a week. After RT, adjuvant chemotherapy (CT) was administered as 150-200 mg / m^2 / day, every 5 days for 5 days. Temozolomide was applied in 6-12 cycles.

Follow-up

During the treatment, a complete blood count, biochemistry tests and a physical examination were performed once a week. Potential side effects were evaluated. After RT, he/she was followed up with a physical examination and MR every 3 months.

Endpoint

The primary endpoint of the study was overall survival (OS). The second endpoint was to determine the effect of DM and BMI on OS.

Statistical Analysis

Descriptive statistics were applied to determine patient and treatment characteristics. Average, median, and standard deviations were calculated in order. Overall survival was defined as the time from the time of diagnosis to death or final control. Progression-free survival was determined as the time from diagnosis until relapse or progression, or until death. Chi-square test was carried out to compare the categorical variables. Kaplan Meier Analysis was carried out for survival analysis. In univariate analysis, the survival curves of the subgroups were evaluated with a log-rank test. In univariate analysis, all variables with $p < 0.10$ were included in the multivariate analysis. Cox regression analysis was performed. $P < 0.05$ was considered statistically significant. Version 13.0 of Statistical Package for Social Sciences Software (SPSS Inc.; Chicago, IL, USA) was utilized in the whole statistical analysis.

RESULTS

Patient and Treatment Characteristics

The results of 174 cases were evaluated retrospectively. Median follow-up was 16.11 months. The median age was 57 (18-84). 37 (21.3%) patients had grad 3, 137 (78.7%) patients had grad 4 pathology. DM was present in 22 (12.6%) of the cases. The median BMI was 27.14. 36.8% of the cases were normal weight, 37.4% were overweight and 25.9% were obese. Treatment and patient characteristics are summarized in **Table 1**.

Survival Analysis

Median survival was 17.28 months. Overall survival for 1, 2, 5 and 10 years was 64.4%, 34%, 17.7% and 10.3%, respectively (**Figure 1**). During the follow-up period, 138 (79.3%) patients died. Being over 65 years of age, KPS <80, presence of diabetes, grad 4 pathology, subtotal excision / biopsy, hypofractionated / whole brain radiotherapy and absence of adjuvant chemotherapy (CT) had negative effects on overall survival (**Table 2**) in univariate analysis. Being over 65 years old, having grad 4 pathology, subtotal excision and not taking adjuvant CT were found to be effective on OS (**Table 3**) in multivariate analysis. Median overall survival in diabetics was 9.65 months, while in non-diabetics 17.74

Table 1. Patient and treatment characteristics

Characteristic		n (%)
Age		
	median	57 (18-84)
	≥65	53 (30.5)
	<65	121 (69.5)
KPS		
	≥80	120 (68.6)
	<80	54 (31.4)
Gender		
	Male	118 (67.8)
	Female	56 (32.2)
Type and extent of surgery		
	GTR	58 (33.3)
	Subtotal/Biopsy	116 (66.7)
Concurrent CT		
	None	6 (3.4)
	Temozolomide	168 (96.6)
RT fraction		
	Conventional	152 (87.4)
	Hypofractionation/whole-brain	22 (12.6)
Adjuvant CT		
	None	28 (16.1)
	Temozolomide	146 (83.9)
Diabetes		
	Nondiabetic	152 (87.4)
	Diabetic	22 (12.6)
Body mass index(kg/m^2)		
	18,5-24,9	64 (36.8)
	25-29,9	65 (37.4)
	≥30	45 (25.9)

KPS: Karnofsky Performance Status, GTR: Gross Total Excision, CT: Chemotherapy, RT: Radiotherapy

Table 2. Factors affecting overall survival in univariate analysis

Variances		Median overall survival	P value
Age			
	≥65	12.32	**<0.001**
	<65	20.14	
KPS			
	≥80	19.51	**<0.001**
	<80	9.65	
Type and extent of surgery			
	Total	28.58	**<0.001**
	Subtotal/Biopsy	15.60	
Pathology			
	Grad 3	33.54	**<0.001**
	Grad 4	15.60	
Adjuvant CT			
	Yes	18.99	**<0.001**
	None	3.77	
RT fraction			
	Conventional	18.99	**<0.001**
	Hypofractionation/whole-brain	7.81	
Diabetes			
	Nondiabetic	17.74	**0.017**
	Diabetic	9.65	
Body mass index(kg/m^2)			
	<30	18.89	0.095
	≥ 30	13.47	

KPS: Karnofsky Performance Status, CT: Chemotherapy, RT: Radiotherapy

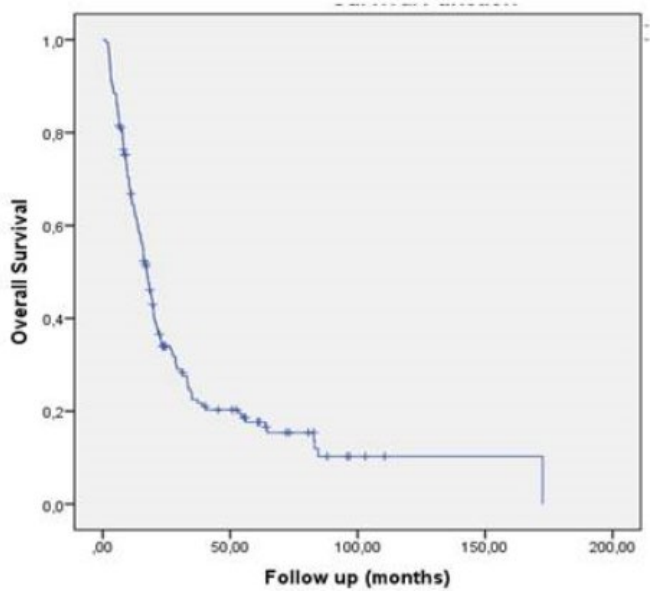

Figure 1. Overall survival curve

Table 3. Multivariate analysis results for overall survival

Variances		Overall (n=157)		
		HR	95%CI	p value
Age				
	<65	1	1.046-2.330	**0.029***
	≥65	1.561		
KPS				
	≥ 80	1	0.990-2.235	0.056
	<80	1.487		
Type and extent of surgery				
	Total	1	1.122-2.476	**0.011***
	Subtotal/Biopsy	1.667		
Adjuvant CT				
	Yes	1	2.754-7.518	**<0.001***
	None	4.550		
RT fraction				
	Conventional	1	0.945-2.664	0.081
	Hypofractionation	1.587		
Body mass index (kg/m^2)				
	<30	1	0.868-1.901	0.211
	≥30	1.284		
Diabetes				
	Nondiabetic	1	0.662-1.886	0.676
	Diabetic	1.118		
Pathology				
	Grad 3	1	1.522-4.372	**<0.001***
	Grad 4	2.579		

KPS: Karnofsky Performance Status, CT: Chemotherapy, RT: Radiotherapy

months (p=0.017) (**Figure 2**). It could not be shown statistically significant relationship between BMI and OS.

DISCUSSION

Diabetes is a metabolic condition that increases the risk of many types of cancer [6]. Many studies have evaluated the relationship between cancer types and DM and BMI. This is not clear in gliomas. Pearson-stuttard et al. showed that alone DM contributes to 2.1% and high BMI contributes to

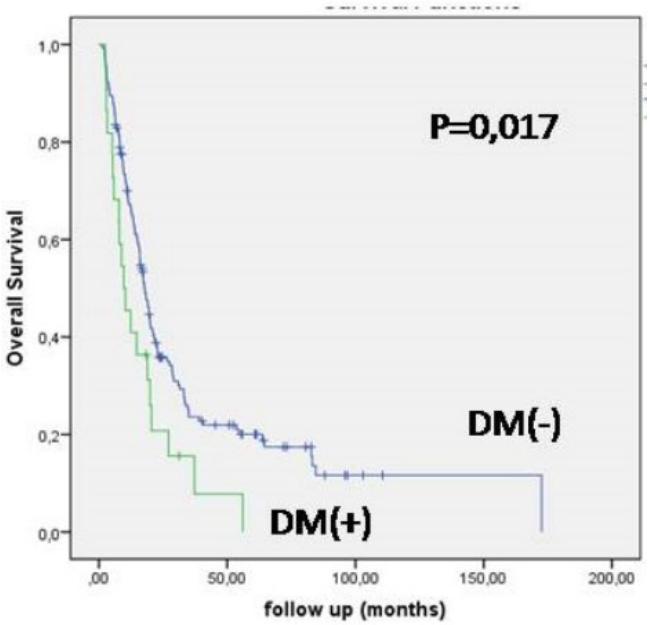

Figure 2. Overall survival curve in patients with and without diabetes in malignant glioma patients

3.9% of all cancer cases in 2012 [10]. As obesity and DM continue to increase all over the world, it is predicted that there will be an increase in cancer mortality and incidence in the coming period. In the case-control study conducted by Barami et al., 15.7% diabetes and 27.7% obesity were observed in the glioma patient group, while this ratio was 16.8% and 32.1%, respectively in the control group. There was no relationship between DM and obesity and GBM risk. However, when the relationship between DM and survival was evaluated, it was associated with worse survival in univariate analyzes, but could not be demonstrated in multivariate analyzes [9]. In the metaanalysis performed by Tong et al., no increase was observed in the risk of brain tumors in diabetic and nondiabetic patients [16]. In our study, although the risk between glioma patients and diabetes and obesity was not examined, pre-existing DM has been shown to negatively affect survival in malignant glioma patients. With all these data, it can be said that diabetes has prognostic value, not predisposing.

It has been stated that hyperglycemia is a poor prognostic factor on survival in metaanalysis performed on glioblastoma [17]. Many mechanisms of action of hyperglycemia are emphasized. The level of insulin rises due to acquired insulin resistance. Insulin resistance, increase of various cytokines, increase of insulin - like growth factor-1 (IGF-1), increase of adipokine balance play a role in cancer development [18]. When Derr et al. classified glioblastoma patients according to their blood glucose levels in their study, they found 14.5 months of survival in patients with glucose <94 mg/dl and 9.1 months in patients with >137 mg/dl (p=0.041) [19].

The increase in obesity causes comorbidities such as cardiovascular disease, DM, cancer [13]. When the relationship between survival and BMI is examined, there are contradictions in the literature. Patharaju et al. showed that the increase in survival occurred when BMI was elevated [20]. However, Chambless et al. showed that DM and high BMI in high-grade gliomas are independent risk factors for poor results in a retrospective study on 171 patients [3]. These results are contradict with Jones et al. study with 1259 patients. In this study, no relationship was found between BMI and survival [12]. Similarly, in a prospective cohort study for brain tumors, could no relationship was found between obesity and glioma risk [21]. In our study, could no relation was found between BMI and survival. This may be due to the fact that weight and height data were evaluated at the first examination before radiotherapy. Patients may also have experienced weight change due to steroid use before and after the operation.

The limitation of our study was that it was retrospective. HbA1c levels and MGMT status of patients could not be determined before treatment due to the retrospective nature. Clear information on hyperglycemic control adequacy could not be obtained.

CONCLUSION

As a result, diabetes is a poor prognostic factor for the survival of malignant glioma patients. It is important to control diabetes and related conditions. In the future, prospective studies should be conducted to investigate the relationship and mechanism of action between both DM and high BMI and the risk and mortality of malignant glioma.

DECLARATION OF CONFLICT OF INTEREST

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Case Report

An unusual cause of acute abdomen in children: Mesenteric pseudocyst in the ileum

Çocuklarda nadir bir akut batın sebebi: İleumda mezenterik psödokist

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ABSTRACT

Intraabdominal cysts and pseudocysts are unusual lesions. Mesenteric cysts in the pediatric age group are more common in boys [62.5%] and most cases are under 10 years of age. Mesenteric cysts are often asymptomatic. Mesenteric cysts rarely recur after removal and patients have a good prognosis. The most common surgical procedure in treatment is excision during laparotomy. We present the surgical method that we apply to the unusual case of ileum mesenteric cyst, which constitutes the clinical picture of the acute abdomen in an 11 years old boy, in the light of the literature.

Keywords: pseudocyst, children, ileum

ÖZ

Karın içi kistler ve psödokistler nadir lezyonlardır. Pediatrik yaş grubundaki mezenterik kistler erkeklerde [%62,5] daha sık görülür ve çoğu vaka 10 yaşından küçüktür. Mezenterik kistler sıklıkla asemptomatiktir. Çıkarıldıktan sonra mezenterik kistler nadiren tekrarlar ve hastalar iyi bir prognoza sahiptir. Tedavide en sık uygulanan cerrahi işlem laparotomi sırasında eksizyondur. 11 yaşındaki erkek çocuğunda akut karın klinik tablosunu oluşturan nadir görülen ileum mezenter kist olgusuna uyguladığımız cerrahi yöntemi literatür eşliğinde sunuyoruz.

Anahtar kelimeler: psödokist, çocuklar, ileum

INTRODUCTION

Intraabdominal cysts and pseudocysts are unusual lesions [1]. This was noticed in 1507 by the Italian anatomist Benevenni when performing an autopsy in an 8-year-old child. In fact, 820 cases were reported in the literature by Tillaux, the first case in 1880 [2]. According to Kurtz et al., The incidence of the disease is approximately 1 / 100.000, but other authors record a lower frequency, about 1 / 250.000 hospital applications. The disease is much more common in children under 10 years of age (1 patient per 4.000-34.000 hospital admissions) [1]. According to Kurtz et al., there was no difference in terms of gender and race. Mesenteric cysts are often asymptomatic [2], but sometimes patients may show symptoms such as abdominal pain or discomfort, abdominal distention, nausea, vomiting, bloating, constipation, or diarrhea [1]. Differential diagnosis required before each operation includes: peritoneal cyst, lymphangioma, endometriosis, acid, pancreatic pseudocyst, hemangioma, cystic mesenteric panniculitis, hydatid cyst, teratoma and urogenital cyst [1]. The surgical procedure recommended in the literature is the excision of the tumor [1]. Mesenteric cysts rarely recur after removal and patients have a good prognosis. The incidence of malignancy is about 3% [1]. Rarely, these may be complicated by rupture or intestinal obstruction [2]. The intestinal volvulus caused by the mesenteric cyst typically affects children with acute abdominal symptoms [2]. The most common locations of mesenteric cysts are: small intestine mesentery (50-80%) and then right colon and large intestine mesentery (15-30%) [1]. The size of mesenteric cysts varies from a few centimeters to 10 cm. Cysts larger than 10 cm are defined as giant mesenteric cysts. The exact etiology of mesenteric cysts is unknown [2]. Clinical imaging methods (Ultrasound, Computed tomography or Magnetic resonance imaging) can help in reaching a definitive diagnosis [2]. Mesenteric cysts in the pediatric age group are more common in boys (62.5%) and most cases are younger than 10 years old [3].

CASE REPORT

This report presents a male patient with an open approach operated intra-abdominal cyst and nonspecific symptoms. The patient was 11 years old and was admitted to Karaman State Hospital Pediatric Emergency Clinic with cramp-like abdominal pain and nausea and vomiting for two days. In addition, the patient complained of fever (38°C) and anorexia. The patient's history included a laparoscopic appendectomy history performed at a private medical center a year ago. As a laboratory finding, neutrophilia and leukocytosis were present. In the physical examination, there was widespread sensitivity in all the quadrants of the abdomen. There were several lymph nodes in the lower quadrant of the mesentery with a short anterior width of 8 mm. In addition, there was no abnormality in the intra-abdominal organs except for a 9 mm diameter nodular lesion in the left adrenal region. The abdomen was explored with a midline incision on the navel passing through the right side of the abdomen. Adhesions between the bowel loops in the distal of the ileum were opened with blunt dissection and scissors. With an 8 cm bowel loop, excision was performed and an ileoileal resection anastomosis was performed to ensure bowel continuity.

Microscopic examination of the excised cyst showed active chronic inflammation, edema, granulation tissue, mesenteric pseudocyst (**Figures 1**-**3**). The cyst of our patient was classified as a mesenteric pseudocyst with first class content according to Beahrs et al., Ros et al., and de Perrot et al. Most such lesions are associated with a post-traumatic or inflammatory event. Abdominal trauma has not been reported in our patient. The patient's history of laparoscopic appendectomy a year ago suggested an inflammatory event in the abdominal wall of this lesion. The patient had a uneventful course after surgery and was discharged 7 days after the operation. Six weeks later, the patient was asymptomatic.

DISCUSSION

Mesenteric cysts have a good prognosis and no recurrence has been observed following complete excision of the cyst [4]. Recently, Ros et al. reviewed 41 cases of mesenteric and omental cysts and proposed another histological classification related to radiological findings. They divided the cysts into five groups:

Lymphangiomas, enteric duplication cysts, enteric cysts, mesothelial cysts, non-pancreatic pseudocysts (they used the term "pseudocysts" for the first time in the classification of mesenteric cysts).

The final classification of intra-abdominal cysts was formed by Perrot et al. [4] in 2000 based on the histological identity of the inner epithelium and consists of 6 groups:

- Lymphatic cysts: simple cyst and lymphangioma (the only exception that usually occurs in the first decade of life (up to 12 years of age) with male dominance) [4];
- Mesothelial cysts: Malignant mesothelioma, simple cyst, benign mesothelioma (this is often associated with a previous pelvic inflammatory process or history of surgery and endometriosis) [4];
- Urogenital cyst;
- Mature cystic teratoma (dermoid cysts);

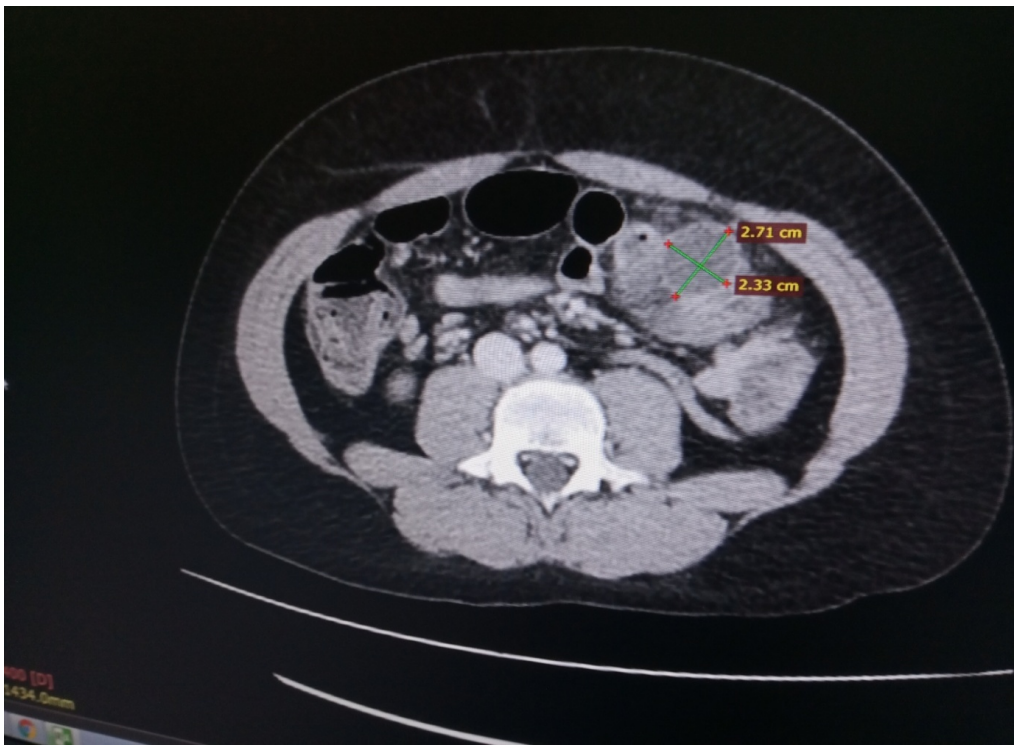

Figure 1. Pseudocyst formation in ileum in contrast-enhanced CT (measuring 2.71x2.33 cm)

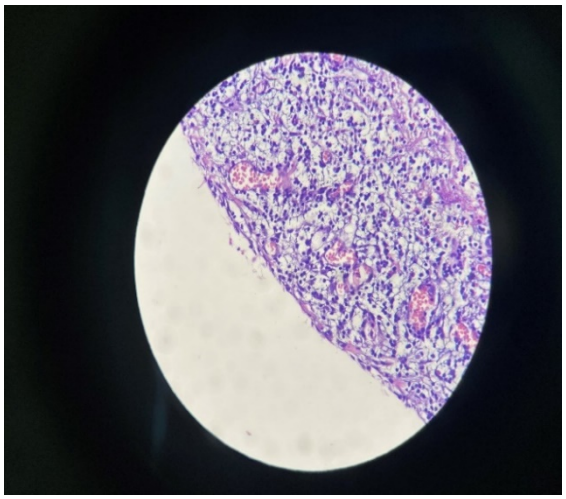

Figure 2. Multiple pseudocyst formations in seroza (x40, H & E)

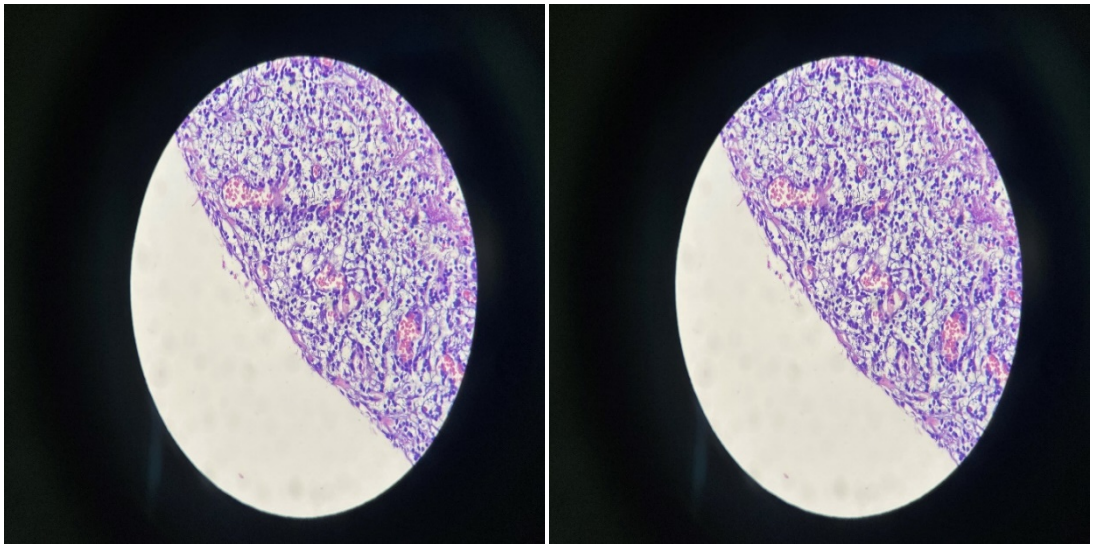

Figure 3. Pseudocyst surface (x200, H&E) covered with foamed histiocytes, not observed in epithelium

- Pseudocysts (inflammatory, traumatic and degenerative). Mesenteric pseudocysts are called non-pancreatic pseudocysts to prevent confusion with the much more common pancreatic pseudocyst [5]. Non-pancreatic pseudocysts are masses without an internal cellular main membrane; they are considered to be a non-absorbent mesenteric or omental hematoma or abscess sequel. It has nothing to do with pancreatitis. Pathologically, pseudocysts are thick-walled, usually hemorrhagic or purulent-containing separated cystic masses [5].

Sonographically, a hypoechoic mass often appears filled with echogenic dead tissues. Computed tomography (CT) and Magnetic resonance (MR) imaging reveals a thick-walled cystic mass that may contain an air-fluid level resulting from hemorrhagic or purulent contents and does not show an increase after contrast [6]. Non-pancreatic pseudocysts have a fibrous wall with no epithelium and a serous (pale yellow) or mucoid (brownish red) content. Their origin may be inflammatory or traumatic [7].

Mesenteric pseudocysts are difficult to diagnose because they exist as a lost mass or in a changing place [8]. In general, the patient has no symptoms and the cyst is discovered by chance in imaging the abdomen for other reasons. Larger lesions are abdominal pain, discomfort, distension, or other nonspecific symptoms [8].

In our case, the diagnosis revealed a defined collection of abdominal pain and vomiting complaints that occurred after laparoscopic appendectomy the first presentation was made a year ago and increased for several days until clinical presentation and imaging. Mesenteric pseudocysts may be secondary to trauma or infection [9] and the internal appearance of the cyst etiology is secondary to inflammation between bowel loops in this patient.

In our case, there was an inflammatory infiltration and an infectious cause was possible because the patient had no history of trauma. Treatment is surgical resection, as in 3% of cases, the only way to prevent the lesion from turning into a malignant mesenteric cyst [9].

CONCLUSION

The case we reported came to the operating table without a proper diagnosis of the disease. Diagnostic imaging methods may allow accurate diagnosis, but it is not always possible to solve the diagnostic problem due to the rarity of the lesion.

DECLARATION OF CONFLICT OF INTEREST

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Original Article

Thiol/disulfide homeostasis in patients with chronic hepatitis B

Kronik hepatit B hastalarında tiyol/disülfit dengesi

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ABSTRACT

Aim: The purpose of this study was to evaluate the relation between chronic hepatitis B (CHB) and the thiol/disulfide balance, used as a marker of oxidative stress.

Materials and Methods: This study was conducted between May 2016 and July 2016 at the Erzurum Regional Training and Research Hospital Infectious Diseases Polyclinic. 63 subjects with CHB and 60 healthy volunteers without any known diseases were included in the study. In term of measuring dynamic thiol/disulfide homeostasis, we used the novel automated assay method developed by Erel and Neselioglu.

Results: Native thiol (SH), total thiol (total SH) and disulfide (SS) levels were determined; measures such as SS/SH, SS/total SH, and SH/total SH were calculated. It is determined that CHB group's SH levels (P=0.041), total SH levels (P=0.043) were lower than the control group's. There is negative correlation between Anti-HBc total IgG and total SH, SH, SH/total SH, there is positive correlation between Anti-HBc total IgG and SS/SH, SS/total SH ratio. There is negative correlation between BMX index and total SH, SH, SH/total SH and positive correlation between SS/total SH, SS/SH. Positive correlation is determined between total protein, albumin and total SH, SH.

Conclusions: In our study thiol levels as an antioxidant were found to be low in CHB patients. Thiol levels were again emphasized as a new marker in hepatitis B. Thiol levels in CHB are thought to shed light to slowing of disease course and improving new treatment efforts with more wide studies.

Keywords: chronic hepatitis B, thiol/disulfide balance, oxidative stress

ÖZ

Amaç: Bu çalışmanın amacı, oksidatif stres belirteci olarak kullanılan tiyol / disülfit dengesi ile kronik hepatit B (KHB) arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Bu çalışma Mayıs 2016 - Temmuz 2016 tarihleri arasında Erzurum Bölge Eğitim ve Araştırma Hastanesi Enfeksiyon Hastalıkları Polikliniğinde yapıldı. Çalışmaya KHB'li 63 hasta ve bilinen herhangi bir hastalığı olmayan 60 sağlıklı gönüllü dahil edildi. Dinamik tiyol /disülfit dengesini ölçmek için Erel ve Neselioğlu tarafından geliştirilen yeni otomatik analiz yöntemini kullanıldı. Doğal tiyolden (SH) sonra, toplam tiyol (toplam SH) ve disülfit (SS) seviyeleri belirlendi; SS/SH, SS/toplam SH ve SH/toplam SH gibi ölçüler hesaplandı.

Bulgular: KHB grubunda, SH seviyelerinin (P=0,041), toplam SH seviyelerinin (P = 0,043) kontrol grubundan düşük olduğunu tespit edildi. Anti-HBc toplam IgG ile toplam SH, SH, SH/toplam SH arasında negatif korelasyon vardı, Anti-HBc toplam IgG ile SS/SH, SS/toplam SH oranı arasında pozitif korelasyon vardı. BMX indeksi ile toplam SH, SH, SH/toplam SH arasında negatif, SS/total SH, SS/SH arasında pozitif korelasyon vardı. Toplam protein, albümin ve toplam SH, SH arasında pozitif korelasyon bulundu.

Sonuç: Çalışmamızda KHB hastalarında antioksidan olarak tiyol düzeyleri düşük bulundu. Hepatit B'de tiyol düzeyinin yeni bir belirteç olduğu tekrar vurgulandı. Gelecekte yapılacak daha geniş çalışmalarla KHB'de tiyol düzeyleri hem hastalığın seyrinin yavaşlatılması hemde yeni tedavi geliştirme çabalarına ışık tutacağı düşünülmektedir.

Anahtar kelimeler: kronik hepatit B, tiyol/ disülfit dengesi, oksidatif stres

INTRODUCTION

Hepatitis B infection is common in our country and in the world and is the leading infection among viral infections that become chronic [1]. In the pathogenesis of chronic viral hepatitis, oxidative stress and immunological damage resulting from direct cytotoxicity of some virus-derived substances are implicated. The liver is one of the most protected organs from the damage caused by oxygen radicals thanks to its various repair mechanisms and protective enzymes as well as some antioxidants it contains. Nonetheless, fibrosis, which develops due to the prolonged inflammatory reaction and subsequently increased collagen synthesis, may result in liver cirrhosis, especially in viral hepatitis. It is generally accepted that free oxygen radicals are involved in the pathophysiology of liver diseases and lead to the progression of the disease [2].

Also, oxidative stress can be simply described as an imbalance between the antioxidant defense of the body and free radical production [3]. Free oxygen radicals lead to disorders in membrane structure and cellular functions by means of denaturation of proteins, damage to nucleic acids, and lipid peroxidation, and play a role in the pathogenesis of many diseases [4]. Free oxygen radicals are influential in reactions caused by various drugs/toxins such as lead poisoning (toxicity), carbon tetrachloride-induced hepatic damage, and in glomerulonephritis, hepatitis B, ischemia, vitamin (C and E) deficiency, and in the pathogenesis of many diseases such as cancer, emphysema, hyper oxidation, bronchopulmonary dysplasia, atherosclerosis, pancreatitis and rheumatoid arthritis [3]. Antioxidants trying to prevent the damaging effects of free radicals, especially thiol groups, cannot preserve the plasma and tissue levels during these affections [5]. Thiols are a class of organic compounds that contain a sulfhydryl group (-SH) which is composed of a hydrogen and a sulfur atom attached to a carbon atom [6]. And they are compose the basic part of the nonenzymatic antioxidant system in the circulation, and are the first molecules responsible for neutralization of oxidant molecules [7]. Among the antioxidants found in plasma, the highest concentration of thiol groups is explained by the high plasma protein levels in adults. Because the primary source of thiol groups found in plasma are cysteine and methionine amino acids in protein structures, especially albumin, as well as reduced glutathione (GSH). The determination of plasma thiol levels is important as it shows how the proteins are affected by SOR-mediated oxidation [8]. While the serum thiol/disulfide levels were previously assessed indirectly, direct measurement possibility has been available with fully-automated calorimetric technique which was found by Erel and Neselioglu in 2014 [9].

The purpose of this study was to evaluate the relation between CHB and the thiol/disulfide balance, used as a marker of oxidative stress, by measuring that exchange

using a novel technique. This study is important as the first, to the best of our knowledge, involving this novel biomarker, previously used in the investigation of different diseases.

METHOD

This study was conducted between May 2016 and July2016 at the Erzurum Regional Training and Research Hospital Infectious Diseases Polyclinic.

The study population included a total of 123 participants; 63 hepatitis B (28 women and 35 men) patients, and 60 healthy volunteers (25 women and 35 men) with no historyof chronic illness or regular drug use.

The study was conducted in accordance with the Declaration of Helsinki 2013 Brasil version and was approved by the Erzurum Regional Training and Research Hospital Ethics Research Committee (2016/9-62). All subjects were provided written informed consent prior to participation in the study.

The patients enrolled in the study was clinically and serologically diagnosed as chronic hepatitis B after 6 months follow up. Blood sample was taken in their routine polyclinical control. Control group was selected from patients referred to our polyclinic with a diagnosis of other than hepatitis B. The patients which were under systemic steroid treatment and with cerebrovascular disease, chronic and acute kidney disease, additional liver disease, acute and chronic systemic disease like malignancy and the patients regularly using antioxidant, antilipid, vitamin drugs, smokers, alcoholics were excluded from the study.

After blood sample was taken, plasma and serum were separated by centrifuging at 1500 rpm for ten seconds. Serum was kept in - 80°C in Eppendorf tubes until they were tested. Afterwards thiol hemostasis parameters were studied from the same blood sample. Patients' synchronous whole blood count biochemical parameters including cholesterols and hepatitis markers, HBV- DNA levels were recorded.

In term of measuring dynamic thiol/disulfide homeostasis, we used the novel automated assay method developed by Erel and Neselioglu, in which both sides of thiol/disulfide balance can be measured as opposed to the method developed by Ellman, which can measure only one side of this balance. This novel method is based on the sulfhydryl groups of proteins turning into a reversible formation of disulfides under oxidative conditions and reduction of disulfide bonds into thiol groups again. The difference between the total thiol and the native thiol is divided by two to obtain the amount of the disulfide bond. Measurements were made using a Cobasc501 (Roche Diagnostics, Mannheim, Germany). Serum thiol/disulfide homeostasis values were presented as mmol/L [10].

From the obtained data, total thiol, native thiol, disulfide, disulfide/total thiol, disulfide/native thiol, native thiol/total thiol levels were determined. Results were compared between CHB patients and healthy subjects.

Total protein (TP), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP) was measured with the Abbott Architect c16000 (USA) autoanalyzer. All CBC analysis was performed in the hematology laboratory of our hospital with the use of a Abbott Cell-Dyn Ruby (USA) autoanalyzer. Hepatitis B markers were performed by Abbott (architect) i2000sr, HBV-DNA RT PCR Rotorgene (Giasymphny) autoanalyzer. All parameters were compared with thiol/disulphide homeostasis. Correlation of whole obtained parameters with thiol/disulfide homeostasis were analyzed.

STATISTICAL ANALYSES

We performed all statistical analyses using SPSS for Windows, version 17.0. Unless otherwise stated, results wereexpressed as mean ± SD. We used the Mann-Whitney U test or independent sample t test between two subject groups, and used the Pearson correlation test or Spearman correlation test, as appropriate. Categorical data were analyzed by Chi-square test. The receiver operating characteristic (ROC) curve analysis assessed the cut-off thiol levels the best diagnostic accuracy for detecting differentiated CHB.

RESULTS

In this cross-sectional study, 63 patients with chronic hepatitis B, and 60 control subjects were evaluated. Mean age ± SD of subjects were 41.2 ± 13.4 in the hepatitis group and 34.9 ± 13.8 in the control group ($p < 0.01$).

There was negative correlation between age and SH, SH/total SH; positive correlation between age and SS/SH, SS/total SH. There is no statistical significance between age, sex and thiol levels.

SH levels (366±66 µmol/L, 392±72 p=0.041), total SH levels (439±80, 470±80 p=0.043) of patients with CHB significantly lower than control subjects (**Figure 1**). All parameters compared between two group were presented (**Table 1**).

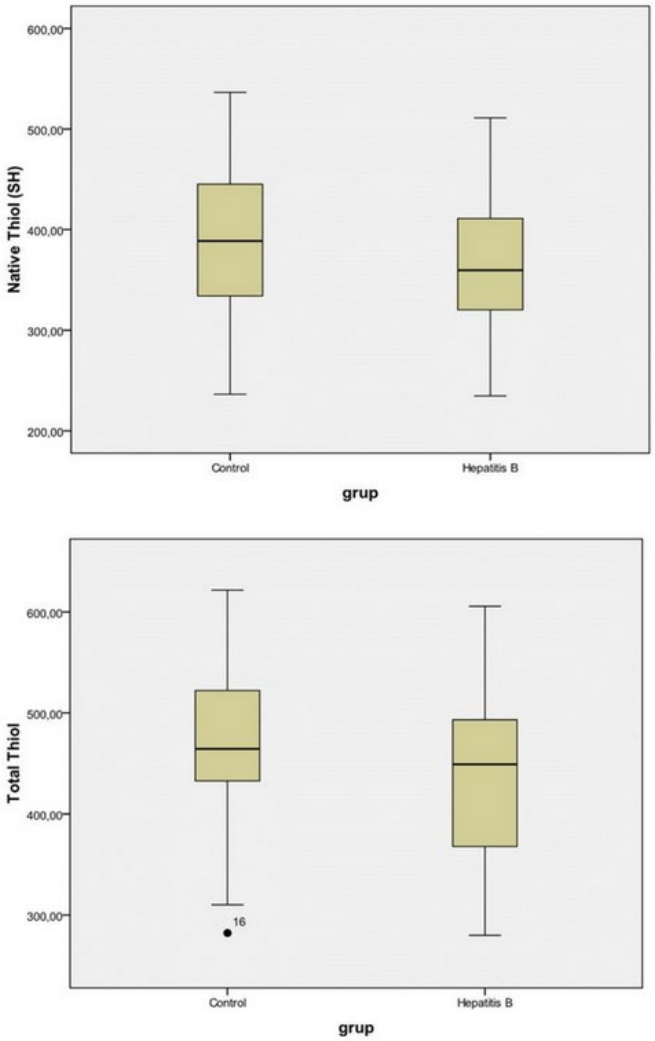

Figure 1. Thiol/disulfide homeostasis according to groups. Native thiol and total thiol level between groups.

Table 1. Demographics and laboratory findings of study population

	Control n (60)	Chronic hepatitis B n (63)	p value
Sex (male), n	60 (35)	63(35)	0,75
Age (years)	34.91±13.87	41.21±13.40	0.01*
BMI (kg/m^2)	26.61±3.97	27.10±3.26	0.45
Total thiol (µmol/L)	470±80	439±80	0.043*
Native thiol (µmol/L)	392±72	366±66	0.041*
%SH/Total SH	83.69±7	83.66±6.7	0.092
SS (µmol/L)	38.67±18	36.64±17.27	0.541
SS/SH ratio (%)	10.17±5	10.16±5	0.996
%SS/Total SH	8.1±3.5	8.1±3.3	0.983
WBC (10^3/µL)	7758.33±1793.42	7233.33±1849.20	0.107
Platelet	259.88±55	273.91±85	0.53
HBV-DNA		903275±4.1	0.000*
ALT (U/L)	20.90±10.19	27.63±23.20	0.000*
AST (U/L)	20.22±9.04	23.85±12.45	0.02*
GGT (U/L)	73.45±22.70	21.19±16.78	0.000*
Albumin (g/dL)	4.36±0.45	4.31±0.40	0.26
AFP	2.2±1.02	2.65±1.96	0.63
TP (g/dL)	7.02±0.40	7.06±0.81	0.09
ALP	25.26±37.16	88.40±39.75	0.000*

BMI body mass index, SS disulfide, SH native thiol, Total SH total thiol, WBC white blood cell, ALT alanine aminotransferase, AST aspartate aminotransferase, GGT gamma glutamyl transferase, TP total protein, ALP alkaline phosphatase, AFP alfa feto protein, HBV-DNA hepatitis B virus deoxy nucleic acid.

* $p < 0.05$ for chronic hepatitis B patients compared with controls

Negative correlation between AntiHBc total IgG and total SH, SH, SH/total, SH; positive correlation between AntiHBc total IgG and SS/SH, SS/total SH were determined.

Negative correlation between BMX index and total SH, SH, SH/total SH was found. Also, there was positive correlation between BMX index and SS/total SH, SS/SH.

There is positive correlation between albumin and total SH, SH and positive correlation between total protein and total SH, SH.

Furthermore, High disulfide levels and low thiol levels in patients with CHB were found to be independent of sex, HBVDNA, HBsAg, antiHBs, AFP, ALP, GGT, AST, ALT, neutrophil and thrombocyte count (**Table 2**).

DISCUSSION

HBV infection is clinically observed in the form of acute infection, chronic infection or primary hepatocellular carcinoma (PHC). While chronic hepatitis is seen in 5-10% of patients, cirrhosis and hepatic failure may also develop in 10% of those with chronic hepatitis. 80% of cases with PHC are associated with chronic HBV infection [11]. Oxidative stress causes various parenchymal injuries ranging from subclinical unicteric hepatitis to necroinflammatory hepatitis (acute, recurrent or chronic), cirrhosis and cancer [12].

In the course of viral hepatitis, it is suggested that reactive oxygen types released by the Kupffer cells and other active macrophages in the inflammatory zone cause peroxidation in cell membrane lipids, resulting in aldehyde products which directly activate stellate (ito) cells to transform into myofibroblasts and as a result of this, an increase in collagen synthesis and fibrosis develop [13]. It has been found that hepatitis B virus causes the release of pro-oxidant cytokines such as reactive oxygen types and tumor necrosis factor alpha (TNF-α) by activating phagocytic cells, and the inhibition of anti-oxidant enzymes such as superoxide

Table 2. Bivariate correlation between thiol/disulphide homeostasis parameters and other variables in chronic hepatitis B

Variables	Native thiol		Total thiol		Disulfide		Disulfide/native thiol		Disulfide/total thiol		Native thiol/total thiol	
	r	p	r	p	r	p	r	p	r	p	r	p
Age	-0.305	0.004	-0.24	0.23	0.114	0.299	242*	.024	.238*	.026	-.238*	.026
Sex	.150	.165	.200	.063	.142	.189	.090	.408	.087	.421	-.087	.422
BMİ	-.317**	.003	-.242*	.025	.143	.191	.221*	.042	.237*	.029	-.237	.029
HBV-DNA	.217	.210	.203	.243	.043	.808	-.045	.799	-.029	.871	.029	.870
Anti-HB total Ig	-.348**	.001	-.249	.022	.195	.076	.289**	.008	.285**	.009	-.285**	.009
HBsAg	-0.17	0.056	-0.179	0.052	-0.06	0.48	-0.01	0.87	-0.12	0.9	0.01	0.9
HbeAg	0.155	0.09	0.13	0.14	0.04	0.61	-0.006	0.95	-0.006	0.95	0.006	0.95
AntiHBs	.122	.265	.111	.312	.044	.688	-.032	.770	-.015	.890	.015	.891
Albumin	.766**	.000	.809**	.000	.202	.061	-.061	.574	-.054	.620	.054	.619
TP	.239	.012	.246	.010	.109	.258	.044	.653	.043	.654	-.043	.655
AFP	.009	.942	-.008	.946	-.040	.738	-.047	.696	-.038	.754	.038	.754
GGT	.158	.094	.151	.108	.079	.406	.036	.706	.035	.708	-.035	.710
ALT	-.037	.703	-.010	.920	.085	.374	.074	.437	.075	.435	-.075	.436
AST	-.021	.825	.001	.993	.039	.679	.035	.710	.035	.704	-.035	.709
PLT	-.027	.769	-.037	.687	-.081	.384	-.085	.358	-.086	.355	.086	.356
BK	.080	.393	.107	.252	.111	.234	.079	.397	.078	.401	-.079	.400

p<0.05 was accepted as statistically significant

dismutase (SOD) by affecting the pro-oxidant and antioxidant balance in the host cell [14].

In recent years, many studies on oxidative stress in chronic viral hepatitis (CVH) have been conducted [3].

A study of Halliwell et al. have indicated that lipid peroxidation may increase in relation to the inflammatory response in viral infections and that the earliest sign of reduced oxidative stress during recovery was an increase in antioxidant level [15]. In another study, Dikici et al. have found that the levels of oxidative enzymes were significantly increased and the levels of antioxidant substances were reduced in patients with acute and chronic viral hepatitis, and have demonstrated that the antioxidant level increased after interferon treatment [16].

The goal in the treatment of CVH is to suppress viral replication, to eliminate or halt cell damage by inhibiting the inflammatory response. The purpose of finding new originating points in the treatment search in order to increase antioxidant response has recently made the antioxidants more important [3]. Duygu et al. have shown that total antioxidant capacity reduced in proportion to the severity of the disease in chronic hepatitis B patients [17]. Bolukbas et al. have shown that oxidative stress was significant in patient groups, who are in the different periods of chronic hepatitis B infection, compared to the control group [18]. Again in another study, Yamamoto et al. have suggested that high oxidative stress accompanied necroinflammation in CVH, cirrhosis, and hepatocellular carcinoma cases [19]. In order to prevent the damage of free radicals, there are defense systems called antioxidants in the body [20].

Thiol group compounds are organic substances that have an important role in defense against oxidative stress with their reductive characteristics. The major thiols found in the plasma are low-molecular-weight thiols including albumin thiols, protein thiols and cysteine, cysteinylglycine, glutathione, homocysteine, and γ-glutamyl cysteine. Oxidative products that form in the organism, such as reactive oxygen types, are reduced by transferring their excess electrons to the compounds containing thiol, and thiol groups are oxidized. The oxidation of thiol groups causes disulfide bonds to form. However, this is a reversible reaction and the resulting disulfide bonds can be reduced to thiol groups again. Thus, dynamic thiol-disulfide homeostasis is obtained. Dynamic thiol-disulfide homeostasis plays a critical role in antioxidant defense, detoxification, apoptosis, regulation of enzymatic activity, and cellular signal transduction [21]. In cases where the neutralizing capacity of antioxidant mechanisms to neutralize the oxidizing agents is not sufficient, damage to the cell membrane, lipids, nucleic acids, proteins, and extracellular matrix components may occur [22,23]. Therefore, when thiol/ disulfide homeostasis shifts towards the disulfide formation, these vital activities are adversely affected and pathologies occur in the structure and functions of many organs [24]. There is also a growing body of evidence demonstrating that an abnormal thiol/ disulfide homeostasis state is involved in the pathogenesis of a variety of diseases, including diabetes, cardiovascular disease, cancer, rheumatoid arthritis, chronic kidney disease,

acquired immunodeficiency syndrome (AIDS), Parkinson's disease, Alzheimer's disease, Friedreich's ataxia (FRDA), multiple sclerosis and amyotrophiclateral sclerosis and liver disorder [3].

By measuring the dynamic thiol-disulfide homeostasis, information on many normal or abnormal biochemical processes can be obtained [21].

The Erel technique that we used in our study is a new system that reveals the total antioxidant response by simultaneously determining the oxidant and antioxidant capacity. Compared to other systems available today, the major advantages of this system is that it is reliable and sensitive, cheap and simple, completely easy and provides automatic measurement and is not affected by serum content such as bilirubin, serum lipids and anticoagulants [25].

its usefulness as a novel and sensitive oxidative stress mediator has been investigated in various diseases [26] However, this study is the first to assess dynamic thiol-disulfide homeostasis in patients with CHB in the literature. In this respect, this study is very important. We found that in CHB group (366±66 µmol/L, 392±72 p=0.041), total SH levels (439±80, 470±80 p=0.043) were lower than the control group.

In a recent study, including patients with pre-diabetes, Ates et al. showed a positive correlation between disulfide and blood glucose concentrations [27]. In a study, including patients with newly diagnosed primary hypertension, there was a positive correlation between disulfide levels and blood pressure. Disulfide was identified as an independent risk factor for hypertension in this study [28]. In another study, an increase was found in a disulfide/thiol ratio in patients with idiopathic recurrent pregnancy loss; however, there was no difference in the disulfide levels [29]. Özşahin et al it is known that excessive production of free oxygen radicals by active neutrophils cause tissue damage. It was shown that both chronic renal failure (CRF) and hemodialysis (HD) patients' circulating neutrophils had a increased oxidative metabolism. Also in Özşahin et al's study it is found that plasma total thiol levels were less when compared with healthy individuals [8]. In other study CRF and CRF+diabetes mellitus (DM) patients' total and free thiol levels informing about antioxidant status were significantly low when compared with control group [21]. Matteuchi E et al. have reported that impairment of thiol redox homeostasis is an important factor in the development of DM and DM-related complications [30]. Mahmut et al.'s study shows that mechanism involving oxidative stress operates in the development of tip 2 diabetes [31]. Kundi et al. demonstrated that thiol levels correlated with the severity of coronary atherosclerosis and the mortality rate was higher in the group with low thiol levels (32). Furthermore, thiol levels were shown to be markedly reduced in patients with migraine [33]. In a study carried out by Erkus et al., a connection between low plasma thiol levels and left ventricular diastolic dysfunction was reported. The authors suggested that increased thiol levels could play a protective role in diastolic dysfunction [34].

In this study, there was no correlation between HBV-DNA level and thiol/disulfide homeostatic. Although there are several studies investigating the correlation between viral load and biochemical markers of hepatitis, there is a small number of studies describing the correlation between viral load and free radical damage in the literature. Kaya et al. have shown that there was a significant increase in malondialdehyde (MDA) levels, an indication of lipid peroxidation (LPO), but there was no correlation between viral load and MDA (an LPO product) and antioxidant enzyme activities [35]. Similarly, Wang et al. have found no correlation between HBV DNA and MDA levels [36].

The main limitation of our study is that it is a cross-sectional study. Age may also be a confounder factor. Because the age ranges of CHB (chronic hepatitis) patients and control group were compatible in our study. There was a positive correlation between age and SH, SH/total SH, and SS/SH and SS/total SH. In a study of Mahmut et al., a significantly negative correlation was determined between the SH level and the total SH level and the age. Researchers have previously shown that oxidative stress levels increased with age [31].

In chronic liver diseases, albumin level decreases and gamma-globulin increases due to necroinflammation and fibrosis [37]. In our study, there was also a positive correlation between albumin and total protein and total SH, SH. Due to the association of albumin with antioxidant capacity, it has been once again verified that it is a valuable parameter in the follow-up of patients with CHB.

The most sensitive indicator showing the encounter of an individual with hepatitis B virus (HBV) is the presence of hepatitis B core antibody (anti-HBc) response [38]. In our study, there was a negative correlation between AntiHBc total Ig G and total SH, SH, SH/total SH, and a positive correlation between SS/SH, SS/total SH. No correlation was found between HBs Ag and thiol/disulfide balance. Anti-HBc total Ig G (+) was found to be significant in the antioxidant capacity that we detected in all patients. It has been once

again emphasized that the effects of oxidative stress should be monitored in all individuals who have experienced hepatitis B virus.

There was a negative correlation between BMX index and total SH and SH, SH/total SH, and a positive correlation between SS/total SH and SS/SH.

Oxidative stress that is not excessive but persistent in chronic viral hepatitis causes mutations by affecting the host cell DNA, stimulates the fibroblastic activity and after a long period of time, complications such as cirrhosis and HSC occur. At the same time, reduced antioxidant capacity may result in exacerbation of the disease and fibrosis in chronic cases [13].

This study examined the thiol/disulfide balance in patients with CHB using a newly developed technique. To the best of our knowledge, this is the first study evaluated the oxidative stress using this marker in CHB.

With this study, it was considered that low thiol levels detected in patients with CHB will be suggestive in terms of ways to increase antioxidant capacity in the search for new treatments. Also, in the future, understanding how host cell DNA sets up the repair pathways in response to oxidative stress due to hepatitis B virus effects will be indicative and invaluable in preventing chronic liver diseases and developing new treatment modalities. Furthermore, the significant correlation between AntiHBc total Ig G (+) and thiol/disulfide hemostasis in our study may be considered to be significant in terms of showing the presence of oxidative stress on isolated AntiHBc total Ig G (+) patient groups once again.

DECLARATION OF CONFLICT OF INTEREST

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Düzeltme Yazısı (Erratum)

Düzeltme: Hemodiyaliz hastalarında hepatit E, hepatit G ve TTV seroprevalansı

Erratum: The seroprevalance of hepatitis E, hepatitis G and TTV in haemodialysis patients

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2) Affiliation of Seda Sabah should be "Bozok Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji Anabilim Dalı, Yozgat".

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Düzeltme Yazısı (Erratum)

Düzeltme: Hemodiyaliz hastalarında okült hepatit B ve hepatit C enfeksiyonu sıklığı

Erratum: Frequency of occult hepatitis B and C infections in hemodialysis patients

Neziha Yılmaz, Aydın Çifci *, Mehmet Balcı, Salih Cesur, Seda Sabah Özcan, S. Süha Şen, Reyhan Öztürk, Çiğdem Kader, Hasan Irmak, Mehmet İbiş, Laser Sanal

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1) The clause "Bu çalışma Bozok Üniversitesi BAP tarafından desteklenmiştir (Proje No: 2014TF/A45)" in article information section should be corrected as "Bu çalışma Bozok Üniversitesi BAP tarafından desteklenmiştir (Proje No: 2014TF/A95)".

2) Affiliation of Seda Sabah Özcan should be "Bozok Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji Anabilim Dalı, Yozgat".

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Orijinal Makale

Bir eğitim ve araştırma hastanesi psikiyatri polikliniğine yönlendirilen adli olguların değerlendirilmesi

Clinical features, cases of psychiatric diagnosis and socio-demographic characteristics of patients with polyclinics of forensic psychiatry in education research hospital

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ÖZ

Amaç: Bu çalışmada adli psikiyatri polikliniğimize yönlendirilen olguların sosyodemografik özellikleri ile yaş ve eğitim durumları gibi özellikleri ön plana çıkarılarak, işledikleri suç kapsamları, madde kullanım durumları ve klinik özellikleri ile psikiyatrik olarak en sık konulan tanılar belirlenmeye çalışılacaktır.

Yöntem: Çalışmaya Eğitim ve Araştırma Hastanesi psikiyatri polikliniğine 01.01.2018 -15.12.2018 tarihleri arasında adli makamlarca rapor düzenlenmesi ve ayaktan başvuru ile yönlendirilen 191 olgu çalışmaya dahil edilmiştir. Bu vakalar yaş, cinsiyet, eğitim durumları gibi sosyodemografik özellikleri ile klinik tanıları ve madde kullanım durumları geriye dönük olarak taranmıştır.

Bulgular: Adli olguların 36'sı kadın (%18,8), 155'i (%81,2) erkek olurken, grubun yaş ortalaması 44,52±16,522 (18-92) yıl olarak saptanmıştır. Eğitim düzeyi 104 (%54,45) ilkokul, 72 (%42,93) orta öğretim, 15 (%2,62) yüksekokul olarak tespit edilmiştir. Vakaların 137'sinin geçmişte psikiyatrik öyküsü bulunurken, bunların 100'üne tanı konmuştur. Uluslararası sınıflandırma (ICID-10) kapsamında değerlendirilen tanı dağılımlarında ilk sırayı 41 (%34,45) kişi ile duygudurum bozuklukları alırken, ikinci sırada 37 (%31,09) kişi ile şizofreni ve sanrılı bozukluklar yer almaktadır. Adalet bakanlığı tarafından, en çok Türk Ceza Kanunu (TCK) 432. maddesi kapsamında değerlendirme istenirken, işlenen suçlar ağırlıklı olarak fiziksel saldırı bazlıdır.

Sonuç: Bu çalışma suç ve ceza ikilisinin, sebep ve sonuç durumları açısından bir çıkarım yapmayı hedeflemiştir. Şiddet içerikli suçların ağırlıklı olduğu durumlarda yoğun olarak pskiyatrik rahatsızlıkların eşlik ettiği, ceza sorumluluğu kapsamında çok azının ceza sorumluluğunun olmadığı, psikiyatri tanı geçmişi olan vakalarda saldırı tipi fiziksel suç işleme oranın daha fazla olduğu ve yoğun olarak sosyal şifa hali ile vakaların takip edildiği sonucuna varılmıştır.

Anahtar kelimeler: adli psikiyatri, madde kullanımı, bağımlılık

ABSTRACT

Purpose: In this study, sociodemographic characteristics of the patients referred to our forensic psychiatry outpatient clinic will be highlighted in terms of their features such as age and educational status, and the scope of crime, substance use and clinical features and the most frequently diagnosed diagnoses will be determined.

Methods: A total of 191 patients who were referred to the psychiatry outpatient clinic of the Training and Research Hospital between 01.01.2018 and 15.12.2018 by judicial authorities and outpatient admissions were included in the study. Sociodemographic features such as age, gender, educational status and clinical diagnoses and substance use cases were retrospectively reviewed.

Findings: Of the forensic cases, 36 (18.8%) were female and 155 (81.2%) were male. The mean age of the group was 44.52 ± 16.522 (18-92) years. The level of education was 104 (54.45%) primary school, 72 (42.93%) secondary school and 15 (2.62%) high school. Of the cases, 137 had a history of psychiatric history, of which 100 were diagnosed. While 41 (34.45%) patients had mood disorders with the first place in the diagnostic distribution evaluated within the scope of international classification (ICID-10), 37 (31.09%) people had schizophrenia and delusional disorders. The Ministry of Justice is most frequently asked for an assessment under the Article 432 of the Turkish Criminal Code, while the crimes committed are predominantly based on physical attacks.

Result: This study aimed to make an inference in terms of cause and effect of crime and punishment duo. In cases where violent crimes were predominant, it was concluded that there were very few psychiatric disorders, no criminal capacity under the scope of criminal capacity and the cases were followed with social healing.

Keywords: forensic psychiatry, drug use, addiction

GİRİŞ

Adli psikiyatri, psikiyatri, çocuk ve ergen psikiyatrisi, nöroloji disiplinleri başta olmak üzere gerçeği değerlendirme yetisini etkileyen diğer klinik tablolar da dahil yasal çerçevede ele alınan konuları değerlendiren, yargılama sürecinde bu konularla ilgili sorulara yanıt aranan ve bilirkişilik yapılan disiplinler arası bir alandır. Bu alanın sınırları, sözü edilen disiplinlerin yanı sıra yasal konular tarafından da belirlenmektedir [1].

Adli psikiyatri hukuk ve tıp bilimi arasında bir köprü oluşturarak kişinin suçu işlediği andaki ruhsal durumunun, ceza sorumluluğunun olup olmadığının belirlenmesi gibi alanlara yardımcı olan bir bilim dalıdır. Hekimlerin görev ve sorumlulukları alanı içerisinde, yetkili makamlarca istenen neticesinde kişinin işlediği suçtan ötürü ceza alıp alamayacağının belirlendiği adli rapor düzenleme de yer almaktadır [2]. Türk Ceza Kanunu (TCK) 32. maddesinde bir kişinin işlediği herhangi bir suçtan dolayı sorumlu tutulabilmesi için, suç sırasında, işlediği suçun hukukî anlam ve sonuçlarını algılayabilme veya bu fiille ilgili olarak davranışlarını işleyeni bağladığı gibi, psikiyatrik açıdan değerlendirildiği andaki durumun sonucu ne kadar yönlendirme yeteneğinin tam olması gerektiği ifade edilmiştir [3]. Bu ifade suçu etkileyebileceğini gözler önüne sermektedir. Değerlendirmenin temeli, akıl hastalıklarının ayırıcı tanısının yapılması, olaydaki etkisinin belirlenmesi olduğundan; değerlendirmelerin uzmanlarca yapılması, uzmanlardan konsültasyon alınması ve psikometrik incelemeler gibi yardımcı yöntemlere dayandırılması gerektiği önerilmektedir [4-6]. Ruhsal durumun etkilediği suç ve ceza kapsamı açısından bir genelleme çıkarılmaya çalışılacak olan bu çalışmada, adli psikiyatri polikliniğimize yönlendirilen olguların sosyodemografik özellikleri ile yaş ve eğitim durumları gibi özellikleri ön plana getirilerek, işledikleri fiili eylemler, madde kullanım durumları ve klinik özellikleri ile psikiyatrik olarak en sık konulan tanılar belirlenmeye çalışılacaktır.

GEREÇ VE YÖNTEM

Geriye dönük olarak gerçekleştirilen bu çalışmada 01.01.2018 tarihi ile 15.12.2018 tarihleri arasında bir eğitim araştırma hastanesi psikiyatri polikliniğine adli makamlarca rapor düzenlenmesi ve ayaktan başvuru ile yönlendirilen 191 olgu çalışmaya dahil edilmiştir. Bu vakalar yaş, cinsiyet, eğitim durumları gibi sosyodemografik özellikleri ile klinik tanıları ve madde kullanım durumları geriye dönük olarak taranmıştır. Hastane adli büro biriminde taranan verilerden kişi bilgileri geliş sebebi, yakınması, tanı ve tedavi durumu ve sonuç değişkenleri belirlenmiştir. Hastane veri tabanı bilgilerinden bu kişilerin geçmişte psikiyatrik öykülerinin olup olmadığı, varsa tanıları, kaç kez başvurdukları, tedavi

Tablo 1. Sosyodemografik Veriler

		N	%
Cinsiyet	Kadın	36	%18,8
	Erkek	155	%81,2
Yaş	18-33	57	%29,8
	34-49	64	%33,5
	50-65	47	%24,6
	66-81	19	%9,9
	82 ve yukarı	4	%2,1
Eğitim Durumu	İlkokul	104	%54,45
	Orta Öğretim	72	%42,93
	Yüksekokul	15	%2,62

Tablo 2. Psikiyatrik Tanı Dağılımları

		N	%
Genel Psikiyatrik Tanı Dağılımı	Madde Kullanım Bozukluğu	2	2%
	Şizofreni	13	13%
	Psikotik Bozukluk	10	10%
	Bipolar	10	10%
	Depresif Bozukluk	35	35%
	Duygu Durum Bozuklukları	2	2%
	Anksiyete Bozuklukları	19	19%
	Uyum Bozukluğu	2	2%
	Zeka Geriliği	3	3%
	Davranış Problemleri	4	4%
Şiddet İçerikli Suçları İşleyen Hastalardaki Psikiyatrik Tanı Dağılımı	Şizofreni	12	%37,5
	Duygu Durum Bozukluğu	7	%21,87
	Anksiyete Bozuklukları	2	%6,25
	Zeka Geriliği	2	%6,25
	Davranım Problemleri	1	%3,12
	Diğer	8	25%

madde kullanım durumlarının olup olmadığına bakılmıştır. Hangi yaş gurubunda hangi suç oranın yüksek olduğu, tanı dağılımının suç oranı ile ilişkili olup olmadığına istatistiksel olarak frekans dağılımlarına SPSS paket program 21.0 kullanılarak Ki-kare yöntemi ile bakılmıştır.

Çalışmanın etik kurul onayı, hastane oluru ve Adalet Bakanlığı onayı alınmış olup Helsinki Deklarasyon'una uygun olarak gerçekleştirilmiştir.

BULGULAR

Çalışmaya psikiyatri polikliniğinde değerlendirilen toplam 191 hasta dahil edilmiştir. Adli olguların 36'sı kadın (%18,8), 155'i (%81,2) erkek olurken, grubun yaş ortalaması 44,52±16,522 (18-92) yıl olarak saptanmıştır. En çok vaka 64 (%33,5) kişi ile 34-49 yaş aralığında yer alırken en az vaka 4 (%2,1) kişi ile 82 yaş ve üzeri yaş aralığında yer almaktadır. Eğitim düzeyi 104 (%54,45) ilkokul, 72 (%42,93) orta öğretim, 15 (%2,62) yüksekokul olarak tespit edilmiştir (**Tablo 1**).

Vakaların 138'nin geçmişte psikiyatrik öyküsü bulunurken, bunların 100'üne tanı konmuştur. Uluslararası sınıflandırma

Tablo 3. Gönderilme Sebebi ve Değerlendirme

		N	%
TCK Gönderilme Sebeplerine Göre Dağılım	432 Toplum için tehlike	39	%20,41
	46/3 Ceza sorumluluğu (eski)	5	%2,9
	5237 Nolu Genel kanun	36	%20,7
	5275-48 Hücre cezası	4	%2,3
	57/1 Koruma tedavi	57	%32,8
	57/1-2 Sosyal şifa sorunsalı	4	%2,09
	57/7 Madde kullanım	1	%0,6
	Diğer	45	%23,5
TCK'na Göre Değerlendirilme Durumu (Konulan Tanı)	32/1(Ceza sorumluluğu Tam Bozulma)	7	%3,66
	32/1-2 (-) (Ceza sorumluluğu Tam)	15	%7,65
	32/2 (Ceza sorumluluğu Azalma)	16	%8,37
	Ayaktan Tedavi	4	%2,09
	Sosyal Şifa Hali	60	%31,47
	Yatırılarak Takip	29	%15,18
	Diğer	60	%31,47

(ICID-10) kapsamında değerlendirilen tanı dağılımlarında ilk sırayı 41 (%34,45) kişi ile duygudurum bozuklukları alırken, ikinci sırada 37 (%31,09) kişi ile şizofreni ve sanrılı bozukluklar yer almaktadır. Bunların dışında madde kullanım bozukluğu 2 (%2), uyum bozuklukları 2 (%2), zeka geriliği 3 (%3), ve davranış problemleri 4 (%4) kişide tespit edilmiştir. Şiddet içerikli suç kapsamında ceza sorumluluğu olup olmadığı yahut, daha evvel işlenmiş suç kapsamında güvenlik tedbirleri hükmolunan vakalarda belirlenen psikiyatrik tanı dağılımlarında şizofreni 12 (%37,5), duygu durum bozuklukları 7 (%21,87), anksiyete bozuklukları 2 (%6,25), zeka geriliği 2 (%6,25), davranım problemleri 1 (%3,12) ve diğer 8 (%25) şeklinde yer almıştır (**Tablo 2**).

Görevli mahkemeler tarafında Türk Medeni Kanunu ve TCK 32/1-2 kapsamında akıl hastalığı nedeniyle, işlediği fiilin hukuki anlam ve sonuçlarını algılayamayan veya bu fiille ilgili olarak davranışlarını yönlendirme yeteneği önemli derecede azalıp azalmadığı ve yazılı derecede olmamakla birlikte işlediği fiille ilgili olarak davranışlarını yönlendirme yeteneği azalıp azalmadığı sorgulanma durumları geliş sebepleri dağılımlarında TCK 432 toplum için tehlike arz eden vaka 39 (%20,41), 46/3 (eski ceza sorumluluğu kanunu) ceza sorumluluğu 5 (%2,9), 5237 sayılı genel kanun 36 (%20,7), 5275-48 hücre cezası 4 (%2,3), 57/1 koruma, tedavi 57 (%32,8), 57/1-2 sosyal şifa hali 4 (%2,09), 57/7 madde kullanım duruma bağlı 1 (%0,6) ve diğer durumlar 45 (%23,5) olarak sınıflandırılmıştır Sorgu kapsamında değerlendirilen olgulara verilen rapor sonuçlarında 32/1 7 (%3,66), 32/1-2 15 (%7,65), 32/2 16 (%8,37), ayaktan tedavi 4 (%2,09), sosyal şifa 60 (%31,47), yatarak tedavi 29 (%15,18) ve diğer durumlar 60 (%31,47) olarak bulunmuştur (**Tablo 3**).

Tablo 4. Suç Unsuru Oranları, Psikiyatri Tanı ve Yaş İlişki Durumları

		N	%
Geliş Sebeplerinde Bariz Suç Unsuru Olanlar	Madde Kullanımı	1	%0,5
	Fiziksel Saldırı	18	%9,42
	Cinsel Taciz	5	%2,61
	Huzuru Bozma	1	%0,5
	Hırsızlık	6	%3,14
	Öldürmeye Teşebbüs	3	%1,57
	Diğer	157	%82,19
		P	
Fiziksel Şiddet Suçluları ve Psikiyatrik Tanı İlişkisi		P=0,000	
Fiziksel Suç İşleyenler ve Yaş ilişkisi		P=0,131	

Hastaneye geliş sebepleri içerisinde bariz suç durumları bildirilen 34 (%17,81) kişiden şiddet içerikli şuç kavramı içeren, 1 (%0,5) madde kullanımı, 18 (%9,42) fiziksel saldırı, 5 (%2,61) cinsel saldırı, 1 (%0,5) huzuru bozma, 6 (%1,01) hırsızlık, 3 (%1,57) öldürmeye teşebbüs olarak tespit edilmiştir. Suç ve psikiyatrik tanı dağılımı arasında (p=0,000) anlamlı bir ilişki tespit edilirken yaş değişkeni arasında anlamlı bir ilişki bulunamamıştır (p=0,131) (**Tablo 4**).

TARTIŞMA

Uzun yıllardır adli olguların suç işlenilen durumlarında psikiyatrik bozukluk birlikteliği sürekli araştırılmış ve bu davranışları sergileyenlerde tedavi edilecek bir hastalığın olduğuna inanılmıştır [7]. Bu inançlar araştırmacıları bu yöne itmiş eğitim düzeyi, ekonomik durum, madde kullanımı, psikiyatrik tanı varlığı gibi bir çok etmenin suç ile ilişkisi araştırılmıştır.

Yapılan çalışmalarda, adli olaylarda görülen erkek oranları kadın olgulara oranla 2-3 kat daha fazladır. Bu çalışama da benzer özellikler göstermiş olup erkek olguların kadın olgulara oranı 4,31'dir [8-10]. İşlediği suçtan ötürü ceza sorumluluğunun olup olmadığının değerlendirilmesinin istendiği bu vakalarda eğitim düzeyin düşük olduğu literatürdeki diğer çalışmalara benzer nitelikte olup ilkokul düzeyinde %54,45 kişi bulunmaktadır [10]. Bu oranın eğitim düzeyinin yineleyici suç işleme davranışı ile ilişkili olduğu yapılan diğer çalışmalarda gösterilmiştir [11,12].

Suçun işlendiği zamandaki yaş durumları için olguların verimli çağlarında olduğunu ifade eden çalışmalar mevcut olup bizim çalışmamızda yaş ortalaması benzer düzeydedir [13].

Dikkat çekilmek istenen asıl konu suç ve psikiyatrik tanı durumu olmakla birlikte literatürde adli olgulardan şizofren hastaların geçmişte şiddet içerikli suçu eyleme dönüştürmeden önce kuruma başvuruların büyük oranda olduğunu göstermiştir. Ulkemizde yapılan benzer bir çalışmada bu oran %87,5 olarak bulunmuştur [14]. Çalışmamızda geçmişte şizofreni tanısı konmuş %13 hasta bulunmaktadır. Öncü ve arkadaşlarının yapmış oldukları çalışmada ceza sorumluluğu olmayan psikiyatrik bozukluğu olanlarda koruma ve tedavi sonrasında yineleyici suç işleme oranını %9 olarak bulmuştur. Bir diğer çalışma başkasına karşı şiddet içerikli davranışlarda bulunma psikotik grupta %10, psikotik olmayan grupta %20 olarak bulmuştur. Çalışmamızda şiddet içerikli suçlarda psikotik grup oranı %37,5 olarak bulunmuştur [15,16].

İlgili makamlarca ceza sorumluluğunun olup olmadığının sorgulandığı TCK32/1 ve 32/2 kapsamında incelemenin yapıldığı bir çalışma bulunmaktadır. Bu çalışmada %33,1'inin ceza sorumluluğunun tam olduğuna, diğerlerinin ise ceza sorumluluğunun kısmen ya da tamamen bozulduğuna karar verilmiş bizim çalışmamızda ceza sorumluluğu tam %7,65, kısmen yada tam bozulmanın görüldüğü %12,03 olarak bulunmuştur [17]. Geliş sebebi diğer oranların karşılaştırılabileceği çalışma bulunmamaktadır.

Çalışmadaki tüm olgular suç dağılımı açısından değerlendirildiğinde en yüksek oranda fiziksel saldırı (darp, şiddet, bıçakla yaralama, adam öldürme gibi) %9,42 bulunmakta iken madde kullanım suçu %0,5 olarak bulunmuştur. Literatürde madde kullanım ilişkisi ile ilgili yapılan bir çalışmada %39,8 ile en çok madde yakalatma tespit edilmiştir bu durumu işlenen suçun doğrudan madde kullanımı ile ilişkilendirilebileceğini belirtmişlerdir [18]. Suç dağılımın geneline bakıldığında benzer özellik gösteren bir çalışmada ceza sorumluluğu olmayan psikotik grubun adam öldürme ve yaralama gibi ağır şiddet suçlarını daha fazla işlediklerini ve bununla birlikte madde kullanım bozukluğu yaygınlığının yüksek olmadığı bildirilmiştir [19,20].

SONUÇ

Psikiyatrik tanı, beraberinde alkol-madde bağımlılığı, düzenli ve devamlı ilaç kullanılmaması kötüye giden ruhsal durum, eğitim düzeyi sosyoekonomik yapı gibi birçok etken şiddeti tetikleyen unsurlar içerisinde sayılabilir. Ruhsal durumun suç işlemedeki etkinliği oldukça yüksektir. Ağır travmatik rahatsızlık, fizyolojik ve patolojik bozukluklar gibi organik etmenler kişinin karar verme mekanizması üzerinde çok etkilidir. Bu sebeple ruhsal durum muayenesi kişinin suç karşısında ceza yükümlülüğünü sorgulatmaktadır. Gerek suç işleyen gerekse mağdur açısından bu sorumluluk çok büyük önem arz etmektedir. Toplum temelli uygulamalarda verilecek herhangi bir karar geri dönüşü mümkün olmayan sonuçlar doğurabilmektedir. Bu çalışma suç ve ceza ikilisinin, sebep ve sonuç durumları açısından bir çıkarım yapmayı

hedeflemiştir. Şiddet içerikli suçların ağırlıklı olduğu durumlarda yoğun olarak psikiyatrik rahatsızlıkların eşlik ettiği, ceza sorumluluğu kapsamında çok azının ceza sorumluluğunun olmadığı ve yoğun olarak geçmiş işlenen suçlar kapsamında hakkında süreli kontrol kararı verilen vakaların takip edildiği, bu takiplerin suçun tekrarlanmaması için oldukça önemli olduğu sonucuna varılmıştır. Literatürde bu kapsamda yapılmış yeterince çalışma olmayışı bazı oranların karşılaştırılmasında kısıtlılığa sebep olmuş bu durum çalışmanın eksikliğini göstermiştir, ancak elde edilen oranlar bu alanda çalışmanın azlığı dikkate alınınca literatüre katkı sağlayacağı düşünülmektedir.

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Case Report

Hyponatremia due to duloxetine use in an elderly woman patient

Yaşlı bir kadın hastada duloksetin kullanımına bağlı hiponatremi

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ABSTRACT

Hyponatremia is a potentially dangerous side effect of antidepressants. Almost every antidepressant can cause hyponatremia. Duloxetine-induced hyponatremia is a side effect that is usually seen in older women. In addition to advanced age and female sex; low body weight, presence of comorbid diseases are other important risk factors for the development of hyponatremia. In this case report we present a patient with depressive disorder who developed hyponatremia with duloxetine treatment which resolved immediately after the cessation of the medication with supportive electrolyte treatment. In our case, the resolution of hyponatremia with supportive electrolyte treatment in addition to the cessation of duloxetine reminds us about the importance of monitoring sodium levels both before and after antidepressant treatment in geriatric populations.

Keywords: hyponatremia, duloxetine, antidepressant side effect

ÖZ

Hiponatremi, antidepresanların potansiyel olarak tehlikeli bir yan etkisidir. Hemen hemen her antidepresan hiponatremiye neden olabilir. Duloksetin kaynaklı hiponatremi genellikle yaşlı kadınlarda görülen bir yan etkidir. İleri yaş ve kadın cinsiyetine ek olarak; düşük vücut ağırlığı, komorbid hastalıkların varlığı hiponatremi gelişimi için diğer önemli risk faktörleridir. Bu olgu sunumunda, ilacın kesilmesinden hemen sonra düzelen duloksetin tedavisi ile hiponatremi gelişen depresif bozukluğu olan bir hasta sunulmaktadır. Bizim olgumuzda, duloksetin kesilmesine ek olarak, hiponatreminin destekleyici elektrolit tedavisi ile çözülmesi bize geriatrik popülasyonlarda antidepresan tedavisinden önce ve sonra sodyum seviyelerinin izlenmesinin önemini hatırlatmaktadır.

Anahtar kelimeler: hiponatremi, duloksetin, antidepresan yan etkisi

INTRODUCTION

Duloxetine is an antidepressant included in the pharmacological class of serotonin-norepinephrine reuptake inhibitors (SNRIs). The drug is approved for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain and stress urinary incontinence. The drug is generally safe and well tolerated across all approved indications in adults at doses ranging from 60 to 120 mg/day. The most commonly reported adverse reactions were nausea, dry mouth, somnolence, constipation, decreased appetite and hyperhidrosis, which occurred mainly in the early stages of the assumption and disappeared after the first weeks of treatment [1].

Hyponatremia is the most common electrolyte imbalance disorder in hospitalized patients, defined as a serum sodium level below 135 mEq/L which is associated with increased mortality, morbidity, and prolonged hospitalization [2]. Normovolemic hyponatremia accounts for approximately 60% of chronic hyponatremia where the most common reason is inappropriate anti-diuretic hormone (ADH) secretion. Inappropriate ADH secretion is known to be responsible for medication as well as medical conditions such as cancer, infection, head trauma. Selective serotonin reuptake inhibitors (SSRIs) and other antidepressant drugs are known to induce inappropriate ADH secretion [3].

In this case study, we presented a patient who developed severe hyponatremia due to the use of duloxetine and we aimed to discuss drug-induced hyponatremia.

CASE PRESENTATION

Our case was an 80-year-old female patient. She had anhedonia, depressive mood and loss of appetite, waxing and waning in severity for the last 30 years. Thus, from time to time she was put on a variety of antidepressant treatment including venlafaxine, escitalopram, mirtazapine and fluoxetine. Over the last couple of years these complaints worsened with the addition of anxiety symptoms.

The patient, whose depressive complaints had increased for the last one month, was hospitalized with the diagnosis of mixed anxiety-depression. Her routine blood tests revealed only a mild creatinine elevation. After her admission to the clinic, she was put on a combination of duloxetine 30 mg/day, sulpiride 50 mg/day and hyosin N-methylbromide-medazepam 10 mg/day treatment. Duloxetine was then increased to 60 mg daily and because she had a history of hypertension she continued to take her antihypertensive treatment which was 50 mg of metoprolol and 10 mg of lercadipine per day. Since an increase in her hepatic enzymes [Alanine aminotransferase (ALT): 91 U/L; Reference value: 0–34 U/L, Aspartate aminotransferase (AST): 71 U/L; Reference value: 0–31 U/L] were observed in the next blood test, duloxetine was reduced to 30 mg for a couple of days. However; sulpiride and hyosin N-methylbromide-medazepam which can elevate hepatic enzymes were discontinued. ALT and AST values returned to normal 3 days after treatment change. About a week later, she had to be consulted to the cardiology doctor because of a sudden edema in her legs. The patient described a mild polydipsia and there was no polyuria. The cardiologist, after a series examination and diagnostic tests concluded that she had a mild aortic insufficiency and a severe tricuspid regurgitation for which an aldactazide treatment was initiated. In the meantime, severe hyponatremia [Serum sodium (Na^+): 114.1 mEq/L; Reference value: 135-145 mEq/L] was added. In addition, the patient's serum potassium (K^+) value was 4.94 mEq/L [Reference value: 3.5-5.3 mEq/L] and creatinine was 1.25 mg/dL [Reference value: 0.6-1.2 mg/dL]. Nephrology consultation was requested and the nephrologist suggested that hyponatremia might be related to duloxetine treatment. Treatment of duloxetine was stopped and electroconvulsive therapy (ECT) was started. In the preparation phase for the ECT, small pulmonary nodule in the subpleural space and atelectasis were detected in her lungs. Since her electrolyte balance deteriorated the drug treatment was stopped and an ECT treatment was planned. The Na^+ value of the patient returned to normal limits (Na^+: 134.4 mEq/L) 10 days after discontinuation of duloxetine with supportive electrolyte treatment. On the first day, 150 ml of 3% hypertonic saline intravenous infusion was administered twice in 5 hours. Then 0.9% isotonic was applied for 4 days. After duloxetine has also been stopped, the patient started to take ECT treatment, which was administered three times per week. The patient was in full recovery when a total of 8 sessions was completed.

DISCUSSION

In this case report, we presented a case of hyponatremia after duloxetine treatment in an elderly female patient who also had renal parenchymal disease.

Inappropriate ADH secretion due to hypothyroidism, diuretic use, renal pathology, lung pathology, brain lesions, and drugs –in this case duloxetine, were possible explanations for the hyponatremia observed in this patient. Since there was no clinical or laboratory evidence, a thyroid dysfunction was easily excluded. Likewise, any central nervous system lesion or pathology was also excluded for the same reason.

The patient was on a diuretic treatment which could readily be the reason for the development of hyponatremia. However, this hyponatremia improved after some time despite the fact that the patient continued to take her diuretic medication until the end of her stay. This suggests that the antidiuretic drug used by the patient is unlikely to be responsible for hyponatremia.

The patient's lung pathology (nodular lesion) and renal pathologies (chronic parenchymal disease) may both cause hyponatremia. However, these are most likely to be chronic conditions which may be expected to lead to hyponatremia long before this occasion. Furthermore, the recovery of hyponatremia soon after its occurrence suggests that it is possibly not related to these chronic conditions but to some temporary etiology like the use of a drug, in this case duloxetine. Indeed, hyponatremia occurred shortly after the initiation of duloxetine in this patient and it gradually aggravated as long as the patient continued to take this drug. Finally, it rapidly recovered after the discontinuation of the drug, which seems to strengthen this temporal relationship.

Almost all antidepressant drugs may cause hyponatremia [4]. Fluoxetine-associated hyponatremia is reported to be the most prevalent among SSRIs. Research findings suggest that, there is not a correlation between the dose of SSRIs and the onset or severity of hyponatremia [5]. However, it is noteworthy that female gender and advanced age are important risk factors for the development of hyponatremia with antidepressant treatment [6].

For the development of hyponatremia with duloxetine; advanced age and female gender, low body weight, history of hyponatremia, presence of comorbid diseases are reported as important risk factors [7]. In our case, all other risk factors were observed except for a low body weight and a history of hyponatremia. Particularly, chronic kidney disease and concomitant diuretic use might have facilitated the development of hyponatremia with the initiation of duloxetine even though they have not led to a serious electrolyte imbalance on their own until then.

Cases of hyponatremia induced by duloxetine have been described in the literature [8,9]. Our patient's presentation is consistent with literature reports of elderly females who developed hyponatremia within days of being initiated on duloxetine [10-12].

The main treatment for antidepressant induced hyponatremia is the cessation of antidepressant medication and supportive treatment [3]. In our case, in addition to the cessation of duloxetine treatment, hyponatremia was managed with adequate fluid-electrolyte treatment and close monitoring of serum electrolytes and renal functions.

This case report underlines the importance of monitoring serum sodium levels before and after antidepressant drug treatment, because the risk of drug-induced hyponatremia can increase in the geriatric population with chronic diseases which commonly end up with multiple pharmacological treatment.

CONCLUSION

Serum Na^+ concentrations should be monitored in the early stages of the duloxetine treatment of patients, especially elderly patients. The use of duloxetine should be remembered in the differential diagnosis of drug-induced hyponatremia.

DECLARATION OF CONFLICT OF INTEREST

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Original Article

Availability of Non-Ionizing Radiation Applications to Dispose Coronavirus from Foods and a Research on Creating Awareness in Protection from Coronavirus (COVID-19)

Koronavirüsü Gıdalardan Bertaraf Etmek İçin İyonize Olmayan Radyasyon Uygulamalarının Kullanılabilirliği ve Koronavirüsten Korunma Konusunda Bilinçlendirme Araştırması (COVID-19)

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ABSTRACT

Coronavirus (COVID-19) is one of the serious respiratory diseases known as a human pathogen. Recently, the world health organization has described this virus as a pandemic. One of the sources of transmission of this virus, which has many ways of transmission, is food. Especially foods pose a potential danger with contamination. The virus's survival even at high temperatures and for long periods led to the search for alternative applications to heat treatments applied to foods. These applications include infrared (IR), ultraviolet-C (UV-C), and microwave radiation. These applications, which are shown as an alternative to heat treatments, have recently found widespread use in foods. It was reported that applications are more effective against viral infections than heat treatments. This review study deals with methods of raising awareness of coronavirus prevention and virus removal from food.

Keywords: coronavirus, food, heat treatment, non-ionizing radiation applications

ÖZ

Koronavirüs (COVID-19), insan patojeni olarak bilinen ciddi solunum yolu hastalıklarından biridir. Son zamanlarda, dünya sağlık örgütü bu virüsü bir salgın olarak tanımladı. Birçok bulaşma yoluna sahip olan bu virüsün bulaşma kaynaklarından biri gıdadır. Özellikle gıdalar kontaminasyonla potansiyel bir tehlike oluşturur. Virüsün yüksek sıcaklıklarda ve uzun süre bile hayatta kalması, gıdalara uygulanan ısıl işlemlere alternatif uygulamalar aramasına yol açtı. Bu uygulamalar arasında kızılötesi (IR), ultraviyole-C (UV-C) ve mikrodalga radyasyonu bulunur. Isıl işlemlere alternatif olarak gösterilen bu uygulamalar son zamanlarda gıdalarda yaygın olarak kullanılmaktadır. Çalışmalarda uygulamaların viral enfeksiyonlara karşı ısıl işlemlerden daha etkili olduğu bildirilmiştir. Bu derleme çalışması, koronavirüs önleme ve gıdalardan virüsün uzaklaştırılması konusunda farkındalığı artırma yöntemleri ile ilgilidir.

Anahtar kelimeler: koronavirüs, gıda, ısıl işlem, iyonlaştırıcı olmayan radyasyon uygulamaları

INTRODUCTION

Coronavirus disease (COVID-19) is a disease that causes serious respiratory conditions such as pneumonia and lung injury [1]. It is the seventh coronavirus identified as a human pathogen. Of these viruses, HKU1, NL63, OC43, and 229E can cause mild symptoms, while SARS-CoV, MERS-CoV, and SARS-CoV-2 (COVID-19) are associated with serious diseases. The path that COVID-19 takes while entering the cell is like the path followed by SARS-CoV. It enters the cell by binding strongly to the receptor binding site (RBA) on the S protein and the angiotensin-converting enzyme 2 (ACE2) receptor on the cell [2].

COVID-19; it is genetically associated with the middle east respiratory syndrome (MERS). Also, its epidemiology is surprisingly similar to Severe Acute Respiratory Syndrome (SARS) [3]. It was first reported in China's Wuhan province (capital of Hubei) in December 2019 [1]. In January 2020, the first case was seen in Thailand. Later, many countries, especially Japan, South Korea, and America, started to report cases. Upon this; The World Health Organization (WHO) declared the coronavirus epidemic as an international health emergency and reported that on February 11, this disease caused by a new type of coronavirus was called coronavirus disease 2019 (COVID-19) [4]. The first case in Turkey reported on 10 March 2020 and has reached 47 029 cases in a month, 1006 has led to death [5].

Although the exact route of transmission is unknown, it is thought to be transmitted by droplet. Also, the fecal-oral route is among the accused transmission routes [6]. Although initially considered to be a zoonosis factor transmitted from the seafood and livestock market in Wuhan in etiology, it has also appeared in families that have never been in Wuhan before and human-to-human transmission has been reported [7].

As the incubation period changes with long intervals such as 2-14 days, it can lead to more infections and outbreaks. COVID-19 causes symptoms such as sore throat, high fever, shortness of breath, dry cough, vomiting, headache, diarrhea, confusion, and tremor [8]. COVID-19 affects men more than 3.25: 1. The average age is 75. In older patients, it worsens faster than younger ones [9]. Although it is generally seen in the elderly, it can also see in children [10].

Clinical criteria, laboratory tests, nasal swab, PCR studies, Serological tests, and CT imaging methods are used for diagnosis. The positive fading of COVID-19 nucleic acid is the priority for the diagnosis of COVID-19. Patients who are not positive for nucleic ascites but are clinically suspicious should be evaluated by CT, and when their characteristic findings are detected, their treatment should be isolated [11]. The most important thing we need to do is to prevent the virus from spreading. Capture, isolate and treat form the basis for this (Watkins J). Persons with contact history should be isolated for 14 days [8].

Healthcare workers involved in COVID-19 prevention and control are more prone to skin and mucous membrane-injuries such as acute and chronic dermatitis, secondary infections, and aggregation of underlying skin diseases. Therefore, standard consensus should be applied for protection. It is also recommended to use moisturizing products because of its highly effective barrier protective properties [12]. They must use gloves, gowns, face shields, goggles, and masks to protect the staff responsible for the treatment and patient care, especially in healthcare institutions. It should be ensured that health facilities are equipped with appropriate air conditioning and ventilation systems. It is important to place known or suspected COVID-19 cases in isolation rooms. It is important to work in special autopsy rooms and using isolation methods in studies on cases known to be COVID-19 during their deaths [13]. In

emergencies, separate areas should be created for COVID-19 patients, training of non-specialist clinicians should be provided, recent developments in treatments should be closely followed, and protocols should be established in the use of ventilators [14]. Since there are no vaccines and antiviral treatments, symptomatic treatments are applied (Watkins J). Although there is no specific treatment, broad-spectrum antibiotics such as moxifloxacin, ceftriaxone, azithromycin; oseltamivir antiviral, and in some cases, it is also recommended with steroids [15].

Remdesivir, chloroquine, abidol, lopinavir/ritonavir, plasma, and antibodies are included in the treatment. Vaccination studies and stem cell therapy studies are ongoing [16]. This infection, which has been effective in more than 170 countries all over the world for more than four and a half months, continues to affect many areas economically and psychologically [17-21].

One of the ways of transmission of coronavirus is also food. Food can be transmitted both in production and at every stage of storage and marketing. For these reasons, it is essential to protect and ensure food safety. For this, necessary measures should be taken in the food industry.

Precautions to be taken in food-producing establishments;

1. Providing hygiene and sanitation in washbasins,
2. Taking one transporter of the symptoms of COVID-19, to the nearest health institution,
3. Used clothes are constantly cleaned and disinfected,
4. The routine washing of work clothes at the appropriate temperature,
5. Use of masks and gloves in dining halls,
6. Ensuring social isolation,
7. Termination of contact,
8. Prevention of collective social activities,
9. Working with the least number of workers considering production planning,
10. Washing the dishes at the appropriate temperature without the opportunity for contamination,
11. Disinfectant and mask should be found in service vehicles,
12. When suppliers come, body temperatures should be checked with a fever meter,
13. Risk assessments should be constantly strengthened,
14. Living areas in the business should be routinely disinfected.

Contamination can consist of the hands, sneezing, and coughing of labors responsible for the manufacturing, packaging, and storing of food, and according to the WHO's findings, consumption of contaminated raw material and unclean food can induce human disease [22-23]. Modern or traditional applications for inactivation of viruses in foods were given below.

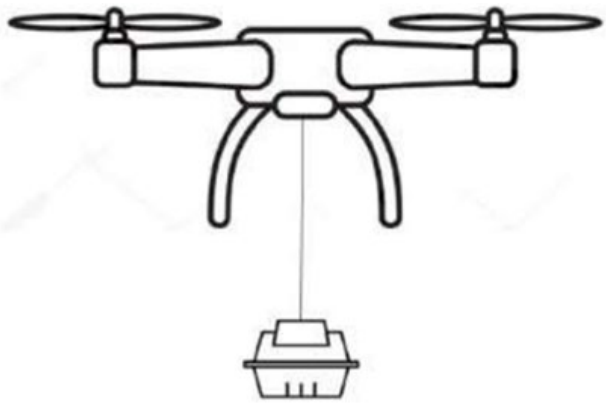
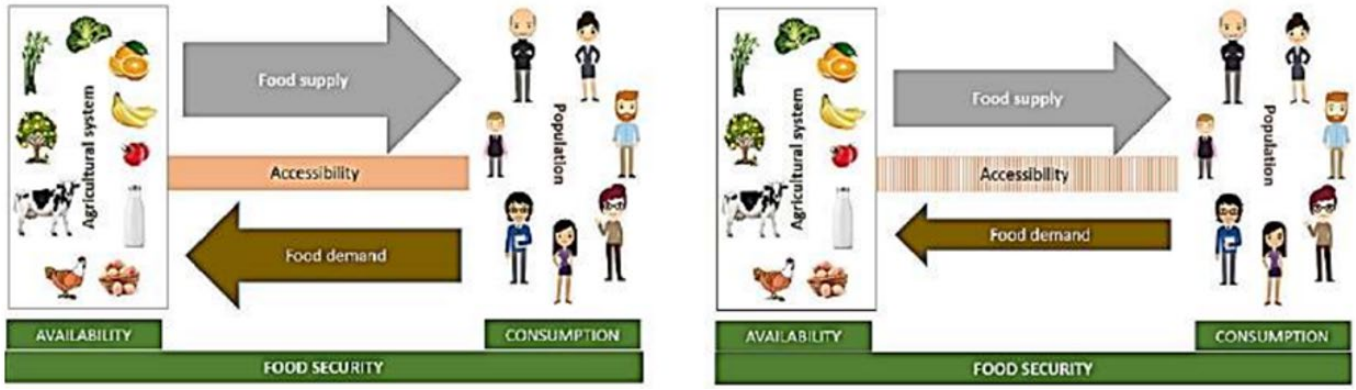


Figure 1. Drone-based system for non-contact food delivery

1. High-temperature treatments should be at minimum 70°C because coronavirus can be active at -20°C or less for 2 years.
2. The virus can be inactivated by ionizing radiation at doses from 2.7 to 3.0 kGy
3. The virus can be inactivated by non-ionized radiation such as ultraviolet-c (uv-c), infrared, and microwave especially uv-c applications for surface sterilization such as egg, fruits, and vegetable surface.
4. High-pressure applications (300-400 MPa, and 5- 22°C temperatures for 5 minutes) such as fish, fruit juice, and pre-cooked meat products.
5. Chlorine, chlorine dioxide ozone gas, sodium, and calcium hypochlorite for 1 minute such as water or food packaging.
6. In the process of the epidemic, the need for food increases due to quarantine applications [24]. For this reason, drones transport systems are developed to maintain contact and social distance during the marketing and retail sale of foods. The system developed for this purpose is given in **Figure 1**.

Moreover, the food supply chain is a link that connects a food system with the consumer's dinner table, including processes such as producing, storage, packaging, and distribution [24-25] (**Figure 2**).

Besides that, recommendations to consumers for protection from the virus were given in **Table 1**.



(a) (b)

Figure 2. Food security system (a) without COVID-19 and (b) with COVID-19. Both supply and demand have been affected, although a greater effect on demand, due to the passability restrictions that affect accessibility. Availability and consumption remain almost stable. The agricultural system includes producers, raw materials, agricultural machinery and inputs, processing plants, and farm and industrialized food. Consumption includes people and different marketing systems.

Table 1. Recommendations to consumers for protection from viruses [26-36]

Material	***Application***	***Precautions***
Food packages	When removing food packages from store shelves	You should use latex gloves. Wash the packages which are purchased from the market with water and disinfectants at home
Bread Bread coming out of the oven	Completely safe	The virus may be contaminated by bread crumbs and knives. Therefore, it should be avoided slicing the bread. Moreover, pre-heat traditional and industrial bread by microwave or traditional method before consumption.
Raw milk and pasteurized milk	Should be boiled before using	should do not use traditional dairy products
Vegetables and fruits	After washing, transfer to the refrigerator	Should be washed
Raw and partially cooked foods	Cross-contamination should not be.	It must be stored separately.
The nuts	Should be roast at home	Should be not consumed as raw
The fruits	Can be dried by microwave	Should be washed which are purchased from the market before consumption
The kitchen	Regularly clean and disinfect	Contamination
Probiotic foods	Should be consumed regularly	May bind directly to the virus, inhibit virus attachment to the host cell, and improving the immune system.

Another stage of the food production chain is the application of heat treatment to foods. Studies have reported that COVID-19 remains alive at high temperatures for a long time. Therefore, it should be investigated in different applications as an alternative to heat treatment. One of these applications is non-ionizing radiation. This radiation does not pose any health risks and even has an effective inactivation mechanism against the virus. These radiations include microwave, infrared and UV-C applications. Microwave applications are now used for purposes such as food preservation, especially in many heat treatments. Microwave can be applied as a pretreatment at processes such as thawing, drying, cooking, and boiling. In the food industry, the IR heating application is applied in the processes of foods such as drying, thawing, pasteurization and sterilization, roasting, peeling, cooking, boiling, etc [37].

It should be remembered that the radiation used in microwave and IR applications is electromagnetic radiation and that the harmful effect of this radiation on both food and human health is minimized. Another radiation application is UV-C. It is used in surface sterilization due to its anti-microbial effect. Also, it is easily used in fruit juices in the application known as cold sterilization in the food industry. In studies conducted, it is reported that UV-C application is effectively eliminated COVID-19. The aforementioned radiation has advantages and disadvantages. Therefore, radiation can be combined by the food material.

CONCLUSIONS

In this review study, the methods to be used for the disposal of COVID-19 from foods have been examined. Due to the

outbreak, the significant change in lifestyle, the increase in working hours, and the ever-decreasing availability of time to cook led to the inevitable triumph of supermarkets and discount stores. Therefore, to prevent the epidemic, food safety needs to be sustainable to balance the increasing supply and demand. To prevent the spread of the food-borne virus;

• Prevention of contact by state quarantine practices and some restrictions,

Use of drones to cut off contact at the supermarkets,

• Non-ionizing radiation applications in foods: Non-ionizing radiation applications have become popular in the food industry in recent years. The most important of these are UV infrared and microwave applications. Especially these processes are widely used in important heat treatment applications such as drying, cooking, heating, surface sterilization in foods. Among these processes, UV application is an application known as cold sterilization application besides being used as an alternative process to pasteurization, especially in providing surface sterilization. This application is used as an alternative to heating treatment as well as to kill microorganisms like bacteria viruses. Therefore, COVID-19 can be used effectively as an alternative to heat treatment in outbreaks. It can also be applied as a final treatment to eliminate contamination from any source during the production process. Another application is infrared radiation. This radiation can be used especially in short wavelength and high-power food processes. Thus, both heat treatment and sterilization process can be provided in foods. Microwave, on the other hand, can be used for pre-heating of foods, defrosting, and sudden heating. Thus, processing time can be shortened. When the applications such as infrared, UV, and microwave are used in combination, it will be supplied effective sterilization in foods,

• The application of these radiations in the food industry to prevent epidemic situations can be easily applied in preventing the transportation of the epidemic with food, and also preventing the transport of other than food with personnel and other carriers.

It was concluded that this virus, which is likely to be transmitted in foods non-ionized radiation applications compared to heat treatment applications such as pasteurization, may prevent the formation of more resistant species to environmental conditions by mutation.

DECLARATION OF CONFLICT OF INTEREST

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Original Article

Effect of curcumin on activation and expression of IRS1, Grb2, K-Ras and Bax in STZ-induced diabetic rat brains

STZ indüklü diyabetik sıçan beyinlerinde kurkuminin IRS1, Grb2, K-Ras ve Bax ekspresyonu ve aktivasyonu üzerindeki etkisi

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ABSTRACT

Aim: Diabetes mellitus leads to development of neuropathy as a secondary complication. The main mechanism of diabetic neuropathy is the dysregulation of energy balance and glucose homeostasis in brain. This study aimed to examine the effects of curcumin as an antidiabetic compound on the expressions of IRS1, Grb2, K-Ras and Bax proteins in diabetic rat brains.

Material and Methods: 16 Wistar albino rats were divided randomly into four groups as: control, curcumin; STZ-treated and STZ+Curcumin treated groups. The rats in STZ group were induced to develop diabetes by intraperitoneal administration of STZ. Then, they were treated with curcumin daily by gavage. Expressions and activation of IRS1, Grb2, K-Ras and Bax were determined by western blot analyses.

Results: Western blot analyses showed that curcumin treatment increased IRS1 tyrosine phosphorylation and it reversed the negative effect of STZ on IRS1 activation. K-Ras expression significantly decreased while Bax expression increased in STZ group ($p<0.05$). No significant changes in the expressions of Grb2 and IRS1 were observed for all groups.

Conclusion: Based on the results, it could be suggested that curcumin treatment significantly reversed the negative effects of STZ on insulin signaling pathway members in STZ induced diabetic rat brains.

Keywords: curcumin, diabetes mellitus, IRS1, insulin signaling, STZ

ÖZ

Amaç: Diabetes mellitus ikincil komplikasyon olarak nöropatiye neden olmaktadır. Diyabetik nöropatinin temel mekanizması beyindeki glukoz homeostasisinin ve enerji dengesinin bozulmasıdır. Bu çalışmanın amacı anti-diyabetik bileşik olarak kurkuminin diyabetik sıçan beyinlerinde IRS1, Grb2, K-Ras ve Bax proteinlerinin ekspresyonları üzerindeki etkisinin belirlenmesidir.

Materyal-Metot: 16 adet Wistar albino sıçan rastgele 4' erli gruplar halinde 4 gruba ayrılmıştır; kontrol grup, kurkumin grup, STZ muamele grup ve STZ+kurkumin muamele grup. STZ gruplarındaki sıçanlarda diyabet, intraperitonel STZ uygulaması ile indüklenmiştir. Ardından hayvanlar, günlük gavaj uygulamasıyla kurkumin ile muamele edilmiştir. IRS1, Grb2, K-Ras ve Bax ekspresyon ve aktivasyonu western blot yöntemi ile belirlenmiştir.

Sonuçlar: Western blot analizleri, kurkumin muamelesinin IRS1 aktivasyonunu arttırdığını ve STZ'nin IRS1 aktivasyonu üzerindeki negatif etkisini geriye çevirdiğini göstermektedir. STZ grubunda K-Ras ekspresyonu belirgin bir derecede azalırken, Bax ekspresyonu artmıştır ($p<0.05$). Tüm gruplarda, Grb2 ve IRS1 ekpresyonlarında herhangi bir değişiklik gözlemlenmemiştir.

Sonuç: Sonuçlar göz önüne alındığında, STZ indüklü diyabetik sıçan beyinlerinde kurkumin muamelesinin STZ'nin insülin sinyali yolağı elemanları üzerindeki negatif etkilerini geriye çevirdiği söylenebilmektedir.

Anahtar kelimeler: kurkumin, diabetes mellitus, IRS1, insülin sinyali, STZ

INTRODUCTION

Diabetes mellitus is a multifactorial complex metabolic disease group characterized by hyperglycemia resulting from the defects in insulin signaling. Uncontrolled diabetes mellitus leads to secondary complications such as diabetic retinopathy, neuropathy and vasculopathy [1]. It has been well documented that there is a strong association between insulin resistance and neuronal disorders. Dysregulation in glucose homeostasis and energy balance induces the pathological processes such as oxidative stress and abnormal inflammatory response that lead to neuronal loss or death in diabetes mellitus [2].

Insulin is the primary anabolic hormone that controls energy balance and glucose homeostasis through complex cellular signaling pathways in body. Insulin receptor substrate (IRS) proteins are the main docking proteins that bind insulin and insulin like growth factor receptors and transmit the signal to the downstream targets such as Growth factor receptor-bound protein 2 (Grb2), Rat sarcoma viral oncogene homolog (RAS), Extracellular signal-regulated kinases (ERK1/2), Phosphoinositide 3-kinase (PI3K) and Protein kinase B (AKT) [3]. IRS1 is the first identified member of this family and it is widely expressed in human tissues. Although tyrosine phosphorylations of IRS1 protein trigger the insulin signaling, serine/threonine (S/T) phosphorylations generally inhibit the signal transduction. Many studies showed that S/T phosphorylation of IRS1 significantly increased in diabetes while tyrosine phosphorylation decreased [4].

Curcumin is a lipophilic polyphenolic compound and a major active component of turmeric. It is isolated from the root of *Curcuma longa* which is a member of curcuminoid family. Curcumin has been used in daily diet for a long time in the history and no side effects have been reported [5]. Numerous *in vivo* and *in vitro* studies have demonstrated curcumin's therapeutic actions in inflammatory diseases, neurodegenerative diseases, liver diseases, depression, cancer, obesity and diabetes [6-8]. It can directly or indirectly interact with many proteins through covalent, non-covalent hydrophobic, and hydrogen bonding to modulate signal transduction and show its functional effects [5].

Many studies showed that blood glucose level can be reduced by curcumin treatment through decrease in hepatic glucose production, inhibiting hyperglycemia-induced inflammation, reduction of insulin resistance and inducing glucose uptake [9]. Peeyush et al. showed that curcumin treatment significantly normalized the diabetic cerebellar disorder in STZ induced diabetic rats [10]. In another study, curcumin enhanced insulin sensitivity and showed an anti-hyperglycemic effect on L6 myotubes and high fat diet induced diabetic rats [11]. Curcumin also has also been shown decrease blood glucose levels by reducing oxidative stress in ob/ob mice [12].

Although, there are numerous studies that shows the beneficial effects of curcumin on insulin-targeted tissues in diabetes, its effects on diabetic brain still needs to be clarified. Therefore, this study aimed to determine the effects of curcumin on IRS1 and IRS1-targeted proteins Grb2 and K-Ras in streptozotocin (STZ)-induced diabetic rat brains.

MATERIAL AND METHODS

Animals and Experimental Design

Animal Ethics Committee of Van Yuzuncu Yil University reviewed and approved our protocol (Date: 02.05.2019, No:04). We used 16, 300–370 g; 8-10 months old male Wistar albino rats. Animals were housed at 23 ± 1 ºC with a 12 h light:12 h dark cycle. Food and water were available *ad libitum*. The rats were divided randomly into four groups as: control, curcumin; STZ-treated and STZ+Curcumin treated groups.

Curcumin (Sigma Aldrich, St. Louis, MO) was dissolved in DMSO. Rats were treated with 10 mg/kg/day curcumin by gavage for 15 days.

Western Blotting

Whole brain tissues were lysed in buffer containing 50 mM HEPES, pH 7.0, 150 mM sodium chloride, 10% (v/v) glycerol, 1.2% (w/v) Triton X-100, 1.5 mM magnesium chloride, 1 mM EGTA, 10 mM sodium pyrophosphate, 100 mM sodium fluoride, 1 mM sodium orthovanadate, 1 mM phenylmethylsulphonyl chloride, 0.15 units/ml aprotinin, 10 µg/ml leupeptin and 10 µg/ml pepstatin A. Samples then were homogenized by sonication. For western blot analysis, 75 µg protein lysates were mixed with SDS loading buffer and heated for 5 minutes at 100 °C. Then, they were kept at room temperature. Protein samples were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, then transferred to polyvinylidene fluoride membranes. The membranes were blocked with 5% (w/v) skim milk powder in PBS containing 0.1% Tween 20. The blots were first labeled with phosphotyrosine (pY) antibody and then stripped off and re-labeled with IRS1 antibody (Santa Cruz Biotech, CA). Blots were also labeled with Bax, Grb2, K-Ras and anti-beta actin antibodies (Santa Cruz Biotech, CA). Beta actin was used as the loading control for the blots. Signal intensity on blots was determined using an enhanced chemiluminescent detection system (BioRad Hercules, CA) according to the manufacturer's instructions.

Statistical Analysis

Statistical analysis was performed using Prism version 8.2.0 software (GraphPad, San Diego, CA). One way-Anova multiple comparison test was used to test the differences between the groups. Differences were considered significant at $p \leq 0.05$.

RESULTS

Effects of Curcumin on the Expression of Cell Survival Proteins in Brain

Western blot analyses showed that tyrosine phosphorylation level of IRS1 significantly increased by the treatment of curcumin in curcumin group compared to control group ($p=0.0267$). No changes in the level of tyrosine phosphorylation of IRS1 in STZ treated group compared to control group was detected (**Figure 1a**). Curcumin treatment led to an increase in the phosphorylation of IRS1 in curcumin+STZ group compared to STZ group ($p=0.003$). Statistically significant change was not observed in tyrosine-phosphorylation level of IRS1 in STZ+Curcumin group compared to Curcumin group (**Figure 1a**). Contrary to activation of IRS1, expression of IRS1 did not seem to be equally increased. It was observed that curcumin and STZ treatments did not affect the expression of IRS1 in rat brain (**Figure 1b**).

After the expression and activation levels of IRS1 were determined, the expression of Grb2 as a downstream target of IRS1 was explored. Although, activation of IRS1 significantly increased in the Curcumin and STZ+Curcumin groups, no statistically significant changes were observed in the expression levels of Grb2 in Curcumin, STZ and STZ+ Curcumin groups compared to control group (**Figure 2a**).

K-Ras is also another downstream target of IRS1. Expression of K-Ras 3-fold decreased in STZ group compared to control group. Although, we observed almost 50% decreased in the level of K-Ras expression in Curcumin and STZ+curcumin groups compared to control group, this reduction was not statistically significant (**Figure 2b**).

Effect of Curcumin on the Expression of Pro-Apoptotic Protein, Bax, in Brain

Results suggested that STZ treatment induced the expression of Bax compared to control and curcumin treated groups ($p<0.05$). In STZ group, Bax expression was 90% and 75% higher than control and curcumin groups, respectively (**Figure 2c**). No statistically significant difference between control, curcumin and STZ+curcumin groups in Bax expression was detected (**Figure 2c**).

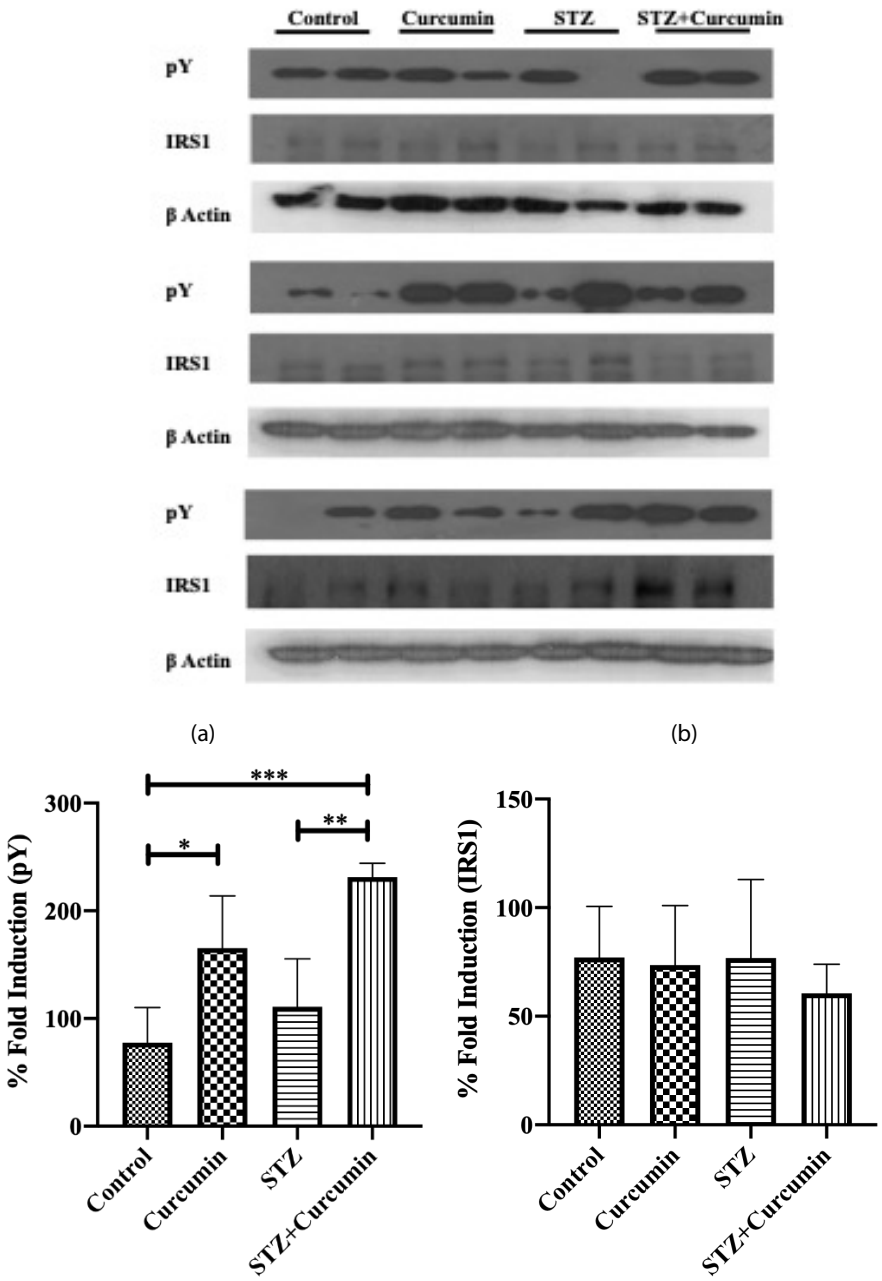

Figure 1. a. Tyrosine phosphorylation levels of IRS1 (*p = 0.0267; **p = 0.0030; ***p = 0.0004) **b.** Expression levels of IRS1. (Error bars represent the standard deviations)

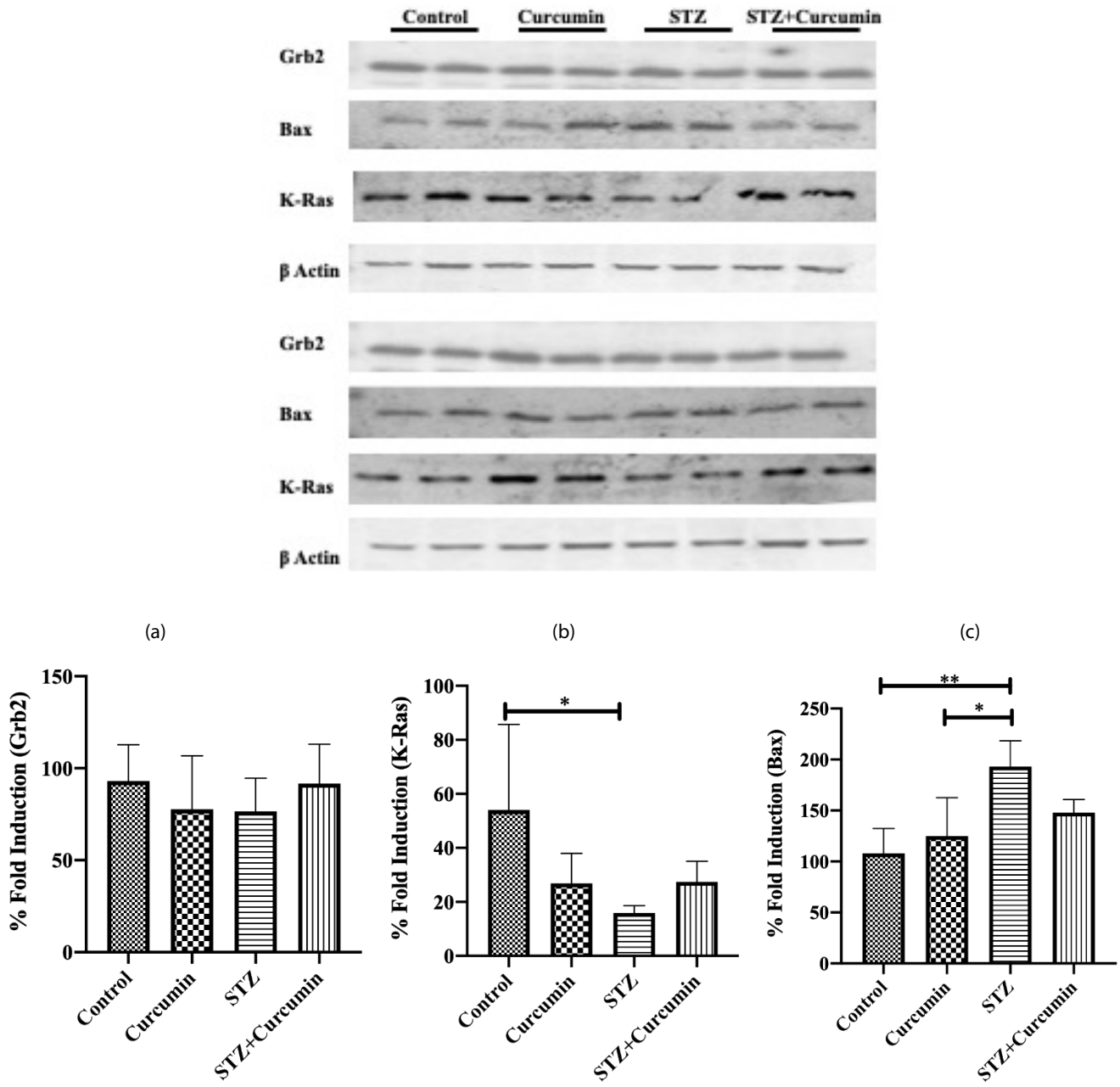

Figure 2. a. Expression level of Grb2 **b.** Expression level of K-Ras (*p = 0.0381) **c.** Expression level of Bax (*p = 0.0151; **p = 0.032) (Error bars represent the standard deviations)

DISCUSSION

Glucose is the primary energy source of the brain. Dysregulation of glucose metabolism leads to the development of neurologic disorders. There are several studies showed that diabetic patients had neuronal damages that were primarily caused by hyperglycemia and impairment in insulin signaling [13,14]. Neuroprotective and anti-diabetic roles of curcumin have been shown in epidemiological studies [15].

Dysregulation of IRS1 signaling is one of the fundamental mechanisms of the development of diabetes. Increased oxidative stress, inflammation and stress activated protein kinases inhibit insulin-induced IRS1 tyrosine phosphorylation in diabetes [16]. Plenty of studies reported that curcumin enhanced the insulin signaling and increased the insulin sensitivity through reduction oxidative stress and decrease in TNF alpha and NFkB activations in STZ induced diabetic rats [9,15]. Curcumin treatment stimulated the level of IRS1 phosphorylation in rat insulinoma cells and improved the high glucose-induced insulin resistance [17]. In accordance with these findings, it was found that curcumin treatment increased tyrosine phosphorylation of IRS1 and it also reversed the negative effect of STZ on IRS1 activation in brain. Based on these observations, it may be

suggested that curcumin could enhance and improve insulin signaling through the activation of IRS1 in STZ induced diabetic and normal rat brains.

During insulin signaling, Grb2 binds to YVNI motifs of IRS1 and PI3K binds to YXXM motifs of IRS1 and activates SOS-RAS-RAF-MEK-ERK and PI3K-AKT pathways respectively [3,18]. Grb2 is one of the members of biological network proteins that are identified by Ingenuity Systems Pathway Analysis (IPA) platform in CAL27 cells after curcumin treatment [19]. On the contrary, no significant change in Grb2 expression in rat brains were observed. However, tyrosine phosphorylation of IRS1 increased after curcumin treatment. Results showed that, curcumin may not affect Grb2 expression via IRS1 signaling in STZ diabetic rat brains and curcumin-induced IRS1 tyrosine phosphorylation can induce PI3K rather than ERK1/2 pathway.

K-Ras is one of the downstream targets of IRS1 and it activates the MAPK pathway which is responsible for the proliferative effects of the insulin signaling [3]. An increasing body of evidence shows that curcumin inhibits cell proliferation [20]. Al et al. showed that curcumin treatment significantly inhibited gastric carcinoma cells and they observed that it led to down regulation of Ras protein and upregulation of ERK1/2 [21]. Another study showed that G2/M arrest was induced by curcumin through the activation of ERK1/2 in Ras overexpressed human adenocarcinoma cells and they suggested that curcumin might have a beneficial effect in treatment of Ras activated cancers [22]. In this study it was also revealed that STZ significantly inhibited K-Ras expression and curcumin treatment reversed this effect in brain.

Previous studies have shown that apoptosis has been the main mechanism that leads to neuronal death in diabetes [23]. Bax is pro-apoptotic protein and Bax expression increased in STZ induced diabetic rats [24]. In accordance with this study, it was found that STZ treatment significantly increased Bax expression and curcumin treatment reversed the negative effects of STZ in brain. It can be suggested that increased free radical production can lead to apoptosis through the elevation of Bax expression after STZ treatment and antioxidant effect of curcumin reduces Bax expression and improves the survival of brain cells.

CONCLUSION

These results suggested that curcumin treatment led to increase in IRS1 activation and reversed the negative effects of STZ in diabetic brain cells through decreasing in Bax expression and elevation of K-Ras expression.

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Original Article

Is mean platelet volume a helpful parameter in diagnosing periprosthetic joint infection?

Ortalama trombosit hacmi periprostetik eklem enfeksiyonunun tanısında faydalı bir parametre midir?

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ABSTRACT

Introduction: Mean Platelet Volume (MPV) is encountered in the literature as a diagnostic marker used to monitor infectious and inflammatory events. We aimed to investigate whether or not there was a change in platelet and MPV parameters in patients diagnosed with periprosthetic join infection (PJI).

Material and Methods: A total of 110 patients were included in the study, consisting of 37 (33.6%) patients with periprosthetic join infection, 38 (34.6%) patients with total knee arthroplasty (TKA), and 35 (31.8%) control group subjects. During the preoperative period and follow-up, MPV, platelet, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were assessed from routine laboratory tests. Statistical analyses of values between and within groups were conducted using Shapiro-Wilk test, One-way ANOVA, Bonferroni's test, Pearson's test, and Chi-square test. $P<0.05$ and $p<0.01$ values were considered statistically significant.

Results: There was no statistically significant difference among the groups according to preoperative platelet and MPV values ($p>0.05$). Postoperative MPV levels were significantly lower and platelet, ESR and CRP levels were significantly high in the PJI group compared to both the control group and the TKA group ($p<0.05$).

Conclusion: MPV is a useful laboratory parameter in the diagnosis of periprosthetic joint infection in patients.

Keywords: Mean Platelet Volume, periprostatic, infection, diagnosis, knee

ÖZ

Giriş: Literatürde Ortalama Trombosit hacminin (OTH) enfeksiyöz ve inflamatuar olaylarda bir tanı belirteci olarak kullanıldığı görülmektedir. Amacımız OTH'nin periprostetik eklem enfeksiyonu tanısında yararlı bir parametre olup olmadığını araştırmaktır.

Araç ve Yöntemler: Çalışmaya 37 (%33,6) periprostetik eklem infeksiyonlu, 38 (%34,6) diz artroplastili ve 35 (%31,8) kontrol grubunu oluşturan 110 hasta dahil edildi. Preoperatif dönem ve kontroller sırasında alınan rutin laboratuvar örneklerinde OTH, trombosit, eritrosit sedimantasyon hızı (ESR) ve C reaktif protein (CRP) değerlerine bakıldı. Sonuçlar grup içi ve gruplar arasında Shapiro-Wilk, One-way ANOVA, Bonferroni, tPearson's, Chi-square testleri ile istatiksel olarak değerlendirildi. $p<0.05$ ve $p<0.01$ değerleri anlamlı kabul edildi.

Bulgular: Preoperatif dönemde grupların trombosit ve OTH değerleri arasında istatiksel fark saptanmadı. Periprostatik eklem enfeksiyonu olan grubun postoperatif OTH düzeyleri hem kontrol hem de TKA grubuna göre anlamlı düşük, trombosit, CRP ve ESR düzeyleri ise anlamlı yüksek saptandı ($p<0.05$).

Sonuç: OTH periprostetik eklem enfeksiyonu tanısında kullanılabilecek faydalı bir laboratuvar parametresidir.

Anahtar kelimeler: Ortalama Trombosit Hacmi, periprostetik, enfeksiyon, tanı, diz

INTRODUCTION

Periprosthetic joint infection (PJI) is a complication encountered by nearly every orthopedics specialist. Its incidence rate after primary knee arthroplasty is between 0.4-2% while its incidence after revision knee arthroplasty surgery is 3.2-5% [1-3]. PJI of the knee remains a major challenge as there is no test with absolute accuracy [4,5]. The diagnosis of PJI is based on a combination of clinical findings, laboratory results from peripheral blood and synovial fluid, microbiological culture, histological evaluation of periprosthetic tissue, and intraoperative findings [4,5].

Mean platelet volume (MPV) is assessed as a part of routine complete blood count (CBC) analysis. MPV is a parameter defined as an indicator of platelet activation and function [6]. Recently, there is increased interest in MPV as a diagnostic marker used in the follow-up of infectious events [7]. Studies reported that infectious events cause various responses in platelet and MPV levels [7,8].

This study aims to evaluate whether or not MPV is a useful parameter in diagnosing periprosthetic knee infection.

MATERIAL AND METHODS

Study Design

This retrospective clinical study was performed with the approval of the Insitutional Review Board and in line with the ethical principles of the Declaration of Helsinki. After approval of the institutional review board, informed consent was obtained from the guardians of all participants.

Setting

Patients were identified from a single tertiary academic medical center.

Participants

Patients who were followed up at our institute between January 2013-October 2018 were included in the study. Inclusion criteria were; procedure of bilateral knee prosthesis, no presence of infection other than PJI, at least six months of regular follow-up, and no clinical history of inflammatory disease and/or surgical intervention which may affect MPV value. Exclusion criteria included presence of systemic disease (dyslipidemia, uncontrolled DM, hypertension, etc.), peripheral circulatory disorders, cerebrovascular diseases, inflammatory arthropathy, alcohol-smoking, liver and/or kidney failure, immunosuppressive drug use, and malignancy.

Groups

TKA Group: Patients who underwent total knee arthroplasty without clinical or laboratory signs of infection.

PJI Group: Patients who were diagnosed with PJI according to Musculoskeletal Infection Society (MSIS) criteria and had growth in intraoperatively collected tissue samples.

Table 1. Demographic Evaluation of Groups

		PJI n=37 (%33.6)	TKA n=38 (%34.6)	Control n=35 (%31.8)	*p*
Age (Year)	*Min-Max (Median)*	58-81 (69)	53-87 (70.5)	22-67 (30)	***0.001*** **
	Mean ±SD	68.27±5.33	70.55±7.71	39.54±15.32	
Gender; n (%)	Woman	28 (75.6)	28 (73.6)	18 (51.4)	*0.082*
	Man	9 (24.3)	10 (26.3)	17 (48.5)	

Control Group: Patients without any pathological condition detected during routine health examinations or laboratory results.

Laboratory and Sample Collecting Methods

Laboratory analyses of peripheral blood samples included platelet count, MPV, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values. Blood samples were collected during the preoperative planning period and six-month postoperative period in the TKA group, during the preoperative planning period before arthroplasty operation and also during the reoperation period after diagnosis of PJI in the PJI group, and during routine health screening in the control group. Inter-group and intra-group comparisons of the blood sample results were made and the data was statistically analyzed.

Biomarkers Measurement

Platelet count (reference range 4–10 x10 9 /L), MPV (reference range 7.5 and 12.0) were analyzed with a hematological blood analyzer LH75 (Beckman Coulter). The serum concentration of CRP (reference range 0–0,5 mg/L) was measured using the immunoturbidimetric method, and ESR (reference range 0-20 mm/h) was also measured using ESR auto analyzer (electra; Italy).

Statistical Analysis

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used when evaluating study data. The normal distribution of quantitative data was tested with Shapiro-Wilk test and graphical investigations. Student t test was used for the comparison of two groups with normal distribution. One-way ANOVA was used for comparison of three or more groups with normal distribution and Bonferroni test for multiple comparison. Paired Samples t-test was used for preoperative and postoperative evaluation of measurements within the group. Pearson's Chi-square test was used for comparison of qualitative data. Diagnostic screening tests (sensitivity, specificity, PPV, NPV) and ROC Curve analysis was used to determine cutoff values. Correlation analysis was performed to assess the relationships between platelet count, MPV, ESR, and CRP values. The value of $p<0.05$ was considered statistically significant.

RESULTS

Demographic Evaluation

A total of 110 patients (74 [67.3%] female, 36 [32.7%] male) were included in the study. Mean patient age was 59.92±17.30 (22-87) years. The PJI group consisted of 37 (33.6%) patients, the TKA group consisted of 38 (34.6%) patients, and the control group consisted of 35 (31.8%) patients (**Table 1**).

In the PJI group, the mean amount of time from initial operation to PJI diagnosis was 11.86±4.2 (7-26) months. Mean follow-up time of the TKA group was 13.12±2.8 (8-20) months.

Patients in the PJI and TKA groups were significantly older than patients in the control group ($p<0.01$). There was no statistically significant difference between the PJI and TKA groups according to age ($p>0.01$). There was no significant difference between the groups according to gender distribution ($p>0.05$) (**Table 1**).

In PJI tissue samples, coagulase-negative staphylococci growth was observed in 11 (29.72%), Staphylococci aureus in 6 (16.21%), anaerobic bacteria in 4 (10.81%), gram negative bacilli in 3 (8.1%), mixed flora in 3 (8.1%), and Enterococcus spp. in 2 (5.4%).

Comparison between Groups

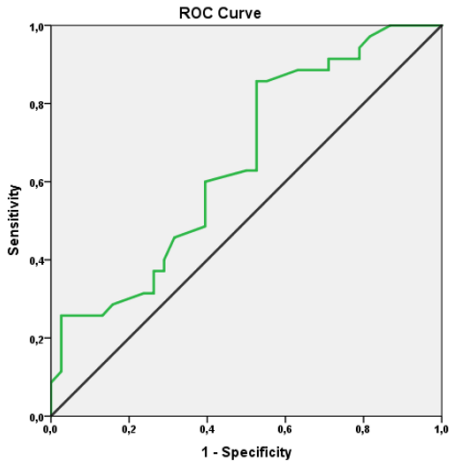
There was no statistically significant difference between the initial samples of the groups according to platelet count, MPV, ESR, or CRP values ($p>0.05$). There was, however, a significant difference between the second samples of the groups ($p<0.01$). In order to determine the group causing this significant difference, results of two-way test showed that platelet count, MPV, ESR, and CRP values of the PJI group were significantly different compared to the other groups; while platelet count, ESR, and CRP values were significantly higher, MPV was significantly lower. According

Table 2. Intra-group Evaluation and Comparison Between Groups

	PNI group (n=37) *Mean±SD (Min-Max)*	**TKA (n=38)** *Mean±SD (Min-Max)*	**Control (n=35)** *Mean±SD (Min-Max)*	**p**
Platelet Count				
First sample	385.30±75.09 (315-412)	383±63.22 (322-403)	380.92±58.17 (325-388)	0.23
Second sample	411.30±102.28 (326-455)	382.13±71.26 (311-401)	380.92±58.17 (325-388)	**0.001****
p	**0.001****	0.258		
MPV				
First sample	7.91±3.18 (6.1-10.7)	8.09±2.89 (6.5-10.8)	8.03±2.11 (6.3-10.1)	0.52
Second sample	7.32±4.48 (5.1-8.2)	7.98±4.89 (5.5-9.8)	8.03±2.11 (6.3-10.1)	**0.001****
p	**0.001****	0.651		
ESR				
First sample	7.98±4.01(5-18)	8.19±4.45 (2-19)	8.89±4.33 (2-15)	0.76
Second sample	54.98±23.77 (16-85)	8.97±12.45 (4-45)	8.89±4.33 (6-23)	**0.001****
p	**0.001****	0.465		
CRP				
First sample	0.15±0.21(0-0.4)	0.22±0.11 (0-0.4)	O.13±0.18 (0-0.3)	0.83
Second sample	4.56±3.32 (1.8-9.7)	0.35±0.16 (0-0.3)	O.13±0.18 (0-0.3)	**0.001****
p	**0.001****	0.489		

Table 3. MPV cut-off value and ROC Curve Results in the PJI group

	Diagnostic Scan					**ROC Curve**		***p***
	Cut off	**Sensitivite**	**Spesifisite**	**Positive Predictive Value**	**Negative Predictive Value**	**Area**	**95% Confidence Interval**	
MPV	***≤ 7.2***	47.37	85.71	78.26	60.00	**0.650**	0.525-0.776	***0.027****



to the two-way test, there was no significant difference between the control group and the TKA group (p>0.05) (**Table 2**).

Intra-group Evaluation

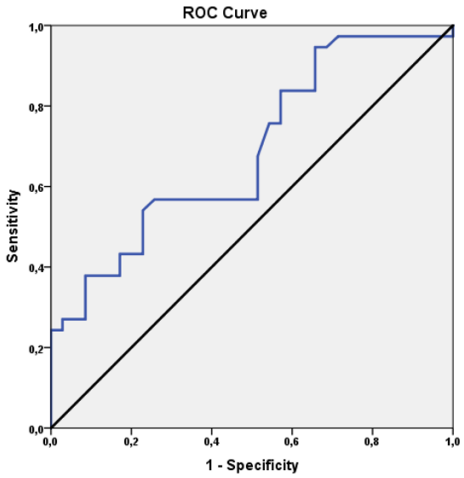
In the PJI group, there was a significant difference between the results of the first and second samples in all parameters (p<0.01). Platelet count, ESR, and CRP were significantly higher in the second sample, and MPV was significantly lower. No significant difference was observed in the intra-group evaluations of the TKA and control groups (p>0.05) (**Table 2**).

MPV Cut-off Value in the PJI Group

MPV values of the PJI group were significantly lower compared to the control group and TKA group. Based on this significance, ROC analysis and diagnostic screening tests were used to determine that cut-off value for MPV was 7,2 and below in the PJI group (**Table 3**).

Table 4. Platelet Count cut-off value and ROC Curve Results in the PJI group

	Diagnostic Scan					ROC Curve		*p*
	Cut off	**Sensitivite**	**Spesifisite**	**Positive Predictive Value**	**Negative Predictive Value**	**Area**	**95% Confidence Interval**	
PLT	**≥ *412***	54.05	77.14	71.43	61.36	**0.688**	0.566-0.810	***0.006****



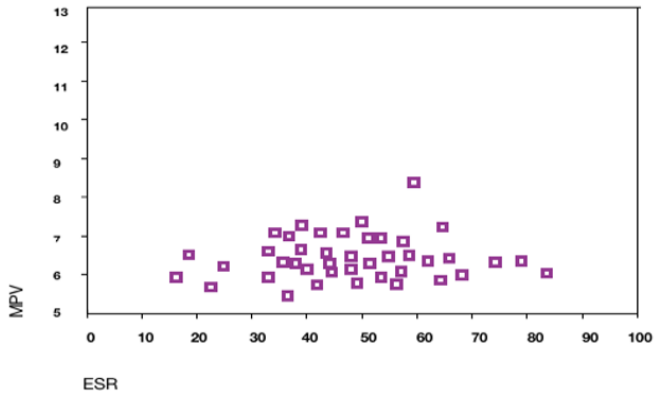


Figure 1. MPV and ESR correlation in the periprosthetic joint infection group

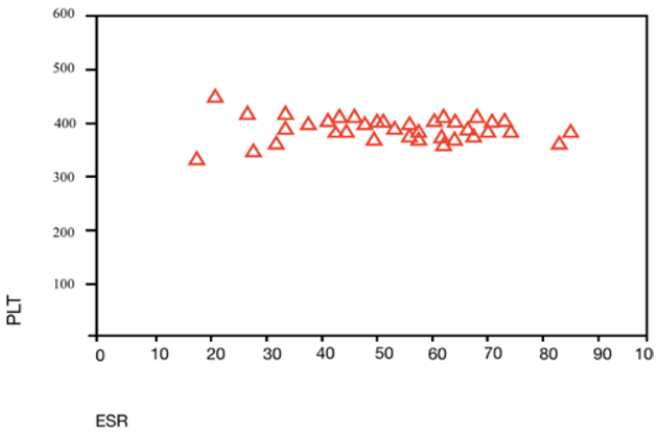


Figure 3. PLT and CRP correlation in the periprosthetic joint infection group

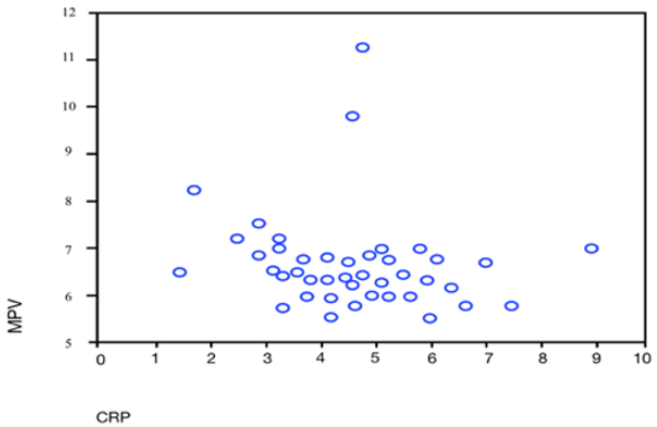


Figure 2. MPV and CRP correlation in the periprosthetic joint infection group

Platelet Cut-off Value in the PJI Group

Platelet count of the PJI group was significantly higher compared to the control group and TKA group. Based on this significance, ROC analysis and diagnostic screening tests were used to determine that cut-off value for platelet count was 7.2 and below in the PJI group (**Table 4**).

Correlation Evaluation

MPV and platelet count were strongly correlated with both ESR and CRP in the PJI group. According to Pearson's correlation test, MPV negatively correlated with ESR and CRP (**Figure 1**, **Figure 2**) and positively correlated with platelet count (**Figure 3**, **Figure 4**).

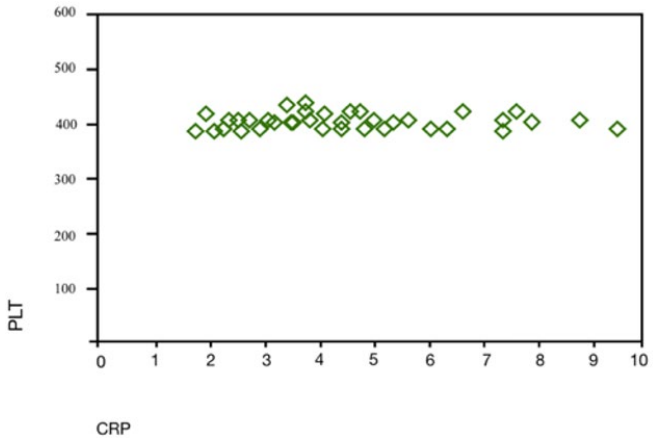


Figure 4. PLT and CRP correlation in the periprosthetic joint infection group

DISCUSSION

Different society groups have previously attempted to standardize the definition of periprosthetic joint infection [9,10]. Although definite evidence or major criteria for infection are similar between the various definitions, the supportive evidence or minor criteria differ and are less agreed upon [11-13]. In recent years, novel laboratory tests are used to diagnose periprosthetic infections. Some of these include serum D-dimer, synovial leukocyte esterase (LE), synovial alpha defensin, and synovial CRP [14,15]. Publications have shown different weights (sensitivity and specificity) for the various tests used and highlight the value of a high pretest probability in the overall diagnosis [16]. The most recent studies have demonstrated that MPV and platelet count have started to be used as independent markers in diagnosis of infection [17,18]. In our study, we found that MPV and platelet count also fluctuate like other known laboratory values, in PJI patients. We found that MPV was lower than normal and platelet count was higher than normal in PJI patients.

Robbins et al. reported that excessive production of proinflammatory cytokines and acute phase reactants affected megakaryopoiesis and suppressed platelet sizes, resulting in smaller platelets released from the bone marrow, as well as inducing thrombopoesis, resulting in thrombocytosis and decreased MPV levels in infections and acute inflammatory events [17].

Zareifar et al. observed decreased MPV and increased platelet count in the active period of patients diagnosed with infection or inflammation and also reported correlation with ESR and CRP [18].

In our study, it was observed that the patients in the PJI group had significantly lower MPV and significantly higher platelet count during their diagnosis period. MPV was also correlated with platelet count, CRP, and ESR.

Kapsoritakis et al. reported that MPV acted similar to negative acute phase reactants in inflammatory diseases, and that it was correlated with CRP and ESR. They concluded that MPV may be used as an independent marker like other indicators [19].

In our study, we also found that MPV and platelet count were in normal ranges in the control group and TKA group, and that correlations with ESR and CRP were statistically significant. Therefore, we identified that MPV and platelet count may be used in laboratory evaluation for diagnosing infection.

Van der Lelie et al. indicated that MPV and platelet count were high in patients with septicemia [20]. However, the blood samples of patients in that study were collected on the first day of septicemia. On the other hand, the literature indicates that decrease in MPV and increase in platelet count occurs after the tenth day [17]. In our study, it was unknown exactly when the periprostatic knee infections of the patients had started. Therefore, the patients of the PJI group with normal or elevated MPV values may have been due to blood samples collected during this time period.

Rodriguez et al. conducted a meta-analysis and reported the prevalence of various microorganisms encountered in patients with periprosthetic joint infection. The most frequently isolated microorganism was coagulase-negative Staphylococcus aureus [21]. In our study, we determined that the types of bacteria observed in the cultures of the patients and their prevalence rates were consistent with the literature.

Limitations

Limitations of our study were that the number of patients were low, the control group consisted of young subjects, and the possibility of low-virulence disease that cannot be detected during examinations or other pathologies which are not yet in the literature but are likely to affect MPV. In addition, follow-up blood samples of patients with knee prosthesis who did not have PJI were collected in the sixth month, which may have caused inflammatory mediators produced in the postoperative period to have affected MPV. Studies have shown that it may take up to three months after operation for inflammatory mediators to return to normal levels [6,7].

CONCLUSION

The results of our study indicate that MPV may be a useful laboratory parameter in the diagnosis of periprosthetic knee infection following knee prosthesis surgery. The likelihood of infection is especially high in patients with MPV of 7.2 or less. However, we must not forget that medicine is a branch of science based on evidence. The more data to support diagnosis, the greater the belief in treatment. Further prospective studies will shed more light on this subject.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective study was approved and consented to participate by the Ethics Committee of Fatih Sultan Mehmet Training and Research Hospital.

DECLARATION OF CONFLICT OF INTEREST

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ORTADOĞU TIP DERGİSİ / YAZIM KURALLARI

YAZARLARIN DİKKATİNE

Tıp dergilerine gönderilecek makalelerin standart gereksinmeleri ile ilgili tüm bilgileri www.icmje.org İnternet adresinde bulabilirsiniz.

Amaç ve kapsam: "Ortadoğu Tıp Dergisi", hakemli, açık erişimli, Mart, Haziran, Eylül, Aralık aylarında periyodik olarak yayımlanan, Meditagem Ltd. Şti.'ye ait bir dergidir. Hedefimiz uluslararası bir tabanda hastalıkların teşhis ve tedavisinde yenilikler içeren yüksek kalitede bilimsel makaleler yayınlamaktır. Hakemli bir dergi olarak gelen yazılar konsültanlar tarafından, öncelikle, biyomedikal makalelere ait Uluslararası Tıp Dergileri Editörleri Komitesi (www.icmje.org) tarafından tanımlanan standart gereksinimler ile ilgili ortak kurallara uygunluğu açısından değerlendirilir. Tıbbın her dalı ile ilgili retrospektif/prospektif klinik ve laboratuar çalışmalar, ilginç olgu sunumları, derlemeler, editöre mektuplar, orijinal görüntüler, kısa raporlar ve cerrahi teknik yazıları yayımlayan bilimsel, uluslararası hakemli bir dergidir. Başka bir dergide yayımlanmış veya değerlendirilmek üzere gönderilmiş yazılar veya dergi kurallarına göre hazırlanmamış yazılar değerlendirme için kabul edilmez.

Online makale gönderimi: Tüm yazışmalar ve makale gönderimleri https://www.editorialpark.com/otd adresi üzerindeki makale gönderim sistemi üzerinden yapılmalıdır.

Açık erişim politikası: Ortadoğu Tıp Dergisi açık erişimi olan bir dergidir. Yazıların tam metnine herkes ulaşabilir. Kaynak gösterilerek tüm makaleler bilimsel çalışmalarda kullanılabilir.

Aşağıdaki rehber dergiye gönderilen makalelerde aranan standartları göstermektedir. Bu uluslararası format, makale değerlendirme ve basım aşamalarının hızla yapılmasını sağlayacaktır.

Bilimsel sorumluluk: Makalelerin her türlü sorumluluğu (etik, bilimsel, yasal, vb.) yazar(lar)a aittir. Editör, yardımcı editör ve yayıncı dergide yayımlanan yazılar için herhangi bir sorumluluk kabul etmez.

Makale dili: Makale dili Türkçe veya İngilizce olmalıdır. İngilizce makaleler gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanı tarafından düzeltilebilir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu amaçla, Türk Dil Kurumu Sözlük ve Yazım Kılavuzu yazım dilinde esas alınmalıdır.

Makalenin başka bir yerde yayımlanmamış olması: Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. 400 kelimeden az özetler kapsam dışıdır. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

Değerlendirme: Dergiye gönderilen makaleler format ve intihal (plagiarism) açısından kontrol edilir. Formata uygun olmayan veya intihal benzerlik oranı yüksek makaleler değerlendirilmeden sorumlu yazara geri gönderilir. Tüm makaleler çift-kör değerlendirme yöntemi kullanılarak en az iki yerli veya yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayına kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir. Makalenin dergiye gönderilmesi veya basıma kabul edilmesi sonrası isim sırası değiştirilemez, yazar ismi eklenip çıkartılamaz.

Basıma kabul edilmesi: Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak basım sırasına alınır. Dergide yayımlanan her makaleye bir DOI numarası atanır.

Yayın hakları devri: https://www.editorialpark.com/otd adresi üzerinden online olarak gönderilmelidir. 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

Makale genel yazım kuralları: Yazılar Microsoft Word programı ile çift satır aralıklı ve 12 punto olarak, her sayfanın iki yanında ve alt ve üst kısmında 2,5 cm boşluk bırakılarak yazılmalıdır. Yazı stili Times New roman olmalıdır. "System International" (SI) birimler kullanılmalıdır. Şekil tablo ve grafikler metin içinde refere edilmelidir. Kısaltmalar, kelimenin ilk geçtiği yerde parantez içinde verilmelidir. Yüzde işareti bitişik yazılmalıdır (Örnek: Türkçe makalelerde %50, İngilizce makalelerde 50% şeklinde). Ondalık sayı ayıracı Türkçe metinlerde virgül (','), İngilizce metinlerde nokta ('.') şeklinde kullanılmalıdır (Örnek: Türkçe: 55,78 İngilizce: 55.78). Derleme 4000, orijinal çalışma 2500, olgu sunumu 1200, editöre mektup 500 kelimeyi geçmemelidir. Özet sayfasından sonraki sayfalar numaralandırılmalıdır.

Yazının bölümleri

1. Sunum sayfası: Yazının Ortadoğu Tıp Dergisi'nde yayınlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığı ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığı, maddi destek ve çıkar ilişkisi durumu belirtmelidir.

2. Başlık sayfası: Sayfa başında gönderilen makale türü (Orijinal çalışma, olgu sunumu, klinik analiz, derleme, editöre mektup, vs.) belirtilmedir. Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1' den itibaren numaralandırılıp, unvanları, çalıştıkları kurum, klinik, şehir ve ülke bilgileri yazar isimleri altına eklenmelidir. Hangi yazarın "sorumlu yazar" olduğu belirtilmelidir. Tüm yazarların e-posta adresleri ve ORCID numaraları eklenmelidir. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir. **2019'DAN İTİBAREN YAZARLARIN ORCID NUMARALARINI BİLDİRMELERİ ZORUNLUDUR.**

3. Makale dosyası:

Çift-kör değerlendirmeye uygunluk: Makale içerisinde yazar ve kurum bilgileri bulunmamalıdır. Yazarların kimliğini veya kurumunu ele verecek bilgiler metin içerisinde bulunmamalı veya uygun bir şekilde gizlenmelidir. Kaynakça kısmında yazar(lar)a ait makaleler sadece yıl bilgisi kalacak şekilde değiştirilmelidir (Örnek: "Yazar 2018.").

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Başlığın hem Türkçe hem de İngilizce versiyonları yazılmalıdır. Çift numaralı sayfaların tepesinde yazılmak üzere kısa başlık (running title) yazılmalıdır.

Özet: Türkçe ve İngilizce yazılmalıdır. Orijinal çalışmalarda özetler, Amaç (Aim), Gereç ve Yöntemler (Material and Methods), Bulgular (Results) ve Sonuçlar (Conclusion) bölümlerine ayrılmalı ve 250 sözcüğü geçmemelidir. Olgu sunumları ve benzerlerinde özetler, kısa ve tek paragraflık olmalıdır (150 kelime), Derlemelerde 300 kelimeyi geçmemelidir.

Anahtar kelimeler: Türkçe ve İngilizce özetlerin sonlarında bulunmalıdır. En az 3, en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden virgül ile ayrılmalıdır ve tamamı küçük harflerle yazılmalıdır. İngilizce anahtar kelimeler "Medical Subject Headings (MESH)" e uygun olarak verilmelidir. (www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler "Türkiye Bilim Terimleri' ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda birebir Türkçe tercümesi verilmelidir.

Metin bölümleri: Orijinal makaleler; Giriş (Introduction), Gereç ve Yöntemler (Material and Methods), Bulgular (Results), Tartışma (Discussion), Sonuç (Conclusion) başlıkları altında düzenlenmelidir. Olgu sunumları; Giriş (Introduction), Olgu (Case), Tartışma (Discussion), Sonuç (Conclusion) başlıkları altında düzenlenmelidir. Şekil, fotoğraf, tablo ve grafiklerin metin içinde geçtiği yerler ilgili cümlenin sonunda belirtilmeli, metin içine yerleştirilmemelidir. Kullanılan kısaltmalar altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak şekil, resim, tablo ve grafik açıklamasında belirtilmelidir. Tablolar, şekiller ve grafikler metin sonuna eklenmelidir. Resim/fotoğraf kalitesi en az 300dpi olmalıdır.

Etik kurallar: Klinik araştırmaların protokolü etik komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda, "Gereç ve Yöntemler" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklarasyonuna (www.wma.net/e/policy/b3.htm) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm insanların bilgilendirilmiş onam formunu imzaladığı metin içinde belirtilmelidir. Ortadoğu Tıp Dergisi gönderilen yazıların Helsinki Deklarasyonuna uygun olarak yapıldığını, kurumsal etik ve yasal izinlerin alındığını varsayacak ve bu konuda sorumluluk kabul etmeyecektir. Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntemler bölümünde Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.

Dergiye gönderilen makalelerin Araştırma ve Yayın Etiğine uygunluğuna dikkat edilmeli, ICMJE (International Committee of Medical Journal Editors) tavsiyeleri ile COPE (Committee on Publication Ethics)'un Editör ve Yazarlar için Uluslararası Standartları dikkate alınmalıdır.

Teşekkür yazısı: Varsa kaynaklardan sonra yazılmalıdır.

Maddi destek ve çıkar ilişkisi: Makale sonunda varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve varsa bu kuruluşların yazarlarla olan çıkar ilişkileri belirtilmelidir. (Olmaması durumu da "Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur" şeklinde yazılmalıdır.

Yayın, direkt ya da indirekt ticari bağlantı içeriyorsa veya çalışmaya materyal desteği veren bir kuruluş varsa, yazarlar kullanılan ticari ürün, ilaç, firma vs. ile ticari hiçbir ilişkisinin olmadığını ya da var ise nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar), editöre sunum sayfasında belirtmek zorundadır.

Kaynaklar: Kaynaklar makalede geliş sırasına göre yazılmalıdır. Kaynaktaki yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 3 isim yazılıp Türkçe makalelerde "ve ark.", İngilizce makalelerde "et al." eklenmelidir. Kaynak yazımı için kullanılan format Index Medicus'ta belirtilen şekilde olmalıdır (www.icmje.org). Kaynak listesinde yalnızca yayınlanmış ya da yayınlanması kabul edilmiş veya DOI numarası almış çalışmalar yer almalıdır. Dergi kısaltmaları "Cumulated Index Medicus" ta kullanılan stile uymalıdır. Kaynak sayısının araştırmalarda 25 ve derlemelerde 60, olgu sunumlarında 10, editöre mektupta 5 ile sınırlandırılmasına özen gösterilmelidir. Kaynaklar metinde cümle sonunda nokta işaretinden hemen önce köşeli parantez kullanılarak belirtilmelidir. Örneğin [4,5]. Kaynakların doğruluğundan yazar(lar) sorumludur. Yerli ve yabancı kaynakların sentezine önem verilmelidir.

4. Şekil ve tablo başlıkları: Şekil başlığı şeklin altına, tablo başlığı tablonun üstüne yazılmalıdır. Şekil, grafik ve tablolar Kaynakça bölümünün arkasına eklenmeli veya her biri ayrı bir dosya olarak gönderim sistemi üzerinden gönderilmelidir.

Makalenin basıma kabulünden sonra "Dizginin ilk düzeltme nüshası" sorumlu yazara ve bilgi için diğer yazarlara e-posta yoluyla gönderilecektir. Düzeltme nüshasında sadece yazım hataları düzeltilecek, ekleme çıkartma yapılmayacaktır. Sorumlu yazar düzeltmeleri 2 gün içinde e-posta ile yayın idare merkezine bildirecektir.

Kaynak Yazım Örnekleri

Dergilerden yapılan alıntı:

Özpolat B, Gürpınar ÖA, Ayva EŞ, Gazyağcı S, Niyaz M. The effect of Basic Fibroblast Growth Factor and adipose tissue derived mesenchymal stem cells on wound healing, epithelization and angiogenesis in a tracheal resection and end to end anastomosis rat model. Turk Gogus Kalp Dama 2013; 21: 1010-19.

Kitaptan yapılan alıntı:

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Tek yazar ve editörü olan kitaptan alıntı:

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Çoklu yazar ve editörü olan kitaptan alıntı:

Schulz JE, Parran T Jr: Principles of identification and intervention. In:Principles of Addicton Medicine, Graham AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998:1-10.

Eğer editör aynı zamanda kitap içinde bölüm yazarı ise:

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag;1988:45-67.

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Kılıç C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Bir internet sitesinden alıntı:

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Diğer referans stilleri için "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References" sayfasını ziyaret ediniz.

Bilimsel sorumluluk beyanı: Kabul edilen bir makalenin yayınlanmasından önce her yazar, araştırmaya, içeriğinin sorumluluğunu paylaşmaya yetecek boyutta katıldığını beyan etmelidir. Bu katılım şu konularda olabilir: 1. Deneylerin konsept ve dizaynlarının oluşturulması, veya verilerin toplanması, 2. analizi ya da ifade edilmesi; 3. Makalenin taslağının hazırlanması veya bilimsel içeriğinin gözden geçirilmesi; 4. Makalenin basılmaya hazır son halinin onaylanması.

Yazının bir başka yere yayın için gönderilmediğinin beyanı: "Bu çalışmanın içindeki materyalin tamamı ya da bir kısmının daha önce herhangi bir yerde yayınlanmadığını, ve halihazırda da yayın için başka bir yerde değerlendirilmede olmadığını beyan ederim. Bu, 400 kelimeye kadar olan özetler hariç, sempozyumlar, bilgi aktarımları, kitaplar, davet üzerine yazılan makaleler, elektronik formatta gönderimler ve her türden ön bildirileri içerir."

Sponsorluk beyanı: Yazarlar aşağıda belirtilen alanlarda, varsa çalışmaya sponsorluk edenlerin rollerini beyan etmelidirler:

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3. Makalenin ana dosyası (Makale başlığı ve kısa başlık (Türkçe ve İngilizce), Özet ve anahtar kelimeler (Türkçe ve İngilizce), makale metni, kaynaklar, tablolar, şekiller. Çift-kör değerlendirmeye uygun olması için yazarları ve kurumlarını ele verecek bütün metinler gözden geçirilmiş olmalıdır.)

4. Şekil ve tablolar (Makale metninin sonuna eklenmeli veya makale gönderim sistemi üzerinden ayrı birer dosya olarak gönderilmelidir. Şekiller en az 300 dpi çözünürlükte olmalıdır.)

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