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25-Hydroxyvitamin D Levels in Preterm Infants ≤32 Weeks Gestational Age and Risk of Late Onset Neonatal Sepsis

Gebelik Yaşı ≤32 Hafta Olan Prematüre Bebeklerde 25-Hidroksivitamin D Düzeyleri ve Geç Başlangıçlı Sepsis Riski

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Abstract

The aim of this study was to evaluate neonatal vitamin D status and effect of vitamin D levels on the development of late-onset sepsis (LOS) in preterm infants with a gestational age of ≤32 weeks. Newborns having a gestational age of ≤32 weeks with culture proven LOS consisted the study group, whereas the control group consisted of gestational age matched newborns hospitalized in the neonatal critical care unit with no evidence of clinical or laboratory infection. 58 (47.5%) had culture proven LOS (study group), while 64 (52.5%) had no signs or symptoms of sepsis (control group). Median 25-hydroxyvitamin D (25-OHD) levels of study group was significantly lower than the median 25-OHD levels of the control group (10.2 ng/ml vs 18.3 ng/ml; p=0.0001). Statistically significant higher rates of low vitamin D levels (25-OHD level <15 ng/ml) were observed in the study group compared to control group (50/58, 86% vs 23/64, 36%; p=0.0001). Preterm infants with low 25-OHD levels were 15.2 (95% confidence interval (CI):5.14-45.10; p=0.0001) times more likely to experience LOS compared with the preterm infants with normal 25-OHD levels. Up to now, there is no established optimal 25-OHD level for adequate immune function for preventing neonatal sepsis in both term and preterm infants, but in this study preterm infants with LOS were found to have significantly lower 25-OHD levels compared to preterm infants at the same gestational age without LOS and low 25-OHD levels seem to increase risk of neonatal LOS.
Keywords: 25-hydroxyvitamin D, preterm infant, season, late-onset sepsis

Özet

Bu çalışmanın amacı, gebelik yaşı ≤32 hafta olan prematüre bebeklerde D vitamini düzeyinin geç başlangıçlı sepsis gelişimine etkisini değerlendirmektir. Çalışma grubunu gestasyon yaşı ≤32 hafta olan ve kültür ile kanıtlanmış geç başlangıçlı sepsis saptanan yenidoğanlar oluştururken, yenidoğan yoğun bakım ünitesinde yatan, ≤32 gebelik haftası olan ve klinik veya laboratuvar enfeksiyon bulgusu olmayan yenidoğanlar kontrol grubunu oluşturmaktadır. 58'inde (%47,5) kültürle kanıtlanmış geç başlangıçlı sepsis (çalışma grubu) varken, 64'ünde (%52,5) sepsis belirti veya semptomu yoktu (kontrol grubu). Çalışma grubunun ortanca 25-hidroksivitamin D (25-OHD) seviyeleri, kontrol grubunun ortanca 25-OHD seviyelerinden anlamlı derecede düşüktü (10,2 ng/ml'ye karşın 18,3 ng/ml; p=0,0001). D vitamini düzeyi düşük bebeklerin oranı çalışma grubunda kontrol grubuna kıyasla istatistiksel anlamlı olarak daha yüksek (25-OHD düzeyi <15 ng/ml) bulundu (50/58, %86'ya karşın 23/64, %36; p=0,0001). 25-OHD düzeyi düşük olan prematüre bebeklerin, normal 25-OHD düzeyine sahip prematüre bebeklere kıyasla geç başlangıçlı sepsis yaşama olasılığı15.2 (%95 güven aralığı (GA):5,14-45,10; p=0,0001) kat daha fazlaydı. Prematüre ve term yenidoğanlarda neonatal sepsisin önlenmesi için yeterli bağışıklık fonksiyonu için belirlenmiş bir optimal 25-OHD seviyesi yoktur ancak bu çalışmada geç başlangıçlı sepsisi olan prematüre bebeklerin, erken başlangıçlı sepsisi olmayan prematüre bebeklere kıyasla önemli ölçüde daha düşük 25-OHD düzeylerine sahip olduğu ve düşük 25-OHD seviyelerinin yenidoğanın geç başlangıçlı sepsis riskini arttırdığı bulunmuştur.
Anahtar Kelimeler: 25-hidroksivitamin D, preterm bebek, mevsim, geç başlangıçlı sepsis

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1. Introduction

Neonatal sepsis is a clinical syndrome characterized by systemic signs and symptoms of an infection with a specific agent grown in blood culture in the first month of life. It is also a major cause of morbidity and mortality in preterm infants. The incidence of neonatal sepsis ranges from one to eight neonates per 1000 live births (1). According to the onset of clinical findings of sepsis, neonatal sepsis could be classified as early-onset (EOS), late-onset (LOS), or very late-onset sepsis (2).

Vitamin D has a key role in immune function. Recent research has suggested that vitamin D plays a role in promoting the normal function of the innate and adaptive immune systems (3). Vitamin D is a lipid-soluble steroid hormone best known for its role in calcium homeostasis and bone health in both children and adults (4). However, it has been the subject with great interest because of its "non-classical" actions in tissues unrelated to calcium homeostasis, particularly in the regulation of both innate and adaptive immune system (5). In addition, vitamin D supplementation has been shown to reduce infections in children and to aid in the prevention of autoimmune disorders (6).

The association of vitamin D deficiency and sepsis has been reported in neonates; however, there is limited data on the association of LOS and vitamin D deficiency in preterm infants (5,7).The aim of this study was to evaluate neonatal vitamin D status and effect of vitamin D levels on the development of LOS in preterm infants with a gestational age of ≤32 weeks. The association between LOS and severity of vitamin D deficiency was secondary outcome of this study.

2. Materials and Methods

This single center retrospective cohort study was conducted between April 2019 and April 2021 at Dörtcelik Children's Hospital. The research has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee. Parental informed consent was obtained from each patient included in the study.

Our center does not have an obstetrics and gyneacology clinic and no births can be given. The patients included in the study consisted of preterm infants born in externally and referred to our hospital. Newborns having a gestational of ≤32 weeks were included in the study. Gestational age was determined primarily through ultrasonographic evaluation in the first trimester, as well as through calculations based on the last menstrual period in pregnancies followed up on, or through clinical evaluation after delivery. Patients with congenital anomalies or malformations, metabolic disease, or who did not have family consent were barred from participating in the study. The study group consisted of newborns with a gestational age of ≤32weeks and culture proven LOS, while the control group consisted of newborns hospitalized in the NICU with a gestational age of ≤32 weeks and no signs of clinical or laboratory infection. Late-onset sepsis was defined as neonatal sepsis diagnosed between postnatal days 4 and 30 (8). Newborns with a gestational of ≤32 weeks and having a history of chorioamnionitis, premature rupture of membranes (PROM) or prolonged premature rupture of membranes (PROM ≥18 hours), maternal urinary tract infection, unknown group B streptococcus status, peripartum maternal fever, fetal tachycardia and EOS were excluded from the study. Also, preterm infants having a history of maternal anticonvulsant (phenitoin, phenobarbital), antifungal (ketoconazole), antituberculosis (rifampicin, isoniazid), anti-retroviral drug or glucocorticoid use and diseases that can affect maternal vitamin D status such as malabsorption, pancreatic insufficiency, nephrotic syndrome, cirrhosis, liver failure, hypoparathyroidism, renal failure were exluded from the study.

Blood samples for calcium (Ca), phosphorus (P), magnesium (Mg), alkaline phosphatase (ALP), parathyroid hormone (PTH), and 25-hydroxy-vitamin D (25-OHD) were obtained from all participants at postnatal six hours of life in the neonatal intensive care unit (NICU).

As no births can be given in our clinic and all the patients hospitalized in the first day of life were born in externally and referred to our hospital. So it was not possible to use cord blood for the measurement of laboratory parameters. Serum 25-OHD and PTH levels were measured by chemiluminescent immunoassay analyzer (Abbott i2000, Abbott Laboratories, USA). Ca, P, Mg and ALP levels were measured using the photometry method on the Beckman Coulter AU 680 analyzer (Danaher Corporation, Brea, CA, USA). Render BC64 device(Render Biotech Co. Ltd. Shenzen, China) was used for analyzing blood cultures.

Maternal demographic data were obtained from medical records. The maternal age at the time of delivery, presence of multiple pregnancies and concomitant maternal diseases and medications used were recorded. The characteristics of newborns, including gestational age, birth weight, sex, mode of delivery, Apgar scores, antenatal steroid use, duration of invasive and non-invasive mechanical ventilation (MV) and total parenteral nutrition (TPN), body weight at discharge, and length of hospitalization were recorded. Also, microorganisms that grew in the blood culture were recorded in the study group. Birth season was classified as summer (June, July, August), fall (September, October, November), winter (December, January, February) and spring (March, April, May). The primary focus of this study was the relationship between neonatal 25-OHD levels and development of LOS. Also, maternal 25-OHD levels and use of vitamin D supplementation could not recorded as all preterm infants included in the study were born in externally and referrred to our hospital as mentioned above.

According to neonatal 25-OHD levels, preterm infants were classified into three groups: Severe vitamin D deficiency (25-OHD levels ≤5 ng/ml), Vitamin D insufficiency (25-OHD levels 5-15 ng/ml) and normal vitamin D (25-OHD levels>15 ng/ml). 25-OHD level ≤15 ng/ml was defined as low vitamin D level (7,9).

Statistical Analysis

Statistical Package for Social Sciences (SPSS) 20.0 for Windows was used to evaluate the data. Qualitative variables were expressed as percentages. Continuous variables with normal distribution were expressed as mean (SD) and compared using t-test. Numerical variables that were not distributed normally were expressed as the median (Interquartile range, IQR). Kruskal Wallis tests were used for the evaluation of continuous variables, while Chi-square test was used for categorical data. Multivariable logistic regression analysis was performed to investigate the association between 25-OHD levels and LOS. A value of $p < 0.05$ was accepted as statistically significant.

3. Results

During the study period, 122 preterm infants having a gestational age of ≤ 32 weeks were included. From these, 58 (47.5%) had culture proven LOS (study group), while 64 (52.5%) had no signs or symptoms of sepsis (control group). There was no significant difference between the groups in terms of gestational age, birth weight, small for gestational age (SGA) infants, sex, mode of delivery, multiple pregnancy, maternal age, antenatal steroid use, accompanying maternal diseases. In contrast to that, first minute and fifth minute Apgar scores were significantly higher in the study group compared to control group. Also there was a significant difference in terms of birth season between the groups. Duration of invasive MV, non-invasive MV and TPN were statistically significant higher in the study group compared to control group. Also, study group was found to have a significantly longer length of hospital stay compared to control group (Table 1).

Table 1. The maternal and neonatal characteristics of the study and control groups

Variables	Study Group n=58	Control Group n=64	p
GA, week *	31 (30, 32)	31 (30, 32)	0.74
Birth weight, gr *	1375 (1115, 1684)	1570 (1200, 1710)	0.08
SGA, n (%)	18 (31)	14 (21)	0.30
Multiple pregnancy, n (%)	14 (24)	14 (20)	0.83
Male sex, n (%)	28 (48)	32 (64)	0.49
Use of antenatal steroid, n (%)	20 (31)	28 (44)	0.19
Delivery with CS, n (%)	50 (86)	58 (90)	0.31
Maternal age, year*	30 (24, 33)	27.5 (23, 35)	0.38
1st min Apgar*	8 (5, 10)	7 (4, 9)	**0.0001**
5th min Apgar *	9 (7, 10)	8 (6, 10)	**0.0001**
Birth season, n (%)			**0.02**
Summer	13 (22)	3(5)	
Fall	15 (26)	16 (25)	
Winter	11 (19)	21 (32)	
Spring	19 (33)	24 (38)	
Duration of TPN, day*	30 (22, 47.5)	15 (10, 27)	**0.0001**
Duration of invasive MV, day *	1 (0, 8)	0 (0, 2)	**0.0001**
Duration of non-invasive MV, day *	3.5 (0, 10.2)	1 (0, 3.8)	**0.0001**
Length of hospital stay, day *	49 (36.5, 67)	31 (20, 41)	**0.0001**
Body weight at discharge, gr *	2415 (2170, 2818)	2250 (2050, 2490)	**0.009**
Maternal disease, n (%)	32 (55)	35 (55)	0.52
Gestational Diabetes	3 (5)	8 (12)	
Preeclampsia	13 (22)	17 (27)	

CS: *Cesarean section,* ***GA:*** *Gestational age,* ***IQR:*** *Interquartile range,* ***MV:*** *Mechanical ventilation,* ***TPN:*** *Total parenteral nutrition,* ***SGA:*** *Small for gestational age*
*** Median (Q1,Q3)***

When the groups were compared for laboratory parameters; the groups did not differ in terms of serum Ca, P, Mg, ALP, PTH levels. In contrast to that, median 25-OHD levels of study group was significantly lower than the median 25-OHD levels of the control group (10.2 ng/ml vs 18.3 ng/ml; p=0.0001). Statistically significant higher rates of low vitamin D levels (25-OHD level<15 ng/ml) were observed in the study group compared to control group (50/58, 86% vs 23/64, 36%; p=0.0001). In the study group, 7 (12%) preterm infants had severe vitamin D deficiency, 43 (%74) had vitamin D insufficiency and 8 (14%) had normal vitamin D levels. In the control group, none of the preterm infants had severe vitamin D deficiency, but 23 (36%) had vitamin D insufficiency and 41 (64%)had normal vitamin D levels (Table 2).

Table 2. Comparison of laboratory findings of the study and control groups

Variables	Study Group n=58	Control group n=64	p
Ca (mg/dl), mean ± SD	8.33 ± 0.81	8.52 ± 0.90	0.23
P (mg/dl)*	5.5 (4.6, 6.3)	5.6 (5, 6.1)	0.51
Mg (mg/dl)*	2.0 (1.8, 2.6)	2.0 (1.8, 2.7)	0.80
ALP (U/L)*	192 (139, 245)	191 (155, 227)	0.78
PTH (pg/ml)*	53 (32, 157)	40 (26, 112)	0.11
25-OHD (ng/ml)*	10.2 (7.2, 13.2)	18.3 (11.5, 20.5)	**0.0001**
25-OHD levels, n (%)			**0.0001**
Low (<15 ng/ml)	50 (86)	23 (36)	
Normal (≥15 ng/ml)	8 (14)	41 (64)	
25-OHD levels, n (%)			**0.0001**
Severe deficiency (≤5 ng/ml)	7 (12)	0 (0)	
Insufficiency(5-15 ng/ml)	43 (74)	23 (36)	
Normal (≥15 ng/ml)	8 (14)	41 (64)	

ALP: *Alkaline phosphatase,* ***Ca:****Calcium,* ***Mg:****Magnesium,* ***P:****Phosphorus,* ***PTH:****Parathyroidhormone,*
25-OHD: *25-hydroxyvitamin D* ****Median (Q1,Q3)***

When the groups' 25-OHD levels were compared according to season, the study group's neonatal 25-OHD levels were significantly lower in all seasons compared to the control group, and this was statistically significant. Furthermore, neonatal 25-OHD levels in the control group were higher in all seasons, with the highest levels found in the summer. In contrast to that, 25-OHD levels of the study group were similar in all seasons (Table 3).

Table 3. Comparison of neonatal 25-hydroxyvitamin D levels in terms of season and group at birth

Season	25-hydroxyvitamin D level (ng/ml)		p
	Study Group Median (min-max)	Control Group Median (min-max)	
Spring	9.9 (4.2-18.3)	18.8 (6.2-47.3)	**0.0001**
Summer	9.3 (4.2-38)	21.1 (17-26)	**0.04**
Fall	10.4 (4.7-17.6)	18.3 (6.5-20.5)	**0.03**
Winter	11.7 (5.7-18.2)	16.2 (7.1-32.3)	**0.02**

The most common microorganism detected in blood culture was coagulase negative *Staphylococcus epidermidis* (n=28, 48%), followed by *Staphylococcus haemolyticus* (n=14, 24%), *Staphylococcus aureus* (n=6, 10%), *Klebsiella pneumonia* (n=4, 7%), *Escherichia coli* (n=4, 7%) and *Pseudomonas aeruginosa* (n=2, 4%). *Staphylococcus epidermidis* was considered as a pathogen as if it was isolated in two separate sets of blood cultures from two different sites.

Multivariable logistic regression analyses revealed that LOS development was more common in the infants with low vitamin D levels, after adjusting the effects of length of hospital stay, duration of invasive MV and TPN. When compared to preterm infants with normal 25-OHD levels, preterm infants with low 25-OHD levels were 15.2 (95% confidence interval [CI]: 5.14-45.1; p=0.0001) times more likely to experience LOS. In addition, after controlling for length of hospital stay, duration of invasive MV, and TPN, the newborn's 25-OHD level was found to be a significant predictor of LOS. Every 1-ng/mL increase in the newborn's 25-OHD level decreased the likelihood of LOS [odds ratio (OR): 0.46, 95% CI: 0.458–0.502, p=0.0001].

4. Discussion and Conclusion

Despite advances in neonatal care, neonatal sepsis remains a significant cause of morbidity and mortality. Neonatal sepsis and other severe infections accounted for nearly 15% of all neonatal deaths worldwide (10). With decreasing birth weight and gestational age, the risk of both EOS and LOS increases (11). Fetal distress, low Apgar scores and need for resuscitation, multiple pregnancy, EOS, frequent blood sampling, entubation, MV, invasive procedures such as catheterization and long-term TPN use especially are known to increase risk for LOS (12).

In this study, preterm infants with a gestational age of ≤32 weeks who had LOS had significantly lower 25-OHD levels than preterm infants with the same gestational age who did not have LOS. Increasing 25-OHD levels also reduces the likelihood of LOS in preterm infants with a gestational age of ≤32 weeks.

Vitamin D has a key role in calcium homeostasis, (4) but in the last years, the immune modulating effects of vitamin D on the innate and adaptive immune system have been great interest for researchers. The active form of vitamin D is 1,25-dihydroxyvitamin D and produced first by hepatic 25-hydroxylation with the cytochrome P450 2R1 and other enzymes, followed by peripheral tissue 1α-hydroxilation with CYP27B1 enzyme (4). Recent research indicates that vitamin D signaling plays an important role in immune system regulation (13). Vitamin D receptors and enzymes involved in vitamin D synthesis are abundant in immune system

cells, and pathogen detection stimulates the production of CYP27B1 via a cytokine network (14). Detection of pathogen-associated antigens and activation of pattern recognition receptors causes antimicrobial peptide production and responses including cytokines, chemokines resulting in wide signalization throughout the immune system. Antimicrobial peptide transcription is directly stimulated by vitamin D receptors bound to vitamin D. Also, vitamin D regulates anti-inflammatory response with the arrangement of dentritic cells (15).Genome-based studies on vitamin D signaling revealed that vitamin D receptors have an important role in the regulation of many different genes associated with immune system functions (16).

Compared to past few years, survival rates of preterm infants have evidently raised with advances in perinatal and neonatal care (17). As a result, rates of very low birth weight (VLBW) and extremely low birth (ELBW) infants has increased. These resulted in an increase of prematurity related morbidities and complications. Therefore, more effort has been given for the prevention rather than the treatment of these morbidities and complications. As vitamin D has many important functions in many systems in the human body, supplementation of vitamin D is given during pregnancy all over the world. In Turkey, regardless of blood 25-OHD levels, vitamin D supplementation is given beginning from the 12th week of pregnancy to end of pregnancy and continued for six months after delivery. The dose of vitamin D is 1200 IU per day given orally (18). The positive correlation of maternal and neonatal vitamin D levels is widely reported in the literature (19-22). In view of these findings, the most important strategy for preventing vitamin D insufficiency during pregnancy is to take vitamin D on a regular basis.

In light of research findings on the wide effects ofvitamin D on many systems, studies on the effect of vitamin D levels on neonatal morbidities such as respiratory distress syndrome, neonatal sepsis, and bronchopulmonary dysplasia were conducted (9,23,24). Studies evaluating the effect of vitamin D deficiency on LOS in preterm infants are very limited (5,7). A recent study evaluating neonatal and maternal vitamin D status and risk of LOS in term newborns reported that neonatal and maternal vitamin D deficiency increases risk of LOS and neonatal vitamin D is an independent predictor for LOS (21).

The study population consisted of preterm infants with a gestational age of ≤32 weeks and levels of 25-OHD were significantly lower in preterm infants with LOS and this finding was similar to results reported by Dogan et al (5). Also, consisted with previous studies evaluating the effect of vitamin D deficiency on the development of EOS in term newborns (1,24,25). In contrast to that, another study found no relationship between cord blood 25-OHD levels and neonatal sepsis in preterm infants (7).

Although, the study and control groups were similar for gestational age and birth weight, frequency of low 25-OHD levels was significantly higher in the study group. A study including preterm infants reported higher frequency of low 25-OHD levels in preterm infants with LOS similar to our results but the study group had lower gestational age and birth weight different from the present study (5). Also, multiple pregnancies are known to increase risk of LOS (12), but the study and the control groups were similar for rate of multiple pregnancy in the present study. EOS is another risk factor for LOS in newborns (12), but in the present study this data was not included.

Parenteral nutrition, existing invasive devices such as endotracheal tubes, urinary catheters, intravascular catheters and orogastric tubes increase the risk of health care associated infections especially in preterm infants. Central venous catheters and peripherally inserted catheters are commonly used for administration of parenteral nutrition. The increased risk of infections caused by the use of central lines were widely reported in the literature. Also use of lipid emulsions is an independent risk factor for bacterial or fungal sepsis (26,27). In addition to prolonged duration of MV, prolonged parenteral nutrition also increase the risk of health care-associated pneumonia in the NICU. Longer

duration of MV causes more frequent insertion of endotracheal tubes which means "to bypass" the initial host defense mechanisms such as the upper airway filtration system and mucociliary clearance system of lower respiratory tract (28). Duration of invasive MV, non-invasive MV and TPN were longer in the study group. After adjusting for the effect of these variables, low 25-OHD levels caused 15-fold increase in the risk of LOS in preterm infants. In a study, it was reported to be 7-fold increase in the risk of LOS in preterm infants (5).

Serum Ca, P, Mg, ALP and PTH levels were similar between the study and control groups in contrast to statistically significant different 25-OHD levels. One study reported lower 25-OHD levels in term newborns with EOS compared to control group but the groups did not differ for serum Ca, P, ALP levels, as our results (29).

One study evaluating the effect of low vitamin D levels on LOS in preterm infants and another study evaluating the role of vitamin D levels on the development of EOS in term infants reported no difference for birth season (5,7). In contrast to that, Ozdemir et al. reported a difference for birth season in term newborns with EOS, similar to our results (29).

Vitamin D can be synthesized from the fetal tissues but maternal vitamin D status is the most important factor on the neonatal 25-OHD levels until neonates are supported for vitamin D from external sources (30). As mentioned above, levels of 25-OHD were significantly lower in the study group compared to control group. In addition to that neonatal 25-OHD levels in the study group were significantly lower in all seasons. Because the season in which the baby is born and the traditional clothing style of women cannot be changed, the most important component is the neonatal 25-OHD level, and the lack of a seasonal effect could be linked to preterm birth, when vitamin D accumulation is highest in the third trimester (26). Cetinkaya et.al reported no difference between the study and control groups for seasonal 25-OHD levels in term newborns. Also, term newborns had significantly higher 25-OHD levels in summer compared to those born in other seasons. These findings support the relation between vitamin D synthesis and exposure to sunlight (1). Our finding was similar with that results. To our knowledge, this is the first study comparing the seasonal 25-OHD levels of preterm infants with LOS and those without LOS.

The present study focused on the relation between neonatal 25-OHD levels and the development of LOS. This study has several limitations. Firstly, due to its retrospective nature, the maternal 25-OHD levels at the time of delivery were not evaluated. Secondly, pregnant women are given vitamin D supplementation beginning from the 12th week of gestation. In the present study, the use of vitamin D supplementation (no usage, irregular use, regular use) was not included. As exposure to sunlight is the most important factor for vitamin D synthesis and use of sun-protective clothing is a major factor this process, these were not included in the study. Another limitation was the small sample size of the study population.

Preterm infants with LOS were found to have significantly lower 25-OHD levels compared to preterm infants at the same gestational age without LOS and low 25-OHD levels seem to increase risk of neonatal LOS. Up to now, there is no established optimal 25-OHD level for adequate immune function for preventing neonatal sepsis in both term and preterm infants. Further studies with larger sample size are needed to achieve precise results. Besides, taking into account the potential negative maternal and neonatal effects of vitamin D deficiency appropriate supplementation should be administered in regions where vitamin D deficiency is frequent.

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Research Article / Araştırma Makalesi

An Evaluation of the Autofluorescence Changes with Wide-Angle Digital Fundus Camera in Chronic Central Serous Chorioretinopathy Patients

Kronik Santral Seröz Koryoretinopati Hastalarında Geniş Açılı Dijital Fundus Kamera ile Otofloresan Değişikliklerinin Değerlendirilmesi

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Abstract

To evaluate the autofluorescence variations and localisation in wide-angle digital fundus camera images of patients with chronic central serous chorioretinopathy (CSCR). A retrospective scan was made of the images of patients diagnosed with chronic CSCR with wide-angle digital fundus angiography and applied at the same time with autofluorescence imaging. The ultra wide area autofluorescence images of 46 patients were examined. The retina was separated as zone 1, zone 2, and zone 3 in respect of disease involvement, and zone 3 represented the peripheral retina. The images of the patients were recorded as hyperautofluorescence (punctate, diffuse) or hypo-autofluorescence (granular, confluent) in respect of the type of autofluorescence involvement. After the exclusion of 2 patients because peripheral images could not be clearly selected, the study evaluations were made of 44 eyes of 44 patients. The mean duration of the disease was found to be 2.7 years. In the result of the examination with wide-angle digital fundus autofluorescence imaging, there was seen to be zone 2 involvement in the 4 quadrants of inferior, nasal, temporal and superior. Peripheral retinal involvement in zone 3 was seen in a total of 7 (15.9%) patients in the form of inferior gravitational defect, in 6 (13.6%) patients together with zones 1 and 2, and in 1 (2.3%) patient together with zone 2. Hyperautofluorescence was determined in 39 (88.6%) patients and hypo-autofluorescence in 5 (11.4%). The involvement frequency was determined as zone 1+2 in 19 (43.2%) patients, followed by zone 1 involvement alone in 16 (36.4%) patients. Common autofluorescence type was detected as hyperautofluorescence in chronic CSCR patients with a high rate of approximately 90%. It has also been shown that in some patients, the disease may also affect the inferior peripheral retina due to the effect of gravity.

Keywords: central serous chorioretinopathy, wide-angle digital fundus autofluorescence, peripheral retina, hyperautofluorescence, hypo-autofluorescence

Özet

Kronik santral seröz koryoretinopatili (CSCR) hastaların geniş açılı dijital fundus kamera görüntülerinde otofloresan değişiklikleri ve lokalizasyonunu değerlendirmek. Geniş açılı dijital fundus anjiyografi ile kronik CSCR tanısı konulan hastaların görüntüleri retrospektif olarak tarandı ve aynı zamanda otofloresan görüntüleme ile uygulandı. 46 hastanın ultra geniş alan otofloresan görüntüleri incelendi. Retina hastalık tutulumuna göre zon 1, zon 2 ve zon 3 olarak ayrıldı ve zon 3 periferik retinayı temsil etti. Hastaların görüntüleri otofloresan tutulum tipine göre hiperotofloresan (punktat, yaygın) veya hipo-otofloresan (granüler, konfluent) olarak kaydedildi. Periferik görüntüler net seçilemediği için 2 hasta dışlandıktan sonra 44 hastanın 44 gözü ile çalışma değerlendirmeleri yapıldı. Ortalama hastalık süresi 2,7 yıl olarak bulundu. Geniş açılı dijital fundus otofloresan görüntüleme ile yapılan inceleme sonucunda alt, nazal, temporal ve üst olmak üzere 4 kadranda zon 2 tutulum olduğu görüldü. Zon 3'te periferik retina tutulumu inferior gravitasyonel defekt şeklinde toplam 7 (%15.9) hastada, zon 1 ve 2 ile birlikte 6 (%13.6) ve 1 (%2.3) hastada ise zon 2 ile birlikte görüldü. Hiperotofloresan 39 (%88.6) hastada ve hipo-otofloresan 5 (%11.4) hastada saptandı. Tutulum sıklığı en fazla 19 (%43.2) hastada zon 1+2, ardından 16 (%36.4) hastada tek başına zon 1 tutulum olarak belirlendi. Kronik SSR hastalarında yaygın otofloresans tipi hiperotofloresans şeklinde ve yaklaşık %90 gibi yüksek bir oranda tespit edilmiştir. Ayrıca bazı hastalarda hastalığın yerçekimi etkisi nedeniyle inferior periferik retinayı da etkileyebileceği gösterilmiştir. Anahtar
Kelimeler: santral seröz koryoretinopati, geniş açılı dijital fundus otofloresansı, periferik retina, hiperotofloresan, hipo-otofloresan

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1. Introduction

Central serous chorioretinopathy (CSCR) is a disease characterised by serous fluid accumulation below the sensory retina in the macular region, which generally resolves spontaneously within 1-6 months, and causes a moderate degree of loss of vision. It is generally seen in males and in the 20-50 years age group (1). In addition, there are also patients who present with persistence of neurosensorial retina detachment or recurrence and chronic CSCR (longer than 4 months) which leads to widespread changes in photoreceptors and the retina pigment epithelium (RPE) with subsequent vision loss (2). The pathophysiology of CSCR has not yet been fully understood and among the theories proposed are choroidal vascular hyperpermeability (3,4), RPE dysfunction(5), and the combination of these two theories(6). Risk factors have been reported to include stress and Type A personality (7), increased sympathetic system activation and the use of sympathomimetic agents (8), the use of glucocorticoids and endogenous hypercortisolism (9). The majority of patients have complaints of clouded vision, metamorphopsia, micropsia, and scotoma in the visual field (10). Optic coherence tomography (OCT), which is used in the diagnosis of CSCR, is useful in the determination of subretinal fluid accumulation, pigment epithelial detachment and retinal atrophy (11, 12).

Although CSCR can be diagnosed from typical clinical findings and the observation of retinal elevation in ophthalmoscopic examination, and subretinal fluid on OCT, or PED, it can be confirmed with the observation of a typical leakage pattern (hyperfluorescence) on fluorescein angiography. Fundus autofluorescence (FAF) is used in the evaluation of some retina diseases, including CSCR. The source of autofluorescence to a large degree is lipofuscin formed with the accumulation in lysosomes of fatty acids with phagocytosis of damaged photoreceptor outer segments and the oxidative destructive products of retinoid and proteins (13,14). This non-invasive method is used as an additional diagnostic tool in CSCR, showing changes in the distribution and density of autofluorescence in the acute and chronic phases of the disease (15). In studies made related to FAF in CSCR, just as hypo-autofluorescence may be seen in acute CSCR patients because oedema blocks the autofluorescence on FAF images of the serous retina detachment area (16,17), hyperautofluorescence may also be seen associated with accumulated photoreceptor chromophores with insufficient phagocytosis made due to the separation of the retina outer segments and RPE (18, 19). In chronic CSCR, hypo-autofluoresence representing RPE damage or subretinal deposit accumulation, and hyperautofluorescence may be observed (19, 20).

Classic fundus imaging systems can visualise the fundus up to 50 degrees. A non-midriatic camera (Optos Tx-200), is a device which can acquire images reaching the ora serrata by retinal scanning of an ultra wide area up to 200 degrees. Similar to the current study, a previous autofluorescence study of CSCR patients made with an ultra wide imaging system (Optos) determined more peripheral retinal findings at the rate of 57% than could be determined with a standard FAF system (21). The aim of this study was to evaluate the types of autofluorescence involvement and localisation in detail up to the periphery in chronic CSCR patients using an ultra wide-angle imaging system.

2. Methods

In this retrospective study was conducted according to the principles of the Declaration of Helsinki and ethics committee approval was obtained from Local Ethics Committee. A retrospective scan was made of the images of patients diagnosed with chronic CSCR (Presence of subretinal fluid for more than 4 months) with wide-angle digital fundus angiography and applied at the same time with autofluorescence imaging. The ultra wide area autofluorescence images of 46 patients were examined.

Patients were excluded from the study if they had another eye disease accompanying CSCR (age-related macular degeneration, diabetic retinopathy, any other macular or retinal

disease), if they had received treatment for CSCR (photodynamic therapy, micropulse laser, anti-VEGF treatment) or if the peripheral retina image could not be evaluated in detail.

Disease involvement on the images was classified in 3 groups as zone 1, zone 2, and zone 3. Zone 1 was defined as a round region 5.4mm in diameter, in the central fovea including the nasal edge of the optic disc and the macular temporal area. Zone 2 was defined as a round region, 16.2 mm in diameter equivalent to 9 optic disc diameters, starting from the inner border of zone 1 and the outer border coinciding with vortex veins. Zone 3 was defined as the region formed of the peripheral retina remaining outside zone 2 (Figure 1) (22). Patients were grouped as those with involvement in zones 1+2, zones 2+3, and zones 1+2+3. Of the patients with involvement in both eyes, the eye with more severe involvement was included in the study. The auto-fluorescence appearance was separated into 4 groups as punctate or diffuse involvement showing hyperautofluorescence and granular or confluent showing hypo-autofluorescence.

Data obtained in the study were analysed statistically using IBM SPSS for Windows vn. 22.0 software. Continuous variables were stated as mean±standard deviation (SD) values and categorical variables as number (n) and percentage (%). A value of $p<0.05$ was accepted as statistically significant.

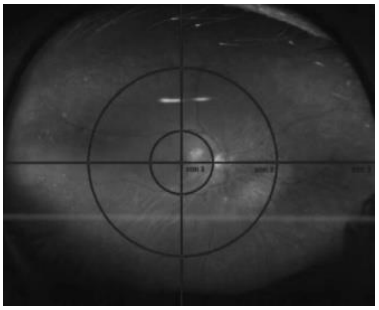

Figure 1. Separation of the retina according to zones

3. Results

The ultra wide area autofluorescence images of 46 patients were examined, and after the exclusion of 2 patients because peripheral images could not be clearly selected, the study evaluations were made of 44 eyes of 44 patients.

The 44 patients comprised 27 (61.4%) males and 17 (38.6%) females with a mean age of 40.4±6.4 years (range, 25-57 years) Table 1. In 7 patients with involvement of both eyes, the eye with more severe involvement was evaluated in the study. The autofluorescence images of 24 right eyes and 20 left eyes were evaluated. The mean duration of the disease was found to be 2.7 years.

The results of the examinations of the ultra wide area autofluorescence images with evaluations of zones 1, 2 and 3 are shown in Table 2.

Table 1. Demographic data of patients

	Age	Gender
Male	43	17
Female	39	27
Total	40.6	44

Table 2. The staging according to autofluorescense

	n	%
Zone 1	16	36,4
Zone 2	2	4,5
Zone 1+2	19	43,2
Zone 2+3	1	2,3
Zone 1+2+3	6	13,6
Total	44	100,0

According to the results, the most involvement was determined in zone 1+2 or in zone 1 only. There was seen to be zone 2 involvement in the 4 quadrants of inferior, nasal, temporal and superior. Zone 3 involvement was seen in the form of inferior gravitational defect only in the inferior quadrant.

Zone 3 involvement of peripheral retina involvement alone was not determined in any patient. Involvement in zone 3 was seen in a total of 7 (15.9%) patients, in 6 (13.6%) patients together with zones 1 and 2, and in 1 (2.3%) patient together with zone 2. The ultra wide area autofluorescence images of the retinal involvements of patients according to zone are shown in Figures 2a-b-c.

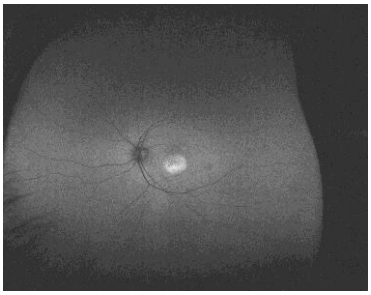

Figure 2a: Involvement of zone 1

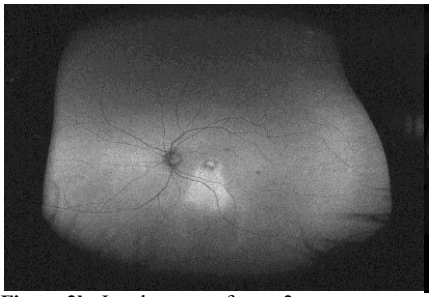

Figure 2b: Involvement of zone 2

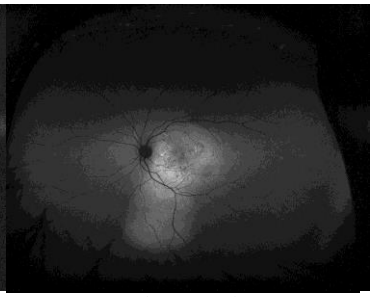

Figure 2c: Involvement of zone 3

Figure 2a-b-c. The retinal autofluorescense according to the zones

Hyperautofluorescence was determined in 39 (88.6%) patients and hypo-autofluorescence in 5 (11.4%). The details of involvement are shown in Table 3.

Table 3. Types of autofluorescense

Tutulum		**n**	**%**	**Total n%**
Hyperautofluorescense	**Punctate**	19	43.2	
	Diffuse	16	36.4	39(%88.6)
	Punctate + Diffuse	4	9.1	
Hypoautofluorescense	**Granular**	4	9.1	5(11.4)
	Confluent	1	2.3	
Total		44	100	44(%100)

As a result of binomial logistic regression performed between the presence of hyperautofluorescence and the duration of the disease, no significant relationship was found($p>0.05$).

4. Discussion

CSCR causes choroidal vascular hyperpermeability and is characterised by focal leakage at the RP level and serous separation of the neurosensorial retina which can be seen on fundus fluorescein

angiography (1,23-25). The source of FAF used in the evaluation of CSCR is to a great degree, lipofuscin, which is formed with the accumulation of the oxidative destructive products of retinoid and proteins in lysosomes and fatty acid with phagocytosis of damaged photoreceptor outer segments (13, 14).

Previous studies have determined CSCR more in males than females (1, 19). Consistent with these findings in literature, 27 (61.4%) of the 44 patients in the current study were male. CSCR has been reported to be seen in the 20-50 years age group (1), and similarly in the current study, the mean age was 40.4±6.4 years, with a range of 25-57 years.

Accumulations showing hyperautofluorescence on blue light autofluorescence imaging in CSCR have been previously reported and have been stated to be due to photoreceptor outer segments that have elongated and fallen (19,26). In recent studies of chronic CSCR, hyperautofluorescence and hypo-autofluorescence involvement types have been examined. In a study by Lee et al, hyperautofluorescence was determined in 63.3% of CSCR patients and minimal changes in 36.4% (18). Zola et al determined 31.25 hyperautofluorescence (19.7% punctate, 11.5% diffuse), 59.9% hypo-autofluorescence (51.0% granular, 8.9% confluent) and mixed patterns in 8.3% of chronic CSCR patients, showing a much higher rate of hypo-autofluorescence (27). Similar to the current study, in a study performed with ultra wide area autofluorescence of 65 eyes with CSCR, Pang et al. (21) reported hyperautofluorescence with subretinal fluid in 19 (29.2%) eyes, hyperautofluorescence with normal RPE and photoreceptors without subretinal fluid in 44 (70%) patients, and hypo-autofluorescence with RPE atrophy and photoreceptor loss in 5 (0.8%) patients. As a result of the study it was said that there could be hyperautofluorescence or a mixed fluorescence image in regions with subretinal fluid, and even if the fluid disappeared, hyperautofluorescence could continue or could change to hypo-autofluorescence together with RPE atrophy. It was also reported in that study that hyperautofluorescence in the periphery could be a useful finding of disease activation. Consistent with the studies of Pang et al and Lee et al, hyperautofluorescence was seen in the majority of the current study patients (39/44, 88.6%) and hypo-autofluorescence in a much smaller proportion (5/44, 11.4%). In the evaluation of the types of autofluorescence, hyperautofluorescence was determined at the higher rate of 43.2% punctate compared to 36.4% diffuse and 9.1% punctate+diffuse, and in the hypo-autofluorescence type, granular involvement was higher at 9.1% than confluent at 2.3%.

The much higher rate of hyperautofluorescence determined in the chronic CSCR patients in the current study was thought to have formed associated with accumulated photoreceptor chromophores as a result of sufficient phagocytosis with separation of retina outer segments and RPE, and the low rate of hypo-autofluorescence was thought to be related to damaged photoreceptors and RPE (18-20). That autofluorescence types in zone 2 were seen in 4 quadrants suggests that the leakage in the disease is not only in the macular region, but can include all the quadrants contained in zone 2. As peripheral retina involvement was determined only in the form of gravitational defect in the inferior, this shows that basically the disease does not involve the periphery, but the inferior quadrant is affected associated with gravity.

This study had some limitations, primarily the low number of patients and that the autofluorescence regions corresponding to hyperautofluorescence or hypo-autofluorescence could not be compared with the areas of subretinal fluid in those regions because the OCT results could not be evaluated. In addition, the duration of the disease, and whether it was chronic active or chronic recurrent type was not reported.

In conclusion, the results of this study, in which the autofluorescence images taken with a wide angle digital fundus camera system of chronic CSCR patients were evaluated, showed that the vast majority of involvement was determined as hyperautofluorescence, peripheral retina involvement was only seen in the inferior quadrant in the form of gravitational defect, and zone 2 involvement

was seen in 4 quadrants. These findings can be considered important in respect of being of guidance for further studies of disease activation and progression.

Ethical approval

All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. The institutional review board/Ethics Committee has approved the study from Eskisehir Osmangazi University with number of 2018-200.

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Research Article / Araştırma Makalesi

Evaluation of Neuromuscular Functions in Hashimoto's Thyroiditis

Hashimoto Tiroiditinde Nöromusküler Fonksiyonların Değerlendirilmesi

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Abstract

Hashimoto's thyroiditis is the most prevalent autoimmune thyroid disease with an increasing incidence. Although the exact causes and pathogenesis of Hashimoto's thyroiditis are not yet fully understood, the literature indicates complex interactions of immunologic, genetic, environmental, and epigenetic factors. It generally leads to hypothyroidism which can cause neuromuscular problems including neuropathy and myopathy. Data on neuromuscular functions of Hashimoto's thyroiditis patients are relatively underreported and not up to date. The current observational study aimed to evaluate neuromuscular functions and sympathetic skin responses (SSR) in patients with Hashimoto's thyroiditis and compare them with healthy participants. In total, 50 patients (25 females, 25 males; mean age, 31.6±4.9 years; range: 25-40 years) including 33 euthyroid, 10 with subclinical hypothyroidism, and 7 with hypothyroidism were included. The control group consisted of 50 healthy individuals (25 females, 25 males; mean age: 31.5±5.1 years; range, 25-40 years). Nerve conduction studies, repetitive nerve stimulation, SSRs and F wave recordings were performed in all participants. There were significant differences in the mean SSR latency and amplitude both in the upper extremities ($p<0.001$ and $p=0.013$, respectively) and in the lower extremities ($p=0.008$ and $p=0.002$, respectively) in the comparison groups. There was a significant difference in comparison groups regarding needle electroneuromyography (EMG) tests ($p=0.012$) and 14% of the patients showed myogenic EMG findings. In addition, a significant correlation was found between EMG findings and anti-TPO levels in the Hashimoto's thyroiditis patients ($r=0.453$; $p=0.001$). No significant differences were found in the nerve conduction studies, routine EMG tests, repetitive nerve stimulations or F wave recordings between patients and control groups. Hashimoto's thyroiditis, can cause negative influences on the proper functioning of neuromuscular systems. SSR, and electrophysiological tests may be beneficial for early detection and investigation of neuromuscular abnormalities in these patients.
Keywords: Hashimoto's thyroiditis, neuromuscular problems, electromyography, autoimmune thyroid disease

Özet

Hashimoto tiroiditi, görülme sıklığı artan en sık görülen otoimmün tiroid hastalığıdır. Hashimoto tiroiditinin kesin nedenleri ve patogenezi henüz tam olarak anlaşılamamasına rağmen, literatür immünolojik, genetik, çevresel ve epigenetik faktörlerin karmaşık etkileşimlerini göstermektedir. Genellikle nöropati ve miyopati gibi nöromüsküler sorunlara neden olabilen hipotiroidizme yol açar. Hashimoto tiroiditi hastalarının nöromüsküler fonksiyonlarına ilişkin veriler nispeten az rapor edilmiştir ve güncel değildir. Bu gözlemsel çalışma Hashimoto tiroiditi olan hastalarda nöromüsküler fonksiyonları ve sempatik deri yanıtlarını (SSR) değerlendirmeyi ve sağlıklı katılımcılarla karşılaştırmayı amaçlamıştır. Çalışmaya 33 ötiroid, 10'u subklinik hipotiroidizmli, 7'si hipotiroidizmli olmak üzere toplam 50 hasta (25 kadın, 25 erkek; yaş ortalaması 31.6±4.9 yıl; dağılım: 25-40 yıl) dahil edildi. Kontrol grubu 50 sağlıklı bireyden (25 kadın, 25 erkek; yaş ortalaması: 31.5±5.1 yıl; dağılım: 25-40 yıl) oluşuyordu. Tüm katılımcılarda sinir iletim çalışmaları, tekrarlayan sinir stimülasyonu, SSRs ve F dalga kayıtları yapıldı. Karşılaştırma gruplarında hem üst ekstremitelerde (sırasıyla $p<0.001$ ve $p=0.013$) hem de alt ekstremitelerde (sırasıyla $p=0.008$ ve $p=0.002$) ortalama SSR gecikmesi ve genliğinde anlamlı farklılıklar vardı. Karşılaştırma gruplarında iğne elektronöromiyografi (EMG) testleri açısından anlamlı fark vardı ($p=0.012$) ve hastaların %14'ünde miyojenik EMG bulguları saptandı. Ayrıca Hashimoto tiroiditli hastalarda EMG bulguları ile anti-TPO düzeyleri arasında anlamlı korelasyon saptandı ($r=0.453$; $p=0.001$). Hastalar ve kontrol grupları arasında sinir iletim çalışmalarında, rutin EMG testlerinde, tekrarlayan sinir stimülasyonlarında veya F dalgası kayıtlarında anlamlı fark saptanmadı. Hashimoto tiroiditi, nöromüsküler sistemlerin düzgün çalışması üzerinde olumsuz etkilere neden olabilir. SSR ve elektrofizyolojik testler, bu hastalarda nöromüsküler anormalliklerin erken tespiti ve araştırılması için faydalı olabilir.
Anahtar Kelimeler: Hashimoto tiroiditi, nöromüsküler problemler, elektromiyografi, otoimmün tiroid hastalığı

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1. Introduction

Hashimoto's thyroiditis, also known as chronic lymphocytic thyroiditis or autoimmune thyroiditis is the most prevalent autoimmune thyroid disease with an increasing incidence. Hashimoto's thyroiditis is characterized by enhanced thyroid volume, lymphocyte infiltration of parenchyma, and the presence of specific autoantibodies against thyroid antigens, namely, thyroid peroxidase (TPO) and thyroglobulin (TG) (1, 2). Hashimoto's thyroiditis is estimated to affect about 10% of the general population, is diagnosed in females up to ten times more often than males; the frequency of disease increases with age and it can also be seen in children and even in infants (3, 4). Although the exact causes and pathogenesis of Hashimoto's thyroiditis are not yet fully understood, the literature indicates complex interactions of immunologic, genetic, environmental, and epigenetic factors. Hashimoto's thyroiditis can also coexist with various other autoimmune disorders such as type 1 diabetes, rheumatologic syndromes, celiac disease, and multiple sclerosis (4, 5). Hashimoto's thyroiditis symptoms may include weight gain, paresthesia, fatigue, constipation, muscle weakness, cramps, hair loss, infertility, and several psychological problems and it generally leads to hypothyroidism (4, 5). Among these, the role of Hashimoto's thyroiditis on the impairment of neural and muscular functions of patients is relatively underreported and not up to date, therefore, further research is required to address the issue. Neuromuscular problems including neuropathy and myopathy are common in patients with hypothyroidism with up to 80% of patients complaining of associated symptoms (6, 7). It has been reported that almost one-third of patients with hypothyroidism develop muscle weakness, myalgia, fatigue, and muscle cramps (8) and most of them may have mononeuropathy or polyneuropathy because of axonal damage or myelin involvement (9). The current study aimed to evaluate neuromuscular functions and sympathetic skin responses (SSR) in patients with Hashimoto's thyroiditis and compare them with healthy participants.

2. Material and Methods

The present observational study was conducted at Neurology Department of İzmir University of Economics Medicalpoint Hospital between January 2014 and December 2021. Patients with a diagnosis of Hashimoto's thyroiditis were included in the study. All patients were examined for systemic disorders such as diabetes mellitus, vasculitis, rheumatic disease, malignancy, and hematologic disorders and only the ones who had not any of these concurrent systemic problems were included. In total, 50 patients (25 females, 25 males; mean age, 31.6±4.9; range:25-40) including 33 euthyroid, 10 with subclinical hypothyroidism, and 7 with hypothyroidism were included in the study. The control group consisted of 50 healthy individuals (25 females, 25 males; mean age: 31.5±5.1 years; range, 25-40 years) with similar age and sex profile to the patient group and with no previous thyroid disorder any current neurological disorder. The study was approved by the Local Clinical Research Ethics Committee. All participants included in the study provided written informed consent.

Electrophysiological studies

Electrophysiological studies were conducted using the Nihon Kohden (Japan) Electromyograph measuring system (Model: MEB-9400K). All study participants underwent electroneuromyography (EMG) performed by a single physiatrist who was blind to the patient groups. Distal motor latencies and motor nerve conduction velocities were calculated using disc surface cup (Ag/AgCl) recording electrodes which were 5 mm in diameter. Sensory conduction velocity, sensory nerve action potential amplitudes, and distal sensory latencies were recorded using ring electrodes. Motor and sensory conduction recordings of ulnar nerve; motor and sensory conduction recordings of median nerve; motor conduction recordings of peroneal and tibial nerve, and sensory conduction recordings of sural nerve were performed. Needle EMG recordings were performed with the left deltoid muscles and rectus femoris muscles. Electrophysiological parameters were assessed according to the normal values of the laboratory. A minimum

ambient temperature of 25°C and distal extremity skin temperature of >32°C were conserved during all electrophysiological studies.

Repetitive nerve stimulation

Repetitive nerve stimulations were recorded from the orbicularis oris muscles. Ten stimuli at 5 Hz stimulation frequency and 10 Hz stimulation frequency were applied to the facial nerve at the tragus, during rest and every minute for 4 minutes after 30 seconds exercise with maximal isometric muscle contraction of the recording muscle. A decrement of more than 10% between the first and fourth motor response was considered as positive. The decrement ratios between the first and fourth (dec1-4) motor response were calculated.

F wave recordings

F wave parameters including minimum f latency, maximum f latency, f latency chronodispersion, and f wave persistency were studied in median, ulnar, peroneal, and tibial nerves of all participants. Recording electrodes placed on the belly tendon montage, wave recording done from a relaxed muscle. The stimulating cathode was proximal to the anodal electrode to prevent anodal block

Sympathetic Skin Responses

SSRs were recorded via the active electrodes placed in the left palm and sole and the reference electrodes on the dorsum of the left hand and foot, by placing the participants in the reclining position. A two-channel recording from foot and hand as lower and upper extremities were obtained simultaneously by stimulating the contralateral median nerve at the level of the wrist. The stimulus was increased to just above the threshold level and applied not regularly to minimize habituation. Five potentials were recorded and the mean values were used for the analyses.

Statistical Analysis

Statistical analysis was performed using the PASW Statistics for Windows, Version 18.0. (SPSS Inc., Chicago, IL, USA). The descriptive statistical data were expressed as numbers and percentiles for categorical variables and as mean, standard deviation, median, and minimum-maximum (range) for numerical variables. The normal distributions of variables were tested by visual (histograms and probability graphics) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk) test methods. For categorical variables, in two group comparisons, the Chi-Square test was used when appropriate. For numerical variables, in two group comparisons, the Mann-Whitney U test was used when data were not normally distributed. The Student's T-test was used when numerical variables are normally distributed. For the analysis of the correlation between needle EMG findings and free T3, free-T4, thyroid stimulating hormone (TSH), anti-thyroid peroxidase (anti-TPO), and anti-thyroglobulin (anti-TG) levels, Spearman's correlation analysis was performed for non-normally distributed variables. A p value of <0.05 was set as statistically significant.

3. Results

The study included a total of 100 participants, of whom 50 had Hashimoto's thyroiditis (33 patients with euthyroid, 10 patients with subclinical hypothyroid, and 7 patients with hypothyroid; mean age, 31.6±4.9 years) and 50 were healthy controls (mean age, 31.5±5.1 years). In the patient group, mean time since the diagnosis of hypothyroidism was 5.1±3.0 years (minimum 1 year and maximum 10 years) and of the patients, 42% were using levothyroxine, 30% have previous history of levothyroxine, and 28% were not using levothyroxine. The demographic and clinical data and the comparison of these parameters between patient and control groups are summarized in Table 1. Accordingly, there were no significant differences between patient and control groups regarding sex ($p=1.000$), age ($p=0.937$), height ($p=0.894$) and weight ($p=0.358$). Biochemistry laboratory test results regarding Hashimoto's thyroiditis namely creatine kinase levels, free T3 and T4 levels, TSH levels, anti-TPO

levels, anti-TG levels were compared between patient and control groups. There were elevated TSH levels (p=0.009), elevated anti-TPO levels (p<0.001), and elevated anti-TG levels (p<0.001) in the patient group as compared with the control group with respect to the normal laboratory range. The differences in creatine kinase levels (p=0.035), and free T3 (p=0.249) and T4 levels (p=0.354) between the patient and control group were not significant.

Facial nerve decrement ratios of the participants were compared between patient and control groups. There was no significant difference between the patient and control groups in facial nerve decrement ratios (%) between responses 1-4 for repetitive stimulations both at 5 Hz (both patient and control mean values were 5, p=0.579) and at 10 Hz (mean values were 8 and 6 for patient and control groups, respectively; p=0.097) frequencies.

F-wave recordings including minimum and maximum f-latency, f-latency chronodispersion and f-wave persistence in median, ulnar, peroneal, and tibial nerves of all participants were performed and are shown in Table 2. F wave recordings of these nerves were similar between the patient and control groups (p>0.05 for all).

SSR and motor and sensory functions of median nerve were measured in all participants and the results are demonstrated in Table 3. According to the collected data, there were significant differences in the mean SSR latency and amplitude both in the upper extremities (p<0.001 and p=0.013, respectively) and in the lower extremities (p=0.008 and p=0.002, respectively) in the comparison groups. For both upper and lower extremities, mean SSR latency was higher and mean SSR amplitude was lower in the patient group than those of the control group. There was no significant difference between the patient and control groups in motor latency (p=0.942), motor distal amplitude (p=0.874), and motor velocity (p=0.485) values of the median nerve. In addition, no significant difference was found between the patient and control groups in the sensory data of the median nerve recorded for both thumb (p=0.208, p=0.684, p=0.402 for latency, amplitude and velocity values, respectively) and index fingers (p=0.296, p=0.496, p=0.289 for latency, amplitude and velocity values, respectively).

Motor and sensory functions of the ulnar nerve were tested in all participants and the findings are shown in Table 4. There was no significant difference between the patient and control groups in ring finger median-ulnar sensory latency difference (p=0.447), motor distal latency (p=0.772), motor amplitude of below sulcus segment (p=0.981), motor amplitude of above sulcus segment (p=0.970), motor velocity of below sulcus segment (p=0.740), motor velocity of above sulcus segment (p=0.539), and sensory data (p=0.972, p=0.959, p=0.505 as latency, amplitude, and velocity, respectively) of the ulnar nerve.

Nerve conduction studies of peroneal, tibial, and sural nerves were performed in all participants and the results are shown in Table 5. There was no significant difference between the patient and control groups in distal motor latency (p=0.948), and motor amplitude (p=0.992; p=0.961) and motor velocity (p=0.883; p=0.581) in the caput fibula 2 cm distal and 9 cm proximal of the peroneal nerve, respectively. Similarly, no significant difference was found between the patient and control groups in motor latency (p=0.830), motor amplitude (p=0.841) and motor velocity (p=0.567) parameters of the tibial nerve, and in sensory latency (p=0.749), sensory amplitude (p=0.646), and sensory velocity (p=0.890) parameters of the sural nerve. There was no significant difference between the patient and control groups in routine EMG tests (p=0.242), whereas there was a significant difference in comparison groups regarding needle EMG tests (p=0.012) and 7% of the patients showed myogenic EMG findings. Further, the correlation analysis between the needle EMG findings and free T3; free-T4; TSH; anti-TPO, and anti-TG levels was performed in the patients with Hashimoto's thyroiditis (Table 6) and a significant correlation was found between EMG findings and anti-TPO levels (r=0.453; p=0.001). No significant correlation was found for the following parameters: free T3, free-T4, TSH, and anti-TG levels.

Table 1. Demographic and clinical data of the patient and control groups

	Patients **N=50**	Controls **N=50**	p
Sex, n (%)			
Female	25 (50.0)	25 (50.0)	1.000*
Male	25 (50.0)	25 (50.0)	
Age, years, Mean±SD	31.6 ± 4.9	31.5 ± 5.1	0.937**
Height, cm, Mean±SD	165.3 ± 3.8	165.2 ± 3.6	0.894**
Weight, kg Mean±SD	65.1 ± 4.7	64.2 ± 4.8	0.358**
Euthyroid, n (%)	33 (66.0)	50 (100.0)	N/A
Subclinical hypothyroidism, n (%)	10 (20.0)	-	N/A
Hypothyroidism, n (%)	7 (14.0)	-	N/A
Creatine kinase level, u/L (29-168), Mean (min-max)	125 (49-1588)	102.5 (39-167)	0.035***
Free T3, pg/mL (1.5-4.6), Mean (min-max)	1.9 (1.1-4.5)	2.7 (1.5-4.5)	0.249***
Free T4, ng/dL (0.7-1.7), Mean (min-max)	1.3 (0.2-1.7)	1.3 (0.7-1.7)	0.354***
TSH, miu/mL (0.35-4.94), Mean (min-max)	4.305 (0.68-11.2)	3.515 (0.68-4.94)	0.009***
Anti-TPO, iu/mL (0-5.6), Mean (min-max)	258.75 (4.3-1349)	3.4 (0.3-5.3)	<0.001***
Anti-TG, iu/mL (0-4.11), Mean (min-max)	78.55 (1.8-283.9)	3.1 (0.9-4.1)	<0.001***

*SD: Standard deviation; N/A: Not applicable; *Chi-Square test; **Student's T-test. ***Mann Whitney U test. T3: triiodothyronine; T4: thyroxine; TSH: thyroid stimulating hormone; anti-TPO: anti-thyroid peroxidase; anti-TG: anti-thyroglobulin.*

Table 2. F-wave recordings of median, ulnar, peroneal and tibial nerves in patient and control groups

	Patients **N=50**	Controls **N=50**	p*
Median nerve minimum f latency, ms, upper limit 26-28	25 (21.3-30.1)	24.1 (21.3-27.9)	0.052
Median nerve maximum f latency, ms, upper limit 30-34	28,8 (24.1-36.1)	27.5 (24.1-31.1)	0.058
Median nerve f latency chronodispersion, ms, should be <4 ms	3.35 (2-7)	3.1 (2-4)	0.132
Median nerve f wave persistency, should be >50%	65 (43-81)	68 (50-81)	0.474
Ulnar nerve minimum f latency, ms, upper limit 27-29	27.65 (23.8-31.1)	26.9 (23.8-28.9)	0.082
Ulnar nerve maximum f latency, ms, upper limit 31-33	30.9 (26.9-35.4)	30.6 (26.9-32.9)	0.069
Ulnar nerve f latency chronodispersion, ms, should be maximum 4 ms	3.5 (2-5.9)	3.5 (2-4.1)	0.152
Ulnar nerve f wave persistence, should be >50%	62 (50-81)	68 (50-81)	0.543
Peroneal nerve minimum f latency, ms, upper limit 46-52	49.6 (43.9-54.8)	49.1 (45.5-51.8)	0.103
Peroneal nerve maximum f latency, ms, upper limit 52-58	54.85 (49.7-60.1)	54.2 (49.9-56.9)	0.066
Peroneal nerve f latency chronodispersion, ms, should be maximum 6 ms	5.3 (3-8.7)	5 (3-6.3)	0.062
Peroneal nerve f wave persistence, %	62 (37-81)	68 (50-81)	0.498
Tibial nerve minimum f latency, ms, should be maximum 45-53	50.2 (45.5-55.5)	49.9 (45.5-52.5)	0.209
Tibial nerve maximum f latency, ms, should be maximum 51-59	54.9 (49.9-61.7)	54.9 (49.9-58.9)	0.204
Tibial nerve f latency chronodispersion (ms), should be maximum 6 ms	5.25 (4-7,4)	5.2 (4-6.4)	0.340
Tibial nerve f wave persistence, %	62 (43-81)	68 (50-81)	0.480

*ms: milliseconds; *Mann Whitney U test; The descriptive statistical data are shown as median (minimum-maximum).*

Table 3. Sympathetic skin responses, and motor and sensory conduction recordings of median nerve in patient and control groups

	Patients **N=50**	Controls **N=50**	p*
Upper extremities sympathetic skin response (5 responses) mean latency, s (1.46±0.04)	1.495 (1.18-2.5)	1.39 (1.18-1.55)	<0.001
Upper extremities sympathetic skin response (5 responses) mean amplitude, mV (2.5±0.3)	2.025 (1.5-3.1)	2.2 (1.5-3.1)	0.013
Lower extremities sympathetic skin response (5 responses) mean latency, s (1.4±0.07)	1.5 (1.15-2.2)	1.415 (1.22-1.59)	0.008
Lower extremities sympathetic skin response (5 responses) mean amplitude, mV (1.6±0.2)	1.3 (0.8-2.5)	1.6 (1.1-2.5)	0.002
Median nerve motor latency, ms	3.61 (3.1-3.95)	3.61 (3.1-3.95)	0.942
Median nerve motor distal amplitude, mV	18.7 (12.1-25.1)	18.7 (12.2-25.1)	0.874
Median nerve motor velocity, m/s	54.4 (50.1-61.3)	55.6 (50.1-61.3)	0.485
Median nerve sensory latency, ms, thumb	3.2 (2.7-4.5)	3.1 (2.7-3.5)	0.208
Median nerve sensory amplitude, mV, thumb	20.5 (10.5-29.1)	20.7 (16.8-29.1)	0.684
Median nerve sensory velocity, m/s, thumb	52.9 (38.9-60.1)	53.55 (50.2-60.1)	0.402
Median nerve sensory latency, ms, index finger	3.25 (2.7-4.3)	3.2 (2.7-3.4)	0.296
Median nerve sensory amplitude, mV, index finger	19.4 (11.9-29.1)	20.15 (14.7-29.1)	0.496
Median nerve sensory velocity, m/s, index finger	53.4 (39.4-59.8)	53.5 (50.7-59.8)	0.289

*SSR: Sympathetic skin response; ms: milliseconds; mV: millivolt; *Mann Whitney U test; The descriptive statistical data are shown as median (minimum-maximum).*

Table 4. Motor and sensory conduction recordings of ulnar nerve in patient and control groups

	Patients **N=50**	Controls **N=50**	p*
Ring finger median ulnar sensory latency difference (>0.3 is pathological)	0.2 (0.1-0.5)	0.2 (0.1-0.3)	0.447
Ulnar nerve motor distal latency, ms	3.1 (2.8-3.6)	3.1 (2.8-3.6)	0.772
Ulnar nerve motor amplitude, mV, below sulcus segment (5 cm distal)	19.45 (12.3-27.8)	19.4 (14.3-27.8)	0.981
Ulnar nerve motor amplitude, mV, above sulcus segment (5 cm proximal)	19.9 (14.1-27.5)	19.9 (15.1-26.8)	0.970
Ulnar nerve motor velocity, m/s, below sulcus segment	57.5 (50.3-62.5)	57.5 (50.3-62.5)	0.740
Ulnar nerve motor velocity, m/s, above sulcus segment	65.1 (57.1-69.9)	65.7 (57.1-69.9)	0.539
Ulnar nerve sensory latency, ms	3.2 (2.7-3.8)	3.2 (2.7-3.8)	0.972
Ulnar nerve sensory amplitude, mV	20.7 (14.9-30.3)	20.5 (14.9-30.3)	0.959
Ulnar nerve sensory velocity, m/s	57.35 (50.1-67.4)	58.2 (51.6-67.4)	0.505

*ms: milliseconds; mV: millivolt; *Mann Whitney U test; The descriptive statistical data are shown as median (minimum-maximum).*

Table 5. Motor conduction recordings of peroneal and tibial nerve, and sensory conduction recordings of sural nerve in patient and control groups

	Patients	Controls	p*
Peroneal nerve distal motor latency, ms	4.63 (3.8-5.2)	4.5 (3.9-5.2)	0.948
Peroneal nerve motor amplitude, mV, caput fibula 2 cm distal	9.85 (4.7-15.2)	9.9 (6.7-15.2)	0.992
Peroneal nerve motor velocity, m/s, caput fibula 2 cm distal	49.25 (45.4-55.4)	49.3 (45.4-55.4)	0.833
Peroneal nerve motor amplitude, mV, caput fibula 9 cm proximal	11.3 (5.3-17.3)	11.3 (7.3-17.3)	0.961
Peroneal nerve motor velocity, m/s, caput fibula 9 cm proximal	58.1 (54.1-62.4)	58.1 (54.3-62.4)	0.581
Tibial nerve motor latency, ms	4.7 (3.7-5.2)	4.7 (3.7-5.2)	0.830
Tibial nerve motor amplitude, mV	10.9 (7.6-18.4)	11.05 (7.6-18.4)	0.841
Tibial nerve motor velocity, m/s	49.7 (43.9-55.1)	50 (45.9-55.1)	0.567
Sural nerve sensory latency, ms	4.15 (3.1-4.9)	4.1 (2.9-4.8)	0.749
Sural nerve sensory amplitude, mV	18.6 (11.3-25.3)	18.6 (11.3-25.3)	0.646
Sural nerve sensory velocity, m/s	49.65 (42.8-57.2)	49.65 (44.3-57.2)	0.890

*ms: milliseconds; mV: millivolt; *Mann Whitney U test; The descriptive statistical data are shown as median (minimum-maximum).*

Table 6. Results of the correlation analysis between the needle electroneuromyography (EMG) findings and biochemistry laboratory test results in the patients with Hashimoto's thyroiditis

		Free T3	Free T4	TSH	anti-TPO	anti-TG
Needle EMG	**r**	0.054	0.048	-0.016	0.453	0.202
	p*	0.708	0.740	0.912	**0.001**	0.160

**Spearman's correlation analysis. TSH: thyroid stimulating hormone; anti-TPO: anti-thyroid peroxidase; anti-TG: anti-thyroglobulin.*

4. Discussion

In the present study, it was found that there was a significant difference in SSRs between the patient and control groups. For both upper and lower extremities, the mean SSR latencies were prolonged, and the mean SSR amplitudes were decreased in the patient group than those of the healthy control group implying the impairment of the sympathetic system function in the patients compared to the controls. Consistently with the current study, in a previous research, Merello et al. (10) reported that patients with autoimmune hypothyroidism showed sudomotor dysfunctions revealed by the abnormal SSR results likely be resulted from a destructed autoimmune reaction. On the other hand, there are some other studies found contrary results regarding SSR measurements. Gautam et al. (11) and Ümit Yemişci et al. (7) found no significant alterations in SSRs between hypothyroid patients and healthy controls in their research. SSR is one of the most frequently used non-invasive techniques for the evaluation of sympathetic fibers dysfunction in neuropathies and sympathetic system disorders in other diseases. It is simple, fast, and easy to apply; however, it has its methodical limitations similar to other electrophysiological procedures (12, 13). In addition to these limitations, variations in the characteristics of the patient groups, sample size, and the stages of the disease may result in controversial SSR measurements. Nevertheless, the literature lacks adequate data in terms of SSR in immunologically mediated disorders which suggest the need for further investigations of SSR in Hashimoto's thyroiditis to have more comparable and insightful clinical data (14). Although SSR alone cannot be used as a diagnostic tool for autonomic dysfunction, it may be utilized in combination with some other methods such as cardiovascular reflexes for the evaluation of autonomic nervous system functions and before the therapeutic interventions, as suggested previously (7, 10).

Apart from SSR measurements, various electrophysiological tests including repetitive stimulations of facial nerve; F-wave recordings of the median, ulnar, peroneal, and tibial nerves; motor and sensory conduction recordings of the median and ulnar nerve; motor conduction recordings of the peroneal and tibial nerve, and sensory conduction recordings of the sural nerve were performed to investigate any abnormalities in the patients with Hashimoto's thyroiditis. In all of these detailed tests, no significant differences were found in the electrophysiological parameters between patients and control groups. In a previous study, Ozata et al. (9) studied the distal latency, nerve conduction velocity, and F responses in the median and peroneal nerves, and they recorded sensory nerve conduction

velocities and sensory potential amplitudes in the sural and median nerves. As consistent with the current study, they could not find any significant difference in the electrophysiological data between patients with subclinical hypothyroidism and controls and they speculated that the results may be associated with the early stage of the disease in these patients. In another study, oppose to these results, researchers measured some extent of electromyographic variations, even in the early stages of subclinical hypothyroidism where they found motor parameters were more affected in the longer nerves and a higher proportion as compared to the sensory nerves and the progression of thyroid insufficiency was correlated with the decline of the motor and sensory amplitudes in all of the studied nerves (15). In two other studies, the hypothyroidism patients displayed a significant tendency of nerve conduction slowness as compared with controls (16, 17). Khedr et al. (18) recorded electrophysiological measurements showing that half of the hypothyroid patients had peripheral nervous system involvement, and a few of them had axonal neuropathy (9%) and myopathy (9%). Similarly, in the current study, 7 of the patients with Hashimoto's thyroiditis (14%) showed myogenic EMG findings. Furthermore, a significant correlation was found between EMG findings and anti-TPO levels in the patients, which supports the association between Hashimoto's thyroiditis and neuromuscular disorders. In addition, despite no statistical significance between the groups, early phase carpal tunnel syndrome was observed in three patients (6% of the patients). It revealed the importance of performing electrophysiological tests in hypothyroid patients, even in the very early stage of disease to detect the nervous system involvement. Eslamian et al. (8) measured similar electrophysiological abnormalities in patients with untreated spontaneous hypothyroidism and suggested early treatment to slow down the progression rate of the neuromuscular complications or minimize their formation.

As expected, there were elevated TSH levels, anti-TPO, and anti-TG levels in the patient group than those in the control group as the indicators of Hashimoto's thyroiditis and may have possible effects on the functioning of the neuromuscular system and thus on the recordings. The differences in creatine kinase levels and free T3 and T4 levels between the patient and control group were not significant and they may not interfere with the test results.

The homogeneity of the comparison groups in the current study was high with no significant difference according to the demographic features. Further, patients with no concurrent disease were recruited in the study which otherwise may interfere recorded neuromuscular data. This matching data between patient and control groups and specific selection of the patients enhances the reliability of the data comparison and the strength of the study. On the other hand, coexisting systemic disorder free selection of the study participants restricted the population of the study and low number of participants in both groups may be insufficient to record and address all of the neuromuscular effects of Hashimoto's thyroiditis.

Even though the current study results did not establish any significant difference in the electrophysiological data of the patient and healthy samples with the exception of SSRs data, it seems that electrophysiological studies may be useful as a tool in the case of early detection of neuromuscular issues in particular individuals with Hashimoto's thyroiditis.

In conclusion, it is well known that thyroid hormones are the main regulators of human metabolism and they are involved in many processes and biological activities of the neuromuscular systems. Hashimoto's thyroiditis, which results from impaired or abnormal thyroid hormones, can cause negative influences on the proper functioning of these systems. SSR and electrophysiological tests may be beneficial for early detection and investigation of neuromuscular abnormalities in patients with Hashimoto's thyroiditis.

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Research Article / Araştırma Makalesi

Evaluation of the TRK-2P Instrument Reliability in Normal and Keratoconus Eyes: A Preliminary Observation

Normal ve Keratokonuslu Gözlerde TRK-2P Cihazının Güvenilirliğinin Değerlendirilmesi: Bir Ön Gözlem

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Abstract

To compare keratometry and corneal thickness measurements by the TRK-2P instrument (Topcon Medical Systems Inc., Oakland NJ) with the anterior cornea keratometry and pachymetry values obtained by the Pentacam-HR instrument (Oculus; Optikgeräte GmbH, Wetzlar, Germany). Patients who had full records of two both instruments in our databases were included in the observational study. Keratoconus diagnosed twenty-three eyes of twelve patients and thirty-two eyes of sixteen patients with no eye problem (controls) were included. The keratometry and the central corneal thickness (CCT) outputs were collected by TRK-2P and Pentacam-HR. The consistency of the mean anterior cornea keratometry and pachymetry data were correlated using the intraclass correlation coefficient (ICC). Means were statistically correlated using a Paired t-test seeking significant correlations (α=0.05). Mean keratometry of TRK-2P and Pentacam-HR were 42.64D±2.02 and 42.79D±1.95 in controls whereas, these were 47.64D±5.24 and 47.16D±4.65 in keratoconus, respectively. The mean differences in keratometry data were 0.14D for controls and 0.48D for keratoconus(p<0.001). Mean CCT of TRK-2P and Pentacam-HR were 560.27±42.18µm and 537.63±36µm in controls whereas, these were 489.67±45.13µm and 470.22±38.14µm in keratoconus, respectively. The mean differences in CCT data were 22.63µm for controls and 19.44µm for keratoconus(p<0.001). ICC values between two instruments for controls and keratoconus, respectively were as follows: 0.987 and 0.983 for keratometry, 0.998 and 0.994 for CCT (p<0.001). TRK-2P produces consistent result outputs in normal and pathological corneas. Also, TRK-2P is a reliable instrument when correlated with a reference high-reliable instrument. However, in terms of monitoring the progression of keratoconus, these instruments cannot be interchangeable alternatives
Keywords: Central corneal thickness, Keratoconus, Pentacam HR, TRK-2P

Özet

Bu çalışmanın amacı TRK-2P cihazı (Topcon Medical Systems Inc., Oakland NJ) ile elde edilen keratometri ve kornea kalınlık değerlerini, Pentacam-HR cihazı (Oculus; Optikgeräte GmbH, Wetzlar, Almanya) ile elde edilen ön kornea keratometrisi ve pakimetri değerleri ile karşılaştırmaktır. Veri tabanlarımızda her iki cihazın tam kayıtlarına sahip olan hastalar bu gözlemsel çalışmaya dahil edildi. On iki hastanın keratokonus tanılı yirmi üç gözü ve herhangi bir göz sorunu olmayan on altı hastanın otuz iki gözü çalışmaya dahil edildi (kontrol). Keratometri ve santral kornea kalınlığı (SKK) çıktıları TRK-2P ve Pentacam-HR ile elde edilmiştir. Ortalama ön kornea keratometrisi ve pakimetri verilerinin tutarlılığı, sınıf içi korelasyon katsayısı (ICC) kullanılarak ilişkilendirildi. Ortalamalar paired t-testi kullanılarak istatistiksel olarak analiz edildi (α=0.05). Ortalama keratometri TRK-2P ve Pentacam-HR kontrollerde 42.64 D±2.02 ve 42.79 D±1.95 iken keratokonusta 47.64 D±5.24 ve 47.16 D±4.65 idi. Keratometri verilerindeki ortalama farklılıklar kontroller için 0.14 D ve keratokonus için 0.48 D idi (p<0.001). TRK-2P ve Pentacam-HR ortalama SKK değerleri sırasıyla kontrollerde 560,27±42,18 µm ve 537,63±36 µm iken keratokonus hastaları için sırasıyla 489,67±45,13 µm ve 470,22±38,14 µm idi. SKK verilerindeki ortalama farklar kontroller için 22.63 µm ve keratokonus için 19.44 µm idi (p<0.001). Kontrol ve keratokonus grupları için iki cihaz arasındaki ICC değerleri sırasıyla keratometri için 0,987 ve 0,983, SKK için 0,998 ve 0.994 idi (p<0.001). Çalışmamızın sonuçları, TRK-2P, normal ve patolojik kornealarda tutarlı sonuç çıktıları üretir. Ayrıca, TRK-2P, yüksek güvenilirliğe sahip referans bir cihazla ilişkilendirildiğinde güvenilir bir araçtır. Ancak keratokonus progresyonunun izlenmesi açısından bu enstrümanlar birbirinin yerine geçebilecek alternatifler olamaz.
Anahtar Kelimeler: Santral kornea kalınlığı, Keratokonus, Pentacam HC, TRK-2P

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1. Introduction

The accuracy of corneal analysis is necessary to diagnose, treatment planning, and maintenance of refractive surgery patients or pathological corneas such as keratoconus, glaucoma. Keratoconus (KC) is a corneal disease characterized by conical protrusion of the cornea. The thickness and durability of the cornea are adversely affected due to the degeneration in eye defects. Also, advanced pathology of KC can be caused to vision loss (1). Periodically analyses of the corneal thickness measurements at the central zone (CCT) and keratometry are as the standard ocular diagnostic parameters used to detect the cornea health (2).

In the past, KC could only be diagnosed in its advanced pathological stages with the slit lamp technique, but with contemporary precise and rapid instrumentation technology, early diagnosis has also become possible. The Pentacam HR instrument (PC-HR) (Oculus; Optikgeräte GmbH, Wetzlar, Germany) is a non-contact, high-resolution rotating 'Scheimpflug' camera system for anterior segment analysis (3-5). Mainly, PC-HR calculates the thickness of the cornea. Besides, the anterior and posterior corneal topography and elevation, total corneal refractive power, corneal power distribution, automatic chamber angle measurement in 360 °, chamber depth measurement, corneal and crystalline lens optical opacities are analyzed with the PC-HR instrument (Pentcam product brochure). Recently introduced all-in-one TRK-2P (TRK-2P; Topcon Medical Systems, Inc., Oakland, NJ) is a 4 in 1 instrument consisting of a refractometer, keratometer, non-contact tonometer, and pachymeter (6). All-in-one TRK-2P provides operator flexibility and time-efficient measurements or analyzes. All-in-one TRK-2P utilizes an optical pachymetry mode as dissimilar with the PC-HR principles to measure CCT, which includes using a tangential slit of light directed onto the cornea surface at aligned angles. Subsequently, CCT is calculated with a trigonometrical function accordance with intersection angles (7). However, there is limited information available on the recently introduced all-in-one TRK-2P instrument (7-10).

The above-mentioned instruments are categorized as non-contact and non-invasive instruments. Manufacturers claim accurate diagnostic outputs of keratometry and CCT for corneal topography analysis instruments. Though all-in-one TRK-2P or PC-HR instruments provide keratometry and CCT outputs, their operating fundamentals are dissimilar. Different types of instruments assessing the anterior segment yield an information about identical parameters. In this case, the agreement of these instruments has utmost importance for assessing the patient data in clinical practice. For this purpose, to understand the correlation among different instruments, specific clinical studies have been designed concerning their interchangeably used. However, interchangeably using instruments is still a controversial issue. Particularly, specialists often seek an information about cutting-edge novel instruments, in the reference of the current standards or well-known instruments. Also, this issue gains more major importance in corneal degeneration such as keratoconus eyes. With these justifications, this observational study aimed to correlate keratometry and corneal thickness outputs by the all-in-one TRK-2P instrument with the anterior cornea keratometry and pachymetry outputs obtained by the PC-HR instrument.

2. Patients and Methods

2.1. Ethical statement

The study protocol adhered to the tenets of the declaration of Helsinki. The protocol was approved by the Human Subjects Office, Office of Non-Invasive Research Compliance – Eskisehir Osmangazi University (Study no. 26, issue date: 15.02.2022 with reference #: 2022/26).

2.2. Sample size estimation

A priori t-test (means: difference between two independent mean, two groups) was selected from the t-test family in G*Power v3.1.7 software (Heinrich Heine Universität, Düsseldorf, Germany). Based on an effect size of 0.6, an alpha-type error of 0.05, and a power of 60%, the findings of a previous

study7 required minimum sample size of 21 per group to identify significant differences between the two research groups in terms of the parameter of each instrument type and keratoconus condition.

2.3. Inclusion criteria

In this study, the patient records between January 2017 – January 2018 were obtained from the database of the department of ophthalmology, Eskisehir Osmangazi University, Eskisehir, Turkey. This observation analyzed the full records of two instruments using the routine clinical examination procedures for a cohort of subjects examined and does not use experimental or new protocols. All data analyzed were collected as a part of the routine diagnosis of KC. Inclusion criteria of the cohort subjects were as follows

A clinical and topographic diagnoses of KC were included in the study. The main inclusion criteria of subjects were no additional ocular problems except refractive errors. For this purpose, ptosis, pterygium, dry eye, cataracts, retinal disease, strabismus, corneal scar, edema, contact lens usage history, previous ophthalmic surgery in any eye, or uncooperative patients were not included in the study. The common inclusion criteria were (1) subjects with no systemically compromised and (2) having fully achievable records with both instruments.

2.4. Ocular examination

All examinations were performed by ophthalmologists with 2-4 years of clinical experience using both instruments registered in the unit per the manufacturers' instructions. At first, automatic refraction, keratometry, and pachymetry outputs were obtained from the all-in-one TRK-2P instrument. Accordingly, keratometry was recorded utilizing the keratometry mode as K1 (flat keratometry) and K2 (steep keratometry). Then, the CCT outputs were collected utilizing the pachymetry mode. In routine diagnostic protocol, triplet optical analyses were obtained from each patient (three-time).

Second, the slit-lamp examination and high-resolution anterior corneal analyses were performed with PC-HR. To measure the corneal power and dioptric equivalents, two-perpendicular meridians (K1 and K2) were considered at the central 3mm of the corneal ring. Outputs were monitored via the software module of the instrument (Oculus; Optikgeräte GmbH, Wetzlar, Germany). Tomographic scans with an analysis quality that appeared as "OK" were recorded. The refractive indexes of both devices use 1.3375 for diopter conversion.

2.5. Statistical analysis

Statistical analyses were conducted utilizing statistical package software (IBM SPSS Statistics for Windows, v20.0. IBM Corp., Armonk, NY). The normality of data was confirmed using the Kolmogorov-Smirnov test. The consistency of the mean anterior cornea keratometry and pachymetry data were correlated using the intraclass correlation coefficient (ICC). Means were statistically correlated using a s t-test seeking significant correlations. Statistical significance was assumed at $p < 0.05$.

3. Results

Twenty-three eyes from twelve KC patients were included in the study according to the criteria whereas, thirty-two eye from sixteen patients was included as healthy controls (Demographic data not shown).

The mean keratometry and CCT outputs are summarized in Table 1. Mean keratometry of all-in-one TRK-2P and PC-HR were 42.64 D ± 2.02 and 42.79 D ± 1.95 in controls whereas, these were 47.64 D ± 5.24 and 47.16 D ± 4.65 in keratoconus, respectively. The mean differences of keratometry data were 0.14 D for controls and 0.48 D for keratoconus ($p<0.001$). Mean CCT of TRK-2P and Pentacam-HR were 560.27 ± 42.18 µm and 537.63 ± 36 µm in controls whereas, these were 489.67 ± 45.13 µm and 470.22 ± 38.14 µm in keratoconus, respectively. The mean differences of CCT data were 22.63 µm for controls and 19.44 µm for keratoconus ($p<0.001$).

Table 1. The mean keratometry and corneal thickness at the central zone values measured by different instruments along with the paired differences between the instruments.

Parameters	Eye	TRK-2P	Pentacam HR	ICC	*p* value
Keratometry (D)	Control (healthy)	42.64D ± 2.02	42.79D ± 1.95	0.987	<0.001
	Keratoconus	47.64D ± 5.24	47.16D ± 4.65	0.983	<0.001
CCT (µm)	Control (healthy)	560.27 ± 42.18	537.63 ± 36.00	0.998	<0.001
	Keratoconus	489.67 ± 45.13	470.22 ± 38.14	0.994	<0.001

CCT: Corneal thickness at the central zone; ICC: In-observation correlation coefficient. D: Dioptry.

ICC values between two instruments for controls and keratoconus, respectively were as follows: 0.987 and 0.983 for keratometry, 0.998 and 0.994 for CCT ($p<0.001$). Accordingly, mean keratometry and CCT outputs obtained with the all-in-one TRK-2P showed a significant relationship with the measurements obtained with the PC-HR for both keratoconus and healthy eyes.

Overall, the conflicting outputs were observed between all-in-one TRK-2P and PC-HR instrument. Concerning PC-HR results, the CCT yielded thicker outputs for keratoconus and healthy eye. Also, keratometry yielded lower in healthy eye (flat keratometry) whereas, higher in keratoconus (Steep keratometry).

4. Discussion

Due to the requirement for precise measurements of anterior segment characteristics, novel reliable measurement instruments have been introduced parallel to the biomedical developments. However, interchangeable usage can occur in clinical practice among the instruments with overlapped modes by operators with intentionally or unintentionally. Thus, ophthalmologists should be informed such these instruments' interchangeability both in normal eyes and eyes with pathologies (7). In a previous study, it has been recommended that further study was needed to assess the agreement of CCT measurements in abnormal corneas such as keratoconus cornea (8). Accordingly, this observational study compared keratometry and corneal thickness measured in normal eyes and keratoconus by the all-in-one TRK-2P with the anterior cornea keratometry and pachymetry obtained by the PC-HR.

In the present study, CCT and keratometry data obtained by the all-in-one TRK-2P and PC-HR instruments in normal and KC eyes were evaluated for the first time. In-observation correlation coefficient values of the observation parameters obtained from TRK-2P and PC-HR instruments showed consistency. There was a strong correlation between the two instruments in both keratoconus and normal eyes. It has been reported that all-in-one TRK-2P and PC-HR were both reliable instruments in previous reports (7,8,11-13). Regarding all-in-one TRK-2P, it has been associated with optical low-coherence reflectometry (Lenstar LS 900) in a previous study and was found to show excellent agreement between the two instruments in terms of CCT outputs in healthy eyes (8). Similarly, the CCT parameter obtained from four optical instruments which included among of the PC-HR and all-in-one TRK-2P instruments were correlated by Özyol & Özyol (7). Regarding their results, it has been recommended that PC-HR and all-in-one TRK-2P instruments could not be used interchangeably with healthy eyes (7).

As mentioned earlier, keratometry readings of proficient instrument shows the radius of the corneal curvature. Notably, keratometry readings are specific parameter in the diagnosis of ectatic disorders as keratoconus. For this reason, keratometry readings have importance for staging, monitoring the progression, and creating treatment plans in KC patients (12). Hashemi et al. (13) have correlated keratometry readings of a handheld auto-refractokeratometer and PC-HR instruments. Regarding their results, two instruments has the worst agreement except for in emmetropic cases (13). Considering the progressive nature of KC, potential reading

errors may occur due to variations of amongst corneal phenotype. Additionally, it has been reported that the keratometry and pachymetry outputs can be affected by different tonometry instruments in KC cases (14-16).

Previously, all-in-one TRK-2P and PC-HR instruments have significantly correlated according to the CCT parameter in healthy eyes (7). Regarding the result of the previous study, the mean differences of CCT data had 13.6 ± 7.5 µm ($p < .001$) (7). In agreement with the previous study, we found a significant correlation that the mean differences of CCT data were 22.63 µm for controls and 19.44 µm for keratoconus ($p< 0.001$). We consider that the disparity of the means of thickness between our results and the previous report might be originated the demographic character of selected cohorts such as age, gender, or body mass index. Additionally, the disparity is considering clinically insignificant.

The ICC values of controls and keratoconus were (ICC= 0.987), and 0.983 for keratometry, while there were 0.998 and 0.994 for CCT, respectively ($p < 0.001$) in the present study. Regardless of the eye condition, excellent repeatability was seen in PC-HR (ICC= 0.987) whereas, high repeatability was seen in all-in-one TRK-2P (ICC= 0.983) for the CCT parameter. Hence, our results were in concordance with the previous correlations. Previously, having excellent-repeatability had been reported for PC-HR with ICC=0.981(7,17), and ICC=0.987 (18). In addition, having excellent-repeatability had been reported for all-in-one TRK-2P with ICC=0.974 (7).

PC-HR is a Scheimpflug imaging topography instrument that uses a single Scheimpflug camera (rotating from 0° to 180°) (19). The utilized camera can capture up to 50 slit-images from the reflected tear-film layer of the anterior segment in approximately 2 s (20, 21). Principally, the electromagnetic energy source of the PC-HR generates the blue-colored light at 470 nm wavelength. The wavelength of energy might be caused by a high amount of scattering of light via corneal reflections (19-22). Therefore, the scattered energy could adversely affect the thickness determination (23, 24). This drawback could be more distinctive in eyes with pathological corneas such as keratoconus (24). According to its manufacturer, all-in-one TRK-2P includes a registered 'Rotary Prism Technology' that provides reliable measurements. Accordingly, automatic refractometry and keratometry modes of all-in-one TRK-2P use this unique rotary prism (6). Principally, the infrared light source of the all-in-one TRK-2P generates electromagnetic energy at a longer wavelength that causes less scattering in corneal tissue (24). However, all-in-one TRK-2P evaluates only two perpendicular meridians of the anterior cornea. Thus, all-in-one TRK-2P does not provide keratometry outputs of the entire cornea whereas PC-HR do.

The sample size of the present study conducted on a group of Turkish population was in agreement with the previous studies (7,16). However, authors considered that the demographic characteristics of the patients is a limitation of this study due to racial characteristics. In addition, the cohort subjects of this study considered that do not reflect the general Turkish population. Within the limitation of this study, this is the first information in the literature associating the CCT and keratometry data obtained by the all-in-one TRK-2P and PC-HR in normal and KC eyes. Further studies are needed to provide data variability of the overlapped instruments on keratoconus or different eye defects.

Currently, PC-HR is known as a reliable and high-precise instrument among ophthalmologists, however, there is no standard technology for corneal topography characterization and it is not also possible to define which instrument provides the most precise measurements (19). To make an examination with the all-in-one instruments reduces the time loss and therefore the clinical workload. Besides its advantages during operation, being accurate and reliable is fundamental.

5. Conclusion

Within the limitations of this observational study, the following conclusions can be

drawn: All-in-one TRK-2P is a reliable instrument when correlated with Pentacam HR as a reference high-reliable instrument. Also, TRK-2P can produce consistent results in normal and pathological corneas.

Approved by the following research ethics committee

Yes. The study protocol was performed in accordance with relevant guidelines and regulations. The protocol was approved by the Human Subjects Office, Office of Non-Invasive Research Compliance – Eskisehir Osmangazi University (Study no. 26, issue date: 15.02.2022 with reference #: 2022/26).

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Research Article / Araştırma Makalesi

Magnetic Resonance Imaging Findings of Pineal Gland Metastasis

Pineal Metastazların Manyetik Rezonans Görüntüleme Bulguları

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Abstract

The pineal gland metastatic disease is relatively uncommon. Our research's objective was to assess pineal gland metastasis findings from magnetic resonance imaging (MRI). We queried the radiology reports of brain MRI examinations performed between September 2010 and December 2019. After identifying cases, patient characteristics including sex, age, diagnosis, survival time, and MRI features including size (largest cross-sectional diameter), T1- Weighted Image (WI) signal, T2-WI signal, contrast enhancement, and additional brain metastatic involvement area were evaluated. Our investigation identified 7 patients with pineal gland metastasis. Underlying malignancies were lung (N 2), breast (N 2), prostate cancer (N 1), neuroblastoma (N 1), and non-Hodgkin lymphoma (N 1). The average survival period after the detection of the pineal gland metastasis is 3.14 ± 3.93 months. The lesions ranged in size from 0.8 to 1.8 cm (mean 1.18±0.38 cm). Six tumors were isointense to gray matter both on T1-WI and T2-WI. One showed heterogeneous signal intensities on T1-WI and T2-WI. 6 out of 7 tumors showed homogenous solid enhancement while one tumor showed heterogeneous enhancement due to necrosis. Two patients had leptomeningeal, one patient had pituitary stalk, one patient had parenchyma, and one patient had calvarium-dural metastases. In the remaining 3 patients, no accompanying metastases were observed in brain. The presence of pineal gland lesions in patients with known malignancy should increase suspicion of metastatic involvement.
Keywords: pineal gland, metastasis, magnetic resonance imaging, pineal, magnetic resonance

Özet

Pineal bez metastazları oldukça nadirdir. Çalışmamızın amacı, pineal bez metastazlarının manyetik rezonans görüntüleme bulgularını değerlendirmektir. Bu çalışmada Eylül 2010 ile Aralık 2019 tarihleri arasında hastane/ radyoloji arşivindeki beyin manyetik rezonans görüntülemelerinin raporları retrospektif olarak tarandı. Olgular belirlendikten sonra, hastaların cinsiyet, yaş, tanı, sağkalım süresi gibi özellikleri ve boyut (en büyük kesit çap), T1 ağırlıklı, T2 ağırlıklı sinyaller, kontrast tutulumu, ek beyin metastatik tutulum alanları gibi özellikler değerlendirildi. Araştırmamızda pineal metastazlı 7 hasta tespit edildi. Altta yatan maligniteler akciğer (N 2), meme (N 2), prostat kanseri (N 1), nöroblastom (N 1), non-Hodgkin lenfoma (N 1) idi. Pineal metastaz saptandıktan sonra ortalama yaşam süresi 3.14 aydı. Lezyonların boyutları 0.8 ile 1.8 cm arasında değişiyordu. Altı tümör, hem T1 ağırlıklı hem de T2 ağırlıklı olarak gri cevhere göre izointens idi. Biri T1 ağırlıklı ve T2 ağırlıklı görüntülerde heterojen sinyal intensitesi gösterdi. 7 tümörden 6'sı homojen solid kontrastlanma gösterirken, bir tümör nekroza bağlı heterojen kontrastlanma gösterdi. İki hastada leptomeningeal, bir hastada hipofiz sapı, bir hastada parankim, bir hastada kalvaryum-dural metastaz vardı. Kalan 3 hastada ise beyinde eşlik eden metastaz izlenmedi. Bilinen malignitesi olan hastalarda pineal lezyonların varlığı metastatik tutulum şüphesini artırmalıdır.
Anahtar Kelimeler: pineal bez, metastaz, manyetik rezonans görüntüleme, pineal, manyetik rezonans

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1. Introduction

The pineal gland is an uncommon location for metastatic disease, although neoplasms from almost every tissue have been reported to metastasize to the pineal gland (1). When we reviewed the literature according to "pineal gland metastasis", we found 43 cases (1-3). In one autopsy study of 130 patients with lung and breast cancers, pineal metastases were discovered in 5 cases (2). In a surgical study by Lassman et al, 10 pineal gland metastasis were found among 191 patients with surgically managed pineal gland tumors of unknown etiology (3). The remaining 28 cases were reported as clinical cases only (1). Melatonin (N-acetyl-5-methoxy-tryptamine) is a molecule produced and released from the pineal gland. Apart from sleep and circadian regulations, melatonin displays inhibitory properties during tumor progression (4-6). The prognosis of pineal gland metastasis is poor because it generally occurs in the late course of widely metastatic systemic cancer (7). Impaired synthesis and secretion of melatonin from suffered pineal tissue may contribute to worsening of prognosis. Thus, pineal metastasis may be more important than just a metastasis site.

Primary tumors of the pineal gland can originate from a wide variety of cell sources, such as pineal parenchymal tumors, germ cell tumors, glial tumors, ependymomas, papillary pineal tumors, meningiomas, and lipomas (1-3). Histological diagnosis maybe not practical because of the highly invasive nature of biopsy and the deep location of the pineal gland. Magnetic resonance imaging (MRI) has an important place in the diagnosis of pineal metastasis as in the diagnosis of many diseases (8).

There is no prior report specifically focused on the radiological findings of pineal gland metastasis. In this article, we aimed to evaluate MRI findings of metastases to the pineal gland.

2. Materials and Methods

Subjects

MRI examinations were performed either on a 1.5 Tesla (T) MRI device (Magnetom vision plus, Siemens, Germany) or a 3T MRI device (GE Healthcare, Waukesha, WI). Conventional brain MRI protocol was as follows: T2-weighted image (WI) (Echo time (TE): 85, Repetition Time (TR):7711, Window Contrast/Window Width (WC/WW): 4434/8868 for 3T, TE: 91, TR:3940,WC/WW: 798/1698 for 1.5T) fluid-attenuated inversion recovery imaging (TE: 37, TR:2095,WC/WW: 3256/6513 for 3T, TE: 88, TR:8001,WC/WW: 474/973 for 1.5T) non-enhanced T1-WI (TE: 11, TR:829,WC/WW: 2082/4165 for 3T, TE: 17, TR:750,WC/WW: 660/1395 for 1.5T), and contrast-enhanced T1-WI (TE:9, TR:820, WC/WW: 5508/11017 for 3T, TE: 17, TR:750,WC/WW: 486/1021 for 1.5T) with a slice thickness: 5 mm. MRI images were transferred to the MR protocol workstation. From conventional MR images, a neuroradiologist with 12 years of experience (SS) and a radiologist with 6 years of experience (NA) evaluated the pineal gland metastasis with consensus. Due to the invasive nature of the biopsy and the deep location of the pineal gland, if the lesion became large on follow-up MRI examination, the pineal gland lesion was accepted as metastasis (Figure 1). MRI features including size (largest cross-sectional diameter), T1- WI signal, T2-WI signal, contrast enhancement, and additional brain metastasis were recorded.

Statistical analysis

Statistical analysis was evaluated with the SPSS v.22 package program (IBM Corp, Chicago, USA). Descriptive statistics were given as a mean ± standard deviation.

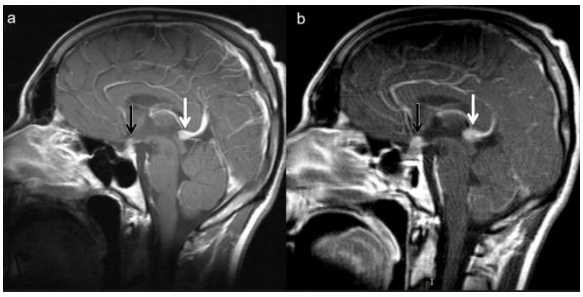

Figure 1. *A pineal lesion that increased in size in 2 months in a 23-year-old man with non-Hodgkin lymphoma. Figure 1a. A nodular lesion is seen on sagittal post-contrast T1-WI image (white arrow). Figure 1b. Sagittal post-contrast T1-WI image 2 months later shows marked progression of the lesion size, suggesting metastasis (white arrow). Also pituitary stalk involvement is progressed (black arrows).*

3. Results

Patient characteristics of these patients as well as their primary neoplasm are described in Table 1. We analyzed 7 patients (age range 23-71 years; mean age 46.28± 16.89 years, 3 male, 4 female) who were diagnosed with pineal gland metastasis from September 2010 to December 2019. Underlying malignancies were lung cancer (N 2), breast cancer (N 2), neuroblastoma (N 1), prostate cancer (N 1), and non-Hodgkin lymphoma (N 1). The survival period after the detection of the pineal gland metastasis ranged from 1 to 12 months (mean 3.14 ± 3.93 months).

The imaging characteristics including size, T1-WI signal, T2-WI signal, contrast enhancement, and additional brain metastasis were described in Table 2.

Table 1. Patients and Disease Characteristics

Patient Number	Sex	Age (years)	Diagnosis	Survival days
1	M	23	Non-Hodgkin lymphoma	1 month
2	F	71	Breast	12 months
3	M	49	Lung	2 months
4	F	25	Neuroblastoma	2 months
5	M	52	Prostate	2 months
6	F	53	Breast	1 month
7	F	51	Lung	2 months

Table 2. Radiologic Manifestations of the Patients

Patient Number	Magnetic Resonance Imaging				
	Size (cm)	T1 signal	T2 signal	Enhancement	Additional brain metastasis
1	1.4	isointense	isointense	homogeneous	infundibular stalk, leptomeninges
2	1.8	heterogenous-hipointense	heterogenous-hyperintense	peripheral (necrotic)	-
3	1.1	isointense	isointense	homogeneous	-
4	1.5	isointense	isointense	homogeneous	-
5	0.8	isointense	isointense	homogeneous	calvarium-dural
6	0.8	isointense	isointense	homogeneous	leptomeninges
7	0.9	isointense	isointense	homogeneous	parenchymal

The lesions ranged in size from 0.8 to 1.8 cm (mean: 1.18±0.38 cm). Six tumors were isointense to gray matter both on T1-WI and T2-WI (Figure 2). One showed heterogeneous signal intensities on T1-WI and T2-WI. 6 out of 7 tumors showed homogenous solid enhancement while one tumor showed heterogeneous enhancement due to necrosis (Figure 3). In contrast-enhanced images, two patients had leptomeningeal metastases, and one of them also had pituitary stalk metastases. One patient had parenchymal metastasis (Figure 4), and one patient had calvarium-dural metastasis. The remaining 3 patients had no other metastases within the brain. Pineal gland lesions and accompanying metastatic lesions were not observed in the previous examinations of our patients (not shown) in our study.

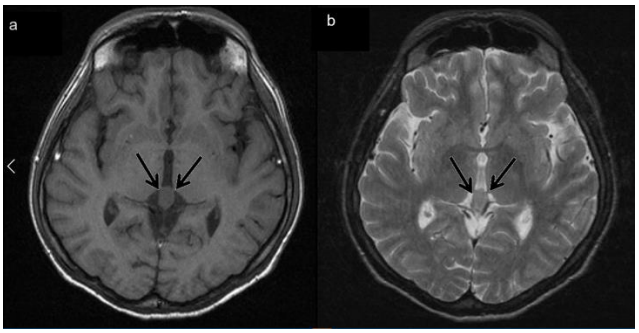

Figure 2. *Tumour is seen as isointense to gray matter both on axial T1-WI (Figure 2a) and on axial T2-WI (Figure 2b) (arrows).*

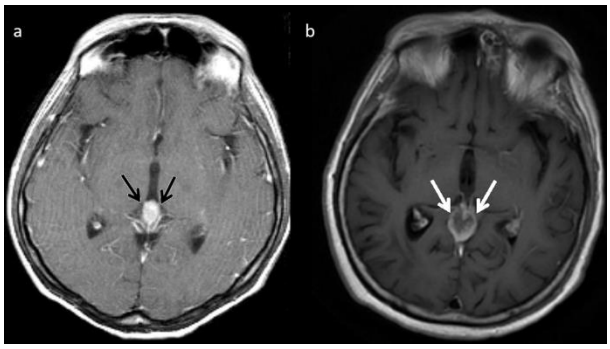

Figure 3. *On post-contrast T1-WI axial image, homogenous solid enhancement is seen within tumour (black arrows) (Figure 3a). Heterogenous enhancement is seen due to necrosis (white arrows) on post-contrast T1-WI axial image (Figure 3b).*

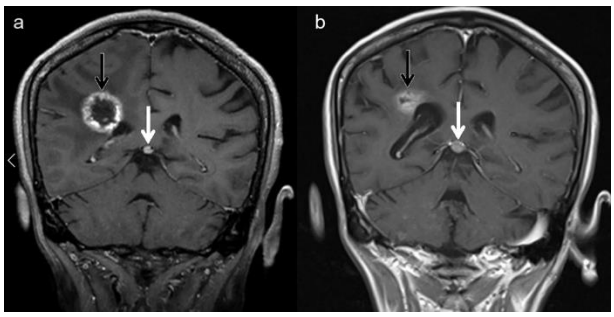

Figure 4*. Progression of pineal lesion size suggesting metastasis is seen (white arrows) in coronal post- contrast enhanced T1-WI images (Figure 4a). An additional parenchymal metastasis is regressed after radiotheraphy (black arrows) in coronal post-contrast T1-WI (Figure 4b)*

4. Discussion

Melatonin is a molecule synthesized and secreted by the pineal gland known as a regulator of sleep and circadian rhythms. The melatonin effect may be impaired in pineal metastases. In the last decade, many more reports have shown that melatonin leads to prolonged survival and improved quality of life in patients when included in chemotherapy or radiotherapy protocols designed to treat cancer (4-6). The diagnosis of pineal gland metastases is therefore important. Pineal gland metastases are most common in lung cancer (9). It has been reported that previously detected pineal gland metastases originate from other tumors such as the esophagus, breast, pancreas, kidney, stomach, liver, colon, melanoma, thyroid, and myeloma (1). Central nervous system lymphoma rarely involves the pineal gland. Kim et al. reviewed reported cases of primary and secondary pineal lymphoma in 2016 and found 10 cases, of whom 2 were secondary, with 1 retroperitoneal primary and 1 gastric primary (10). Since then, two additional cases of pineal lymphoma have been reported, one presenting with masses in the adrenal gland, the other one presenting as primary pineal lymphoma (11,12). When we look at the literature, pineal gland metastases are observed less frequently.

Brain MRI of isolated pineal gland metastasis secondary to acute lymphocytic leukemia revealed a well-defined solid lesion with intense enhancement after contrast. In this case, significant diffusion restriction of the lesion was detected on diffusion-weighted images (13). The diffusion restriction feature of the cases was not included in our study. Mostly homogeneous enhancement was observed in our patients, and heterogeneous enhancement was observed in pineal gland metastasis of breast cancer in one patient of our study.

In the literature, hydrocephalus is the prominent finding in the brain MRI image of a lung adenocarcinoma metastasizing to the pineal gland. And in this case, the diagnosis was made as a result of a biopsy several times (14). Hydrocephalus was not observed in our patients. Our patients did not have a pathological diagnosis, and most of them showed progression in the lesions during their follow-up. In addition, pineal gland lesions and accompanying metastatic lesions were not observed in the previous examinations in our study.

Heterogeneous contrast enhancement was observed in the pineal gland metastasis of esophageal neuroendocrine tumor on contrast-enhanced T1-weighted examination, and calcification was detected on computed tomography in the literature (15). In our study, there were no calcifications in pineal metastasis, and in our patients, heterogeneous contrast enhancement was present in one of the 7 patients. The primary of this patient was breast cancer. And in the literature ring-like enhancement and hypointensity in T2-weighted examinations were observed in a patient with pineal gland metastasis of gastric adenocarcinoma (16). In our 6 of 7 patients, the signal feature was observed as isointense in T2-weighted examinations.

Due to the absence of the blood-brain barrier in the pineal gland, the basis of extracranial malignant tumors reaching the pineal region is considered to be hematogenous metastasis (1). In one study, it was mentioned that metastasis of the pineal gland may arise mainly from tumor cells entering the pineal gland via the posterior choroidal artery (2). Due to the proximity of the pineal gland to the third ventricle and quadrigeminal cistern, tumor cells may also reach the pineal gland via cerebrospinal fluid pathways. Primary pineal gland tumors can arise from a wide variety of cells (17). Histological diagnosis maybe not be practical due to the invasive nature of the biopsy and the deep location of the pineal gland. The presence of pineal gland lesions in patients with known malignancy increases suspicion of metastatic involvement. In the literature, some patients could not be diagnosed pathologically with an invasive procedure at one time, and more than one intervention was needed (18). Diagnosis may be made alone based on imaging. MRI has an important place in the differential diagnosis. The metastatic pineal tumors are generally significantly enhanced because of the absence of the blood-brain barrier. However, the metastatic lesions showed different degrees of

enhancement, such as heterogeneous enhancement, peripheral enhancement, or less obvious enhancement. To distinguish metastases from other tumors located in the pineal gland through imaging maybe not always possible. In these circumstances, a follow-up MRI examination needs to be considered.

One limitation of our study is the absence of a pathological diagnosis of pineal gland metastases. Another limitation of our study is the small number of patients in our study due to the rarity of pineal gland metastases. Studies that can be performed with homogeneous patient groups with a larger number of patients and with the same primary may provide more specific MRI findings in the future.

The prognosis of pineal gland metastasis is poor because it generally occurs in the late course of widely metastatic systemic cancer (5). Impaired synthesis and secretion of melatonin from suffered pineal gland may contribute to worsening of prognosis. Most of the patients in the present study died within a few months. Due to the anti-cancer effect of melatonin, melatonin may be replaced if pineal gland metastasis is discovered.

5. Conclusion

In conclusion, although uncommon, the pineal gland should not be overlooked as a site of metastases. Histological diagnosis maybe not be practical due to the invasive nature of the biopsy and the deep location of the pineal gland. Diagnosis may be made alone based on imaging. The presence of pineal gland lesions in patients with known malignancy should increase suspicion of metastatic involvement. However, a confident diagnosis through imaging maybe not always possible. In these circumstances, a follow-up MRI examination should be made.

Ethical approval

Ethical approval for this study was obtained from the ethics committee (No. E-25403353-050.99-142914, decision no: 18, Date: 12.01.2021). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Research Article / Araştırma Makalesi

Nitrate and Diuretic Treatments in Acute Heart Failure within 30 Minutes: A Cross Sectional Study in Emergency Department

Akut Kalp Yetersizliğinde İlk 30 Dakika İçinde Nitrat ve Diüretik Tedavileri: Acil Serviste Kesitsel Bir Çalışma

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Abstract

Diuretics and nitrates form the cornerstone of emergency treatment, and more recently, some observational studies have highlighted the importance of the concept of 'time' in the treatment of Acute Heart Failure (AHF). We aimed to investigate clinical manifestations, phenotypes, and outcomes of patients with AHF and required early diuretics and nitrates administration. Patients who presented to the ED with signs and symptoms of acute heart failure were included in the study. The clinical features of the early (30 minutes and less) and delayed (over 30 minutes) treatment groups were evaluated according to the duration of diuretic and nitrate treatment. The median age of the 719 patients was 73 years [66–80 IQR] and 395 (54.9%) were male. Furosemide treatment was administered to 682 (94.9%) patients, and 537 (74.7%) patients received glycerol trinitrate treatment. In-hospital mortality rates were high in patients who received early treatments of both furosemide and nitrate (OR: 5.802, 95% CI: 1.885–17.831, p = 0.001 and OR: 5.229, 95% CI: 1.355–20.115, p = 0.013, respectively). The 3-month mortality rates were also high in patients who received early furosemide treatment (OR: 1.864, 95% CI: 1.078–3.223, p = 0.026). Patients who were started diuretics and nitrates in the early period (<30 min) had shorter stays in the ED. In-hospital mortality was higher in early treatment group.
Keywords: heart failure, furosemide, nitrates, emergency department

Özet

Akut Kalp Yetmezliğinin (AKY) tedavisinde diüretikler ve nitratlar, acil tedavinin temel taşını oluşturur ve yakın zamanlarda, bazı gözlemsel çalışmalar, 'zaman' kavramının önemini vurgulamıştır. AKY bulunan, erken diüretik ve nitrat uygulaması gerektiren hastaların klinik belirtilerini, fenotiplerini ve sonuçlarını araştırmayı amaçladık. Acil servise akut kalp yetmezliği belirti ve bulguları ile başvuran hastalar çalışmaya dahil edildi. Erken (30 dakika ve altı) ve gecikmeli (30 dakika üzeri) tedavi gruplarının klinik özellikleri diüretik ve nitrat tedavisinin süresine göre değerlendirildi. 719 hastanın medyan yaşı 73 idi [66-80 IQR] ve 395'i (%54.9) erkekti. 682 (%94,9) hastaya furosemid tedavisi, 537 (%74,7) hastaya gliserol trinitrat tedavisi verildi. Hem furosemid hem de nitratın erken tedavisini alan hastalarda hastane içi ölüm oranları yüksekti (OR: 5.802, %95 GA: 1.885-17.831, p = 0.001 ve OR: 5.229, %95 GA: 1.355–20.115, p = 0.013, sırasıyla). Erken furosemid tedavisi alan hastalarda 3 aylık mortalite oranları da yüksekti (OR: 1.864, %95 GA: 1.078–3.223, p = 0.026). Erken dönemde (<30 dk) diüretik ve nitrat başlanan hastaların acil serviste kalış süreleri daha kısaydı. Hastane içi mortalite erken tedavi grubunda daha yüksekti.
Anahtar Kelimeler: kalp yetersizliği, furosemid, nitratlar, acil servis

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1. Introduction

Acute heart failure (AHF) is a life-threatening condition highly associated with morbidity and mortality. It is also one of the leading causes of hospitalizations in subjects aged >65 years and is associated with high mortality and rehospitalization rates and represents a significant economic burden on the healthcare system. In-hospital mortality ranges from 4% to 10%. Post-discharge 1-year mortality is reported to be 25-30% with up to more than 45% deaths or readmission rates1. The majority of patients with AHF initially present to the emergency department (ED). Furthermore, early diagnosis of AHF in the ED and prompt initiation of appropriate treatment strategy may influence clinical outcomes2–4. In patients with AHF, diuretics and nitrates form the cornerstone of treatment, and more recently, some observational studies have highlighted the importance of the concept of 'time' in the treatment of AHF. Although the management of acute coronary syndrome is similar for almost every patient, a single treatment approach or a fixed treatment program and timing do not seem appropriate for every AHF patients. Most patients with AHF present with worsening signs and symptoms of congestion, but only a minority of patients with low cardiac output findings. However, precipitating factors, underlying heart disease, clinical characteristics, and comorbidities may differ greatly in patients presenting with similar clinical picture and also, may effect physician's treatment approaches5,6. Although early initiation of diuretics in AHF treatment has been recommended, the appropriate timing, patient management, and optimal practices are still unclear and data on nitrates are not available.

In this study, we aimed to examine the clinical manifestations, and outcomes of patients who presented to the ED with AHF and required time interval to treatment ≤30 min diuretics and nitrates administration.

2. Methods

This is a cross sectional and observational study. It included patients aged ≥18 who presented to the ED of a tertiary university hospital between October 2015, and September 2016; were diagnosed with de novo heart failure (HF) and/or acutely decompensated HF (ADHF), and for whom treatment was recommended (Figure 1). The study was conducted with the approval of the local ethics committee (date: October 27, 2015; number: 56). Signed informed consent was obtained from the patients who participated in the study or from their relatives if they were unconscious. Patients aged <18, those with trauma, pregnant women, patients with known HF who presented to the emergency department for reasons other than HF complaints and symptoms, chronic renal failure (CRF) without urine output, N-terminal proBNP (NT-proBNP) levels <300 pg/mL and those who (or whose relatives) did not give their consent were excluded from the study.

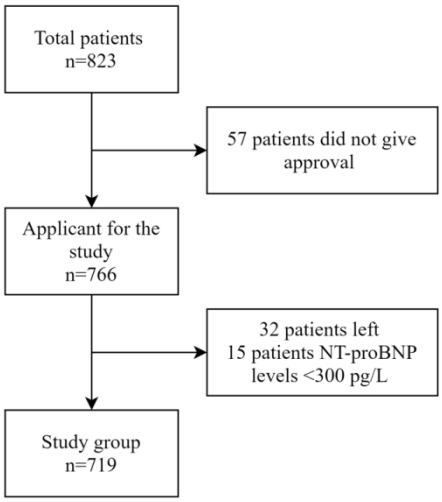

Figure 1. Flow chart of the patients participating in the study.

We recorded information from the patients regarding demographic data, comorbidities, medications, vital signs, the presence of typical signs and symptoms of HF, bedside echocardiography, chest X-ray, electrocardiography and laboratory findings, treatments and interventions performed in the ED, ED outcome (discharge/intensive care admission/hospitalization/death), and the duration of stay in the ED, intensive care unit, and hospital.

One or both nitrate or furosemide added to treatment if indicated by clinical findings. The time of treatment initiation (door-to-furosemide time and door-to-nitrate time) were recorded. No recommendations were made to the healthcare team during the diagnosis and treatment stages because of the nature of study. Patients with a time interval to treatment ≤30 min were assigned to the "early" treatment group and those with a difference of >30 min were assigned to the "delayed" treatment group. The primary outcome was ED visit that require IV therapy, re-hospitalization, and all-cause mortality in the following 3 months. The secondary outcome was to evaluate clinical factors causing a delay in administering diuretic and nitrate treatments.

During follow-up, patients were contacted via phone-call at 90th day. Presentations to the ED due to HF; hospitalizations due to HF; and the cause and date of death, were recorded.

Statistical Analysis

Continuous data were given data that do not fit into normal distribution were given as Median [25.-75. interquartile range], categorical data were given as a percentage (%). We used Shapiro Wilk's test to determine if the data fit into a normal distribution, Mann-Whitney U test is used when two groups did not. Cross-tables were analyzed with Pearson Chi-Square and Fisher Exact Chi-Square tests. Logistical regression analysis was used to determine risk factors. We used the IBM SPSS Statistics 21.0 program (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) to run the analyses.

3. Results

De novo HF was diagnosed in 373 (51.9%) patients and ADHF in 346 (48.1%) patients. The median age of the 719 patients was 73 years [66–80 IQR]. Of the patients, 395 (54.9%) were male and 324 (45.1%) were female. The median age was 72 years [65–78 IQR] for men, whereas it was 73 years [68–82 IQR] for women ($p < 0.001$). The median age of de novo patients was 73 years [64–80], and it was 73 years [66–77] in the ADHF group. The number of female patients was 189 (50.7%) among the de novo HF patients and 135 (39.0%) among the ADHF patients ($p = 0.002$). Based on the medical history, there were 516 (71.8%) patients with hypertension, 260 (36.2%) patients with diabetes mellitus, 119 (16.6%) patients with chronic kidney disease (CKD), 180 (25.0%) patients with chronic obstructive pulmonary disease, and 305 (42.4%) patients with coronary artery disease (CAD). The number of active smokers was 201 (28.0%). 512 (71.2%) patients' systolic blood pressure was higher than 140 mmHg.

The most common symptom was dyspnea in 714 (99.3%) patients followed by orthopnea in 688 (95.7%) patients, fatigue in 476 (66.2%) patients, palpitations in 353 (49.1%) patients, paroxysmal nocturnal dyspnea in 341 (47.4%) patients, and increased swelling in the legs and body in 249 (34.6%) patients.

Nitrate treatment was started earlier in patients with a history of CAD [odds ratio (OR): 1.568, 95% confidence interval (CI): 1.071–2.294, $p = 0.020$]. Although there was no statistically significant difference, furosemide and nitrate treatments were started delayed in cases with de novo HF so that it could be clinically significant (50.5% vs. 54.6%, $p = 0.337$; 48.8% vs. 58.1%, $p = 0.055$, respectively). In the evaluation of the vital parameters, it was observed that both systolic blood pressure and diastolic blood pressure were higher in patients in whom treatment with diuretics and nitrates were initiated in the early period ($p < 0.001$ in both groups). Increased heart rate was found to be statistically significant in the early treatment groups for both furosemide and nitrate ($p =$

0.037 and p = 0.001). In addition, oxygen saturation was lower and respiratory rates were higher in the early treatment group (Table 1).

While the left ventricular EF (LVEF) was determined to be 30.0 [20.0–50.0] % in the entire patient group, 407 (56.6%) of patients had HFrEF, 118 patients (16.4%) had HFmrEF, and 194 patients (27.0%) had HFpEF.

Table 1. Baseline Characteristics of Study Patients

	Furosemide Group (n=682)			Nitrate Group (n=537)		
	Early 0-30 minutes (n=499)	**Delayed >30 minutes (n=183)**	**p**	**Early 0-30 minutes (n=389)**	**Delayed >30 minutes (n=148)**	**p**
Age, years [IQR]	73 [65-79]	73 [67-80]	0.238	74 [66-80]	73 [68-80]	0.458
Female, *n(%)*	221 (44.3%)	87 (47.5%)	0.450	167 (42.9%)	72 (48.6%)	0.234
De novo, *n(%)*	252 (50.5%)	100 (54.6%)	0.337	190 (48.8%)	86 (58.1%)	0.055
Comorbidities, *n(%)*						
HT	357 (71.5%)	138 (75.4%)	0.316	282 (72.5%)	114 (77.0%)	0.286
DM	181 (36.3%)	72 (39.3%)	0.462	151 (38.8%)	43 (42.6%)	0.428
CRF	86 (17.2%)	25 (13.7%)	0.263	67 (17.2%)	20 (13.5%)	0.297
COPD	134 (26.9%)	41 (22.4%)	0.238	105 (27.0%)	37 (25.0%)	0.640
CAD	298 (59.7%)	100 (54.6%)	0.234	240 (61.7%)	75 (50.7%)	**0.020**
AF	98 (19.6%)	33 (18.0%)	0.637	75 (19.3%)	22 (14.9%)	0.235
Smoker	142 (28.5%)	48 (26.2%)	0.565	109 (28.0%)	34 (23.0%)	0.237
Medication, *n(%)*						
Furosemide	251 (50.3%)	86 (47.0%)	0.444	198 (50.9%)	65 (43.9%)	0.148
Spironolactone	90 (18.0%)	29 (15.8%)	0.505	66 (17.0%)	23 (15.5%)	0.691
Nitrate	61 (12.2%)	23 (12.6%)	0.904	49 (12.6%)	19 (12.8%)	0.940
ACEI	119 (23.8%)	37 (20.2%)	0.317	98 (25.2%)	30 (20.3%)	0.232
ARB	86 (17.2%)	36 (19.7%)	0.462	71 (18.3%)	27 (18.2%)	0.998
Vitals [IQR]						
SBP, *mmHg*	150 [140-170]	140 [120-160]	**<0.001**	160 [140-170]	150 [130-160]	**<0.001**
DBP, *mmHg*	90 [80-100]	80 [80-90]	**<0.001**	90 [90-100]	90 [80-98]	**<0.001**
Heart rate, *bpm*	100 [85-117]	95 [80-115]	**0.037**	100 [86.5-120]	94.5 [80.5-112]	**0.001**
SpO2, *%*	89 [85-92]	90 [88-93]	**<0.001**	89 [85-91.5]	90 [88-92]	**<0.001**
Respiratory rate	28 [24-32]	24 [22-32]	**0.002**	28 [24-32]	24 [22-32]	**0.001**

IQR: Interquartile range, HT: Hypertension, DM: Diabetes mellitus, CRF: Chronic renal failure, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blockers, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SpO2: Oxygen saturation

The evaluation of laboratory parameters, additional treatments administered, and interventions performed in the ED according to whether they were administered or performed early or delayed are provided in Table 2. In the furosemide group, oxygen therapy was given at a higher rate in patients whose treatment was started early (OR: 1.966, 95% CI: 1.130–3.420, p = 0.016). In patients who received early furosemide treatment, nitrates were also started early (OR: 1.496, 95% CI: 1.010–2.218, p = 0.045), and in those receiving early nitrate treatment, furosemide was also started early; however, no significant difference was found (p = 0.05). Patients underwent noninvazive mechanical ventilation were more likely to be included in the early treatment group for both furosemide and nitrate (OR: 4.588, 95% CI: 2.112–9.953, p < 0.001 and OR: 2.769, 95% CI: 1.397–5.479, p = 0.002, respectively). ED and hospital outcomes regarding treatment times were shown on Table 3.

Table 2. Echocardiographic findings, laboratory parameters, chest x-ray findings, and ED treatment

	Furosemide Group (n=682)			Nitrate Group (n=537)		
	Early 0-30 minutes (n=499)	**Delayed >30 minutes (n=183)**	**p**	**Early 0-30 minutes (n=389)**	**Delayed >30 minutes (n=148)**	**p**
LVEF % [IQR]	35 [20-50]	30 [20-50]	0.425	35 [20-50]	35 [20-50]	0.814
HFrEF, *n(%)*	273 (54.7%)	107 (58.5%)	0.712	215 (55.3%)	80 (54.1%)	0.961
HFmrEF, *n(%)*	85 (17.0%)	29 (15.8%)		69 (17.7%)	27 (18.2%)	
HFpEF, *n(%)*	141 (28.3%)	47 (25.7%)		105 (27.0%)	41 (27.7%)	
Laboratory parameters, [IQR]						
pH	7.40 [7.35-7.45]	7.41 [7.36-7.45]	0.084	7.40 [7.35-7.44]	7.41 [7.36-7.45]	0.369
Lactate, *mmol/L*	1.9 [1.3-2.6]	1.6 [1.2-2.4]	**0.004**	1.7 [1.3-2.5]	1.6 [1.0-2.4]	**0.008**
Base excess, *mmol/L*	-3.1 [-6.2 - -1.0]	-3.0 [-5.2 - -0.4]	0.124	-3.1 [-6.0 - -0.9]	-3.0 [-5.3 - -0.9]	0.352
Hemoglobin, *g/dL*	12.0 [10.5-13.8]	11.7 [10.4-13.7]	0.196	12.1 [10.6-14.0]	11.7 [10.4-13.2]	**0.022**
Sodium, *mEq/L*	138.0 [134.0-140.0]	139.0 [135.0-141.0]	0.283	138.0 [135.0-140.0]	139.0 [134.0-141.0]	0.914
Potassium, *mEq/L*	4.73 [4.30-5.10]	4.73 [4.35-5.20]	0.364	4.70 [4.28-5.20]	4.60 [4.30-5.08]	0.371
BUN, *mg/dL*	27.7 [18.3-43.4]	25.7 [18.5-44.5]	0.763	27.0 [18.2-41.0]	25.5 [18.3-42.8]	0.739
Creatinine, *mg/dL*	1.25 [0.95-1.68]	1.20 [0.94-1.63]	0.473	1.25 [0.95-1.67]	1.22 [0.91-1.65]	0.606
NT-proBNP, *pg/mL*	6860 [3058-15550]	7410 [3180-14856]	0.820	6823 [3091-15440]	6898 [2994-13508]	0.728
hs-Troponin T, *ng/L*	41.0 [22.0-77.0]	38.0 [23.0-70.0]	0.667	41.0 [21.0-75.0]	37.5 [24.3-63.8]	0.864
ED Treatment and interventions in hospital, *n(%)*						
Oxygen	465 (93.2%)	160 (87.4%)	**0.016**	368 (94.6%)	133 (89.9%)	**0.050**
Nitrate	401 (80.4%)	134 (73.2%)	**0.045**			-
Furosemide			-	388 (99.7%)	147 (99.3%)	0.476
Inotrope	15 (3.0%)	3 (1.6%)	0.425	N/A	N/A	-
NIMV	77 (15.4%)	7 (3.8%)	**<0.001**	65 (16.7%)	10 (6.8%)	**0.003**
Endotracheal intubation	7 (1.4%)	1 (0.5%)	0.689	6 (1.5%)	0 (0%)	0.195
Ultrafiltration	26 (5.2%)	4 (2.2%)	0.088	19 (4.9%)	3 (2.0%)	0.136
Coronary angiography	68 (13.6%)	28 (15.3%)	0.578	56 (14.4%)	21 (14.2%)	0.951

IQR: Interquartile range, LVEF: Left ventricular ejection fraction, HFrEF: Heart failure with reduced EF, HFmrEF: Heart failure with mildly reduced EF, HFpEF: Heart failure with preserved EF, BUN: Blood urea nitrogen, NIMV: Non-invasive mechanical ventilation

Table 3. Emergency and hospital outcomes regarding treatment times.

	Furosemide Group (n=682)			Nitrate Group (n=537)		
	Early 0-30 minutes (n=499)	**Delayed >30 minutes (n=183)**	**p**	**Early 0-30 minutes (n=389)**	**Delayed >30 minutes (n=148)**	**p**
Time in ED, *min*	274.0 [200.0-373.0]	330.0 [270.0-416.0]	**<0.001**	280.0 [200.0-374.5]	345.0 [275.0-450.0]	**<0.001**
Hospital admission, *n(%)*	335 (67.1%)	97 (53.0%)	**0.001**	258 (66.3%)	76 (51.4%)	**0.001**
ICU admission, *n(%)*	161 (32.3%)	46 (25.1%)	0.073	124 (31.9%)	33 (22.3%)	**0.029**
Time in hospital, *days*	6.0 [4.0-10.0]	6.0 [4.0-11.0]	0.828	7.0 [4.0-10.0]	6.0 [5.0-10.0]	0.338
90 days ED readmission, *n(%)*	206 (45.6%)	76 (42.9%)	0.550	166 (46.0%)	68 (47.6%)	0.750
90 days hospital admission,	215 (47.8%)	70 (39.5%)	0.062	174 (48.2%)	61 (42.7%)	0.261

n(%)						
In-hospital exitus, *n(%)*	44 (8.8%)	3 (1.6%)	**0.001**	26 (6.7%)	2 (1.4%)	**0.013**
90 days exitus, *n(%)*	80 (16.0%)	17 (9.3%)	**0.026**	53 (13.6%)	12 (8.1%)	0.080

ED: Emergency department, ICU: Intensive care unit

It was observed that patients who received early furosemide treatment were hospitalized at a high rate (OR: 1.811, 95% CI: 1.283–2.566, p < 0.001). On the other hand, both hospitalization and intensive care unit admission rates were high those receiving nitrate (OR: 1.866, 95% CI: 1.271–2.739, p = 0.001 and OR: 1.631, 95% CI: 1.050–2.531, p = 0.029, respectively). In-hospital mortality rates were high in patients who received early treatments of both furosemide and nitrate (OR: 5.802, 95% CI: 1.885–17.831, p = 0.001 and OR: 5.229, 95% CI: 1.355–20.115, p = 0.013, respectively). The 3-month mortality rates were also high in patients who received early furosemide treatment (OR: 1.864, 95% CI: 1.078–3.223, p = 0.026).

4. Discussion

Diuretics, which are the foundation of HF treatment, and vasodilator treatments that lead to symptomatic relief have been evaluated in many different7,8.The necessity of starting HF treatment in the early period has been defined in several guidelines. In recent years, studies on door-to-diuretic time have been performed, and these studies report that diuretic treatment initiated within a time of ≤60 min reduces the in-hospital mortality2. It has also been shown that treatment initiated at or before 90 min reduces the length of hospital stay and all-cause mortality9. In addition, it was reported in another study that diuretic treatment initiated at 60 min or before did not lead to significant differences in terms of clinical outcomes10. In our study, we evaluated patients who received treatment within and after 30 min, and we could not find any previous evaluations in the literature based on this time. Although there are remain questions regarding the use of glyceryl trinitrate in the acute treatment of HF, it has been observed that it is used in treatment because patients are usually hypertensive and there is a need to reduce the afterload1,11,12. Besides, the effect of individual patient profiles in heart failure on the timing of diuretic and nitrate therapy administered in the ED is not well defined.

In previous studies, when vital parameters were evaluated, systolic blood pressures, diastolic blood pressures, and heart rate were found to be high in patients receiving early treatment2,10. Approximately three quarters of patients hospitalized for AHF have a history of chronic HT and more than one half have an initial systolic blood pressure (SBP)>140 mmHg at the time of hospital admission13. In present study, approximately 75% of the patients had a diagnosis of HT and 71.2% of the patients had SBP>140 mmHg. Presence of a diagnosis of HT did not affect the timing of diuretic and/or nitrate therapy. However, it was observed that the blood pressure level at the time of admission to the ED was related to the timing of both diuretic and nitrate treatment. In addition, the prognostic effect of heart rate in AHF and its effect on treatment management in ED admission are still debate and unclear. In individuals with chronic HF, elevated resting HR was reported to be associated with increased risks of cardiovascular disease and mortality14. In the hyperacute phase of AHF, tachycardia is a mostly beneficial physiological compensatory response. In contrast to the predictive role of this parameter in chronic HF and clarity on rate control, the role of heart rate in AHF is much more controversial and the details of the relationship between the pathophysiology of AHF and HR are still unknown15. In our study, it was observed that the heart rate affects the timing of treatment at the time of admission to the ED, and the patient profile with a higher heart rate was treated with diuretic and nitrate therapy earlier. In a recent study, it was reported that simple combined admission measurement of SBP and heart rate predicted a higher risk for 1-year all-cause mortality in the elderly population hospitalized for the first time for AHF16.

Limitations

The present study also has some limitations. First, it is a single-center study. Second, the treatment was not administered in a randomized controlled manner, and it was an observational study. Third, although healthcare professionals treating the patients received similar training, treatment may have been delayed in patients with possibly atypical presentations.

5. Conclusion

According to our study, patients who were started on diuretics and nitrates in the early period (<30 min) had shorter stays in the ED and were hospitalized more. In-hospital mortality was higher in the early treatment group. Since the early treatment group consists of clinically more critical patients, there is a need for more such studies and definitive clinical guidelines

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Research Article / Araştırma Makalesi

Pelvic Lymphomas in the Differential Diagnosis of Gynecological Diseases: 10 Years of Experience of the Tertiary Center

Jinekolojik Hastalıkların Ayırıcı Tanısında Pelvik Lenfomalar: Üçüncü Basamak Merkezin 10 Yıllık Deneyimi

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Abstract

It was aimed to raise awareness about pelvic lymphoma among gynecologists by evaluating and sharing the clinical features of 12 patients diagnosed with pelvic lymphoma in the obstetrics and gynecology clinic of Eskisehir Osmangazi university.The clinico-pathological data of 12 patients who were presented to our clinics with gynecological complaints and diagnosed with lymphoma between 2010 and 2020 were analyzed retrospectively from their files.In our study, extranodal primary pelvic lymphoma was detected in ten patients, while nodal lymphoma was diagnosed in two patients. The most common histological lymphoma type detected in patients was diffuse large B-cell lymphoma seen in ten patients (83.3%). It was the cervical involvement that was most commonly observed in four patients (33.3%) with primary pelvic lymphoma. Total abdominal hysterectomy was performed as a gynecological surgical procedure in two patients, while a staging surgical procedure was performed in addition to total abdominal hysterectomy in five patients. Frozen pathology method was used in only four of the patients who underwent surgical procedure. While the diagnosis of lymphoma was made by minimally invasive tissue biopsy in five patients (41.6%), it could be made after surgery in seven patients (58.3%).Keeping pelvic lymphomas in mind in the differential diagnosis of patients who are evaluated with non-specific gynecological complaints and a preliminary diagnosis of pelvic mass may prevent some unnecessary extensive oncological surgeries. Increasing awareness of pelvic lymphoma among gynecologists can help prevent delays in diagnosis and treatment

Keywords: Pelvic lymphomas, atypical diagnosis, pelvic mass

Özet

Üniversitemiz kadın doğum polikliniğinde pelvik lenfoma tanısı konulan 12 hastanın klinik özelliklerinin değerlendirilip paylaşılarak jinekologlar arasında pelvik lenfoma konusunda farkındalık yaratılması amaçlanmıştır.2010-2020 yılları arasında jinekolojik şikayetlerle Eskişehir Osmangazi Üniversitesi kadın doğum bölümüne başvuran ve lenfoma tanısı alan 12 hastanın klinikopatolojik verileri dosyalarından retrospektif olarak incelendi.Çalışmamızda 10 hastada ekstranodal primer pelvik lenfoma saptanırken, iki hastada nodal lenfoma tanısı konuldu. Hastalarda en sık saptanan histolojik lenfoma tipi, on hastada (%83.3) görülen diffüz büyük B hücreli lenfoma idi. Primer pelvik lenfomalı dört hastada (%33.3) en sık görülen servikal tutulumdu. İki hastaya jinekolojik cerrahi olarak total abdominal histerektomi, beş hastaya total abdominal histerektomiye ek olarak evreleme cerrahisi uygulandı. Cerrahi işlem uygulanan hastaların sadece dördünde frozen patoloji yöntemi kullanıldı. Lenfoma tanısı beş hastada (%41.6) minimal invaziv doku biyopsisi ile konulurken, yedi hastada (%58.3) cerrahi sonrası konulabildi.Non-spesifik jinekolojik şikayetleri olup pelvik kitle ön tanısı alan hastaların ayırıcı tanısında pelvik lenfomaların akılda tutulması gereksiz yere yapılacak onkolojik ameliyatların önüne geçebilir. Jinekologlar arasında pelvik lenfoma farkındalığının artması, tanı ve tedavide gecikmelerin önlenmesine yardımcı olabilir.

Anahtar Kelimeler: Pelvik lenfomalar, atipik tanı, pelvik kitle

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1. Introduction

Lymphomas are hematological malignancies arising from mature and precursors of T and B lymphocyte cells and plasma cells. Lymphomas can be divided into two main groups as Hodgkin and non-Hodgkin and can be seen in all age groups. Non-Hodgkin lymphomas constitute 90% of lymphomas [1,2]. While the incidence of non-Hodgkin lymphomas in the United States is 19.6/100,000, it is predicted that 4.3% of all new cancer cases will be non-Hodgkin lymphoma for 2021 [3]. Less than one-third of non-Hodgkin lymphomas involve the extranodal area. The most common extranodal involvement sites are the gastrointestinal tract, skin, bone, central nervous system, and testis, while more rarely kidney, bladder, prostate, and genital system organs [4-7]. Although primary lymphoma in the female genital tract is extremely rare, it constitutes approximately 0.2-1.5% of all extranodal lymphomas [7-10]. Lymphomas with nodal involvement present itself with bone marrow and peripheral blood involvement together with a mass in lymphoid or visceral organs [11]. While most patients have B symptoms (fever, weight loss, malaise, and sweating), lymphadenopathy and laboratory changes, the definitive diagnosis is made by histological tissue biopsy. Patients with primary pelvic lymphomas apply to gynecology clinics with different clinical findings than lymphomas with nodal involvement. While few patients have B symptoms, most patients complain of irregular vaginal bleeding, vaginal discharge, and pelvic pain. After their initial evaluation in gynecology clinics, a preliminary diagnosis of pelvic mass, gynecological malignancy or uterine leiomyoma is made and surgery is planned. This causes delays in the diagnosis and treatment of the disease. Biopsy and immunochemotherapy are primarily used instead of surgery in the diagnosis and treatment of lymphomas.

The majority of literature studies on pelvic lymphomas consist of case reports. Case series are very few. Considering pelvic lymphomas in the differential diagnosis of gynecological diseases is a distant possibility for gynecologists. Therefore, in our study, it was aimed to raise awareness about pelvic lymphoma among gynecologists by evaluating and sharing the clinical features of 12 patients diagnosed with pelvic lymphoma in the obstetrics clinic of our university.

2. Material and Method

The medical data of 12 patients who presented to the gynecology clinic of Eskisehir Osmangazi University, which was a tertiary center, with various gynecological complaints and were diagnosed with pelvic lymphoma as a result of the evaluations between 2010 and 2020, were retrospectively analyzed from their files. Ethics committee approval was obtained before starting the study. Etic commitee approval number is 2020/13

Demographic data such as age, gravida, parity, and menopause status were examined from the files of the patients. The complaints of the patients at the time of admission to the gynecology clinic, and the histopathological findings after clinical examination and diagnostic procedures were reviewed from their files. The histopathological type, sites of involvement, and surgical procedures of lymphomas were examined retrospectively from their files. Staging information was made according to the Ann Arbor Staging System [11,12]. In addition, the general survival information of the patients was reviewed.

Statistical analyzes were performed by using the statistical software package SPSS version 22.0 (SPSS, Inc. Chicago, IL). The data were expressed as median and range for continuous variables. Binary variables were reported as counts and percentages.

3. Result

In our study, extranodal primary pelvic lymphoma was detected in ten patients, while nodal lymphoma was diagnosed in two patients. While the mean age of the patients was 50.41 ± 14.58, the mean gravida was 3.41 ± 2.6. While seven of the patients (58.3%) were in the premenopausal period, five of them (41.6%) were found to be postmenopausal. Demographic data of the patients were shown in Table 1.

The patients mostly applied to the gynecology service with complaints of pelvic pain, irregular menstrual bleeding, and vaginal discharge. Other clinical complaints of the patients were shown in Table 2.

Table 1. Clinical characteristics of the patients

Age	**50.41 ±14.58**
Gravida	3.41 ±2.6
Parity	2.75 ±2.56
Ca125	29.75 ±29.05
Diabetes Mellitus (n%)	6 (50%)
Hypertension (n%)	4 (33.3%)
Menopause Status	
Pre-menopausal (n%)	7 (58.3%)
Post-menopausal (n%)	5 (41.6%)

Table 2. Complaints of patients applying to the clinic

Complaints	
Pelvic pain	5 (41.6%)
Postmenopausal bleeding	2 (16.6%)
Irreguler bleeding	7 (58.3%)
Vaginal discharge	5 (41.6%)
Difficulty urinating	2 (16.6%)
Post coital bleeding	4 (33.3%)
Symptoms of B	3 (25%)
No complaints	1 (8.3%)

The most common histological lymphoma type detected in patients was diffuse large B-cell lymphoma seen in ten patients (83.3%). According to the Ann Arbor Classification, six patients (50%) were in Stage 1, while three patients (25%) were detected in Stage 2, and the remaining three patients had advanced stage tumors. In our study, it was the cervical involvement that was most commonly observed in four patients (33.3%) with primary pelvic lymphoma. Total abdominal hysterectomy was performed as a gynecological surgical procedure in two patients, while a staging surgical procedure was performed in addition to total abdominal hysterectomy in five patients. Frozen pathology method was used in only four of the patients who underwent surgical procedure. While the diagnosis of lymphoma was made by minimally invasive tissue biopsy in five patients (41.6%), it could be made after surgery in seven patients (58.3%). The clinical features of lymphomas are shown in Table 3. While four patients died due to lymphoma, eight patients are still alive. The overall survival of the patients was found to be 48.08±47.17 months.

Table 3. Clinicopathological characteristics of the patients

Histology	
Diffuse large B cell lymphoma (n%)	10 (83.3%)
Folicular lymphoma (n%)	1 (8.3%)
Hodgkin mixed celluler (n%)	1 (8.3%)
stage	
1 (n%)	6(50%)
2 (n%)	3(25%)
3 (n%)	1(8.3%)
4 (n%)	2(16.6%)
Site of involvement	
Ovary(n%)	2 (16.6%)
Uterus(n%)	1 (8.3%)
Cervics(n%)	4 (33.3%)

Mixed involvement(n%)	3 (25%)
Pelvic lymph node (nodal involvoment) (n%)	2 (16.6%)
Surgery treatment	
Total hysterectomy + bilateral salpingooferectomy (n%)	2 (16.6%)
Total hysterectomy + bilateral salpingooferectomy +omentectomy+ pelvic paraaortic lymph node dissection (n%)	5 (41.6%)
Frozen	4 (33.3%)
Diagnostic for lymphoma (n%)	1 (25%)
Diagnostic for malingnite (n%)	3 (75%)
Diagnostic method	
Biospy	5 (41.6%)
Surgery	7 (58.3%)
Overall survival (mean±std)	48.08±47.17

Preliminary diagnoses of pelvic mass, cervical cancer, and leiomyoma were considered primarily in the clinical examination and ultrasonographic evaluation of the patients. While myomas prolapsing the vagina were observed in two of the gynecological examinations, hydronephrosis, which is an oncological emergency of lymphomas, was observed as a clinical finding in two patients. One of our patients was diagnosed with lymphoma concurrent with endometrial cancer. The clinical features of the patients were shown in Table 4.

4. Discussion

In patients with pelvic pain, irregular menstrual bleeding, vaginal discharge, and pelvic mass findings on ultrasonography, gynecological diseases, especially gynecological malignancies, are considered in the foreground and extensive abdominopelvic surgical procedures are performed. The inclusion of pelvic lymphomas will prevent delays in the diagnosis and treatment of lymphoma and contribute to the prognosis in a good way, despite the fact that they are very rare in the differential diagnosis of pelvic mass and gynecological diseases.

In lymphomas with nodal involvement, involvement of gynecological organs is seen in approximately 30-40% of patients with advanced disease. Primary pelvic lymphoma involving gynecological organs constitutes only 1.5% of all extranodal lymphomas [13,14]. In advanced state nodal-involvement lymphomas, classical clinical B symptoms, fever, weight loss, sweating and malaise, as well as multiple lymph node involvement facilitate the diagnosis, while non-specific symptoms are seen in primary pelvic lymphoma. This causes the diagnosis to be made after complex surgical procedures. Due to its rarity, failure to provide standardization in treatment and delays in clinical diagnosis cause poor prognosis [10,14-17]

In our study, extranodal non-Hodgkin primary pelvic lymphoma was detected in ten of our patients. The most common complaints were irregular bleeding (58%), pelvic pain (41%), and vaginal discharge (41%). These rates were followed in accordance with the literature data [10, 13, 18].

In rare case reports in the literature, it has been stated that Cancer antigen 125 (Ca125) value can be used in the diagnosis, treatment, and follow-up of advanced lymphoma cases [16]. A moderate increase in Ca125 value was observed in our two postmenopausal patients. This not very high increase in Ca125 is of limited use in differential diagnosis because it increases in many gynecological and non-gynecological diseases.

Diffuse large B-cell lymphoma was detected histologically in 83.3% of our primary pelvic lymphomas. Diffuse large B-cell type is the most common type in the literature [19,20]. Although different rates are given in many studies, the most common site of involvement is expressed as the ovary [10,19]. In our study, cervix involvement was most frequently followed by involvement of more than one focus.

Table 4. All characteristics of the patients (Ct: chemotherapy, Dblcl:Diffuse b large cell lymphoma)

Patient	Pre-diagnosis	Ultrasound finding	Places of involvement	Diagnostic method	Treatment	Clinic finding	Histological diagnosis	Stage	Alive	Overall survival
1	Pelvıc mass	6 * 4 cm right adnexial solid mass	ovary	surgery	Tah+bso+Ct	-	Dblcl	1	yes	135
2	Pelvic mass	7 * 5 cm semisolid mass in the left adnex	ovary	surgery	Tah+bso+bpplnd +omentectomy+Ct	-	Dblcl	2	yes	48
3	leiomyoma	4 cm degenerated myoma	Uterus Ovary Cervics	surgery	Tah+bso+Ct	-	Dblcl	1	yes	60
4	Endometrium ca	7 * 5 cm uterine myoma	Cervics	surgery	Tah+bso+bpplnd +omentectomy+Ct	-	Endometrioid ca+Dblcl	Endcas3a+lenfomas1	yes	108
5	Cervics ca	cervical enlargement	Cervics	biopsy	Ct	hydronephrosis	Dblcl	1	yes	24
6	Cervics ca	cervical enlargement	Cervics	biopsy	Ct	-	Follicular+Dblcl	4	ex	8
7	vaginal myoma	9 * 9 cm fibroids in the vagina	Cervics	biopsy	Ct	mass with vaginal bleeding	Dblcl	3	ex	10
8	leiomyoma	enlarged uterus and cervix	Uterus	biopsy	Ct+Rt	Hydronephrosis+ kidney failure	Dblcl	2	ex	10
9	Pelvic mass	10*6 cm right adnexial solid mass	Right obturatory lymph node	surgery	Tah+bso+bpplnd +omentectomy+Ct	Endometrial hyperplazi	Dblcl (Nodal)	1	yes	24
10	leiomyoma	10*7 cm left adnexial solid mass	Left external lymph node	surgery	Tah+bso+bpplnd +omentectomy+Ct	-	hodgkin mixed cellular type	2	yes	120
11	Pelvic mass	7*4 cm right adnexial solid mass	Ovary+fallopian tuba+retroperitoneal	surgery	Tah+bso+bpplnd +omentectomy+Ct	extensive involvement of the lungs and abdomen	Dblcl	4	ex	6
12	Vaginal myoma	5*5 cm fibroids in the vagina	Cervics+uterus	biopsy	surgical excision+Ct	mass with vaginal bleeding	Dblcl	1	yes	24

While lymphoma was diagnosed in the final pathology after abdominal hysterectomy operation in seven of our patients, this rate was found to be 62% in the study of Dimitros *et al.* [19]. Of the patients who underwent abdominal hysterectomy, surgery was performed due to the diagnosis of pelvic mass in 4, leiomyoma in 2, and endometrial ca in one patient. It is seen that the diagnosis of our patients applying to the clinic is mostly in the form of pelvic mass, cervical mass, uterine and vaginal leiomyoma, as in the literature [10].

Imaging methods do not have sufficient sensitivity in diagnosing pelvic lymphoma [19-21]. On ultrasonographic imaging, a non-specific pelvic mass image of solid consistency is seen in the majority of our patients. The diagnosis of lymphoma can be made mainly by pathological examination of tissue samples and immunohistochemical staining. For this purpose, ultrasound-guided biopsy may be useful [22-24].

In patients with a preliminary diagnosis of myomas prolapsing the vagina, cervical mass, and uterine leiomyoma, it is possible to diagnose with biopsy before complex surgery. In our study, lymphoma was diagnosed by biopsy in five patients.

Although ultrasonography, biochemical tumor markers, and clinical examination findings provide important information in the diagnosis of malignant ovarian diseases, the diagnosis of lymphoma can mostly be made after complex surgery. Frozen method during abdominal surgery can be helpful in the diagnosis of lymphoma, although it is not definitive. In our study, frozen was applied to four patients and lymphoma diagnosis was made in only one patient. In case of suspected lymphoma diagnosis, hemato-pathologist support will increase the diagnosis rate.

The addition of surgery to immunochemotherapy in the treatment of pelvic lymphomas has not been shown to contribute positively to the survey of the disease [19]. Complex abdominal surgery causes delay in diagnosis and treatment [6-8,10,15,16,25-26]. In many studies, immunochemotherapy [Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (CHOP) + rituxumab] is recommended as primary therapy.

In conclusion, keeping pelvic lymphomas in mind in the differential diagnosis of patients who are evaluated with non-specific gynecological complaints and a preliminary diagnosis of pelvic mass may prevent some unnecessary extensive oncological surgeries. Increasing awareness of pelvic lymphoma among gynecologists can help prevent delays in diagnosis and treatment.

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Research Article / Araştırma Makalesi

Why Pediatricians Need to Consult An Otolaryngologist: Analysis of 3774 Patients

Pediatristler Neden Bir Kulak Burun Boğaz Uzmanına Danışır: 3774 Hastanın Analizi

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Abstract

A multidisciplinary approach may be necessary in the diagnosis and management of certain patients; therefore, interdisciplinary consultations have an important place in the medical practice. Diagnosis and management of children with ear, nose and throat (ENT) disorders take part in the practices of both otorhinolaryngologists and pediatricians. The aim of this study to investigate the reasons for pediatric ENT consultations, and examine them in relation with the pediatric age groups and the site of the requests. All pediatric consultations requested from the Otorhinolaryngology Department by the Pediatrics Department [outpatient, inpatient, intensive care unit (ICU) and pediatric emergency room (ER)] in 2021 were examined and included in the study. The pediatricians consulted a total of 3774 children in one-year period. The most common reason for consultation was hearing and/or speech evaluation (19.6%). The frequency of consultations for hearing and/or speech evaluation was significantly higher in early childhood (24.6%) ($p<0.001$) and lower in adolescents (10.7%) ($p<0.001$). The majority of the children consulted were in early childhood (38%) and middle childhood (28.5%). Most of the consultations were requested for outpatients (71.4%). Hearing and/or speech evaluation (26.6%) was the most common reason for outpatient consultations. Respiratory disorders (25.7%) in inpatients, prolonged intubation in the intensive care unit (47.1%) and foreign body (42.7%) in the emergency department were the most common reason for consultation. Pediatric consultations make up a large volume of work particularly in tertiary and higher health centers. Pediatric otorhinolaryngology units of these centers must be armed with equipment suitable for pediatric examination and surgery as well as an audiovestibular unit laboring audiologists and speech-language therapists.
Keywords: Pediatric Emergency Medicine; Otorhinolaryngologic Diseases; Consultation; Pediatricians

Özet

Bazı hastaların tanı ve tedavisinde multidisipliner bir yaklaşım gerekli olabilir; bu nedenle disiplinler arası konsültasyonların tıp pratiğinde önemli bir yeri vardır. Kulak burun boğaz (KBB) rahatsızlığı olan çocukların tanı ve tedavisi hem kulak burun boğaz uzmanlarının hem de pediatristlerin uygulamalarında yer alır. Bu çalışmanın amacı, pediatrik KBB konsültasyonlarının nedenlerini araştırıp, yaş ve talep edile yer ile olan ilişkisini belirlemektir. Pediatri bölümü [ayaktan hasta, yatan hasta, yoğun bakım (YBÜ) ve çocuk acil servisi (AS)] tarafından KBB bölümüne 2021 yılında konsülte edilen tüm pediatrik hastalar incelenerek çalışmaya dahil edildi. Pediatristler bir yıllık süre içinde toplam 3774 hastayı konsülte etti. En sık konsültasyon nedeni işitme ve/veya konuşma değerlendirmesiydi (%19,6). İşitme ve/veya konuşma değerlendirmesi için konsültasyon sıklığı erken çocukluk döneminde anlamlı olarak daha yüksek (%24,6) ($p<0,001$) ve adolesanlarda daha düşüktü (%10,7) ($p<0,001$). Konsülte edilen çocukların çoğunluğu erken çocukluk (%38) ve orta çocukluk (%28,5) yaş grubundaydı. Konsültasyonların çoğu ayaktan hastalar için istendi (%71,4). İşitme ve/veya konuşma değerlendirmesi (%26,6) ayaktan, solunum bozuklukları (%25,7) yatan, uzamış entübasyon (%47,1) yoğun bakım, yabancı cisim (%42,7) ise acil servis konsültasyonlarının en sık sebebiydi. Pediatrik konsültasyonlar, özellikle üçüncü basamak ve üzeri sağlık merkezlerinde büyük bir iş yükü oluşturmaktadır. Bu merkezlerin KBB üniteleri, pediatrik muayene ve cerrahiye uygun ekipmanlar yanı sıra odyolog ve konuşma-dil terapistlerini de bünyelerinde bulunduran bir odyovestibüler ünite ile donatılmalıdır.
Anahtar Kelimeler: Pediatrik Acil Tıp; Kulak Burun Boğaz Hastalıkları, Konsültasyon; Pediatristler

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1. Introduction

A multidisciplinary approach may be necessary in the diagnosis and management of certain patients; therefore, interdisciplinary consultations have an important place in the medical practice. Consultations may be requested for outpatients, inpatients, intensive care unit (ICU) patients or for the patients who are admitted to emergency room (ER).

The diagnosis and management of children with ear, nose and throat (ENT) disorders take part in the practices of both otorhinolaryngologists and pediatricians. Pediatricians may consult children with the otorhinolaryngologists for any congenital or acquired conditions of the ear, upper aero-digestive system, head and neck, nose and paranasal sinuses, as well as for the diagnosis, treatment and rehabilitation of hearing, speech, language and voice disorders. Therefore, nearly all tertiary pediatric medical centers agree that an on-site pediatric otorhinolaryngologist is needed in those centers (1).

The aim of this study is to investigate the reasons for pediatric ENT consultations, and examine them in relation with the pediatric age groups and the site of the requests including pediatric outpatient clinics, pediatrics hospital, ICU and ER, in our 3810-bed quaternary medical center.

2. Material and Methods

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee of X University, XXX Hospital (Date:06/04/2022, decree no:2519). Due to the retrospective nature of the study, informed consents were not obtained from the subjects.
All consultation requests to the Otorhinolaryngology Department from the Pediatrics Department (outpatient, inpatient, intensive care unit and pediatric emergency room) between January 1, 2021 and December 31, 2021 were examined using the

hospital's electronic records, and included in the study. Repeated consultations of the patients were excluded if they were requested with the same reason. Pediatric consultations requested from other departments were not included. The gender, age, the reason for consultation, and the site of consultation request (outpatient, inpatient, ICU or ER) were recorded.

The patients included in the study were classified according their ages into groups as following: neonates (birth - 27 days), infants (1 month - 12 months), toddlers (13 months - 24 months), early childhood age (25 months - 71 months), middle childhood age (72 months - 143 months) and adolescents (144 months – 18 years).

2.1. Statistical analysis

The statistical analyses were made using SPSS ver. 14.0 software (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as frequencies (n) and percentages (%). Chi-square test was used for comparisons of independent groups in terms of categorical variables. For continuous variables, Kolmogorov-Smirnov test was used to assess the assumption of normality. The variables that did not have a normal distribution are expressed as median (minimum-maximum). A p value <0.05 was considered as statistically significant.

3. Results

A total of 3774 children's consultations were included in the study, there were 1543 (40.9%) female and 2231 (59.1%) male patients. Of the consulted children, 42 (1.1%) were neonates, 326 (8.6%) were infants, 282 (7.5%) were toddlers, 1434 (38%) were in early childhood, 1074 (28.5%) were in middle childhood, and 616 (16.3%) were adolescents. There were 2693 (71.4%) requests for outpatients, 811 (21.5%) requests for ER patients, 183 (4.8%) requests for inpatients, and 87 (2.3%) requests for ICU patients.

When all patients were considered, the most common reason for consultation was hearing and/or speech evaluation (n=740, 19.6%). This was followed by sleep disorders (snoring, mouth breathing, sleep apnea, etc.) in 686 (18.2%), infection in 551 (14.6%), foreign body in 353 (9.4%), trauma in 234 (6.2%) and other reasons in 1210 (32%) patients.

Table 1. The reasons for pediatric consultations in relation with the age groups.

	Neonate (n=42)*	Infant (n=326)*	Toddler (n=282)*	Early Ch. (n=1434)*	Middle Ch. (n=1074)*	Adolescence (n=616)*	AP (n=3774)**
Hearing and/or speech evaluation	9 (21.4)	60 (18.4)	33 (11.2)	353 (24.6)	219 (20.4)	66 (10.7)	740 (19.6)
Sleep disorders	0 (0)	20 (6.1)	32 (11.3)	332 (23.2)	229 (21.3)	73 (11.9)	686 (18.2)
Infection	2 (4.8)	48 (14.7)	65 (23)	197 (13.7)	168 (15.6)	71 (11.5)	551 (14.6)
Foreign body	0 (0)	8 (2.5)	45 (16)	212 (14.8)	65 (6.1)	23 (3.7)	353 (9.4)
Trauma	0 (0)	10 (3.1)	28 (9.9)	82 (5.7)	55 (5.1)	59 (9.6)	234 (6.2)
Breathing disorders	12 (28.6)	102 (31.3)	34 (12.1)	26 (1.8)	14 (1.3)	9 (1.5)	197 (5.2)
Recurrent epistaxis	0 (0)	3 (0.9)	5 (1.8)	42 (2.9)	56 (5.2)	38 (6.2)	144 (3.8)
Vertigo	0 (0)	0 (0)	0 (0)	6 (0.4)	37 (3.4)	75 (12.2)	118 (3.1)
Otalgia	0 (0)	3 (0.9)	3 (1.1)	26 (1.8)	33 (3.1)	18 (2.9)	83 (2.2)
Nasal congestion	0 (0)	0 (0)	0 (0)	5 (0.3)	24 (2.2)	53 (8.6)	82 (2.2)
Epistaxis	0 (0)	0 (0)	2 (0.7)	26 (1.8)	23 (2.1)	24 (3.9)	75 (2)
Chronic cough	0 (0)	1 (0.3)	0 (0)	27 (1.9)	22 (2)	13 (2.1)	63 (1.7)
Head and neck mass	4 (9.5)	11 (3.4)	7 (2.5)	13 (0.9)	18 (1.7)	9 (1.5)	62 (1.6)
Ear wax	0 (0)	9 (2.8)	4 (1.4)	20 (1.4)	16 (1.5)	9 (1.5)	58 (1.5)
Hoarseness	0 (0)	2 (0.6)	1 (0.4)	19 (1.3)	20 (1.9)	7 (1.1)	49 (1.3)
Prolonged intubation	0 (0)	21 (6.4)	3 (1.1)	7 (0.5)	3 (0.3)	7 (1.1)	41 (1.1)
Dysphagia	0 (0)	5 (1.5)	1 (0.4)	8 (0.6)	12 (1.1)	9 (1.5)	35 (0.9)
Facial paralysis	0 (0)	0 (0)	1 (0.4)	6 (0.4)	10 (0.9)	17 (2.8)	34 (0.9)
Chronic headache	0 (0)	0 (0)	0 (0)	1 (0.1)	12 (1.1)	16 (2.6)	29 (0.8)
Chronic nasal discharge	0 (0)	1 (0.3)	4 (1.4)	6 (0.4)	10 (0.9)	3 (0.5)	24 (0.6)
Ankyloglossia	0 (0)	9 (2.8)	4 (1.4)	7 (0.5)	2 (0.2)	0 (0)	22 (0.6)
Choanal atresia	9 (21.4)	6 (1.8)	2 (0.7)	1 (0.1)	0 (0)	0 (0)	18 (0.5)
Tracheostomy problems	0 (0)	2 (0.6)	2 (0.7)	6 (0.4)	4 (0.4)	3 (0.5)	17 (0.5)
Otorrhagia	0 (0)	2 (0.6)	3 (1.1)	4 (0.3)	5 (0.5)	3 (0.5)	17 (0.5)
Hemoptysis	0 (0)	0 (0)	3 (1.1)	0 (0)	5 (0.5)	9 (1.5)	17 (0.5)
Ear malformations	5 (11.9)	1 (0.3)	0 (0)	0 (0)	2 (0.2)	0 (0)	8 (0.2)
Post-tonsillectomy hemorrhage	0 (0)	0 (0)	0 (0)	1 (0.1)	6 (0.6)	1 (0.2)	8 (0.2)
Velopharyngeal insufficiency	1 (2.4)	2 (0.6)	0 (0)	1 (0.1)	2 (0.2)	0 (0)	6 (0.2)
Sudden hearing loss	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.2)	1 (0.2)	3 (0.1)

*AP: All patients; Ch: Childhood; *N (%) within the age group; **N (%) in all patients included.*

The most common reason for consultation in neonates was respiratory disorders (wheezing, stridor, dyspnea, etc.) (n=12/42, 28.6%). This was followed by choanal atresia and hearing and/or speech evaluation (n=9, 21.4% for both). Of all neonates, 26 (62%) were outpatients, 1 (2%) was an inpatient, 1 (2%) was consulted from the ER, and 14 (34%) were in the ICU.

Similar to neonates, respiratory disorders were the most frequent cause of ENT consultations in infants (n=102/326, 31.3%). Hearing and/or speech evaluation (n=60, 18.4%) and infection (n=48, 14.7%) were the second and third most common causes. Of the infants, 213 (65%) were outpatients, 51 (16%) were inpatients, 29 (9%) were consulted from ER, and 33 (10%) were ICU patients.

Infection was the most common reason for consultation in toddlers (n=65/282, 23%). Foreign body was in the second place (n=45, 16%). These were followed by respiratory disorders (n=34, 12.1%), hearing and/or speech evaluation (n=33, 11.7%), and sleep disorders (n=32, 11.3%). Toddlers were consulted most frequently as outpatients (n=153, 54.3%), 32.2% of them were consulted from the ER, 11% were inpatients and 2.5% were ICU patients.

In early childhood, the most common reason for consultation was hearing and/or speech evaluation (n=353/1434, 24.6%) followed by sleep disorders (n=332, 23.2%), foreign body (n=212, 14.8%) and infection (n=197, 13.7%). Of the early childhood patients, 1023 (71.4%) were outpatients, 41 (2.8%) were inpatients,

356 (24.8%) were ER patients and 14 (1%) were ICU patients.

For middle childhood patients, the most common reason for consultation was sleep disorders (1074/229, 21.3%). This was followed by hearing and/or speech evaluation in (n=219, 20.4%) and infection (n=168, 15.6%). The patients in this age group were most frequently consulted on an outpatient basis (n=847, 79%). The number of inpatients was 33 (3%), the number of ER patients was 186 (17.3%), and the number of ICU patients was 8 (0.7%).

Adolescents were consulted most frequently for vertigo (75/616, 12.2%), followed by sleep disorders (n=73, 11.9%), infection (n=71, 11.5%), and hearing and/or speech evaluation (n=66, 10.7%). Of the adolescents, 431 (70%) were outpatients, 26 (4.2%) were inpatients, 11 were ICU patients (1.8%) and 148 (24%) were ER patients.

The frequency of consultations for hearing and/or speech evaluation was significantly higher in early childhood (24.6%) ($p<0.001$) and lower in adolescents (10.7%) ($p<0.001$). The frequency of sleep disorders as the cause of consultations was significantly higher in early childhood (23.2%) and middle childhood (21.3%) ($p<0.001$ and $p=0.002$, respectively). Similarly, the frequency of consultations due to infection was significantly higher in early childhood (23.4%) ($p<0.001$) and middle childhood (21.6%) ($p=0.001$). The consultations due to foreign body were significantly higher in toddlers (16%) and in early childhood (14.8%) ($p<0.001$) and significantly lower in infants (2.5%) and in middle childhood (6.1%) ($p<0.001$). The frequency of consultations for respiratory disorders was significantly higher in neonates (28.6%), infants (31.3%) and toddlers (12.1%), while it was lower in early childhood (1.3%), middle childhood (1.3%) and adolescents (1.5%) ($p<0.001$).

The most common reason for outpatient consultations (n=2693) was hearing and/or speech evaluation (n=717, 26.6%). This was followed by sleep disorders (n=680, 25.3%), infection (n=406, 15.1%), recurrent epistaxis (143, 5.3%), respiratory disorders (117, 4.3%), and vertigo (105, 3.9%) (Table 2). Of the outpatients consulted, 1023 (38%) were in early childhood. There were 847 (31.5%) patients in middle childhood group, 431 (16%) patients in adolescence group, 213 (7.9%) patients in infant group, 153 (5.7%) patients in toddler group, and 26 (1%) patients in neonate group.

The most common reason for inpatient consultations was breathing disorders (n=47/183, 25.7%). This was followed by infection (n=46, 25.1) and hearing and/or speech evaluation (n=23, 12.6%) (Table 2). Of the hospitalized patients, 51 (27.9%) were infants, 41 (22.4%) were in early childhood, 33 (18%) were in middle childhood, 31 (16.9%) were toddlers, 26 (14.2%) were adolescents and 1 (0.5%) was a neonate.

The most common reason for intensive care consultations was prolonged intubation (n=41/87, 47.1%). This was followed by respiratory disorders (n=23, 26.4%) and choanal atresia (n=7, 8%) (Table 2). Of the intensive care patients, 33 (37.9%) were infants, 14 (16.1%) were neonates, 14 (16.1%) were in early childhood, 11 (12.6%) were adolescents, 8 (9.2%) were in middle childhood and 7 (8%) of them were toddlers.

The most common reason for ER consultations was foreign body (n=346/811, 42.7%), followed by trauma (n=227, 28%), infection (n=94, 11.6%), and epistaxis (n=61, 7.5%) (Table 2). Of the ER patients, 356 (43.9%) were in early childhood, 186 (22.9%) were in middle childhood, 148 (18.2%) were adolescents, 91 (11.2%) were toddlers, 29 (3.6%) were infants, and 1 (0.1%) was a neonate. Among the foreign body consultations, the most common was a foreign body in the nose (58.4%). This was followed by foreign bodies in the external ear canal (22.2%), oropharynx (14.4%), and larynx (5%).

Table 2. The sites of the pediatric consultation requests.

	Outpatient clinic N=2693 (%)*	Hospitalized patients N=183 (%)*	ICU N=87 (%)*	ER N=811 (%)*
Hearing and/or speech evaluation	717 (26.6)	23 (12.6)	0 (0)	0 (0)
Sleep disorders	680 (25.3)	6 (3.3)	0 (0)	0(0)
Infection	406 (15.1)	46 (25.1)	5 (5.7)	94 (11.6)
Foreign body	7 (0.3%)	0 (0)	0 (0)	346 (42.7)
Trauma	0 (0)	5 (2.7)	2 (2.3)	227 (28)
Breathing disorders	117 (4.3)	47 (25.7)	23 (26.4)	10 (1.2)
Recurrent epistaxis	143 (5.3)	1 (0.5)	0 (0)	0 (0)
Vertigo	105 (3.9)	1 (0.5)	0 (0)	12 (1.5)
Otalgia	65 (2.4)	7 (3.8)	0(0)	11 (1.4)
Nasal congestion	82 (3)	0 (0)	0 (0)	0 (0)
Epistaxis	0 (0)	12 (6.6)	2 (2.3)	61 (7.5)
Chronic cough	63 (2.3)	0 (0)	0 (0)	0 (0)
Head and neck mass	47 (1.7)	10 (5.5)	3 (3.4)	2(0.2)
Ear wax	57 (2.1)	1 (0.5)	0 (0)	0 (0)
Hoarseness	48 (1.8)	1 (0.5)	0 (0)	0 (0)
Prolonged intubation	0 (0)	0 (0)	41 (47.1)	0 (0)
Dysphagia	25 (0.9)	9 (4.9)	1 (1.1)	0 (0)
Facial paralysis	12 (0.4)	4 (2.2)	0 (0)	18 (2.2)
Chronic headache	28 (1)	1 (0.5)	0 (0)	0 (0)
Chronic nasal discharge	23 (0.9)	1 (0.5)	0 (0)	0 (0)
Ankyloglossia	22 (0.8)	0 (0)	0 (0)	0 (0)
Choanal atresia	11 (0.4)	0 (0)	7 (8)	0 (0)
Tracheostomy problems	5 (0.2)	5 (2.7)	3 (3.4)	4 (0.5)
Otorrhagia	5 (0.2)	0 (0)	0 (0)	12 (1.5)
Hemoptysis	11 (0.4)	3 (1.6)	0 (0)	3 (0.4)
Ear malformations	8 (0.3)	0 (0)	0 (0)	0 (0)
Post-tonsillectomy hemorrhage	0 (0)	0 (0)	0 (0)	8 (0.2)
Velopharyngeal insufficiency	6 (0.2)	0 (0)	0 (0)	0 (0)
Sudden hearing loss	0 (0)	0 (0)	0 (0)	3 (0.4)

(%) within clinics; ICU: Intensive care unit; ER: Emergency room.*

Nasal fracture (n=117/227, 51.5%) was the most common cause of trauma-related consultations from the ER. This was followed by intraoral injury (tongue trauma, soft palate laceration, etc.) in 32 patients (14.1%), lip laceration in 26 patients (11.5%), and maxillofacial trauma in 21 patients (9.3%).

In the neonate group, the most common reason for consultation from the ER was infection (n=1, 100%.). Trauma was the most common reason for ER consultation in infants (n=10, 34.5%) and adolescents (n=57, 38.5%). foreign body was the most frequent cause of ER consultation in toddlers (n=45, 49.5%), early childhood (n=208, 58.4%) and middle childhood (n=62, 33.3%).

The frequency of consultation in the emergency department due to respiratory disorders (n=3, 10.3%) was higher in infants than in other groups (p=0.004). Foreign body consultations were higher in the early childhood group (n=208, 58.4%), whereas foreign body consultations in the middle childhood group were less frequent (n=62, 33%) (p<0.001 p=0.002, respectively). Trauma-related consultations were less frequent in the early childhood group (n=79, 22.2%) and more frequent in the adolescent group (n=57, 38.5%) (p=0.001 and p=0.002, respectively).

4. Discussion

Our results indicated that including the holidays, the pediatricians consulted more than 10 children per day to otorhinolaryngology clinic in our 3810-bed hospital, and the most frequent reason for consultation was hearing and/or speech evaluation. In fact, this number is bigger than most of the reported daily ENT consultation requests; for example, Sher et al. (2) reported

that the monthly number of pediatric ENT consultations ranged from 13 consults per month to 69 consults per month in their academic hospital in New York, serving a catchment area of 19 counties.

Although pediatric otorhinolaryngology has been established as a subspecialty of otorhinolaryngology in many countries including USA, otorhinolaryngology does not have any legal subspecialties in our country. Turkish otorhinolaryngologists have founded subspecialty societies as well as subspecialty clinics including otology, rhinology, head and neck surgery, allergy, plastic surgery and pediatric otorhinolaryngology, however, there is currently no legal regulation regarding these subspecialties.

The most common reason for pediatric consultations was evaluation of hearing and/or speech, in 19.6% of all consultations. The rate of consultation for evaluation of hearing and/or speech was higher in neonates, infants, in early childhood and middle childhood, however the group causing a significant difference was early childhood group ($p<0.001$) (Table 1). There is a newborn hearing screening program in our country, the neonates who cannot pass the screening tests are consulted to otorhinolaryngology, and most of the consulted neonates were the ones who did not pass the newborn hearing screening tests.

High frequencies of consultations for hearing and/or speech evaluation in the early and middle childhood may be related to middle ear problems in these ages. Demir et al. (3) reported that 12% of 973 children who applied to pediatrics outpatient clinic with non-otorhinolaryngological complaints had external or middle ear disorders including otitis media with effusion (6.9%), impacted cerumen (3.8%) and even congenital cholesteatoma (0.1%).

Articulation problems are common in early and middle childhood, and they might have been the reason for consulting otorhinolaryngology in the heading of evaluation of hearing and/or speech problems. Our result indicates that any pediatric otorhinolaryngology outpatient clinic must hold an audiology unit, including a speech-language pathologist.

Sleep disorders which include mouth breathing, snoring and sleep apnea were the second most common cause for otorhinolaryngology consultations. Sleep disorders were most frequent reasons in the early and middle childhood consultations ($p<0.001$ and $p=0.002$, respectively, Table 1). In fact, the most frequent cause of snoring and sleep apnea in these age groups is adenoid and tonsillar hypertrophy. Since we did not analyze the otorhinolaryngologic diagnoses in our study, we cannot provide data about the presence of those disorders in the consulted children. This is a limitation of our study.

In our study, the third most frequent cause of all pediatric consultations was infection (14.6%), and the frequency of consultations due to infection was significantly higher in early (23.4%) ($p<0.001$) and middle childhood (21.6%) ($p=0.001$). Infection was one of the most frequent cause for consultation in hospitalized patients (Table 2), and we assume that complicated head and neck infections may be a reason for this. Upper respiratory tract infections were reported as the first cause for emergency pediatric consultations, and it was reported that pediatricians referred their patients to otorhinolaryngology if they had recurrent acute otitis media (4,5).

The majority (71.4%) of the consulted children were outpatients in our study. In contrast, Sandra et al. (6) reported that only 1.94% of their pediatric consultation cases were referred. In fact, outpatient consultations have been increasing in our hospital in the recent years, probably due to medicolegal considerations. Sher et al. (2) of USA reported that otolaryngology consult volume increased by 144% in four years in their academic institution.

In our study, the most frequent cause for pediatric outpatient consultations were hearing and/or speech evaluation, sleep disorders and infection, in rank order (Table 2). Sandra et al. (6) reported the most common causes of outpatient pediatric consultations as infectious causes, including otitis and tonsillitis. Hearing and/or speech

problems were not mentioned as the cause of pediatric outpatient consultations in that study (6). It seems that pediatricians treat most of the childhood infections in our hospital, and only refer the children with complicated head and neck infections to otorhinolaryngology.

Breathing disorders were the most common cause of consultation in inpatients in our study, followed by infection. Prolonged intubation and breathing disorders were the most common reasons in ICU patients. Choi et al. (7) reported airway evaluation as the most frequent cause for ENT consultation in inpatients.

The most common reason for ER consultations was foreign body (42.7%) in our study (Table 2). Similarly, Topuz (8) reported that nasal foreign body was the most common reason for ENT consultations in children. In fact, nasal foreign bodies constituted the majority of the foreign bodies in our study (58.4%). We found trauma as the second cause of ER consultations (28%), followed by infection (11.6%). Choi et al. (7) reported that infection was the most frequent cause of pediatric consultations from ER followed by facial lacerations and airway evaluation. Sahin et al. (4)] reported that the most common ER pediatric consultation cause was upper respiratory tract infections in two hospitals included in their study. It seems that pediatric consultation patterns differ in different countries and between the institutions in the same country.

Pediatric age has been divided into six age groups due to children's different anatomical and physiological characteristics and response to medications by age (9). In our study, the majority of the consultations (66.5%) were requested for the children in the early and middle childhood. Our result is in agreement with Sandra et al. (6), who reported that 53.4% of 309 pediatric consultations were requested for the children between the 3 and 12 years of age.

Infant consultations were relatively small in our study (1.1%). Most of the consulted infants (62%) were outpatients, and the most frequent cause for consultation was respiratory problems including stridor and dyspnea in 31.3% of the cases. The reasons at the second rank were hearing and/or speech evaluation (18.4%) (Table 2). Most of the infants were outpatients, and we suppose that this is due to referral of the patients from other hospitals in our country.

It is interesting that the most common cause for consultation was vertigo in adolescents (12.2%). It has been reported that the exact incidence of vertigo in adolescence is not known, and the majority of them are diagnosed with migraine (10).

Our study has some limitations. First, the otorhinolaryngological diagnoses and the management of the consulted children were not examined. Second, our study includes the data of only one year, 2021, and was performed during COVID-19 pandemic, therefore our data may not reflect out-of-pandemic conditions and cannot provide any information on the alterations of the volume of consultations in time.

In conclusion, pediatric consultations make up a large volume of work particularly in big health centers. Pediatric otorhinolaryngology units of these centers must be armed with equipment suitable for pediatric examination and surgery as well as an audiovestibular unit laboring audiologists and speech-language therapists.

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Akut Gastroenteritli Hastaların Klinik Örneklerinde Salmonella, Shigella ve Campylobacter Türlerinin Kültür Yöntemi ve Moleküler Yöntem ile Tespit Edilmesi

Detection of Salmonella, Shigella and Campylobacter Species in Clinical Samples of Patients with Acute Gastroenteritis by Culture and Molecular Method

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Özet

Akut gastroenterit (AGE), tüm dünyada yaygın olarak görülen enfeksiyon hastalıkları arasındadır. Campylobacter, Salmonella, Shigella türleri AGE'nin bakteriyel etkenleri arasında ilk sıralarda bulunmaktadır. Bu çalışmada, laboratuvarımıza gönderilen gaita örneklerinde kültür yöntemi ve moleküler yöntemle Campylobacter, Salmonella ve Shigella sıklığını saptamak ve her iki yöntemin kıyaslanması amaçlanmıştır. 2019-2020 yılları arasında Namık Kemal Üniversitesi Tıp Fakültesi Hastanesi'ne ishal yakınması ile başvuran, ayaktan erişkin ve çocuk hasta örnekleri dahil edilmiştir. Dışkı örnekleri Campylobacter, Salmonella ve Shigella türlerinin tespiti için konvansiyonel kültür yöntemleri ve polimeraz zincir reaksiyonu (PZR) yöntemi ile çalışılmıştır. Çalışmamızda 400 (%77 yetişkin, %23 çocuk) hastaya ait dışkı örneği değerlendirilmiştir. Örneklerin kültür ile değerlendirilmesinde 14 örnekte (%3.5) etken saptanmış; 10'u (%2.5) Campylobacter spp., 4'ü (%1) Salmonella spp. olarak tiplendirilmiş, Shigella spp. izole edilememiştir. Kültür yöntemi ile Campylobacter spp. ve Salmonella spp. sıklığı çocuklarda sırasıyla %6.5 ve %2.2, yetişkinlerde %1.3 ve %0.7 olarak saptanmıştır. Örneklerin PZR ile değerlendirilmesinde 38 örnekte (%9.6) etken saptanmış; 33'ünde (%8.3) Campylobacter spp., 5'inde (%1.3) Salmonella spp. varlığı tespit edilmiş, hiçbir örnekte Shigella spp. saptanamamıştır. Kültürde üreme saptanan 14 dışkı örneğinin tamamında PZR yönteminde de aynı etken mikroorganizma tespit edilmiştir. 24 örnekte ise kültürde üreme saptanmayıp sadece PZR'de Campylobacter spp. veya Salmonella spp. saptanmıştır. Gaita kültürü AGE tanısında altın standart yöntem olmasına rağmen araştırmamız sonucunda PZR'nin hem hızlı sonuç vermesi hem de saptama oranının yüksek olması nedeniyle kültüre avantajlı olduğu görülmüştür. Bu nedenle moleküler yöntemlerin rutin tanıda kullanılmasının faydalı olacağı kanaatindeyiz.

Anahtar Kelimeler: Campylobacter, Salmonella, Shigella, PZR

Abstract

Acute gastroenteritis (AGE) is among the most common infectious diseases all over the world. Campylobacter, Salmonella and Shigella species are among the first bacterial agents of AGE. In this study, it was aimed to determine the prevelance of Campylobacter, Salmonella and Shigella by culture method and molecular method in stool samples sent to our laboratory and to compare both methods. Samples of adult and pediatric patients who applied to the Namık Kemal University Medical Faculty Hospital with the complaint of diarrhea between 2019-2020 were included. Stool samples were studied by conventional culture methods and polymerase chain reaction (PCR) method for the detection of Campylobacter, Salmonella and Shigella species. In our study, stool samples of 400 (77% adults, 23% children) patients were evaluated. In the evaluation of the samples by culture, agents were detected in 14 samples (3.5%), 10 (2.5%) were Campylobacter spp., 4 (1%) were Salmonella spp, Shigella spp. could not be isolated. By culture method, Campylobacter spp. and Salmonella spp. prevalence was 6.5% and 2.2% in children, and 1.3% and 0.7% in adults, respectively. In the evaluation of the samples by PCR, the causative agent was found in 38 samples (9.6%); Campylobacter spp. was found in 33 (8.3%) and Salmonella spp. was found in 5 (1.3%) samples, Shigella spp. not detected. The same causative microorganism was detected in the PCR method in all 14 stool samples with growth in the culture. In 24 samples, no growth was detected in the culture, only by PCR method, Campylobacter spp. or Salmonella spp. detected. Although stool culture is the gold standard method in the diagnosis of AGE, as a result of our research, PCR was found to be advantageous to culture because of its rapid results and high detection rate. Therefore, we believe that it would be beneficial to use molecular methods in routine diagnosis.

Keywords: Campylobacter, Salmonella, Shigella, PCR

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1. Giriş

Akut gastroenterit (AGE), çocukluk çağında sık görülmekle beraber her yaş grubunu etkileyen ve tüm dünyada yaygın olarak görülen enfeksiyon hastalıkları arasındadır(1). Özellikle gelişmekte olan ülkelerde önemli bir morbidite ve mortalite nedenidir (2). Etiyolojisi çoğunlukla enfeksiyöz kaynaklı olup *Campylobacter*, *Salmonella*, *Shigella* türleri AGE'nin bakteriyel etkenleri arasında ilk sıralarda bulunmaktadır (3).

Bakteriyel gastroenteritlerin tanısında laboratuvar testlerine ihtiyaç vardır ve altın standart yöntem kültürdür (4,5). *Campylobacter*, *Salmonella* ve *Shigella* türleri üretilmeleri durumunda laboratuvar tarafından bildirimi zorunlu hastalıklar grubuna girmektedir(6). Günümüzde hemen hemen bütün mikrobiyoloji laboratuvarlarında rutin gaita kültüründe *Salmonella* ve *Shigella* için değerlendirme yapılırken *Campylobacter* türleri selektif besiyeri gerektirmesi ve mikroaerofilik ortama ihtiyaç duyması nedeniyle her laboratuvarda rutin olarak çalışılmamaktadır(7). Kültür yöntemi beraberinde antibiyogram yapılabilmesi açısından avantaj sağlarken sonuçların 72-96 saatte raporlanması olumsuz yönüdür. Kültüre alternatif olarak moleküler yöntemler de AGE tanısında kullanılmakta ve hızlı sonuç alınmaktadır (8,9).

Bu çalışmada laboratuvarımıza gönderilen gaita örneklerinde kültür yöntemi ve moleküler yöntemle *Campylobacter, Salmonella* ve *Shigella* sıklığını saptamak ve her iki yöntemi kıyaslamak, ayrıca bölgemize ait epidemiyolojik veri elde etmek amaçlanmıştır.

2. Gereç ve Yöntem

Çalışmamıza, 01.11.2019-01.04.2020 tarihleri arasında ishal yakınması ile Namık Kemal Üniversitesi Tıp Fakültesi Hastanesi'ne başvuran, AGE ön tanısıyla gaita kültürü istenen erişkin ve çocuk hasta örnekleri dahil edilmiştir. Dışkı örnekleri *Salmonella* ve *Shigella* türlerinin tespiti için %5 koyun kanlı agar, Eosin Methylene Blue (EMB) agar ve hektoenterik agara ekim yapılarak 37°C'de 24-48 saat inkübe edilmiştir. *Campylobacter* spp. tespiti için modifiye kömür sefoperazon deoksikolat agar (modifiye CCDA) kullanılmış, 42°C'de mikroaerofilik ortamda 72 saat inkübe edilmiştir. İzole edilen izolatlar konvansiyonel yöntemler (gram boyama, TSI agar, üre agar, antiserum, oksidaz, hippurat hidrolizi vb) ve Vitek MS otomatize identifikasyon sistemi (Biomerieux, Fransa) ile tanımlanmıştır. Moleküler çalışma için dışkı örnekleri -80˚C'de bekletilmiş, RINA™ Robotik Nükleik Asit Ekstraksiyon Kitleri kullanılarak gerçek zamanlı polimeraz zincir reaksiyonu (PZR) temelli RINA™ M14 cihazı (Bioeksen, Türkiye) ile çalışılmıştır. Çalışmamızda ayrıca kültürde veya PZR testinde *Campylobacter* spp., *Salmonella* spp. ya da *Shigella* spp. saptanan numunelerin laboratuvar bilgi yönetim sisteminden (LBYS) retrospektif olarak gaita direk mikroskobi sonuçları incelenerek mikroorganizma varlığı-lökosit birlikteliği açısından değerlendirilmiştir. Tekrarlayan numuneler çalışmaya dahil edilmemiştir.

Çalışmamızın etik kurul onayı Tekirdağ Namık Kemal Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan alınmıştır (30.10.2019 tarih, 2019/23 karar no).

İstatistiksel Analiz

Çalışmada elde edilen veriler SPSS 22.0 (SPSS INC, Chicago, IL, USA) programına kaydedildi ve istatistiksel analizleri yapıldı. Kategorik veriler yüzde olarak verildi. Kategorik değişkenlerin bulunduğu bağımsız grupların karşılaştırılmasında Ki-Kare testi kullanıldı. p değerinin 0.05'in altında olduğu durumlar istatistiksel olarak anlamlı sonuçlar olarak değerlendirildi.

3. Bulgular

Çalışmamızda 400 yetişkin ve çocuk hastaya ait dışkı örneği değerlendirilmiştir. Çalışmaya dahil edilen dışkı örneklerinin %77'sinin (n=308) yetişkin, %23'ünün (n=92) çocuk; %55'inin (n=220) kadın, %45'inin (n=180) erkek hastaya ait olduğu görülmüştür.

400 dışkı örneğinin kültür ile değerlendirilmesinde; 14 örnekte (%3.5) etken saptanmış, 10'u (%2.5) *Campylobacter* spp., 4'ü (%1) *Salmonella* spp. olarak

tiplendirilmiş, *Shigella* spp. izole edilememiştir. *Campylobacter* türlerinin 4'ü *Campylobacter jejuni*, 3'ü *Campylobacter coli* olarak tespit edilmiş, 3 örnekte ise tür ismi saptanamamıştır. Bu 10 izolatın 6'sı çocuk hastalardan, 4'ü ise yetişkin hastalardan izole edilmiştir. *Salmonella* türlerinin 2'si *Salmonella enteritidis*, 2'si *Salmonella typhimurium* olarak bulunmuştur. *S.enteridis* izolatları çocuk, *S.typhimurium* ise yetişkin hastalara ait dışkı örneklerinden tespit edilmiştir. Böylece kültür yöntemi ile *Campylobacter* spp. ve *Salmonella* spp. sıklığı çocuklarda sırasıyla %6.5 (6/92) ve %2.2 (2/92), yetişkinlerde %1.3 (4/308) ve %0.7 (2/308) olarak saptanmıştır.

400 dışkı örneğinin PZR ile değerlendirilmesinde; 38 örnekte (%9.6) etken saptanmış, 33'ünde (%8.3) *Campylobacter* spp., 5'inde (%1.3) *Salmonella* spp. varlığı tespit edilmiş, hiçbir örnekte *Shigella* spp. saptanamamıştır. Kültürde üreme saptanan 14 dışkı örneğinin tamamında PZR yönteminde de aynı etken tespit edilmiştir. 24 örnekte ise kültürde üreme saptanmayıp sadece PZR'de *Campylobacter* spp. veya *Salmonella* spp. saptanmıştır (Tablo 1). Kültür ve PZR yönteminin etken mikroorganizma tespiti açısından istatiksel olarak karşılaştırılmasında her iki yöntem arasında anlamlı fark saptanmamıştır (toplam grupta p=0.096, *Campylobacter* spp'de p=0.121, *Salmonella* spp.'de p=0.561).

Kültür ve/veya PZR testinde etken saptanan 38 dışkı örneğinin 10'unda (%26.3) mikroskobik incelemede lökosit saptanmış, 28'inde (%73.7) ise lökosit görülmemiştir (Tablo 2).

Tablo 1. Değerlendirilen dışkı örneklerinin kültür ve PZR sonuçları

Etken	Kültür		Pzr		*p* değeri
	n	%	n	%	
***Campylobacter* spp.**	10	2.5	33	8.3	
***Salmonella* spp.**	4	1	5	1.3	
***Shigella* spp.**	0	0	0	0	
Toplam	14	3.5	38	9.6	0.096

Tablo 2. Mikroorganizma saptanan dışkı örneklerinin lökosit varlığı ile birlikteliği (n)

Etken	Kültür		Pzr	
	Lökosit (+)	Lökosit (-)	Lökosit (+)	Lökosit (-)
***Campylobacter* spp.**	2	8	8	25
***Salmonella* spp.**	2	2	2	3
***Shigella* spp.**	0	0	0	0
Toplam	4	10	10	28

4. Tartışma ve Sonuç

Akut gastroenterit, tüm dünyada önemli bir sağlık sorunu olarak karşımıza çıkmakta, özellikle gelişmekte olan ülkelerde ciddi morbidite ve mortaliteye neden olmaktadır. Tüm yaş gruplarında görülmekle beraber beş yaş altı çocuklar daha sık etkilenmektedir (10).

Birçok mikroorganizma gastroenterite neden olmaktadır. Bakteriyel etkenler arasında *Campylobacter*, *Salmonella* ve *Shigella* türleri ilk sıralarda yer almaktadır. Dünyada farklı yaş gruplarını içeren farklı çalışmalarda *Campylobacter* spp. sıklığı %1.7-10.4, *Salmonella* spp. sıklığı %0.4-19.5, *Shigella* spp. sıklığı %0-12.6 olarak bildirilmektedir. Ek olarak *Campylobacter* türlerinin *Salmonella* ve *Shigella* türlerinden çok daha sık görüldüğü belirtilmektedir(11-13). Ülkemizde ise oranlar *Campylobacter* spp'de %0.6-12.9, *Salmonella* spp.'de %0.5-8.4, *Shigella* spp.'de %0-9.8 arasında

değişmektedir(14-18). *Campylobacter* türlerinin neden olduğu gastroenteritlerde % 90-95 *C.jejuni* izole edilirken *Salmonella* türlerinde %57.3-74.1 oranında *Salmonella enteritidis* etkendir(19,20). *Shigella* türlerinde ise gelişmekte olan ülkelerde *Shigella flexneri* daha sık görülmekteyken gelişmiş ülkelerde *Shigella sonnei* daha sık görülmektedir (21,22).

Güney ve ark(7) ayaktan ve yatan hastalara ait toplam 379 dışkı numunesini değerlendirdikleri çalışmada kültürde etken olarak %3.7 *Campylobacter* ve %2.9 *Salmonella* türü izole etmişlerdir. *Campylobacter* spp. olarak izole ettikleri 14 suşun 13'ünü *C.jejuni* ve birini *C.coli* olarak tanımlamışlardır. *Salmonella* izolatlarının dördünü *S.enteridis*, dördünü *S.paratifo B* ve geri kalan üçünü de *S.typhimurium* olarak tiplendirmişlerdir. Ağralı(16) ishal yakınması olan 487 çocuk hastaya ait dışkı örneğinde yaptığı çalışmada 32 örnekte bakteriyel patojen saptamış, en sık *Salmonella* spp. (19 örnek), ikinci sırada *Campylobacter* spp. (7 örnek) izole etmiştir. Yazıcı ve ark(23) gastroenterit ön tanılı 80 hastaya ait dışkı örneklerinin kültüründe %4.5 oranında *C.jejuni,* %2.5 oranında *Salmonella* spp. saptamışlar, bakteriyel gastroenterit etkenleri arasında ilk sırada *C.jejuni*'yi tespit etmişlerdir. Bu üç çalışmada da hiçbir örnekte *Shigella* spp. izole edilememiştir (7,16,23). Kara ve ark(14) akut gastroenterit nedeniyle başvuran çocuklarda *Salmonella* ve *Shigella* sıklığını değerlendirdikleri çalışmada toplam 2425 hastaya ait dışkı numunesi incelemişlerdir. Etken olarak 77 hastada *Shigella* spp. (%3,2) ve 36 hastada *Salmonella* spp. (%1,5) saptamışlardır. *Salmonella* türlerinde en sık *S.enteritidis*, *Shigella* türlerinde ise *S.sonnei* tespit etmişlerdir. Yaptığımız çalışmada kültür yöntemi ile örneklerin %2,5'inde *Campylobacter* spp., %1'inde *Salmonella* spp. izole edilmiş, hiçbir numunede *Shigella* spp. tespit edilmemiştir. Etkenlerin sıklıkları ve tür dağılımları çalışmalara benzer saptanmıştır. Hem çocuklarda hem de yetişkinlerde en sık AGE etkeni olarak *Campylobacter* türleri tespit edilmiştir. Yine benzer şekilde çocuk hastalarda yetişkinlere göre *Campylobacter* ve *Salmonella* sıklığının daha fazla olduğu görülmüştür. Ek olarak çalışmamızda ve benzer birçok çalışmada *Shigella* spp. izole edilememesinin dışkı numunelerinin laboratuvara gereken sürede ulaştırılmamış olmasına bağlı olabileceğini düşünmekteyiz.

Kültür yöntemi tanıda altın standart test olmasına rağmen sonuçların 72-96 saatte raporlanması AGE tanısında moleküler yöntemler gibi daha hızlı yöntemleri gündeme getirmiştir(8,9). Özellikle *Campylobacter* türlerinin sık karşılaşılan etkenler olmasına rağmen kültürde üretilmesinin diğer etkenlere göre daha zor ve zaman alıcı olması moleküler yöntemlerin önemini arttırmıştır (24,25). Özcan ve ark(25) diyareli olgularda dışkıda etkene ait genetik yapıyı saptayan moleküler yöntemlerin duyarlık ve özgüllüklerinin yüksek olduğunu bildirmişlerdir. Platts-Mills ve ark (26) enfeksiyöz ishalli hastalara ait dışkı örnekleri ile yaptıkları çok merkezli çalışmada kültür yöntemi ile *C.jejuni/C.coli* DNA'larını saptayan PZR yöntemini karşılaştırmış, kültür yönteminin duyarlılığının oldukça düşük olduğunu saptamışlardır. Harrington ve ark(27) *Campylobacter, Salmonella* ve *Shigella* türlerinin tespitine yönelik yaptıkları çok merkezli çalışmada PZR yönteminin kültüre göre tanıda daha faydalı olduğunu saptamışlardır. İbrahim ve ark(19) 300 dışkı örneğinde kültür ve PZR yöntemini karşılaştırdıkları çalışmada kültür metodu ile *Campylobacter* türlerini %1, *Salmonella* türlerini %0.33, *Shigella* türlerini %0 olarak saptarken PZR metodu ile bu oranları sırasıyla %1.7, %2.33 ve %1.33 olarak tespit etmişlerdir. Göktaş ve ark(5) 471 hastaya ait dışkı örnekleri ile yaptıkları çalışmada multipleks PZR metoduyla bakteriyel gastroenterit etkenlerini değerlendirmişlerdir. 149 örnekte (%31,6) bakteriyel etken saptamış, bunların 108'i (%23) *Salmonella* spp., 8'i (%3.5) *Campylobacter* spp., 33'ü diğer bakteriyel etkenler olarak tespit edilmiş, *Shigella* spp. hiç izole etmemişlerdir. Çalışmalarının sonucunda gastroenterit tanısında, özellikle sanitasyonun kötü olduğu, düşük sosyoekonomik düzeyli bölgelerde hızlı tanı için PZR testlerinin rutinde faydalı olduğu kanısına varmışlardır.

Yaptığımız çalışmada kültür yöntemi ile etken saptanma oranı %3.5 iken PZR ile bu oran %9.6'ya yükselmiş, fakat iki yöntem arasında

etken tespiti açısından istatistiksel olarak anlamlı bir fark olmadığı görülmüştür (p=0.096). Bununla birlikte özellikle *Campylobacter* türlerinde PZR metodunun kültüre göre etken saptama oranının istatistiksel olarak anlamlı olmasa da (p=0.121) çok daha yüksek olduğu tespit edilmiştir. Çalışmamızda iki yöntem arasında anlamlı fark tespit edilmemesine pozitif örneklem sayımızın az olmasının neden olduğu kanısındayız. Literatüre bakıldığına *Campylobacter* türlerinin kültürde tespit edilebilmesi için kan içeren ya da içermeyen seçici besiyerleri kullanmak gerektiği, hatta bir kan içeren besiyerinin yanında bir de kömür içeren besiyerinin kullanılmasının izolasyon şansını %15'e kadar arttırabileceği bildirilmektedir. Bu nedenle laboratuvarların böyle bir kombinasyonu kullanması önerilmektedir (28). Bizim çalışmamızda sadece kömür içeren tek besiyeri kullanmamıza bağlı *Campylobacter* türlerinin kültür ile izolasyonunda sıkıntı yaşadığımızı düşünmekteyiz. Etken saptama oranlarına bakıldığında ise moleküler yöntemlerin rutin tanıda kullanılmasının daha faydalı olacağı ortadadır. Aynı gün içerisinde sonuç vermesi ayrıca önemli bir avantajdır. Testin maliyet etkinliği, deneyimli personel gerektirmesi gibi dezavantajları düşünüldüğünde ise en azından belirli bölgelerde ve 3. basamak hastanelerde çalışılmasının hasta yararına olacağı kanaatindeyiz.

Kültür ve moleküler yöntemlere ilaveten dışkının mikroskobik incelenmesi lökosit varlığının gösterilmesi açısından ishalli hastalarda önemlidir. Fakat her zaman kültür pozitifliği ve dışkıda lökosit varlığı birbirine eşlik etmemektedir. Özellikle *Campylobacter* spp. kaynaklı enterit ile dışkıda lökosit varlığı arasında yakın bir ilişki saptanmadığı bildirilmektedir(7). Yaptığımız çalışmada tüm numunelerin direk mikroskobik incelemesi yapılmamış, kültür ve/veya PZR testi pozitif saptanan numunelerde lökosit varlığı araştırılmıştır. Kültür ve/veya PZR testinde pozitif sonuç görülen 38 numunenin %76,3'ünde dışkının mikroskobik incelemesinde lökosit saptanmazken sadece %23,7'sinde lökosit görülmüştür. Saptadığımız bu sonuca dayanarak dışkıda lökosit olmamasının hem *Salmonella* hem de *Campylobacter* türlerine bağlı AGE'de tanıyı ekarte ettirmediği, mutlaka kültür ya da moleküler yöntemlerle tanının doğrulanması gerektiği ortadadır.

Çalışmamızın kısıtlılığı kültürde etken saptanan hastalarda etken saptanma sıklığı çocuk ve yetişkin olarak gruplandırılmış fakat PZR yöntemiyle saptanan hastalar bu şekilde ayrılamamıştır.

Sonuç olarak, AGE'de gereksiz tedaviden kaçınmak, hastalığın yayılmasını önlemek, enfeksiyon kontrolü ve epidemiyolojik önlemlerin alınması açısından hızlı ve doğru tanı gereklidir. Yaptığımız çalışma da dahil olmak üzere dünyada ve ülkemizde yapılan birçok çalışmada *Campylobacter* türlerinin bakteriyel gastroenterit etkenleri arasında ilk sırada görüldüğü bildirilmesine rağmen mikrobiyoloji laboratuvarlarının birçoğunda sadece *Salmonella* ve *Shigella* için kültür çalışmaları yapılmaktadır. Laboratuvarların gerekli alt yapıyı hazırlayarak *Campylobacter* spp.'yi de rutin kültür çalışmalarına eklemelerinin AGE'nin tanı ve tedavi sürecine katkı sağlayacağını düşünmekteyiz. Ek olarak AGE tanısında dışkının mikroskobik incelenmesinde lökosit varlığına bağlı kalmadan mutlaka ek yöntemlerle patojen araştırması yapılmasının gerekli olduğu da saptanmıştır. Gaita kültürü AGE tanısında altın standart yöntem olmasına rağmen araştırmamız sonucunda PZR'nin hem hızlı sonuç vermesi hem de saptama oranının yüksek olması nedeniyle kültüre avantajlı olduğu görülmüştür. Tüm bunlar değerlendirildiğinde moleküler yöntemlerin rutin tanıda kullanılmasının daha faydalı olacağı, maliyet etkinlik açısından düşünüldüğünde ise en azından belirli bölgelerde ve 3. basamak hastanelerde çalışılmasının hasta yararına olacağı kanaatindeyiz. Ayrıca örnek vermeden önce hastaların bilgilendirilmesinin, varsa dışkının kanlı ve/veya mukuslu bölgelerinden kültür kaplarına alınmasının ve alınan örneklerin bekletilmeden laboratuvara ulaştırılmasının her üç patojenin laboratuvarda tespit oranını arttıracağı unutulmamalıdır.

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Research Article / Araştırma Makalesi

Factors Affecting the Perioperative Blood Transfusion Need in Geriatric Hip Fractures

Geriatrik Kalça Kırıklarında Perioperatif Kan Transfüzyon İhtiyacına Etki Eden Faktörler

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Abstract

Hip fractures are an important cause of hospitalization and long hospital stays in the elderly. Allogeneic blood transfusion(ABT) affects patient health and also has economic effects.Therefore, more data on blood management are needed to improve patient outcomes, and optimize resource use. In this study,our primary aim was to determine the predictive factors affecting the need for ABT after geriatric hip fractures. A total of 596 hip fractures patients who were treated surgically in our clinic between 2011 and 2021 were analyzed. Age, gender, fracture type ,ASA score, surgical delay time, anesthesia type, surgery type, use of antiaggregants or anticoagulants, complications and hemoglobin (Hg), hematocrit (Hct), creatinine and INR levels at the time of admission were obtained. Binary logistic regression was employed to determine the risk factors. The receiver operating characteristic(ROC) curve was used to determine the appropriate cut-off point . While the mean Hg value of the patients who underwent ABT was 10.6±1.2 g/dl at the time of admission (p<0.001), the mean Hct value was 31.6±3.7%(p<0.001) and the mean creatinine was 1.25±0.88mg/dl (p=0.007). The outcomes of the regression analysis showed that the preoperative Hg level (p<0.001, OR:0.113, CI:0.068-0.190) and the preoperative Hct level (p=0.016,OR: 0.841, CI:0.730-0.968) were predictive factors for ABT. The ROC analysis showed that, a cut-off value of ≤11.9 g/dl was found for preoperative Hg and ≤35.5% for preoperative Hct. The main factors determining the need for blood transfusion are the Hg and Hct values at the time of admission. A Hg level of ≤11.9 g/dl and a Hct level of ≤35.5% can be safely used as a cut-off value.
Keywords: geriatric hip fractures, blood transfusion, cut-off value, predictors

Özet

Kalça kırıkları geriatrik hastalarda hastaneye yatışların önemli bir nedenidir. Allojenik kan transfüzyonu (AKT) hasta sağlığını etkiler ve ayrıca ekonomik etkileri vardır. Bu nedenle, hasta sonuçlarını iyileştirmek ve kaynak kullanımını optimize etmek için kan yönetimi hakkında daha fazla veriye ihtiyaç vardır. Bu çalışmada birincil amacımız geriatrik kalça kırıkları sonrası AKT ihtiyacını etkileyen prediktif faktörleri belirlemekti. Yöntemler: Kliniğimizde 2011-2021 yılları arasında cerrahi olarak tedavi edilen toplam 596 kalça kırığı hastası analiz edildi. Yaş, cinsiyet, kırık tipi, ASA skoru, cerrahi gecikme süresi, anestezi tipi, ameliyat tipi, antiagregan veya antikoagülan kullanımı, komplikasyonlar ve başvuru anındaki hemoglobin (Hg), hematokrit (Hct), kreatinin ve INR değerleri belirlendi. Risk faktörlerini belirlemek için ikili lojistik regresyon kullanıldı. Uygun kesme noktasını belirlemek için ROC eğrisi kullanıldı. AKT uygulanan hastaların başvuru anında ortalama Hg değeri 10,6±1,2 g/dl iken (p<0,001), ortalama Hct değeri %31,6±3,7 (p<0,001) ve ortalama kreatinin değeri; 1,25±0,88mg/dl (p=0,007). Regresyon analizi sonuçları, preoperatif Hg seviyesinin (p<0,001, OR:0.113, CI:0.068-0.190) ve preoperatif Hct seviyesinin (p=0.016,OR:0.841, CI:0.730-0.968) AKT için prediktif faktörler olduğunu gösterdi. ROC analizi, preoperatif Hg için ≤11,9 g/dl ve preoperatif Hct için ≤35.5'lik bir cut-off değerinin bulunduğunu gösterdi. Kan transfüzyonu ihtiyacını belirleyen ana faktörler başvuru anındaki Hg ve Hct değerleridir. ≤11,9 g/dl'lik bir Hg seviyesi ve ≤35.5'lik bir Hct seviyesi, cut-off değeri olarak güvenle kullanılabilir.
Anahtar Kelimeler: geriatrik kalça kırıkları, kan transfüzyonu, cut-off değer, prediktörler

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1. Introduction

The prevalence of geriatric hip fractures is increasing worldwide, rendering it a major public health problem. Of the 9 million osteoporotic fractures that occurred worldwide in 2000, 1.6 million were hip fractures [1]. Even if the incidence of hip fractures remains unchanged, this number is expected to rise to 6.26 million by 2050 [2]. Hip fractures are an important cause of hospitalization and long hospital stays in the elderly [3]. In addition, it is known that the rates of early and late mortality and major complications are high after geriatric hip fractures [4].

The relationship between low postoperative hemoglobin levels after geriatric hip fractures and poor functional outcomes in the early term, long hospital stays, and high readmission and mortality rates has been demonstrated [5, 6]. Allogeneic blood transfusion (ABT) is a known risk factor for immunosuppression that increases the risk of infection; excessive transfusion affects patient health and also has economic effects [7-9]. For these reasons, a "restrictive transfusion policy" has been recommended [10-12]. However, the indications for ABT in patients operated for geriatric hip fractures are not standardized and are controversial. Therefore, more data on blood management are needed to improve patient outcomes, reduce the need for perioperative ABT, and optimize resource use.

In this study, our primary aim was to determine the predictive factors affecting the need for ABT after geriatric hip fractures. In addition, we aimed to obtain evidence to help predict the perioperative blood requirement at admission. By managing the process better this way, we believe that patients can receive optimal medical care and avoid unnecessary costs.

2. Patients and Methods

A total of 743 hip fracture patients who were treated surgically in our clinic between January 2011 and June 2021 were retrospectively reviewed. After excluding those who were younger than 60, who had hip fractures following a high-energy trauma, had pathological fractures, had applied to the hospital after the first 12 hours, who had to undergo a second surgery for any reason within the first 30 days, and those who had insufficient or inconsistent perioperative data, 596 patients (205 males, 391 females) were included in the study. The flowchart for patient selection is shown in Figure 1. The hospital database, patient files, and radiological images of the patients were reviewed. Patients' age, gender, fracture type (intracapsular-extracapsular), American Society of Anesthesiologists (ASA) score, surgical delay time, anesthesia type (regional-general), surgery type (internal fixation-arthroplasty), use of antiaggregants or anticoagulants, need for ABT, postoperative complications, need for postoperative intensive care, and hemoglobin (Hg), hematocrit (Hct), creatinine and INR levels at the time of admission were obtained. Based on our standard approach for ABT transfusion in our clinic, transfusion was indicated for all patients included in the study. Allogeneic blood transfusion was performed in patients whose Hg levels fell below 8 mg/dl, and in those whose Hg levels were between 8-9 mg/dl and were symptomatic (chest pain, extreme weakness, palpitations) or had abnormal vital signs (tachycardia, hypotension).

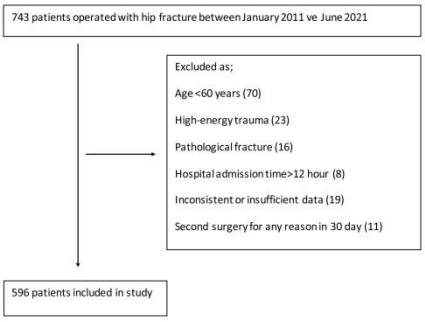


Figure 1. *Flowchart demonstrating the exclusion criteria.*

Age, Hg, Hct, creatinine, and INR values were analyzed as continuous data. In this way, we aimed to investigate the existence of a cut-off value that could predict the need for ABT. Preoperative radiological images of the patients were examined, and femoral neck fractures were grouped as intracapsular and trochanteric fractures as extracapsular fractures. Detailed preoperative data regarding comorbidities and ASA scores were obtained through the evaluation of anesthesiology notes, consultation information, and patients' files. The ASA scores were grouped as 1-2 or 3-4 based on previous literature [13]. The date of presentation and the date of surgery were checked to determine the surgical delay in days and it was analyzed as continuous data. The type of surgery was determined by examining the patients' postoperative radiological images. The preferred methods for internal fixation were classified as proximal femoral nail (PFN), dynamic hip screw (DHS), and cannulated screw. Data on the use of antiaggregants and anticoagulants such as warfarin, low-molecular-weight heparin (LMWH), clopidogrel, acetyl salicylic acid, rivaroxaban, and dabigatran were analyzed. Postoperative complications were classified as life-threatening major complications (mortality, pulmonary embolism, cardiac arrest, myocardial infarction, sepsis, acute renal failure, cerebrovascular accident) and minor complications (urinary tract infection, deep vein thrombosis, pneumonia, peripheral nerve damage, superficial wound infection). The 30-day mortality rate was determined by the collected data from the national data system and telephone questionnaires. Permission was obtained from the local ethics commission prior to the study (15.06.2021/25).

Statistical analysis

The continuous data were expressed as mean±standard deviation, while the categorical data were given as a percentage (%). The Shapiro-Wilk test was used to assess the normality of the data. In the comparison of the two groups that exhibited a normal distribution the independent samples t-test was used, whereas groups without a normal distribution were compared using the Mann-Whitney U test. Pearson's and Yate's chi-squared, and Pearson's exact chi-square tests were used in the analysis of the created cross tables. Binary logistic regression was employed to determine the risk factors. The receiver operating characteristic (ROC) curve was used to determine the appropriate cut-off point for the independent markers and calculate the sensitivity and specificity values. IBM SPSS Statistics for Windows v.21.0 (IBM Corp., Armonk, NY, USA) and MedCalc v.20.0 software were used in all analyses. The level of statistical significance was set at $p<0.05$.

3. Results

The mean age of the patients was 78.3 years (range: 60 to 102 years). In terms of fracture type, 359 patients (60.2%) were operated on for extracapsular and 237 (39.8%) for intracapsular fractures. Arthroplasty was performed in 256 (43%) patients, PFN in 251 (42.1%), DHS in 68 (11.4%), and cannulated screw in 21 (3.5%) patients. While 523 (87.8%) of the patients had an ASA score of 1 or 2, 73 (12.2%) had an ASA score of 3 or 4. The majority (64.8%) of the patients were given regional anesthesia and the rest (34.2%) general anesthesia. Allogeneic blood transfusion was performed in 238 patients (39.9%). Forty-two patients (7%) developed major complications, while 143 (24%) suffered from minor complications. Forty-eight patients (8.1%) needed postoperative intensive care. The mean surgical delay was 3.2 days (range: 1 to 9 days). The average 30-day mortality rate was 6.5%.

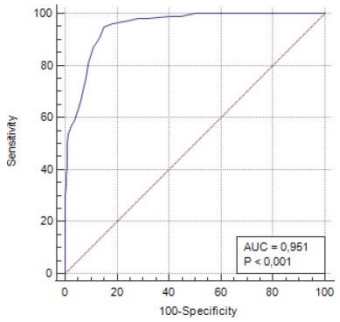
Allogeneic blood transfusion

Of the patients who underwent ABT, 77 (32.4%) were males and 161 (67.6%) were females, albeit the difference was insignificant ($p=0.442$). While the mean age of the 238 patients who underwent ABT was 78.9±8.0 years, the mean age of the 358 patients that did not require ABT was 78.0±8.4 years ($p=0.158$). Of the 238 patients who underwent ABT, 106 (44.5%) were performed arthroplasty, 103 (43.3%) PFN, 26 (10.9%) DHS, and three (1.3%) fixation with cannulated screws. There was no significant

relationship between the type of surgery and ABT (p=0.140). Of the patients who underwent ABT, 153 (64.3%) had extracapsular fractures and 85 (35.7%) intracapsular fractures. Again, no significant relationship was detected between fracture type and ABT (p=0.118). The ASA score was 1 or 2 in 87.8% of the patients who underwent ABT and in 87.7% of those who did not undergo ABT (p=1.000). Of the patients who underwent ABT, 66.8% did not use any antiaggregant or anticoagulant, while 15.5% used acetylsalicylic acid, 10.9% clopidogrel, 4.2% warfarin, 1.3% rivaroxaban, 0.8% dabigatran, and 0.4% LMWH. There was no significant relationship between antiaggregant or anticoagulant use and ABT (p=0.707). General anesthesia was performed on 31.9% of the patients who underwent ABT and regional anesthesia on 68.1% (p=0.198). The mean surgical delay was 3.4±1.7 days in patients who underwent ABT and 3.1±1.7 days in those who did not (p=0.058). No significant relationship was observed between the 30-day mortality rate and ABT (p=0.090). Minor complications were seen in 22.3% of the patients who underwent ABT, while major complications developed in 7.6%, again demonstrating an insignificant relationship with ABT (p=0.480 and p=0.819, respectively). Intensive care was needed for 10.1% of the patients who underwent ABT and for 6.7% of the patients who did not (p=0.183).

While the mean Hg values of the patients who underwent ABT were 10.6±1.2 g/dl at the time of admission, the values were 12.9±1.1 g/dl in those who did not receive ABT (p<0.001). The mean Hct value in the patients who underwent ABT was 31.6±3.7% at the time of admission and 38.3±3.7% in the patients who did not undergo ABT (p<0.001). The mean creatinine values in patients who underwent ABT was 1.25±0.88 mg/dl at the time of admission. The values were measured as 1.15±0.94 mg/dl in patients who did not undergo ABT (p=0.007). In patients who underwent ABT the mean INR value at the time of admission was 1.11±0.36, whereas the mean INR was 1.09±0.28 in patients who did not undergo ABT (p=0.438). Patients who underwent ABT were hospitalized for a mean period of 10.4±3.5 days. On the other hand, the length of hospitalization in those who did not undergo ABT was 8.8±3.5 days (p<0.001). The univariate analysis for predictive factors affecting ABT is given in Table 1.

The Hg, Hct, and creatinine levels, which were found to be significant as a result of the univariate analysis, were evaluated with multivariate logistic regression. The outcomes of the regression analysis showed that the preoperative Hg level (p<0.001, OR: 0.113, CI: 0.068-0.190) and the preoperative Hct level (p=0.016, OR: 0.841, CI: 0.730-0.968) were predictive factors for ABT. The results of the multivariate analysis are summarized in Table 2. ROC analysis was performed to determine the cut-off value for the Hg and Hct values found to be significant as a result of the multivariate analysis and to calculate the sensitivity and specificity values. As a result, a cut-off value of ≤11.9 g/dl was found for preoperative Hg (p<0.0001, sensitivity: 94.96, specificity: 84.92) and ≤35.5% for preoperative Hct (p<0.0001, sensitivity: 89.92, specificity: 77.09) (Figs. 2 and 3).



Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0,951
Standard Error [a]	0,00785
95% Confidence interval [b]	0,931 to 0,967
z statistic	57,469
Significance level P (Area=0.5)	<0,0001

[a] DeLong et al., 1988
[b] Binomial exact

Youden index

Youden index J	0,7987
Associated criterion	≤11,9
Sensitivity	94,96
Specificity	84,92

Figure 2. *ROC analysis to determine the cut-off value for preoperative hemoglobin*

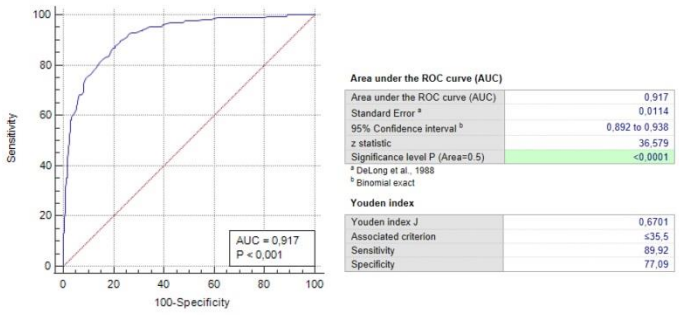


Figure 3. *ROC analysis to determine the cut-off value for preoperative hematocrit.*

Table 1. Results of the univariate analysis for predictive factors affecting allogeneic blood transfusion (ABT).

	Non-ABT (n=358)	ABT (n=238)	p
Gender			
Male	128 (35.8%)	77 (32.4%)	0.442
Female	230 (64.2%)	161 (67.6%)	
Age (years)	78.0±8.4	78.9±8.0	0.158
Surgical delay time (days)	3.1±1.7	3.4±1.7	0.058
Surgery type			
Arthroplasty	150 (41.9%)	106 (44.5%)	
DHS	42 (11.7%)	26 (10.9%)	0.140
PFN	148 (41.3%)	103 (43.3%)	
Cannulated screw	18 (5.0%)	3 (1.3%)	
Fracture type			
Extracapsular	206 (57.5%)	153 (64.3%)	0.118
Intracapsular	152 (42.5%)	85 (35.7%)	
ASA score			
1-2	314 (87.7%)	209 (87.8%)	1.000
3-4	44 (12.3%)	29 (12.2%)	
Antiaggregant–anticoagulant use			
ASA	70 (19.6%)	37 (15.5%)	
Dabigatran	2 (0.6%)	2 (0.8%)	
Clopidogrel	26 (7.3%)	26 (10.9%)	
LMWH	1 (0.3%)	1 (0.4%)	0.707
Rivaroxaban	4 (1.1%)	3 (1.3%)	
Warfarin	16 (4.5%)	10 (4.2%)	
None	239 (66.8%)	159 (66.8%)	
Anesthesia type			
General	134 (37.4%)	76 (31.9%)	0.198
Regional	224 (62.6%)	162 (68.1%)	
Major complication			
Yes	24 (6.7%)	18 (7.6%)	0.819
No	334 (93.3%)	220 (92.4%)	
Minor complication			0.480
Yes	90 (25.1%)	53 (22.3%)	
No	268 (74.9%)	185 (77.7%)	
Hospitalization in ICU			
Yes	24 (6.7%)	24 (10.1%)	0.183
No	334 (93.3%)	214 (89.9%)	
Length of hospital stay (days)	8.8±3.5	10.4±3.5	**<0.001**
Preoperative Hg (g/dl)	12.9±1.1	10.6±1.2	**<0.001**
Preoperative Hct (%)	38.3±3.7	31.6±3.7	**<0.001**
Creatinine (mg/dl)	1.15±0.94	1.25±0.88	**0.007**
INR	1.09±0.28	1.11±0.36	0.438

ASA: acetylsalicylic acid, DHS: dynamic hip screw, Hg: hemoglobin, Hct: hematocrit, ICU: intensive care unit, INR: international normalized ratio, LMWH: low-molecular-weight heparin, PFN: proximal femoral nail. Significant p values are written in bold.*

Table 2. Results of the multivariate analysis.

Multivariate predictor	Regression coefficient	Odds ratio	95% Confidence interval		p
			Lower	Upper	
Hemoglobin at admission	-2.177	0.113	0.068	0.190	**<0.001**
Hematocrit at admission	-0.173	0.841	0.730	0.968	**0.016**

**Significant p values are written in bold.*

4. Discussion

We retrospectively analyzed 596 individuals to determine the ABT rate in geriatric hip fracture patients and the predictive factors affecting it. Our sample size was relatively small, however, we had a great range of relevant confounders in our study. In addition, we aimed to form a homogeneous study group by excluding the patients aged less than 60 years and those who had fractures as a result of a high-energy trauma. To produce a more reliable regression model, the confounders were analyzed as continuous variables where possible. In particular, we investigated for a cut-off value by not grouping the preoperative Hg and Hct values and analyzing them as continuous variables. In this way, we wanted to create evidence to predict the need for ABT in geriatric patients presenting with hip fractures, since the first step in the management of ABT is to predict the possible need. Good management of transfusion can prevent complications caused by anemia, while also preventing the risks of transfusion and effectively reducing the economic burden [14-17].

In our study, the rate of ABT application was 39.9%. In a study by Hou et al., where 220 geriatric patients with trochanteric fractures were examined, the rate of ABT was reported as 40.5% [18]. In another study, Shokoohi et al. reported an ABT rate of 32.6% among 919 patients [19]. The blood transfusion rate in our study is in line with the literature.

Contrary to some studies from the literature [18-21], age was not found as a predictive factor for perioperative ABT in our study. The mean age of the patients that underwent ABT was 78.9 years, while the mean age of the patients who did not receive ABT was 78.0 years. In the ABT group, 72.7% of the patients were 75 years of age or older whereas this rate was 65.6% among those that did not undergo ABT, exhibiting an insignificant difference. We believe that the lower preoperative Hg and Hct values in older patients may have caused the difference in other studies.

Several studies in the literature have suggested that preoperative anemia is a predictive factor for perioperative need for ABT [3, 18-25]. Hou et al. stated that values of 12.4 g/dl and below pose a risk for ABT [18], while Shokoohi et al. reported that the ABT rate was six times higher in patients who were anemic at first admission [19]. In Robbins and Steingold's study, only one of nine patients with a Hg level above 11g/dl needed ABT [24]. Kurdy and Hokan recommended blood preparation for patients with a Hg value below 12 g/dl [25], whereas Adunsky et al. suggested that patients with a Hg value above 12g/dl can be operated without blood preparation [3]. In our study, a preoperative Hg value of ≤11.9 g/dl was found to be a strong predictive factor for ABT, a finding in parallel with previous studies.

Contrary to some studies in the literature [3, 18, 19], we found no relationship between the type of surgical technique and ABT. Although PFN application is considered to be minimally invasive and is thought to cause less bleeding due to small incisions, it may cause a high amount of hidden bleeding as reported by Foss and Kehlet [26]. The reason for this is the opening of the medullary cavity and proximal reaming [18]. We believe that the relatively low number of patients who were performed DHS or cannulated screws compared to the other groups may be the reason for not finding a difference in terms of

ABT in these surgery types, where lower bleeding is anticipated.

Some researchers suggested a relationship between the fracture type and ABT [19], whereas some reported otherwise [27] as we did. In our study, complications were grouped as major and minor, and no relationship was observed between ABT and complications. Shokoohi et al. reported a relationship between transfusion rate and chest infection, urinary tract infection, and superficial and deep wound infection [19]. In patients who were operated on for hip fracture, Koval et al. reported a relationship of transfusion with urinary tract infection [9], Carson et al. with chest infection [10], and Levi and Sandberg with wound infection [8]. On the other hand, Johnson et al. found no relationship between infection and transfusion again in patients who were operated on for hip fractures [28]. Although the immunomodulatory effects of ABT are known, its mechanism is still not clear. Similarly, the relationship between ABT and infection is still controversial.

In our study, we did not observe a relationship between ABT and 30-day mortality. Similarly, Shokoohi et al. did not report a relationship between transfusion and 28-day and 180-day mortality rates [19]. Carson et al. also failed to demonstrate a relationship between transfusion and 60-day mortality [10]. In Foss and Kehlet's study conducted on patients with hip fractures, the mortality rate was lower in the restricted transfusion group than in the liberal transfusion group [26]. In our study, a restrictive transfusion policy was followed as explained in the Patients and Methods section.

The main limitations of this study are its retrospective design and limited number of patients. In addition, intraoperative blood loss and surgical time were not analyzed separately. The fact that our study may not reflect the general trend since it was performed at a single center may be considered another limitation. However, we strengthened our study by analyzing almost all potential predictors examined in the literature. In addition, by analyzing the Hg and Hct values as continuous variables, we were able to determine a cut-off value for ABT, which was one of the main objectives of our study.

In conclusion, the main factors determining the need for blood transfusion in geriatric patients operated on for hip fractures are the Hg and Hct values at the time of admission. A Hg level of ≤11.9 g/dl and a Hct level of ≤35.5% can be safely used as a cut-off value in predicting the need for transfusion.

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Research Article / Araştırma Makalesi

Asemptomatik Bireylerde Cervical Lordozis; Sistematik Derleme ve Meta-Analiz

Cervical Lordosis in Asymptomatic Individuals; Systematic Review and Meta-Analysis

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Özet

Servical omurga omurganın en büyük sagittal hareketine sahiptir ve servical omurga dizilimi torasik sagittal dizilimi etkileyerek fonksiyon ve duruş bakımından oldukça önemlidir. Servical lordozun önemli klinik ve cerrahi etkileri vardır. Servical spinal hastalık bulgusu olmayan bireylerde cervical lordozisin yaş ve cinsiyet ile ilişkisini değerlendirip, cervical lordozisin varlığını ve kapsamını incelemektir. Arama algoritmamızda, 2017 ile 2021 tarihleri arasında yayınlanan araştırmalar dahil edildi. Uygun araştırmalar CINAHL Complete, MEDLİNE, OVİD, Clinical Key ve Google Scholar veritabanları kullanılarak 1 Nisan 2021-25 Mayıs 2021 tarihleri arasında tarama yapıldı. Sadece İngilizce ve Türkçe çalışmalar dahil edildi. Tarama sonrası toplam10.138 başlık ve özet bulundu. Bunların içinden 51 tam metin makale analiz edildi. Analizimize dahil etme- hariç tutma kriterlerimizle toplamda 5 makale dahil edildi. Çalışmaların iki tanesi prospective, iki tanesi retrospective ve bir tanesi de observetional kesitsel türde olduğu belirlendi. Yapılan metaanaliz sonucu cinsiyete göre total eğim lordoz acıları arasında %1'lik bir farklılık olduğu belirlendi. Kadınlarda servikal lordoz açıları arasındaki eğim %2'lik farklılık gösterdi. Aynı şekilde erkeklerde de servikal lordoz açıları arasındaki eğim %2'lik bir farklılık gösterdiği analiz edildi. Servical lordoz stabilizasyonu veya restorasyonu içeren cerrahi müdahalelerde cinsiyet ve yaşa bağlı değişen lordoz eğimleri göz önünde bulundurulmalıdır.
Anahtar Kelimeler: Servical lordozis or C2- C7 lordozis, yaş, cinsiyet, asemptomatik bireyler

Abstract

The cervical spine has the greatest sagittal movement of the spine and the cervical spine alignment is very important in terms of function and posture by affecting the thoracic sagittal alignment. Cervical lordosis has important clinical and surgical implications. The aim of this study is to evaluate the relationship of cervical lordosis with age and gender in individuals without signs of cervical spinal disease and to examine the presence and extent of cervical lordosis. Our search algorithm included studies published between 2017 and 2021. Eligible studies were searched using Pubmed, OVID, Clinical Key and Google Scholar databases between April 1, 2021 and May 25, 2021. Only English and Turkish studies were included. After scanning, a total of 10,138 titles and abstracts were found. Of these, 51 full-text articles were analyzed. A total of 5 articles were included in our analysis with our inclusion-exclusion criteria. It was determined that two of the studies were prospective, two were retrospective and one was observational cross-sectional. As a result of the meta-analysis, it was determined that there was a 1% difference between total slope lordosis pains according to gender. The slope between the cervical lordosis angles in women showed a 2% difference. Likewise, it was analyzed that there was a 2% difference in the slope between the cervical lordosis angles in men. Gender and age-related lordosis gradients should be considered in surgical interventions involving cervical stabilization or restoration.
Keywords: Servical lordozis or C2- C7 lordozis, age, gender, asymptomatic individuals

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1. Giriş

Cervical lordoz duruş ve fonksiyon açısından büyük önem taşır. Yedi omurdan oluşan servical vertebralardan atlas (C1) ve eksen (C2) bu bölgede üstün özelliklere sahip ilk iki omur iken sonrasında tipik beş omur (C3-C7) bulunur [1]. Kafanın ağırlığını dengeleyerek günlük yaşam aktiviteleri sırasında boynun fleksiyon ve ekstensiyon hareketlerine izin verir. Nefes alma, çiğneme, seslendirme, göz hareketleri, bakış gibi birçok işlemin etkinliği ve yürüme ve koşma sırasında şok emilimi için önemlidir. [2].

İnsan doğumdan yaşlılığa kadar olan dönemde omurganın sagital dizilimi sürekli değişir. Anne karnında fetus pozisyonda omurga sagital planda tek eğimli olup; "C" şeklindedir. Bütün omurga kifotik görünümdedir. Kafa ile beden kontrolünün sağlanmasından sonra sagital düzlemde ilk servikal lordoz oluşumudur. Ayakta durmaya başlamasından sonra lomber lordoz gelişir. [3]. Omurganın sagital düzlemde sahip olduğu bu fizyolojik eğrilikler, insan vücudu ayakta dururken ve yürürken her zaman minimum enerji harcamasında sabit bir duruş elde etme eğiliminde olduğundan, omurganın sagital dengesini korumak kritik önem taşır [4].

Omurganın diğer bölümlerine göre en hareketli kısım olan ve aynı zamanda başın kütlesini destekleyen servikal omurga, sagital omurga dengesinde çok önemli bir rol oynar. Servikal sagital denge (CSB), servikal omurganın sagital düzlemde nasıl durduğunu tanımlar [5]. Bu alanı çevreleyen araştırmalar, sagital düzlemdeki servikal omurga uyumsuzluğunun baş ağrısı, boyun ağrısı ve sağlıkla ilgili kötü yaşam kalitesi ile nasıl ilişkili olduğunu anlamak için hayati önem taşımaktadır. Kafa kütlesinin normal hizasından herhangi bir sapma, servikal omurganın biyomekanik dengesizliğine ve kas enerji harcamasında artışa ve çeşitli bozukluk ve komplikasyonlara neden olabilir. Araştırmanın derinleşmesiyle birlikte, sagital düzlem hizalaması, yetişkin spinal deformitesi ayarında giderek daha kritik bir parametre olarak kabul edilmektedir. [5,6,7]. Servical lordoz onarımı gerektiren cerrahi girişimlerde komplikasyon gelişiminin önüne geçmek için servical lordoz gelişmesinde yaş ve cinsiyet farklılıklarının hesaba katılması gerekmektedir. [8]. Servical omurga eğriliğinin önemli klinik etkileri vardır. Omurga deformitesinin tedavisinde iyi klinik sonuçların uygun hizalama gerektirdiği açıkça ortaya çıkmıştır [9]. Ancak spinal deformite için uygun tanısal değerlendirme ve optimal tedavi yaklaşımlarının sağlıklı bireylerin araştırılmasına dayandırılması gerekir [10]. Bu çalışmanın sonuçları, servikal omurgada sagital dengenin değerlendirilmesi veya bir füzyon açısının planlanması için ideal CL'nin normal bir referans değeri olarak hizmet edebilir. [11].

Normal lordoz için yapılan araştırmalarda bir takım öneri ve model öne sürülmüştür. Yochum ve Rowe L. [12], C1 ila C7 Cobb açısını kullanarak "normal lordoz" için 35° ila 45° (ortalama 40°) aralığı önerirken, ancak kitaplarında, bu aralığın neden veya nasıl geliştirildiğine dair herhangi bir referans veya sebep verilmemiştir. Gore ve ark.[13] , C2'den C7 vertebraya kadar posterior tanjant yöntemini kullanarak 200 asemptomatik denekte ortalama 21.3° lordoz derecesi olarak kabul etti. Benzer şekilde, Owens ve Hoiris [1], 22.3°'yi ortalama servikal lordoz olarak buldu. Asemptomatik bireylerde servical omurga genellikle lordotik hizadadır. Servikal eğrilik açısından yaş ve cinsiyetin oynadığı rol konusunda araştırmalar oldukça az sayıdadır. Bu araştırmalarda da cinsiyetler arasında çok az fark ve asemptomatik deneklerde artan yaşla birlikte lordoz da genel bir artış olduğunu bildirmiştir [14].Yine farklı bir çalışmada genç- yetişkin ve kadın – erkek tüm bireylerin servical lordozunun benzer olmasına rağmen yaş ve cinsiyetler arasında belirgin farklılıklar olduğunu ortaya koymuştur [11].

Servical omurga, üzerindeki basınç yükünü farklı şekilde dağıtır. Biyomekanik olarak, lordotik konfigurasyon omur gövdesi uç plakları üzerindeki stres, büyük sıkıştırma yüklerine dayanabilir ve en aza indirilebilir [15]. Servikal parametreler üst (O–C2) ve alt servikal eğrilikler (C2–C7), C7 eğimi, spino-kraniyal açı ve dikey servikal kaymadır [16].

Servical lordoz ölçümü için dört güvenilir ve tahmini çizgi çizimi yöntemleri vardır. Bunlar; Cobb C2-C7 yöntemi, İshihara indeksi, Harrison C2-C7 arka tanjant yöntemi ve eğrinin altında kalan Cobb yöntemi. [17].

1.Servikal lordoz - (foramen magnum C0-C7) Foramen magnum ile C7 alt uç plakası arasındaki tam servikal Cobb açısı.

2.Üst servikal lordoz- (foramen magnum C0-C3) Foramen magnum ve C3 üst uç plakası arasındaki üst servikalin Cobb açısı.

3.Orta-alt servikal lordoz - (C2-C7) - C2 alt uç plakası ve C7 alt uç plakası arasındaki Cobb açısı.

4.Alt servikal lordoz (C3-C7)- C3 üst uç plakası ve C7 alt uç plakası arasındaki Cobb açısı.

Yukarıdaki ölçümler servikal lordoz çalışmalarında yaygın olarak kullanılmıştır. Bu dört ölçüm kullanılarak mevcut sonuçların diğer araştırmacılar tarafından elde edilen lordoz açıları ile karşılaştırılması mümkün olmuştur. [18].

2. Gereç ve Yöntemler

Yöntem

Bu çalışma sistematik derleme ve meta-analiz niteliğinde yapılmıştır. Asemptomatik gönüllülerde servical omurga ölçümleri ile ilgili makaleler bulmak için PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement) kriterleri esas alındı. [19]. Tespit edilen makalelerin başlıkları ve özetleri gözden geçirildi. Potansiyel olarak dahil edilebilecek herhangi bir makale tam metin olarak gözden geçirildi.

Uygunluk Kriterleri

Bu sistematik derleme ve meta-analiz için uygun olan çalışmaların seçimi PEOS'a göre belirlendi (Tablo1). Çalışmalar, aşağıdaki kriterleri karşılamaları halinde;

1. Nisan 2017 ile Mayıs 2021 tarihleri arasında yayınlanan araştırmalar dahil edildi.
2. Asemptomatik servical lordoz ölçümleri alınan yetişkin (18 yaş üstü) bireyler ve sevical lordozun normal ölçümlerini karşılaştırmak için semptomatik bireyler dahil edildi.
3. C2-C7 lordoz açılarının ve / veya lordotik eğriliği olan bireylerin oranını gösteren bir şema bulunması

Dışlanma kriterleri olarakta;

1.Segmental lordotik açıları bildirilmiş ancak global lordozu bildirmemiş

2.Servical lordoz ölçümleri bildirmemiş

3. Bireylerin semptomatik bilgilerinden bahsedilmemiş hastalar.

Tarama Stratejisi

Çalışmada Pubmed, OVİD, Clinical Key ve Google Scholar veritabanları kullanıldı. 2017 ile Ocak 2021 tarihleri arasında yayımlanan araştırma makalaleleri dahil edilerek bu çalışma için arama 1 Nisan 2021 tarihinde başlandı. Bu veri tabanlarında "Servical lordozis" or "C2- C7 lordozis", "age", "gender", "asemptomatic individuals", anahtar kelimelerinin değişik kombinasyonları ile tarama yapıldı. Olgu sunumu, derleme ve tez niteliğinde olan araştırmalar kapsam dışı bırakıldı. İngilizce ve Türkçe dilinde yayınlanmış olan makaleler tarandı.

Çalışmaların Seçimi

Dahil etme kriterine dayanarak iki araştırmacı tarafından başlıklar ve özetler gözden geçirilerek tam metin seçimleri bağımsız olarak yapıldı. Dahil edilen makale seçiminde herhangi bir tutarsızlık olduğu durumlarda tartışma yolu ile çözüldü. Uygun makalelerin referans listeleri gözden geçirildi.

Verilerin Elde Edilmesi (Çekilmesi/Çıkarılması)

Araştırma verileri araştırmacılar tarafından geliştirilen veri çekme aracı ile elde edildi. Bu araç ile araştırmaların yazar ve yayın yılları, çalışma deseni, asemptomatik bireylerin cervical lordosis ölçümlerinin cobb açısı veya arka tanjant çizgisi ile elde edilen veriler alındı. Veriler standart bir form kullanılarak; çalışma tasarımı ve konumu, dahil etme /

hariç tutma kriterleri, hasta demo grafileri ve çalışma sonuçları iki araştırmacı tarafından bağımsız olarak yapıldı ve karşılaştırılarak tek bir metine dönüştürüldü. Farklı veri olduğu durumlarda ilgili makale yeniden kontrol edilerek, doğru verilerin çekilmesi sağlandı.

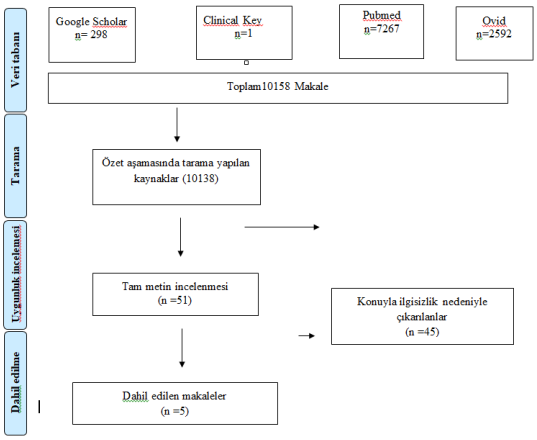
İstatiksel Analiz

Meta-analiz çalışmasındaki hesaplamaların yapılması için Comprehensive MetaAnalysis (CMA) istatistik paket programı kullanıldı ve I^2'nin %50'den fazla olması, istatistiksel olarak önemli bir heterojenliği gösterdiği kabul edildi**.** Bu sistematik derlemede araştırmalar arasındaki heterojenlik, Cochran Q ve Higgins I^2 testleri ile değerlendirildi. I^2'nin %50 ve daha fazla olması durumunda Random Effect, az olması durumunda da Fix Effect sonuçları alındı. Her bir sonuç değişkeni için %95 güven aralığı (CI) ve Tahmini Oranlar hesaplandı. P< 0.05 değeri istatistiksel olarak anlamlı kabul edildi.

4. Bulgular

Tarama Bulguları

Tarama sonucunda toplam 1038 çalışmaya ulaşıldı. Bu çalışmalar sırası ile başlık, özet ve tam metine göre yapılan incelemeler sonucunda 56 makaleye ulaşıldı. Tekrar eden kayıtların çıkarılması, alınma ölçütlerine göre inceleme sonucunda 5 makale ile veri çekme işlemi yapıldı. Makalelerin seçimi ve alınma süreci ile ilgili açıklamalar şekil 1'de gösterilmiştir.



Şekil 1. *Prizma akış şeması*

a) Kadın eğim

Model		Effect size and 95% İnterval			Test of null(2-Tail)		Heterogeneity				T au-squared			
Model	**Number Studies**	**Point estimate**	**Lower limit**	**Upper limit**	**Z -value**	**P - value**	**Q value**	**df (Q)**	**P-Value**	**I-Squared**	**Tau squared**	**Standart error**	**Variance**	**Tau**
Fixed	4	0,156	0,119	0,202	-10,52	0,000	17,2	3	0,00	83,1	0,53	0,54	0,24	0,7
Random	4	0,154	0,077	0,285	-4,26	0,000								

b) Erkek eğim

Model		Effect size and 95% İnterval			Test of null(2-Tail)		Heterogeneity				T au-squared			
Model	**Number Studies**	**Point estimate**	**Lower limit**	**Upper limit**	**Z -value**	**P - value**	**Q value**	**df (Q)**	**P-Value**	**I-Squared**	**Tau squared**	**Standart error**	**Variance**	**Tau**
Fixed	4	0,199	0,155	0,252	-8,97	0,000	16,2	3	0,001	81,5	0,44	0,45	0,2	0,7
Random	4	0,203	0,110	0,345	-3,69	0,000								

c) Total eğim

Model		Effect size and 95% İnterval			Test of null(2-Tail)		Heterogeneity			T au-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z -value	P - value	Q value	df (Q)	P-Value	I-Squared	Tau squared	Standart error	Variance	Tau
Fixed	5	0,099	0,079	0,124	-17,3	0,000	29,8	4	0,00	86,6	0,54	0,45	0,2	0,7
Random	5	0,092	0,048	0,168	-6,48	0,000								

Şekil 2- Cinsiyete göre CMA sonuçları

Çalışmaların ve Katılımcıların Özellikleri

Sistematik derleme ve meta-analize dahil edilen çalışmalardan iki tanesi prospektif, iki tane retrospective tanımlayıcı ve bir tanesi observetional türde idi (Tablo 2). Çalışmalarda toplam 733 asemptomatik kişiler yer almıştır. Çalışmaların ikisi İsrail, ikisi Çin ve bir tanesi Brezilya' da yapılmıştır.

Tablo 1. PEOS

Sorunun bileşenleri	Tanımı / açıklama	Anahtar kelimeler*	Alternatif tarama terimleri*
Katılımcılar (P: Patient / Problem / Population)	Herhangi bir semptom göstermeyen kişiler	Asemptomatik individuals,	
Maruz kalma (E: Exposure)	Cinsiyet ve yaş	Female, male, age	
Sonuçlar (O: Outcomes)	Asemptomatik bireyler Kadın Erkek Yaş	Asemptomatik individuals, female, male,age	
Çalışmanın deseni (S: Study design)	- Prospektif KesitselÇalışmalar - Observetional Çalışmalar -Retrospektif çalışmalar		

Tablo 2: Kalite Değerlendirme Puanları

Yazarın Adı, Çalışmanın Yılı	Çalışmanın Türü	Kalite Puanı
Nasreddine et all.2017	Prospective Kesitsel Çalışma	Evet: 5/6 Hayır:3/2
Zhu et all. 2020	Prospective Kesitsel Çalışma	Evet: 5/7 Hayır:3/1
Been et all. 2017	Retrospective Kesitsel Çalışma	Evet: 7/7 Hayır:1/1
Hu et all. 2020	Retrospective Kesitsel Çalışma	Evet: 6/7 Hayır:2/1
Ezra et all. 2020	Observetional Kesitsel Çalışma	Evet: 6/7 Hayır:2/1

Meta Analiz Bulguları

Bu sistematik derleme ve meta-analize alınan çalışmalarda cervical lordozis asemptomatik kişilerde; cinsiyete göre eğim ve total eğim olarak kategorize edildi (Şekil 2). Çalışmaların dört tanesinde cinsiyete göre cervical lordotik eğrilikler bildirildi

[11,18,20,21]. Bu çalışmaların birleştirilmiş sonuçlarındaki kadın eğim açıları arasında %15'sinde farklılık olduğu bildirildi (%95 CI: 0,077-0,285; z= -4,259; p< 0.001; I^{2}= %83). Aynı çalışmalarda erkek eğim açıları arasında %20'sinde farklılık olduğu bildirildi (%95 CI: 0,110-0,345; z= -3,691; p<0.001; $I^{2=}$ %82). Beş çalışmanın birleştirilmiş sonuçlarına göre [11,18,20,21,22] total eğim açıları arasında %1'inde farklılık olduğu bildirildi (%95 CI: 0.048-0,168; z= -2,543; p< 0.001; I^{2}= %87).

5. Tartışma

Omurga bir bütün olarak ele alındığında, hareket açıklığı en fazla olan kısmı servical omurgalardır. Bu nedenlede başın ağırlığını destekleyerek birçok fonksiyonun yapılmasında rol oynar. Karmaşık bir yapıda olması sebebiyle servikal omurga, dejenerasyonlara karşı daha hassastır. [23]. Bu çalışma asemptomatik bireylerde yaş ve cinsiyetin cervical lordozis eğrilikleri üzerine etkilerinin olup olmadığı incelenmesi amacı ile sistematik derleme ve meta analiz niteliğinde yapılmıştır. Çalışmada 5 araştırmanın cinsiyet üzerine birleştirilmiş sonuçları sunulmuştur. Elde edilen sonuçlar ile kadın erkek arasındaki servikal lordoz farklılığı değerlendirildi. Çalışmalarda kadınlarda üst servical lordoz (C1-C3) daha lordotikken erkeklerde alt cervickal eğriliğin (C4-C7) daha lordotik olduğu bildiridi [24].

Bu sistematik derleme ve meta-analizde; herhangi bir semptom göstermeyen kadın ve erkeklerde servikal lordoz total eğrilikleri arasında %1 lik fark olduğu bildirildi. Been ve ark. nın yapmış olduğu çalışmada kadın ve erkek cervikal lordoz açılarının benzer olduğu sadece kadınların erkeklere göre üst servikal lordozu (FM-C3) daha büyükken alt servikal lordozu (C3-C7)ise daha küçüktür.

Servikal lordotik eğrilik, yaşın ilerlemesiyle servikal lordozun arta bileceği de bazı çalışmalar tarafından bildirilmiştir. Hu ve ark. [22], yapmış olduğu çalışmada 6 yıllık zaman aralığında üç farklı yaş grubu olarak değerlendirilmiş ve anlamlı bir fark bulunmamıştır. Her üç yaş grubunda da C0-C2 açısında ve C2-C7 açısında anlamlı bir fark bulunamamış ancak 60 yaş üzeri hiçbir semptom göstermeyen kişilerde C2-C7 açılarında birtakım düşüşler olduğu bildirilmiş. Farklı bir çalışmada Guo ve ark. yapmış olduğu metaregrasyon analizinde servikal lordoz ile yaş arasında anlamlı bir ilişki bulunmamıştır. Aynızamanda Guo ve ark.'nın [2] yapmış olduğu metaanaliz çalışmasında uygunluk kriterleri doğrultusunda semptomatik ve asemptomatik bireyler arasında da anlamlı bir fark bulunmamıştır. Başka bir çalışmada boyun ağrısı şikayeti olan 700 bireyin boyun ağrısı ile servikal lordoz eğriliği ile arasında bir ilişki bulunmamıştır [25,26].

McAviney ve ark.'nın [14] yapmış olduğu çalışmada 300 bireyin boyun röntgenlerine bakılmış ve servikal ağrı ile servikal lordoz eğriliği arasında önemli bir ilişki olduğu bulunmuştur. Ancak genel olarak bakıldığında semptomlar ve lordoz arasında bir ilişki bulunmamıştır.

6. Sonuç

Servical lordoz ile sağlıklı yaşam kalitesi arasında bir etkileşim olduğu şüphesiz. Sagittal dengesizliği belirlemek ve servikal lordozun doğru hizlanmasını sağlamak için servikal omurga yapısını bilmek önemlidir. Ortalama lordotik eğrilik, C2–C7 posterior tanjant yöntemi kullanıldığında 18° ve Cobb C2–C7 yöntemiyle 13° olarak tahmin edilir. Çalışmada total eğim açılarındaki %1'lik farklılık, p<0.05 servikal lordozun kadın ve erkek arasında farklılığın anlamlı olduğunu göstermiştir. Erkeklerin kadınlara göre lordoz eğimleri daha fazladır. Servical lordoz stabilizasyonu veya restorasyonu içeren cerrahi müdahalelerde cinsiyet bağlı değişen lordoz eğimleri göz önünde bulundurulmalıdır.

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Şizofreni Tanılı Hastalarda Nörobilişsel Bozulmanın Yaşam Kalitesiyle İlişkisi

The Relationship of Neurocognitive Impairment and Quality of Life in Patients Diagnosed with Schizophrenia

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Özet

Bilişsel işlev bozukluğu şizofreninin temel bir özelliğidir. Bilişsel yürütücü işlevler dahil olmakla çeşitli alanlarda, farklı şiddetlerde kendini belli edebilir. Aynı zamanda nörobilişsel bozuklukların yaşam kalitesi üzerine de negatif etkileri mevcuttur. Çalışmamız şizofreni hastalarında nörobilişsel bozulmanın, hastalık süresi, yaşam kalitesi ve sosyodemografik özellikler ile ilişkisini araştırmayı amaçlamıştır. Çukurova Üniversitesi Tıp Fakültesi Balcalı Hastanesi Ruh Sağlığı ve Hastalıkları Anabilim Dalı'nda ayaktan ya da yatarak tedavi gören şizofrenik bozukluk tanısı almış 100 hasta bu çalışmanın örneklem grubunu oluşturmaktadır. Ayrıca genel toplumdan cinsiyet ve yaş olarak benzer 80 sağlıklı kişi kontrol grubu olarak çalışmaya dahil edilmiştir. Kontrol grubuna tarafımızca oluşturulan sosyodemografik veri formuna ek olarak Frontal Değerlendirme Bataryası (FDB), Dünya Sağlık Örgütü Yaşam Kalitesi Ölçeği Kısaltılmış Versiyonu (WHOQOL-BREF) ölçekleri hasta grubuna ise bu ölçeklere ek olarak Pozitif ve Negatif Sendrom Ölçeği (PANNS) uygulanmıştır. Hastalığının ilk 5 yılında olanlar ile 5 yıldan fazla süredir hasta olanların FDB puan ortalaması arasındaki fark istatiksel olarak anlamlı bulunmuştur (p=0,008). Hastaneye yatış sayısına göre yaşam kalitesi (p=0,001) ve FDB (p=0,02) ölçek puan ortalamaları arasında anlamlı fark bulunmuştur. Eğitim durumuna göre hasta grubunda yaşam kalitesi (p=0,001) ve FDB (p<0,001) ölçek puan ortalamaları arasında anlamlı fark bulunmuştur. Aile öyküsü olanlar ile olmayanların yaşam kalitesi (p=0,01) ve FDB (p=0,01) ölçek puan ortalamaları arasındaki fark anlamlı bulunmuştur. Çalışmamızın sonucuna göre hastalığın ilk beş yılında, eğitim düzeyi yüksek olanlarda, çalışanlarda nörobilişsel etkilenmeler daha az görülmüş olup, yaşam kalitesi daha yüksektir. Hastaneye yatış sayısı arttıkça bilişsel işlevlerde daha çok etkilenme görülmüştür. Hastalık süresi ve PANSS ölçek puanları yüksek olan hastalarda bilişsel işlevlerdeki bozulmanın daha fazla olduğu saptanmıştır. Hastalığın ilk yıllarında erken tanı, tedavi ve rehabilitasyon ile olguların eğitim hayatı ve istihdamlarında iyileşme sağlanarak daha kaliteli yaşam sürmeleri için sosyal destek çalışmaları yapılmalıdır.
Anahtar Kelimeler: Şizofreni, Nörobiliş ,Hastalık Süresi, Yaşam Kalitesi

Abstract

Cognitive dysfunction is a core feature of schizophrenia. It can manifest itself in various fields, with different intensities, including cognitive executive functions. At the same time, neurocognitive disorders have negative effects on quality of life. Our study aimed to investigate the relationship of neurocognitive impairment with disease duration, quality of life and sociodemographic characteristics in patients with schizophrenia. 100 patients diagnosed with schizophrenic disorder who are treated as outpatients or inpatients in Çukurova University Faculty of Medicine Balcalı Hospital, Department of Psychiatry constitute the sample group of this study. In addition, 80 healthy people from the general population with similar gender and age were included in the study as a control group. In addition to the sociodemographic data form created by us for the control group, Frontal Evaluation Battery (FEB), World Health Organization Quality of Life Scale Shortened Version (WHOQOL-BREF) scales and Positive and Negative Syndrome Scale (PANNS) was applied. The difference between the mean FDB score of those who were in the first 5 years of their disease and those who were sick for more than 5 years was found to be statistically significant (p=0.008). A significant difference was found between the mean scores of the quality of life (p=0.001) and FDB (p=0.02) scales according to the number of hospitalizations. A significant difference was found between the mean scores of quality of life (p=0.001) and FDB (p<0.001) scale scores in the patient group according to education level. The difference between the quality of life (p=0.01) and FDB (p=0.01) scale mean scores of those with and without a family history was found to be significant. According to the results of our study, neurocognitive effects were observed less in the first five years of the disease, in those with higher education levels, and in workers, and the quality of life was higher. As the number of hospitalizations increased, cognitive functions were more affected. It was determined that cognitive dysfunction was more common in patients with higher disease duration and PANSS scale scores. In the first years of the disease, early diagnosis, treatment and rehabilitation, and social support studies should be carried out in order to improve the education life and employment of the patients and to lead a better quality life.
Keywords: Schizophrenia, Neurocognision,İllness duration, Quality of Life

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1. Giriş

Şizofreni toplumun % 1'ini etkileyen, sanrı ve varsanı gibi pozitif semptomlar; sosyal içe çekilme, duygulanımda küntleşme, düşünce içeriğinde fakirleşme ve konuşma miktarında azalma gibi negatif semptomlar; bellekte, dikkatte, yürütücü işlevlerde bozulma gibi bilişsel belirtilerle giden; düşünce, algılama, duygu ve davranışı etkileyen; farklı klinik tablolarla kendini gösteren psikiyatrik bir hastalıktır(1).

Şizofreninin akut belirtilerinin farmakolojik müdahalelerle kontrol altına alınabilmesiyle birlikte araştırmacılar hastaların uzun vadede yaşam kalitelerini ve işlevselliklerini ölçebilmek ve iyileştirebilmek üzerine yoğunlaşmıştır. Yaşam kalitesi günümüzde öznel iyi oluşu, işlevsel durumu, kaynaklara ve fırsatlara erişimi içeren çok boyutlu bir yapı olarak değerlendirilmektedir. Yapılan araştırmalara rağmen şizofrenide yaşam kalitesinin belirleyicilerinin anlaşılması zor olmaya devam etmektedir. Bir meta-analizde yaşam kalitesi ile genel psikopatoloji arasında güçlü bir ilişkinin olduğu ifade edilmiştir(2).

Araştırmalar şizofreni tanılı bireylerde hafif bilişsel bozulmanın erken çocukluk döneminde ortaya çıktığını göstermektedir. Ayrıca, psikoz öncesi dönemden psikoz başlangıcına kadar en yüksek bilişsel bozulmanın ergenlik, prodrom ve ilk psikotik dönem arasında olduğunu ortaya koymaktadır. Hastaların yaşam kalitelerinin etkilenmesinde bilişsel fonksiyonlardaki bozulmanın da önemli rolü vardır. Şizofreni hastalarında nörobiyolojik süreçleri, tedaviye yanıtı ve prognozu anlamak için bilişsel fonksiyonlarla ilgili çalışmalar önem taşımaktadır(3).

Genel olarak bilişsel işlevler iki alan üzerinden değerlendirilmektedir: Sosyal ve sosyal olmayan. Sosyal olmayan biliş; dikkat/uyanıklık, çalışma belleği, öğrenme, hafıza, işleme hızı, muhakeme ve problem çözme gibi daha yaygın olarak kabul edilen zihinsel yetenekleri içerir. Ayrıca işitsel ve görsel algısal süreçleri de içermektedir. Sosyal biliş ise psikolojik süreçlerle ilişkilidir. Diğer insanlar ve kendimiz hakkındaki bilgilerin algılanması, kodlanması, depolanması, düzenlenmesi ile ilgili alanları kapsamaktadır(4). Bilişsel bozukluklar psikozun erken dönemlerinden başlar ve çoğu hastada hastalığın seyri boyunca devam eder(5).

Şizofrenide nörobilişsel bozulmanın yaşam kalitesi üzerinde olumsuz etkileri konusunda çalışmalarda bulunmaktadır. Şiddetli pozitif ve negatif semptomlar, bilişsel fonksiyonlarda bozulma; azalmış yaşam kalitesi ile ilişkilendirilmiştir(6). Çalışmaların sonucuna göre bilişsel bozukluklar, pozitif ve negatif semptomlar yaşam kalitesini önemli düzeyde etkilemektedir. Aynı zamanda işsizlik, yoksulluk, sosyal izolasyon ve damgalanma gibi faktörlerin de yaşam kalitesi üzerine olumsuz etkileri bulunmaktadır(6).

Sosyodemografik özelliklerin bilişsel bozulma üzerinde etkisinin olduğuna dair çalışma bulguları da bulunmaktadır(7).Şizofreni hastalarında yaşam kalitesi ile sosyodemografik özelliklerin ilişkisinin araştırıldığı çalışmalarda; evli, kadın ve eğitim düzeyi yüksek olguların yaşam kalitesinin daha iyi olduğu bulunmuştur(8).Hastalarda hastalık ile geçen süre uzadıkça yaşam kalitesinin kötüleştiği klinik çalışmalarda gösterilmiştir(9).

Çalışmadaki ilk hipotezimiz nörobilişsel bozulma şiddeti arttıkça yaşam kalitesinin düşecektir. İkinci hipotezimiz ise hastalık süresi uzadıkça nörobilişsel bozulmanın şiddeti artacaktır. Çalışmada şizofreni hastalarında nörobilişsel bozulma ve yaşam kalitesinin hastalık süresi ve sosyodemografik özelliklerle ilişkisinin araştırılması amaçlanmıştır.

2. Yöntem

Verilerin Toplanması

Çukurova Üniversitesi Tıp Fakültesi (ÇÜTF) Balcalı Hastanesi Ruh Sağlığı ve Hastalıkları Anabilim Dalı'nda 01.08.2020-01.12.2020 tarihleri arasında ayaktan ya da yatarak tedavi gören Şizofrenik bozukluk tanısı almış 100 hasta ve 80 sağlıklı birey bu çalışmanın örneklem grubunu oluşturmaktadır. ÇÜTF girişimsel olmayan klinik araştırmalar etik kurulunun 04.09.2020 tarihli toplantısında 33 karar no ile etik kurul onayı alınmıştır.

Çalışmanın güç analizi G Power 3.1.9.7 programı ile yapılmıştır. Orta etki büyüklüğü (Cojen's d = 0,50), 0,95 güç ve 0,05 hata payı (p = 0,05) ile tek bir grupta bulunması gereken minimum örneklem büyüklüğü 79 olarak hesaplanmıştır. Ayrıca çalışmaya şizofreni hastaları ile sağlıklı bireyler arasında nörobilişsel işlevler ve yaşam kalitesi değerlerinin karşılaştırılması ve farklılıkların belirlenmesi için genel toplumdan cinsiyet ve yaş olarak benzer 80 sağlıklı kişi kontrol grubu olarak çalışmaya dahil edilmiştir. Şizofreni hastalarında tanısal değerlendirme için Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) ölçütleri ve Structured Clinical Interview for DSM Disorders-I (SCID- I) kullanılmış, kontrol grubunda psikopatolojinin dışlanması için SCID I-II kullanılmıştır. Ek ruhsal hastalık varlığının yaşam kalitesi üzerine karıştırıcı etkisinden, mental retardasyon ve demans tanısı olanlar özbildirim ölçeklerini doldurmaya ve klinik görüşmeye uyum sağlayamayacağından dolayı çalışmaya dahil edilmedi. Ayrıca 18 yaş altındakiler ve okur yazar olmayan hastalar çalışma dışı bırakılmıştır.

Çalışmaya katılmayı kabul eden hasta ve kontrol gruplarına çalışma ile ilgili bilgilendirme yapılmış ve yazılı onamları alınmıştır. Kontrol grubuna tarafımızca oluşturulan sosyodemografik veri formuna ek olarak Frontal Değerlendirme Bataryası (FDB), Dünya Sağlık Örgütü Yaşam Kalitesi Ölçeği Kısaltılmış Versiyonu (WHOQOLBREF) ve Hasta grubuna ise yukarıda sıralanan ölçeklere ek olarak Pozitif ve Negatif Sendrom Ölçeği (PANNS) uygulanmıştır.

Kullanılan Ölçekler ve Veri Toplama Formu

Veri Toplama Formu

Araştırmacılar tarafından hazırlanan veri toplama formunda hastaların güncel sosyodemografik ve klinik verilerinin değerlendirilmesi amaçlanmıştır. Veri toplama formunda hastaların yaş, cinsiyet, eğitim durumu, medeni durumu, çalışma durumu ve yaşadığı yer gibi sosyodemografik verilerin yanı sıra, tıbbi hastalık öyküsü, ailede ruhsal bozukluk öyküsü, sigara, alkol, madde kullanımı, hastalık başlangıç yaşı, toplam hastalık süresi, toplam hastane yatış sayısı, özkıyım, daha önce elektro konvulzif terapi (EKT) uygulanma durumu ve kullanılan ilaç türü gibi klinik özelliklerin sorgulanması amaçlanmıştır.

Pozitif ve Negatif Sendrom Ölçeği (PANSS)

Şizofreni hastalarının son 1 hafta içerisindeki semptomlarını ve işlevselliğini değerlendirmeyi amaçlayan toplam 30 madde ve 3 alt boyuttan oluşan, uygulama süresi ortalama 30 dakika süren yarı yapılandırılmış bir ölçektir. Ölçek, Kay ve arkadaşları tarafından 1987'de geliştirilmiştir. 164 Kostakoğlu ve arkadaşları tarafından 1999 yılında "Pozitif ve Negatif Sendrom Ölçeği"nin Türkçe geçerlilik ve güvenirlilik çalışması yapılmıştır(10).

Dünya Sağlık Örgütü Yaşam Kalitesi Ölçeği Kısa Form- (WHOQOLBref (TR)

Dünya Sağlık Örgütü (DSÖ) tarafında kişinin iyilik halini ölçen ve kültürler arası kıyaslamalara olanak veren geniş kapsamlı bir yaşam kalitesi ölçeği WHOQOL100 oluşturulmuştur(11). Bu ölçeğin 26 sorudan oluşan kısa formu WHOQOL-BREF ise WHOQOL-100'ün geçerli, güvenilir ve pratik bir alternatifidir. İlk iki soruda genel algılanan yaşam kalitesi ve algılanan sağlık durumu sorgulanırken, diğer 24 soru ile bedensel, ruhsal, sosyal ve çevre alanları olmak üzere 4 alan değerlendirilmektedir. Her soru 1-5 arası skorlanan likert tipi bir ölçektir. Toplam skordan alınan puan arttıkça, orantılı olarak yaşam kalitesi de artmaktadır(12). WHOQOL-BREF'in geçerlik ve güvenilirlik çalışması ülkemizde Eser ve arkadaşları tarafından yapılmıştır(13).

Frontal Değerlendirme Bataryası (FDB)

FDB, frontal lob fonksiyonlarını kısa sürede (ortalama 10 dakikada) ölçen değerlendirme, tanı ve ayırıcı tanı metodudur. 2000 yılında Dubois ve ark tarafından geliştirilen ölçeğin, Türkçe geçerlik güvenirliği 2009 yılında Tunçay ve ark. tarafından yapılmıştır(14).

İstatiksel Analiz

Katılımcılardan elde edilen veri IBM Statistical Package for the Social Sciences (SPSS) 22.0 paket programı ile analiz edilmiştir. Sosyo-demografik değişkenler betimleyici istatistikler ile gösterilmiştir. Kategorik değişkenlere ki-kare analizi ile bakılmıştır. Hastalığa ilişkin bilgiler betimleyici istatistikler ile gösterilmiştir. Verilerin gruplarda normalite testi için analizlerinde Kolmogorov Smirnov testi kullanılmıştır. Sayısal verilerin analizinde katılımcıların ölçek puanlarının ve sosyodemografik özelliklerinin dağılımına bakılarak gruplar arasındaki farkların karşılaştırılmasında bağımsız gruplarda t testi, Mann-Whitney U testi, ANOVA ve Kruskall Wallis testi kullanılmıştır. Ölçekler arasındaki ilişki değişkenlerin dağılımlarına bağlı olarak Pearson korelasyon, Spearman korelasyon analizleri ile incelenmiştir. Yapılan analizlerde $p<0,05$ istatistiksel olarak anlamlılık sınır değeri kabul edilmiştir.

3. Bulgular

Katılımcıların yaş ortalamalarına bakıldığında hasta grubu için ortalamanın 34,76±10,58; kontrol grubu için 33,80 ±8,69 olarak belirlenmiştir. İki grup yaş, cinsiyet, eğitim düzeyi gibi sosyodemografik özellikler açısından benzerdi. Katılımcıların sosyodemografik verileri tablo-1' de yer almaktadır.

Tablo 1. Grupların sosyodemografik özellikleri

Ort. SS= ortalama standart sapma

	Hasta n %		Kontrol n %		p
Cinsiyet					
Erkek	69	69	53	66,33	
Kadın	31	31	27	33,77	**0,695**
Medeni Durum					
Bekar	84	84	59	73,8	
Evli	16	16	21	26,2	**0,091**
Çalışma Durumu					
Çalışmıyor	82	82	19	23,8	
Çalışıyor	18	18	61	76,3	<0,001
Yaşadığı Yer					
İl Merkezi	81	81	73	91,2	
İl Merkezinden Küçük	19	19	7	8,8	**0,52**
Eğitim Düzeyi					
İlkokul	14	14	12	15	
Ortaokul	16	16	11	13,8	
Lise	42	42	36	45	
Üniversite	28	28	21	26,3	**0,956**
Ailede Ruhsal Bozukluk					
Var	52	52	19	23,7	
Yok	48	48	61	76,3	0,001
	Ort.	**SS**	**Ort.**	**SS**	
Yaş	**34,76**	**10,58**	**33,80**	**8,69**	**0,58**

Hasta grubundaki katılımcıların ortalama hastalık süresi 12,06±8,13 yıldır. En düşük hastalık süresi 1 yıl, en yüksek hastalık süresi ise 43 yıldır. Hastalık ilk tanı yaşı ise ortalama 24,74±8,48 yıldır.

Hastalıkla geçirilen süre gruplandırıldığında; hastalık süresi katılımcıların %25'inde 0-5 yıl, %23'ünde 6-10 yıl, %19'unda 11-15 yıl, %19'unda 16-20 yıl aralığında ve %14'ünde 20 yıl üzeri olarak belirlenmiştir. Hastalıkla ilgili diğer veriler tablo- 2'de yer almaktadır

Tablo 2. Şizofreni Tanılı Hastaların Hastalık Özellikleri

	n	%
Özkıyım		
Var	35	**35**
Yok	65	**65**
EKT		
Var	44	**44**
Yok	56	**56**
Sosyal Destek		
Var	92	**92**
Yok	8	**8**
İlaç Uyumu		
Var	95	**95**
Yok	5	**5**
İlaç Türü		
Antipsikotik Oral	33	**33**
Antipsikotik Depo	7	**7**
Kombine	60	**60**
Hastalık Süresi		
0-5 Yıl	25	**25**
6-10 Yıl	23	**23**
11-15 Yıl	19	**19**
16-20 Yıl	19	**19**
> 20 Yıl	14	**14**

	Ort.	**SS**	Minimum-Maximum
Hastalık İlk Tanı Yaşı	24,74	8,48	**15-49**
Hastalık Süresi (Yıl)	12,06	8,13	**1-43**
Hastanede Yatış Sayısı	2,57	3,87	**0-30**
PANSS (+)	22,44	10,03	**7-49**
PANSS (-)	25,67	10,44	**7-49**
PANSS Genel Psikopatoloji	52,40	20,07	**16-103**
PANSS Toplam	**100,51**	**38,69**	**30-191**

n: *Örneklem sayısı,* ***PANSS:****Pozitif Negatif Sendrom Ölçeği,* ***SS:****Standart sapma,* ***Ort:*** *Ortalama*

WHOQOL-Bref ölçeğinde toplam ölçek puanının parametrik dağılım gösterdiği görülmüş olup bağımsız gruplar t testi uygulanmıştır (p<0,001). WHOQOL toplam puanları hasta grubunda ort: 49,80±12,46; kontrol grubunda ort: 79.43±8,53'tür. Kontrol grubunda WHOQOL-Bref toplam ölçek puanı daha yüksek bulunmuş olup hasta grubu ile ortalama puanları arasında anlamlı fark bulunmuştur (t=-18,87, p<0,001).

Frontal Değerlendirme Bataryası'nın FDB 1 benzerlikler (konseptualizasyon), FDB 2 kelime akıcılığı (mental fleksibilite), FDB 3 motor seriler (programlama), FDB 4 çelişen yönergeler (interferansa duyarlılık), FDB 5 yap-yapma (inhibitör kontrol), FDB 6 yakalama davranışı (çevresel otonomi) ve FDB toplam puanları ile grupların dağılımı araştırıldığında normalden sapma gösterdiği tespit edildi. Bu nedenle Frontal Değerlendirme Bataryası'na göre gruplar

arasındaki farklılıklar Mann Whitney-U testi ile araştırıldı. Hasta grubu ile kontrol grubunun konseptualizasyon, mental fleksibilite, programlama, interferansa duyarlılık, çevresel otonomi ve toplam ölçek puanları açısından ortalamaları arasında istatistiksel olarak anlamlı farklılık bulundu.

Buna göre şizofreni hastalarının Frontal Değerlendirme Bataryası'nın tüm alt grupları ve toplam puanları kontrol grubundan düşüktü.

Hasta ve Kontrol Gruplarının Ölçek Puanlarına dair diğer veriler tablo -3'te yer almaktadır.

Tablo 3. Hasta ve Kontrol Gruplarının Ölçek Puanları

Ölçek	Hasta n=100		Kontrol n=80		
	Ort.	**SS**	**Ort.**	**SS**	Önemlilik
WHOQOL Genel Sağlık Durumu	8,60	3,08	15,50	2,12	**U=276, Z=-10,58,** p<0,001*
WHOQOL Fiziksel Alan	10,64	2,99	16,98	1,68	**U=246,50, Z=-10,81,** p<0,001*
WHOQOL Psikolojik Alan	10,10	2,91	15,86	2	**U=360,50, Z=-10,496,** p<0,001*
WHOQOL Sosyal Alan	8,29	3,13	15,16	2,58	**U=393, Z=-10,435,** p<0,001*
WHOQOL Çevresel Alan	12,16	2,46	15,91	1,89	**U=880, Z=-8,995,** p<0,001*
WHOQOL Toplam	49,80	12,46	79,43	8,53	**t=-18,87,** p<0,001**
FDB 1 Benzerlikler (Konseptualizasyon)	1,90	0,81	2,86	0,34	**U=1229, Z=-8,79,** p<0,001*
FDB 2 Kelime Akıcılığı (Mental Fleksibilite)	1,30	0,98	2,75	0,43	**U=910, Z=-9,35,** p<0,001*
FDB 3 Motor Seriler (Programlama)	2,15	0,82	2,96	0,19	**U=1641,50, Z=-7,99,** p<0,001*
FDB 4 Çelişen Yönergeler (Interferansa Duyarlılık)	1,99	0,99	2,89	0,35	**U=1702, Z=-7,53,** p<0,001*
FDB 5 Yap-Yapma (Inhibitör Kontrol)	1,97	0,95	2,84	0,37	**U=1780,50, Z=-7,14,** p<0,001*
FDB 6 Yakalama Davranışı (Çevresel Otonomi)	2,54	0,73	3	0	**U=2600, Z=-5,85,** p<0,001*
FDB Toplam	**11,85**	**4,22**	**17,30**	**1,03**	**U=577, Z=-10,** p<0,001*

n**= Örneklem sayısı, **SS**= Standart sapma, **WHOQOL**= DSÖ Yaşam KalitesiÖlçeği, **FDB**= Frontal Değerlendirme Bataryası, ***= Mann-Whitney U Testi, *= Student t Testi*

Hasta grubunda WHOQOL Genel Sağlık alt boyutu puanlarının FDB puanları ile ilişkisi incelendiğinde: FDB 1, FDB 2, FDB 4 ve FDB 5 alt boyutunun WHOQOL Genel Sağlık alt boyutu ile zayıf şiddette pozitif yönlü ilişkisi olduğu saptanmıştır (FDB 1 r=0,36; p<0,001 / FDB 2 r=0,29; p=0,003 / FDB 4 r=0,38; p<0,001 / FDB 5 r=0,29; p=0,003). FDB 3, FDB 6 ve FDB toplam puanlarının WHOQOL Genel Sağlık alt boyutu puanı ile orta şiddette pozitif yönlü ilişkisi bulunmuştur (FDB 3 r=0,46; p<0,001/ FDB 6 r=0,43; p<0,001 / FDB toplam r=0,48; p<0,001).

FDB puanları ve hastalıkla ilgili diğer veriler tablo- 4'te yer almaktadır.

Tablo 4. Hastalığa ilişkin özelliklerin FDB puan ortalamaları ile ilişkisi

	FDB1	FDB2	FDB3	FDB4	FDB5	FDB6	FDBT
Hastalık yılı	r=-0,19	r=-0,14	r=-0,24	r=-0,14	r=-0,21	r=-0,26	**r=-0,22**
	p=0,052	p=0,13	**p=0,01**	p=0,16	**p=0,03**	**p=0,008**	p=0,02
Başlangıç	r=0,22	r=0,020	r=0,05	r=0,04	r=0,17	r=0,20	**r=0,13**
Yaşı	**p=0,02**	p=0,84	p=0,5	p=0,65	p=0,07	**p=0,03**	**p=0,17**
Yaş	r=-0,005	r=-0,10	r=-0,09	r=-0,02	r=-0,02	r=0,01	**r=-0,05**
	p=0,96	p=0,30	p=0,33	p=0,77	p=0,78	p=0,88	**p=0,57**
Eğitim	r=0,38	r=0,40	r=0,44	r=0,47	r=0,41	r=0,51	**r=0,54**
	p<0,001	**p<0,001**	**p<0,001**	**p<0,001**	**p<0,001**	**p<0,001**	p<0,001
PANSS	r=-0,44	r=-0,26	r=-0,49	r=-0,45	r=-0,41	r=-0,58	**r=-0,53**
Negatif	**p<0,001**	**p=0,008**	**p<0,001**	**p<0,001**	**p<0,001**	**p<0,001**	p<0,001
PANSS	r=-0,38	r=-0,22	r=-0,49	r=-0,37	r=-0,34	r=-0,53	**r=-0,49**
Pozitif	**p<0,001**	**p=0,02**	**p<0,001**	**p<0,001**	**p<0,001**	**p<0,001**	p<0,001
PANSS	r=-0,44	r=-0,28	r=-0,48	r=-0,44	r=-0,41	r=-0,60	**r=-0,55**
Genel	**p<0,001**	**p=0,005**	**p<0,001**	**p<0,001**	**p<0,001**	**p<0,001**	p<0,001
Psikopatoloji							
PANSS	r=-0,44	r=-0,28	r=-0,50	r=-0,44	r=-0,42	r=-0,60	**r=-0,56**
Toplam	**p<0,001**	**p=0,005**	**p<0,001**	**p<0,001**	**p<0,001**	**p<0,001**	p<0,001
WHOQOL	r=0,36	r=0,29	r=0,46	r=0,38	r=0,29	r=0,43	**r=0,48**
Genel Sağlık	p<0,001	p=0,003	p<0,001	p<0,001	p=0,003	p<0,001	**p**<0,001

***FDB**=Frontal Değerlendirme Bataryası, **FDB 1**= Benzerlikler (Konseptualizasyon), **FDB 2**= Kelime Akıcılığı (Mental Fleksibilite), **FDB 3**= Motor Seriler(Programlama), **FDB 4**= Çelişen Yönergeler (İnterferansa Duyarlılık), **FDB 5**= Yap-Yapma (İnhibitör Kontrol), **FDB 6**= Yakalama Davranışı (Çevresel Otonomi), **FDBT**= Frontal Değerlendirme Bataryası Toplam, **PANSS**= Pozitif ve Negatif Sendrom Ölçeği, **WHOQOL**= DSÖ Yaşam Kalitesi Ölçeği, **r**= Spearman korelasyon*

4. Tartışma

Çalışmamızın en önemli bulgusu şizofreni hastalarında nörobilişsel bozulma arttıkça yaşam kalitesinde belirgin bir azalmanın ortaya çıktığının gösterilmesidir. Çalışmamızda vaka ve kontrol grubu incelendiğinde vaka grubunda WHOQOL-BREF tüm alt boyutlarında ve toplam puanda ortalama puan daha düşük bulunmuş olup yaşam kalitesi daha kötü tespit edilmiştir. Yılmaz tarafından 2015 yılında yapılan "Mizaç ve karakterin şizofreni hastalarında sosyal işlevsellik, yaşam kalitesi ve klinik belirtiler üzerine etkisi" isimli çalışmada benzer şekilde WHOQOL-BREF yaşam kalitesi puanları genel sağlık alt grubu dışında kontrol grubunda daha yüksek bulunmuştur(15).

WHOQOL-BREF alt boyut puanları ile FDB alt boyut puanları arasında pozitif yönde zayıf veya orta düzeyde ilişkiler (FDB 2 ile WHOQOL-BREF Psikolojik, Sosyal ve Çevresel alt boyutu hariç) saptanmıştır. WHOQOL-BREF Toplam puanı ile FDB puanları incelendiğinde; FDB 2 ve FDB 5 ile WHOQOL-BREF Toplam puanı arasında pozitif yönlü zayıf ilişki bulunmuştur. FDB 1, FDB 3, FDB 4, FDB 6 ve FDB Toplam puanları ile WHOQOL-BREF Toplam puanı arasında pozitif yönlü orta düzeyde ilişki bulunmuştur. Araştırmamız literatürdeki verilerle ile parelel olarak; şizofrenin, sosyal işlevsellik ve yaşam kalitesini bozan, iş ve çalışma hayatını etkileyen kronik bir hastalık olduğunu teyit eder niteliktedir(16). Yaşamdaki günlük işleri yapabilme, yürütücü işlev bozukluklarının olmaması sağlıklı ve kaliteli yaşam için yüksek önemdedir.

Hastaların yaşam kalitesi ölçeğinin alt boyutları incelendiğinde sosyal alan algısının en düşük, çevresel alan algısının ise en yüksek olduğu bulunmuştur. Bir araştırmada hastaların ruhsal, bedensel, sosyal ve çevresel yaşam kalitesi alt ölçeklerinden alınabilecek alt ve üst puanlar değerlendirildiğinde orta düzeyde ve bedensel alan alt ölçek puanının en yüksek, sosyal alan alt ölçek puanının ise en düşük olduğu görülmüştür(17). Ülkemizde 2009 ve 2010 yıllarında yapılan ayrı çalışmalarda hastaların yaşam kalitelerinin genel olarak orta-orta düzeyin üzerinde ve

çevresel alan alt ölçek puanı en yüksek, sosyal alan alt ölçek puanı ise en düşük olarak bulunmuştur(18).Bu çalışmaların sonuçları araştırmamızla benzerlik göstermektedir. Şizofreni hastaları ile yapılan bir çalışmada şizofreni hastalarının yaşam kalitesi algılarının tüm alanlarda düşük olduğu tespit edilmiştir(19). Başka bir araştırmada ise şizofreni hastalarının yaşam kalitesi algılarının tüm alanlarda sağlıklı kontrollerden daha düşük olduğu, şizofreni hastalarının sosyal ilişkilerden daha az doyum elde ettiği ve yaşam kalitesini psikopatolojik belirtilerdense toplumsal değişkenlerin daha çok etkilediği görülmüştür(20).Şizofreni hastalarında, yaşam kalitesinin iyi olması tedavi edici etkide bir ölçüt olup, yaşam kalitesinin kötü olması uzun dönemde farmakolojik, ruhsal toplumsal tedavi ve sağlık bakım maliyetleri gibi alanları olumsuz etkilemektedir(21).

Araştırmamızda WHOQOLBref'in alt boyutları hasta grubunda incelendiğinde genel sağlık, fiziksel, psikolojik, sosyal, çevresel alan ve toplam puan ortalamaları Güneş tarafından yapılan bir başka çalışmaya göre daha düşük saptanmıştır(22). Bu iki çalışmanın sosyodemografik verileri incelendiğinde Güneş tarafından yapılan çalışmada olguların istihdam ve evlilik oranlarının daha yüksek olduğu görülmüştür. Evliliğin şizofrenide olumlu prognoz kriteri olduğu bilinmektedir(23).2004 yılında yapılan bir araştırmada istihdam edilen şizofreni hastalarında daha iyi sosyal işlevsellik, daha az semptom, benlik saygısında ve yaşam kalitesinde artış olduğu belirtilmektedir(24).Bu çalışmalarda yaşam kalitesi puanları arasındaki farkların olguların istihdamı, medeni durumu, araştırmaların farklı zaman ve bölgelerde uygulanmış olmasından kaynaklandığı düşünülmektedir.

Bir başka araştırmada(25) WHOQOLBref alt ölçek puanları çalışmamızla karşılaştırıldığında genel sağlık alt puanı dışında diğer alan ortalamaları Elegbede ve ark tarafından yapılan çalışmada (25) daha yüksek bulunmuştur. Toplum tabanlı sosyal yönü eksik olan orta ve üst sınıfın ulaşabildiği Nijerya sağlık sitemininde hastaların sağlık harcamalarının %70'ini kendi imkanlarıyla ödedikleri göz önüne alındığında yaşam kalitesi puanlarının yüksek çıkması sağlık sektörünün hizmet verdiği sosyoekonomik sınıf farklılığından kaynaklanabileceği düşünülmüştür(26).

Çalışmamızda cinsiyete göre WHOQOL-BREF puan ortalaması incelendiğinde cinsiyetler arasında anlamlı fark bulunmasa da kadınlarda yaşam kalitesinin erkeklere oranla daha yüksek olduğu görülmüştür. Çalışma durumu açısından bakıldığında çalışan bireylerde yaşam kalitesi çalışmayan bireylere kıyasla daha yüksek bulunmuştur ve bu fark anlamlıdır. Eğitim açısından WHOQOL-BREF puan ortalaması incelendiğinde üniversite çıkışlılarda diğer eğitim gruplarına kıyasla yaşam kalitesi puanları anlamlı derecede yüksek bulunmuştur. Ailede psikiyatrik hastalık öyküsü olmayanlarda yaşam kalitesi puanları ailede ruhsal hastalık olanlara kıyasla anlamlı derecede yüksek bulunmuştur. Özkıyım girişiminde bulunan olgularda yaşam kalitesi puan ortalaması, özkıyım girişiminde bulunmayan olgulara kıyasla daha düşük bulunmuştur, ama bu fark anlamlı değildir. Hastalık yılına göre ilk 5 yıl ve sonrasını incelediğimizde hastalığın ilk 5 yılı yaşam kalitesi 5 yıl sonrasına kıyasla daha yüksek olarak bulunmuştur, ama bu fark anlamlı değildir. Yatış sayılarına göre inceleme yapıldığında 5'ten fazla hastaneye yatışı olan olguların yaşam kalitesi diğer gruplara kıyasla anlamlı derecede düşük bulunmuştur.2019 yılında yapılan bir çalışmada(25) cinsiyet değişkenine göre değerlendirme yapıldığında kadınlarda yaşam kalitesinin erkeklere kıyasla anlamlı derecede daha iyi olduğu, medeni durum açısından karşılaştırma yapıldığında evli grupta yaşam kalitesinin bekar gruba kıyasla anlamlı olarak daha iyi olduğu, eğitim düzeyi yüksek olan hasta grubunda yaşam kalitesi değerlerinin anlamlı derecede daha iyi olduğu, çalışma durumu açısından çalışan grupta yaşam kalitesi pualarının daha yüksek olduğu (fark anlamlı değildir), hastalık yılına göre ilk 5 yıl ve sonrasını incelediğimizde hastalığın ilk 5 yılı yaşam kalitesinin diğer yıllara kıyasla daha yüksek olduğu (fark anlamlı değildir) bulunmuştur. Elegbede ve ark tarafından 2019 yılında yapılan çalışma(25) sonuçları cinsiyet, medeni durum, eğitim düzeyi, çalışma

durumu, hastalık yılı değişenleri açısından çalışmamızla benzerlik göstere de, puan ortalamaları bu çalışmada daha yüksektir. Nijerya'da orta-üst sınıfın sağlık hizmetinden faydalandığı düşünüldüğünde puan ortalamalarının benzer olmaması ülkelerin sağlık sistemlerindeki farklılıklar ile açıklanabilmektedir. Her iki çalışmada da şehir ve kırsal bölgede yaşayan hasta grubunda yaşam kalitesi puanları arasında anlamlı fark yoktur. Bu durum globalleşen dünyada kır ve kent arasındaki farkın giderek azalmasının sebebidir. Aynı çalışmada ilaç tedavileri açısından kombine tedavi uygulananlar ile oral veya depo antipsikotik uygulananlar arasındaki fark anlamlı olup, kombine ilaç kullanan hastalarda yaşam kalitesi puanı daha düşük bulunmuştur. Bizim çalışmamızda da kombine tedavi alanlarda yaşam kalitesi puanı daha düşük (anlamlı değildir) bulunmuştur. Kombine tedavi genellikle monoterapiden fayda göremeyen daha ağır klinik seyir gösteren hastalada uygulandığından her iki çalışmada kombine tedavi kullanan olguların yaşam kalitesinin düşük bulunması beklenen bir sonuçtur.

2013 yılında Gaziantep Üniversitesi Tıp Fakültesi Psikiyatri Polikliniği tarafından yapılan başka bir çalışma sonucuna göre de şizofreni hastalarında WHOQOL-BREF puanlarının medeni durum değişkenine göre değerlendirmesi yapıldığında çalışmamızda da olduğu gibi iki medeni durum arasında anlamlı bir fark bulunmasa da WHOQOL-BREF puanlarının evli grupta daha yüksek olduğu bulunmuştur(27). Ruhsal hastalıkların prognozunda aile tutumunun önemli etkenlerden biri olduğu, aile ortamının yaşam kalitesine pozitif yönde etki ettiği, sağaltım sürecinde aile bireylerinin desteğinin göz ardı edilmemesinin gerektiği bir çok araştırmada tespit edilmiştir(23).

Tarafımızca yapılan çalışmada FDB'nin tüm alt grupları ve toplam puanları hasta grubu ile kontrol grubu arasında karşılaştırıldığında hasta grubununda puanların anlamlı ölçüde düşük olduğu görülmüştür. 2009 yılında N.Tunçay tarafından yapılan FDB ölçeğinin Türk toplumunda geçerlilik güvenilirliği çalışmasında FDB altıncı alan dışında tüm skorlarda anlamlı ilişki saptanmıştır ($p<0,05$). Tüm skorlarda olgular kontrol bireylerden daha düşük puanlar almıştır(14). Yıldırım Beyazıt Üniversitesi tarafından 2020 yılında yayınlanan çalışma sonuçlarına göre FDB'nin tüm alt grupları ve toplam puanları hasta grubu ile kontrol grubu arasında karşılaştırıldığında kontrol grubundaki puanlar daha yüksek olarak saptanmıştır(28). Yurt dışında yapılan çalışmalar incelendiğinde; bir çalışmada FDB total skoru şizofreni grubunda kontrol grubuna kıyasla anlamlı derecede düşük saptanmıştır(29). Fransa'da Lallart ve arkadaşları tarafından yapılan başka bir çalışma sonucun da şizofreni hastalarında FDB puan ortalaması kontrol grubuna kıyasla düşük bulunmuştur(30).Yurt içi ve yurt dışındaki çalışmalar verilerimizi destekler niteliktedir. Bu konuda geçmişte yapılmış birçok çalışma olmasına rağmen bizim çalışmamızın en güçlü yönü örneklem sayısının yeterli olması ve güç analizinin yapılmış olmasıdır. Çalışmamızın en önemli kısıtlılığı yaşam kalitesi ölçeğinin hastanın özbildirimine dayalı olması ile sonuçların yeterince güvenilir olmayabileceğidir. Ayrıca diğer kısıtlılığı ise tek bir ruh sağlığı merkezinden alınan örneklemle yapılan kesitsel bir çalışma olmasıdır.

Şizofreni hastalarında nörobilişsel bozulmanın, hastalık süresi ve yaşam kalitesiyle ilişkisini araştırdığımız çalışmamızda: hipotezlerimizden birincisi olan" nörobilişsel bozulma şiddeti arttıkça yaşam kalitesinin düşecektir " FDB'nin tüm alanlarında doğrulanmıştır. İkinci hipotezimiz olan "hastalık süresi uzadıkça nörobilişsel bozulmanın şiddeti artacaktır" ise FDB'nin proğramlama, inhibitör kontrol ve çevresel otonomi alanlarında doğrulanmıştır. Böylelikle yürütücü işlev bozukluklarının yaşam kalitesi üzerine olumsuz etkileri gösterilmiş olup şizofreni tanılı hastaların yaşam kalitesi değerlendirilirken bu alanın da özellikle dikkate alınmasını önermekteyiz.

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Research Article / Araştırma Makalesi

The Effect of Initiation of Antihypertensive Medication on MPV Level in Newly Diagnosed Hypertensive Patients

Yeni Tanı Konulan Hipertansif Hastalarda Antihipertansif İlaç Başlanmasının MPV Düzeyine Etkisi

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Abstract

Platelet activation is a factor involved in the pathogenesis of hypertension. It also contributes to the development of thrombotic events and target organ damage due to hypertension. Mean platelet volume is an easily measurable parameter indicating platelet activation. To evaluate whether there is any change in MPV levels after starting antihypertensive medication in newly diagnosed hypertensive patients. 79 patients who were started on antihypertensive medication were evaluated retrospectively. 24.1% of the patients had microalbuminuria. MPV values before and after (5.8±3.6 months) the start of the antihypertensive drug were compared statistically. A statistically significant decrease in mean MPV value was found after starting antihypertenive medication (8.92±1.76 fL vs. 8.38±1.60 fL, p<0.001). The mean MPV value was higher in the microalbuminuric group than in the normoalbuminuric group (9.24±1.10 fL vs. 8.49±1.75 fL, p=0.028). A significant decrease in mean MPV level was detected in the first year following the initiation of antihypertensive medication in newly diagnosed hypertensive patients.
Keywords: Hypertension, Mean platelet volume, Microalbuminuria

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Özet

Trombosit aktivasyonu hipertansiyon patogenezinde rol oynayan bir faktördür. Ayrıca, trombotik olayların gelişimine ve hipertansiyona bağlı hedef organ hasarına katkıda bulunur. Mean platelet volume, platelet aktivasyonunu gösteren kolay ölçülebilir bir parametredir. Bu çalışmanın amacı, yeni tanı almış hipertansif hastalarda antihipertansif ilaç tedavisine başlandıktan sonra MPV düzeylerinde herhangi bir değişiklik olup olmadığını değerlendirmektir. Antihipertansif ilaç tedavisine başlanan 79 hasta retrospektif olarak değerlendirildi. Hastaların% 24.1'inde mikroalbüminüri vardı. Antihipertansif ilacın başlamasından önceki ve sonraki MPV değerleri (5.8=3.6 ay) istatistiksel olarak karşılaştırıldı. Antihipertansif ilaç tedavisine başlandıktan sonra ortalama MPV değerinde istatistiksel olarak anlamlı azalma saptandı (8.92=1.76 fl'ye karşılık 8.38=1.60 fL, p<0.001). Ortalama MPV değeri mikroalbüminürik grupta normoalbüminürik gruba göre daha yüksekti (9.24=1.10 fLvs. 8.49 = 1.75 fL, p = 0.028). Yeni tanı konulan hipertansif hastalarda antihipertansif ilaç başlanmasını takip eden ilk yıl içinde ortalama MPV düzeyinde anlamlı bir azalma tespit edildi.
Anahtar Kelimeler: Hipertansiyon, Mean platelet volüm, Mikroalbuminüri

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1. Introduction

Mean platelet volume (MPV) is known as a marker that indicates platelet activation(1-3). Large platelets contain active and dense granules with greater thrombotic potential (3). Therefore, an increased MPV level may be a marker for an increased risk of prothrombotic conditions. An increase in the risk of prothrombosis due to platelet activation is a factor involved in the pathogenesis of hypertension (4-5). Significant relationships between hypertension and MPV levels have been shown in various studies (1,5-8). In addition, it was found that MPV levels were higher in those with target organ damage due to hypertension than in those without (5,6,9).

The aim of this study is to investigate whether there is a change in MPV levels after starting antihypertensive treatment in newly diagnosed hypertensive patients without any other known cardiovascular disease.

2. Materials and Methods

Newly diagnosed hypertensive adult patients not using antihypertensive medication admitted to the nephrology outpatient clinic of the University of Health Sciences-Keçiören Educational and Research Hospital between 01/01/2017-30/06/2019 were included in this retrospective study. Diabetic patients were excluded from the study. Patients who had estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m², who had a history of active infection, malignancy or coronary arter disease were also excluded from the study.

The study protocol was approved by the ethics committee of the Keçiören Education and Research Hospital.

The age, gender, name and number of the newly started antihypertensive drugs of the patients were obtained from the records. Patients' laboratory data as serum creatinine, eGFR, lipid profile, uric acid and spot urine albumin-to-creatinin ratio levels evaluated before antihypertensive medication initiation were also obtained from the medical records. Platelet count and MPV values evaluated before and within the first 1 year (1-12 months) after starting to take antihypertensive medication were found from the medical records.

Blood samples were taken from the antecubital vein into dipotassium ethylenediaminetetraacetic (EDTA) tubes and were analyzed in the same analyzer (BC-6800-Mindray North America Hematology Analyzer) in the same laboratory within one hour. Mean platelet volume measurement was performed based on platelet histogram.

The eGFR was calculated by 4-variable MDRD equation described by the National Kidney Foundation as follows: eGFR (mL/min/1.73 m²) = 175× (Scr)$^{-}$ -1.154 × (Age)$^{-}$-0.203 × (0.742 if female) × (1.212 if African American) (10).

The definition of normoalbuminuria and microalbuminuria is that the daily excretion of albumin should be below 30 mg and 30-300 mg, respectively (11).

Data analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Results were expressed as mean±SD for continous variables and as numbers and percent for categorical variables. Mean platelet volume values before and after the antihypertensive drug began were compared by Paired Samples T-test. Spearman correlation test was used to evaluate correlations between variables. A p-value <0.05 was considered statistically significant.

3. Results

Seventy-nine newly diagnosed hypertensive patients were included in the study. The most commonly started antihypertensives were renin angiotensin system (RAS) blockers (58.2%). Combined antihypertensive medication was started in 49.4% of patients. Demographic and labarotory properties of the patients were given in Table 1.

Table 1. Demographic and laboratory characteristics of patients

Number	**79**
Gender (F/M) (%)	68.4/31.6
Age (years)	53.4±10.8
Number of antihypertensive drug	
1 drug (%)	50.6
2 or more drug (%)	49.4
Antihypertensive drug	
RASi (%)	58.2
CCB (%)	44.3
Beta blocker (%)	1.3
Alpha blocker (%)	1.3
Diuretic (%)	40.5
Follow-up period (months)	5.8±3.6
Serum creatinine (mg/dl)	0.80 ±0.14
eGFR (mL/min/1.73 m²)	94±15
Uric acid (mg/dl)	5.2±1.3
Total cholesterol (mg/dl)	217±37
Triglyceride (mg/dl)	163±104
LDL-cholesterol (mg/dl)	137±35
HDL-cholesterol (mg/dl)	48±9
Albuminuria (mg/day)	50±96
Microalbuminuria (%)	24.1

RASi: renin angiotensin system inhibitors, CCB: calcium channel blocker
eGFR: estimated glomerular filtration rate, LDL: low density lipoprotein HDL: high density lipoprotein

Although the mean MPV value was higher in women, this difference was not statistically significant (9.15±1.89 fL vs. 8.42±1.36 fL, p=0.088). There was no correlation between MPV value and age, lipid profile, uric acid, eGFR and albuminuria amount.

The mean MPV value was found to be higher in the microalbuminuric group than in the normoalbuminuric group (9.24±1.10 fL vs. 8.49±1.75 fL, p=0.028).

The number of platelet and MPV values were evaluated on average 5.8±3.6 months after starting to take the antihypertensive drug. The initial mean MPV value of patients before the drug was started was 8.92±1.76 fL. A statistically significant decrease in mean MPV value was found after starting antihypertensives (8.38±1.60 fL, p<0.001). The mean number of platelets before and after the start of the drug was similar (274±55*10³/µL vs. 277±62*10³/µL, p=0.565) (Table 2).

Table 2. MPV and platelet values before and after the start of antihypertensive medication

	Before	**After**	**p**
MPV (fL)	8.92±1.76	8.38±1.60	<0.001
Platelet (*10³/µL)	274±55	277±62	0.565

MPV: mean platelet volume

4. Discussion

In this study, a significant decrease in the mean MPV value was observed within the first year after starting to take antihypertensive medication in newly diagnosed hypertensive patients. In addition MPV value was higher in microalbuminuric hypertensives than in normoalbuminuric hypertensive patients.

Mean platelet volume is a parameter that indicates the platelet size. Large platelets contain dense granules with greater thrombotic activity (3). Therefore, the

increase in MPV is also a predictor of increased platelet activation (1-3). The presence of a prothrombotic state is a mechanism involved in the pathogenesis of hypertension (4-5). The relationship between MPV and hypertension has been shown in various studies (1,5-8,12,13). Gang et al.(7) followed normotensive individuals for about 9 years and reported that high MPV level was associated with an increased incidence of hypertension independent of other risk factors such as age, sex, serum creatinine, waist circumference. Mean platelet volume values were found to be higher in hypertensive patients than in normotensives (5,6,13). Patients with masked hypertension have higher MPV values than normotensives too (12). It has been also reported that prehypertensive individuals have a higher MPV value than normotensives (13). In addition, a significant relationship between MPV and the severity of hypertension has been detected. The mean MPV value is lower in hypertensives whose blood pressure is under control than in resistant hypertensive individuals (14).

Increased platelet activity plays an important role in the development of atherosclerosis. It has been reported that platelet activation may be associated with cardiovascular morbidity and mortality in hypertensive patients, and increased MPV may be an indicator of this condition (15,16,17). Microalbuminuria is a marker of endothelial damage that develops as a result of atherosclerosis and is associated with an increased risk of cardiovascular disease (18-20). Also, microalbuminuria is an early marker of kidney damage, which is the target organ in hypertensive patients (21,22). In various studies, it has been shown that there is an association between increased platelet activity and the risk of target organ damage in hypertensive patients (5,6,9). Significant positive correlations were found between MPV and subclinical target organ damage, such as microalbuminuria, left ventricular hypertrophy and carotis intima-media thickness in hypertensive patients (5). Ates et al.(9) reported that MPV levels were higher in hypertensive patients with proteinuria than in those without proteinuria. We also found a higher mean MPV value in microalbuminuric hypertensive patients than in normoalbuminuric ones. In this study, we did not detect any correlation between MPV and albuminuria levels that before the initiaition of antihypertensive medication, but we were unable to evaluate the relationship between MPV and albuminuria after medication because there were no control albuminuria values after antihypertensive therapy was started.

It has been shown in various clinical studies that MPV levels increase in hypertensive patients and in various clinical conditions associated with hypertension. However, there are no clinical studies showing the effect of antihypertensive therapy on MPV. In the study involving prehypertensive patients, it was found that 20 week-lifestyle changes provided a significant reduction in MPV levels (23). We found a significant decrease in mean MPV level of newly diagnosed hypertensive patients within one year (mean 5.8±3.6 months) after antihypertensive treatment was started.

Assessment of platelet activity requires difficult, time-consuming and expensive methods (24). However, MPV value measured during routine blood count is an easier and cheaper method of assessing platelet activity. A high MPV level can easily indicate the presence of platelets that are larger and have high thrombogenic activity. Many preanalytical and analytical factors, such as the method of blood collection, the anticoagulant used, the temperature of the blood being analyzed, can affect the mpv value (25,26). In addition, no standard cut off value is known for MPV and there is no standardization in comparing intercenter MPV values. However, in this study, all blood samples were obtained in a similar way and were studied with the same analyzer in the same laboratory within an hour after they were taken.

The most important limitation of this study is the small number of patients included in the study. In addition, due to the retrospective nature of the study, it was not possible to investigate whether there was a relationship between the mpv levels and the initial blood pressure values and the rate of decrease in blood pressure after treatment. However, it is known from the records that all patients enrolled in the study had their blood pressure

under control after starting to take antihypertensive medication. Another limitation of this study is the patients did not have control albuminuria values within one year after starting to take antihypertensive medication, so the relationship between the decrease in mpv and albuminuria levels could not be evaluated.

In conclusion, in this study, a significant decrease was detected in the MPV levels measured in the first year following the initiation of antihypertensive drug in the newly diagnosed hypertensive patients without other diseases. In newly diagnosed hypertensive patients, controlling blood pressure independently of antihypertensive agent may lead to a decrease in MPV level, thus reducing the risk of prothrombotic states, and may be associated with a reduction in endothelial damage and early atherosclerosis. In future studies, it may be useful to investigate whether the decrease in MPV level is accompanied by improvement in endothelial dysfunction after blood pressure control.

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Research Article / Araştırma Makalesi

Vertebral Arter DiseksiyonuTanılı Hastaların Retrospektif Değerlendirilmesi

Retrospective Evaluation of Patients Diagnosed with Vertebral Artery Dissection

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Özet

Kraniyoservikal arter diseksiyonları nadir görülen ancak genç inme hastalarda önemli bir etiyolojik faktördür. Etiyopatogenezde genetik ve çevresel faktörler sorumlu tutulmaktadır. Diseksiyonun neden olduğu nörolojik patolojiler endotelyal hasar nedeniyle meydana gelir. Vertebral arter (VA) sistemine ait diseksiyonlarının insidansı karotid arter diseksiyonlarına kıyasla daha düşüktür. VA diseksiyonları görece daha nadir görülmekle birlikte doğru tanı ve tedavinin gecikmesi fatal sonuçlanabilir. Bu çalışmada, kliniğimizde son sekiz yılda vertebral arter diseksiyonu tanısı ile takip edilmiş olan hastaların değerlendirilmesi ve prognozlarının araştırılması amaçlandı. Bu çalışma SBÜ İzmir Bozyaka Eğitim ve Araştırma Hastanesi Nöroloji Kliniğinde yapıldı. Çalışmaya 1 Ocak 2013 – 1 Ocak 2021 tarihleri arasında servikal arter diseksiyonu tanısıyla takip edilen 15 hasta dahil edildi. Hastalara ait veriler hastane bilgi yönetim sisteminden retrospektif olarak incelendi. Çalışmaya 8'i (%53,3) erkek 15 hasta alındı. Hastaların yaş ortalaması 45,3±15,57 (min-max:24-78) yıldı. Eşlik eden komorbid hastalıklar; hipertansiyon (n=7), diyabetes mellitus (n=2), hiperlipidemi (n=2) ve geçirilmiş serebrovasküler hastalıktı (n=1). Hastaneye en sık başvuru şikayetleri; baş dönmesi (n=12), konuşma bozukluğu (n=4), bulantı ve kusma (n=3), güçsüzlük (n=3) idi. Hastalardan dördünde travma, ikisinde ise boyun bölgesine masaj uygulanma öyküsü vardı. 5 (%33,3) hastada sağ, 9 (% 60) hastada sol vertebral arter diseksiyonu saptanmıştı. Hastaların takiplerinde büyük bölümünün (%80) sekelsiz iyileştiği kaydedildi. Elli yaş altında tüm inmelerin dörtte birinde karotis veya vertebral arterlerin diseksiyonu rol oynar. Bu nedenle genç inme hastalarında, servikal arter diseksiyonu ayırıcı tanıda akla gelmelidir. Ayrıca acil servis, nöroloji ve radyoloji klniklerinin multidisipliner çalışması ile hastalar etkin tedavi planı için yakından izlenmelidir.
Anahtar Kelimeler: Diseksiyon, Servikal arter diseksiyonu, İnme

Abstract

Craniocervicalartery dissection is a rare but important etiological factor in young stroke patients. Genetic and environmental factors are responsible in the etiopathogenesis. The neurological problems caused by dissections occurs due to endotelial damage. The incidence of dissections of vertebral artery (VA) is low, compared to carotid artery dissections. Although vertebral artery dissections are rare, delayed diagnosis or treatment may result in high mortality. This study was aimed to evaluate the patients who were followed up with the diagnosis of vertebral artery dissection in the last eight years and to investigate their prognosis. This study was conducted at University of Heath Sciences, Izmir Bozyaka Training and Research Hospital. Fifteen patients with the diagnosis of VA dissection between January 2013 and 2021 were included in the study. The data of the patients were analyzed retrospectively from hospital information management system. Fifteen patients, 8 (53.3%) male, were included in the study. The mean age was 45.3±15.57 (min-max:24-78) years. Recorded comorbid diseases were hypertension (n=7), diabetes mellitus (n=2), hyperlipidemia (n=2), cerebrovascular disease (n=1). The most common complaints were dizziness (n = 12), speech problem (n=4), nausea and vomiting (n=3), weakness (n=3). Four patients had a history of trauma and two patient had a history of neck massage. Right VA dissection was detected in 5 (33.3%) patients, and left VA dissection in 9 (60%) patients. It was noted that most of the patients (80%) were fully-recovered in the follow-up. Dissection of the carotid or vertebral arteries is the cause for one-fourth of all strokes under 50 years of age. Therefore, cervical artery dissections should be considered in the differential diagnosis of acute ischemic stroke in young adults. In addition, the patients should be closely monitored for effective treatment plan with the multidisciplinary approaches of emergency department, neurology and radiology clinics.
Keywords: Dissection, Cervical artery dissections, Stroke

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1. Giriş

Kraniyoservikal arter diseksiyonları nadir görülen ancak özellikle 50 yaş altında inme tanısı alan hastalarda önemli bir etiyolojik faktördür (1). Servikal arter diseksiyonları (SAD), tüm yaş gruplarındaki iskemik inmelerin %1-2'sinde saptanırken, gençlerde iyi tanımlanmış bir inme nedenidir. SAD saptanan genç hastalar, tipik olarak klasik inme risk faktörlerine sahip değildir. Elli beş yaşından genç hastalarda SAD, hastaların %9-25'inde inme nedeni olarak ortaya koyulmaktadır (2,3). Kranioservikal arter diseksiyonlarıspontan ya da post-travmatik olarak gelişebilir. Etiyolojisinde genetik ve çevresel faktörler sorumlu tutulmaktadır. Hipertansiyon, hiperlipidemi, ateroskleroz, ilişkili bulunan sistemik hastalıklardır. Ayrıca sigara alışkanlığı da diseksiyonlarla ilişkili bulunmuştur (4). Diseksiyonlarla ilişkili olarak gelişen nörolojik bulgular ve inmenin patofizyolojisindenendotelyal hasar sorumludur. Endotelyal yapıdaki bozulma trombosit ve pıhtılaşma kaskatını aktive ederek trombüs oluşumuna ve sekondertromboembolik durumlara neden olmaktadır (4,5).

Posttravmatik diseksiyonlar majör travmalar sonrası oluşabildiği gibi basit fiziksel aktiviteler ya da öksürüğe sekonder de gelişebilir. Karotid arter diseksiyonlarında yıllık insidans 2-3/100.000 iken vertebral arter diseksiyonlarında 1-1,5/100.000 olarak bildirilmiştir (6). Vertebral arter (VA) sistemine ait diseksiyonların insidansı, karotid arter diseksiyonlarına kıyasla daha düşüktür. VA diseksiyonları görece daha nadir görülmekle birlikte doğru tanı ve tedavinin gecikmesi fatal sonuçlanabilir (7).

Bu çalışmada, Sağlık Bilimleri Üniversitesi, İzmir Bozyaka Eğitim ve Araştırma Hastanesi, Nöroloji kliniğinde son sekiz yıl içinde vertebral arter diseksiyonutanısı ile takip edilmiş olan hastaların retrospektif gözden geçirilmesi ve uzun dönem izlemde prognozlarının araştırılması amaçlandı.

2. Gereç ve Yöntem

Retrospektif-kesitsel olarak planlanan çalışmamızda 1 Ocak 2013 – 1 Ocak 2021 tarihleri arasında Sağlık Bilimleri Üniversitesi, İzmir Bozyaka Eğitim ve Araştırma Hastanesi, Nöroloji Kliniğinde vertebral arter diseksiyonu tanı almış, tanıya yönelik tetkik ve tedavisi yapılan hastalara ait veriler hastane bilgi yönetim sisteminden yararlanılarak değerlendirildi. Bu hastaların epikrizleri ve poliklinik izlem kayıtları incelendi. Hastaların demografik özellikleri, başvuru zamanı ve nörolojik muayene bulguları, nörogörüntüleme özellikleri, tedavi ve klinik izlemleri kaydedildi.

Etik Kurul Onayı

Çalışmanın etik kurul onayı Sağlık Bilimleri Üniversitesi, İzmir Bozyaka Eğitim ve Araştırma Hastanesi etik kurulundan alınmıştır (Etik kurul karar tarihi: 09.06.2021 Referans no: 2021/100).

İstatistiksel Analiz

Çalışmadan elde edilen verilerin istatistiksel analizi SPSS 24.0 paket programı (IBM Corp.;Armonk, NY, USA) ile yapıldı. Kategorik değişkenler yüzde ile, sürekli değişkenler ortalama±standart sapma (SD) olarak ifade edildi.

3. Bulgular

Çalışmaya vertebral arter diseksiyonu tanısıyla izlenen, tedavi ve izlem süreci hastanemizde tamamlanan 15 hasta alındı. Hastaların 8'i (%53,3) erkek olup tüm hastaların yaş ortalaması 45,3±15,57 (min-max:24-78) yıldı. Hastalarda kaydedilen komorbid hastalıklar; hipertansiyon (HT) (n=7), diabetes mellitus (DM) (n=2), hiperlipidemi (n=2) ve geçirilmiş serebrovasküler hastalıktı (SVH) (n=1). Hastalardan 5'i aktif sigara kullanıcısıydı.

Hastaların yatış sırasında yapılan rutin biyokimyasal incelemeleri, hemogram, sedimentasyon, vaskülitik markerları (ANA, ANCA paneli, anti-dsDNA, antikardiyolipin antikorları, lupus antikoagülanı), koagülasyon testleri ve tiroid fonksiyon testleri normaldi.

Hastaneye başvuru şikayetileri; baş dönmesi (n=12), konuşma bozukluğu (n=4), bulantı ve kusma (n=3), güçsüzlük (n=3), dengesizlik (n=2) idi. Bunların yanında boyun ağrısı

(n=2), baş ağrısı (n=2), göz kapağında düşme (n=1), bilinç bulanıklığı (n=1) görüldü. Hastalardan dördünde travma, ikisinde ise boyun bölgesine masaj uygulanma öyküsü vardı.

Vasküler görüntüleme yöntemi olarak; vertebral arter doppler ultrasonografi (USG) (n=15), Manyetik rezonansanjiografi (MR-A) (n=3), Bilgisayarlı Tomografi Anjiografi (BT-A) (n=12) kullanılmıştı. Vertebral arter diseksiyonu tanısı konulan bu 15 hastanın nörogörüntüleme bulguları incelendiğinde 5hastada (%33,3) sağ, 9 hastada (% 60) sol vertebral arter diseksiyonu saptanırken, 1 hastada (%6,66) ise sol vertebral ve baziler arter diseksiyonu mevcuttu. Hastaların 1'inde V1, 2'sinde V2, 1'inde V3, 2'sinde V2-V3, 7'sinde vertebral arterin V3-V4 segmentlerinde, 2'sinde V4 segmentinde diseksiyon saptandı.

Ondört hasta (%93,3) şikayetlerinin akut döneminde başvurmuşken, hastalardan biri kliniğimize diseksiyon tanısının 1. ayında başvurmuştu. Bu hastaya ilk değerlendirmenin yapıldığı merkezde ikili antiagregan (asetilsalisilik asit ve klopidogrel) tedavi başlanmıştı. Kliniğimizdeki izleminde de antiagregan tedavi ile devam edildi. Akut gelişen nörolojik semptomlar nedeniyle şikayetin 1. saatinde acil servise başvuran bir hastaya, akut serebrovasküler hastalık tanısı ile intravenöz trombolitik (r-tPA) tedavi uygulandı. Yapılan ileri tetkikler sonrasında VA diseksiyonu tanısı koyulan bu hasta, izlemde varfarinle antikoagule edildi. Benzer şekilde akut dönemde başvuran diğer hastalar da varfarin ile antikoagule edildi. Fakat hastalardan birinde etkin INR düzeyi elde edilememesi, birinde ise klinik izlemi sırasında hematemez ve yaygın ekimotik lezyonlar gelişmesi nedeniyle varfarine devam edilemedi, antiagregan tedavi ile takip edildi. Tüm hastalar poliklinik izleminde (6.-12. Ay aralığında) Doppler USG veya boyun BT-A ile tekrar değerlendirilmişti ve tümünde diseksiyon görünümünde düzelme izlendi. Hastaların takiplerinde büyük bölümünün (%80) sekelsiz iyileştiği, diğer hastaların ise hemiparezi (n=2) ve serebellar sendrom bulguları (n=1) şeklinde hafif sekel bulguların kaldığı görüldü. Hastalara ait demografik, klinik ve radyolojik veriler Tablo 1'de sunulmuştur.

Tablo 1: Demografik, klinik ve radyolojik veriler

Hasta no	Yaş	Cinsiyet	Diseksiyon lokalizasyonu	Şikayet	Komorbid Hastalık	Nörolojik muayene	Tedavi	NÖROLOJİK DEFİSİTİ
1.	32	E	Sağ VA (V3-V4)	Dengesizlik	-	Sağa ataksi	Varfarin	Sekelsiz
2.	31	E	Sağ VA (V3-V4)	Dengesizlik, Baş dönmesi	-	Sağ serebellar sendrom	Varfarin	Sekelsiz
3.	24	K	Sağ VA (V3)	Baş ağrısı Baş dönmesi	-	Konfüzyon Sağ serebellar sendrom	1.Varfarin 2.ASA (varfarin intoksikasyonu)	Sekelsiz
4.	57	E	Sol VA (V2-V3)	Baş ağrısı Baş dönmesi	Hipertansiyon	Sol serebellar sendrom	Varfarin	Sekelsiz
5.	39	E	Sağ VA (V1)	Baş dönmesi kusma	Hipertansiyon	Sol serebellar sendrom	Varfarin	Sekelsiz
6.	60	E	Sol VA (V4)	Baş dönmesi Sağ yanlı güçsüzlük	Hipertansiyon	Sağ hemiparezi	Varfarin	Sağ hemiparezi
7.	37	K	Sol VA (V3-V4)	Kusma Sağ yanlı güçsüzlük	-	Sağ serebellar sendrom	r-tPA Varfarin ASA (İNR etkin olmadığı için)	Sağ serebellar sendrom
8.	31	K	Sol VA (V3-V4) + Baziler arter	Baş dönmesi, konuşma ve yutma güçlüğü	-	Bulber tutulum, quadriparezi	Varfarin	Sekelsiz

9.	57	E	Sol VA (V3-V4)	Baş dönmesi	Hipertansiyon	Sol hemiparezi ve serebellar sendrom	Varfarin	Sol hemiparezi
10.	59	K	Sol VA (V2-V3)	Baş dönmesi	İskemik Serebrovasküler Hastalık	Sol serebellar sendrom	Varfarin	Sekelsiz
11.	30	E	Sol VA (V3-V4)	Baş dönmesi	-	Sol serebellar sendrom	ASA ve Klopidogrel	Sekelsiz
12.	48	E	Sağ VA (V2)	Baş dönmesi Kusma	Diabetes mellitus Hipertansiyon Hiperlipidemi	Sağ hemihipoestezi Nistagmus	Varfarin	Sekelsiz
13.	33	K	Sol VA (V3-V4)	Baş dönmesi Konuşma bozukluğu	-	Sol hemiparezi Sol hemihipoestezi Dizartri	Varfarin	Sekelsiz
14.	78	K	Sol VA (V2)	Baş dönmesi Konuşma bozukluğu Sol yanlı güçsüzlük	Hipertansiyon	Sol serebellar Sendrom Sol hemiparezi	Varfarin	Sekelsiz
15.	64	K	Sol VA (V4)	Baş dönmesi Konuşma bozukluğu	Diabetes mellitus Hipertansiyon Hiperlipidemi	Sola ataksi Dizartri	Varfarin	Sekelsiz

4. Tartışma

Elli yaş altında tüm inmelerin dörtte birinde karotis veya vertebral arterlerin diseksiyonu rol oynar (8). VA diseksiyonları, karotid arter diseksiyonlarından daha seyrek görülür (5,6). Kadınlarda servikal arter diseksiyonlarının, özellikle ekstrakraniyal lokalizasyonda erkeklere oranla fazla olduğu ve kadınlarda diseksiyonun erkeklere göre beş yıl daha erken geliştiği bildirilmiştir (8). Son 8 yıla ait vertebral arter diseksiyonu tanılı olgu deneyimlerini sunmayı amaçladığımız çalışmamızda cinsiyetler arasında VA diseksiyonu benzer sıklıkta (7 kadın, 8 erkek) saptanmıştır. Hastaların yaş ortalaması 45±15,5 yıl saptanmış olup, literatürle uyumlu bulunmuştur. Yusuf Babashovave ark.'nın çalışmasında da VA diseksiyonu saptanan hastalarda yaş ortalaması 40,8 yıl olduğu bildirilmiştir (9). Çalışmamızda kadın ve erkek hastaların yaş ortalamaları arasında fark saptanmamıştır. Vertebral arterlerdeetkilenen taraf açısından literatürde anlamlı bir fark saptanmamış olmakla birlikte 15 vakamızın 10'unda sol tarafta vertebral arter diseksiyonu saptanmıştır.

Travma olmaksızın spontan gelişen VA diseksiyonunda altta yatan bağ dokusu hastalığı araştırılmalıdır. Bağ dokusu hastalıklarından fibromüsküler displazi, Tip 4 Ehler Danlos Hastalığı, Marfan Sendromu VA diseksiyonlarına yatkınlık yarattığı bildirilmiştir (10,11). Çalışmamızda bilinen bağ dokusu hastalığı olan hasta yoktu. Fizik muayene ve yapılan etiyolojiye yönelik tetkiklerde bağ doku hastalıkları açısından patolojik bulgu saptanmadı. Servikal arter diseksiyonlarında travma öyküsünün varlığı çeşitli çalışmalarda yaklaşık %40 oranında bildirilmiştir (9,12). Çalışmamızda 6 (%40) hastada VA diseksiyonunun travmaya sekonder geliştiği saptandı. Bu hastalardan birinin uzun süredir esrar kullanımının olması dikkat çekiciydi. Diğer hastalarda ayrıntılı tetkiklere rağmen etiyolojik neden saptanamamıştır.

VA diseksiyonunda başvuru şikayeti hastaların önemli bir kısmında ense lokalizasyonunda, nadiren de tüm başı içine alan baş ağrısı gibi nonspesifik bulgular olabileceği gibi hastaların %60'ı vertebrobaziler sistem iskemisini düşündüren bulgularla başvururlar (13,14). Saeed ve ark.'nın VA diseksiyonlarında erken semptomları retrospektif olarak inceledikleri çalışmalarında hastaların %88'inin ağrısının olduğunu ve özellikle oksipital başağrısı yaşadıklarını vurgulamışlardır (15). Çalışmamızda saptanan en sık başvuru şemptomları baş dönmesi, bulantı-kusma gibi posterior arteriyel dolaşım yetmezliğini telkin eden bulgulardı. Kaydedilen diğer başvuru bulguları ise baş ağrısı, bilinç değişikliği ve

hemiparezi idi. Vertebral arterde etkilenen segment incelendiğinde, olgularımızdan üçü haricinde V3, V4 ya da V3-V4 segmentinde diseksiyon olduğu kaydedildi. Literatürde V2 ve V3 segmentlerinin daha sık etkilendiği gösterilmiştir (16). Ülkemizden yayınlanmış, sadece vertebral arter diseksiyonlarını inceleyen az sayıda çalışma vardır. Çabalar ve ark.'nın çalışmasında da benzer şekilde önde gelen başvuru semptomları baş dönmesi, baş ağrısı ve boyun ağrısıdır (17).

Vertebral arter diseksiyonuna ikincil lateral medulla (Wallenberg sendromu) olmak üzere beyin sapı, talamus, serebral veya serebellar hemisferlere ait iskemi görülebilir (7). Tanıda altın standart, kateter anjiografidir. Son zamanlarda ulaşım kolaylığı nedeniyle MR-A kateter anjiografinin yerini almıştır ancak VA diseksiyonlarında sensitivite ve spesifitesinin düşük olduğu unutulmamalıdır (9). BT-A'da diseksiyon açısından oldukça spesifik olmakla birlikte kontrast madde gerekliliği açısından kısıtlayıcı olabilir (18). Klinik pratikte genellikle hastanenin sahip olduğu cihazların özellikleri ve ulaşılabilirliklerine göre nörogörüntüleme yöntemine karar verilmektedir. Hastalarımızın tümü Doppler USG, 12'si BT-A ve 3'ü MR-A tetkikleri ile değerlendirilmişti. Hastalarımızın takip sürecinde nörogörüntülemede Doppler USG ve BT-A kullanılmıştı.

Diseksiyonda oluşan iskemik hasardaki temel mekanizma; damarın daralıp tıkanmasına ya da arterden artere emboliye bağlıdır. Antikoagülan tedavi, diseksiyonun ortaya çıkardığı lümen tıkanıklığına sekonder gelişecek taze trombüs formasyonunu engellemek için önerilir (19). Aslında diseksiyonlarda uygulanacak tedavi konusunda yapılmış yeterli sayıda randomize kontrollü çalışma yoktur. 'Cervical Artery Dissection in Stroke Study' (CADISS) çalışması ve çok yakın zamanda yayınlanan uzun dönem sonuçları ile diseksiyonda antikoagulan/antiplatelet tedavi arasında hem rekürren inmeyi önlemede ve hem de rezidüel darlık ya da oklüzyon oranları konusunda anlamlı fark saptanmadığı bildirilmiştir (20,21). Akut iskemik inme semptomları ile başvuran uygun hastalarda etiyolojik araştırma yapılmaksızın ilk 4.5 saatlik tedavi penceresinde ise r-tPA yapılmalıdır (22). Diseksiyonlarda r-tPA deneyimi henüz olgularla sınırlıdır. Hastalarımızdan birine de r-tPA tedavisi uygulandı, komplikasyon yaşanmadı ve kısa sürede sekelsiz olarak düzeldi. Hastalarımızın 3'ü farklı nedenlerden dolayı antiagregan tedavi ile izlenirken diğerleri varfarin ile antikoagüle edilerek izlendi. Literatürde antikoagule edilen hastaların izleminde kontrol MR-A ile damarın rekanalizasyonu gösterildiğinde antiagregan tedaviye geçilmesi önerilmektedir (8). Hastalarımıza poliklinik izlemlerinde yapılan vertebral arter Doppler USG veya boyun BT-A incelemelerinde tümünde rekanalizasyon sağlandığı görülmesi üzerine antiagregan tedaviye geçilmiştir.

Vertebral arter diseksiyonları, arka dolaşım sistemi ile ilişkili semptomlar ve boyun ağrısı ile başvuran genç hastalarda mutlaka ayırıcı tanıda akla gelmelidir. Erken tanı ve tedavi mortalite ve morbiditeyi azaltmak için şarttır. Akut dönemde yaklaşık %10 mortalite ile sonuçlandığı bilinmektedir. İntrakraniyal diseksiyonlarda; subaraknoid hemoraji veya beyin sapı infarktı birlikteliği mortalite ile ilişkili bulunmuştur (15,23,24). Başlangıçtaki inmenin ağırlık derecesi, kollateral dolaşımın yetersizliği ve bilateral tutulum kötü prognostik faktörler arasında yer almaktadır (25). Hayatta kalan hastalarda prognoz sıklıkla iyidir, hastaların %88'inde tama yakın düzelme bildirilmiş (24). Hastalarımızın %80'i sekelsiz iyileşirken, diğer hastaların takiplerinde dizartri, ılımlı hemiparezi ve serebellar sendrom bulgularının sekel kaldığı izlenmiştir. Olgu serimizde diseksiyonların intraserebral hemoraji komponenti veya subaraknoid hemoraji birlikteliği olan ve kaybedilen hasta yer almamaktadır.

Çalışmamızın en önemli kısıtlılığı görece az hasta sayısına sahip olması, tek merkezli ve retrospektif dizaynıdır. Ancak 3. Basamak bir hastanenin 8 yıllık verilerinin değerlendirilmiş olması nedeniyle literatüre önemli katkı sağlayacağı kanısındayız.

Sonuç olarak özellikle genç inme olgularındadiseksiyon tanısı mutlaka akla gelmeli, acil servis, nöroloji ve radyoloji kliniklerinin multidisipliner çalışması ile hastalar etkin tedavi planı için yakından izlenmelidir.

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Research Article / Araştırma Makalesi

The Anti-Cytoplasmic and Anti-Mitotic Autoantibodies; Are These Antibodies Associated with Diseases?

Anti-Sitoplazmik ve Anti-Mitotik Otoantikorlar; Bu Antikorların Hastalıklarla İlişkisi Var Mı?

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Abstract

Examination of antinuclear antibody (ANA) is used in diagnosis of systemic autoimmune diseases, and the indirect immunofluorescence (IIF) assay using HEp-2 cells is the gold standard method. HEp-2 allows the detection of multiple target antigen-directed autoantibodies. The guide "The International Consensus on ANA Patterns (ICAP)", characterizes the patterns into three groups: nuclear, cytoplasmic, and mitotic. The majority of these are associated with autoimmune diseases, but some are rarely seen in autoimmune diseases or may be associated with conditions other than autoimmune disease. There is no consensus on how to report cytoplasmic and mitotic patterns-negative or positive. We aimed to examine the characteristics of patients that had cytoplasmic or mitotic staining in ANA evaluation by IIF. In our Medical Microbiology Laboratory, 18985 ANA tests of 16940 patients were studied between 01.01.2015-31.12.2019. Cytoplasmic or mitotic pattern was detected in 393 (2.07%) tests belonging to 385 patients. Cytoplasmic patterns suggestive of anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), anti-Jo-1 and anti-ribosomal P-protein were not included. The most common patterns were anti-midbody, anti-spindle fibers, and anti-vimentin patterns. There were 66 rheumatology patients that were negative for ANA but had cytoplasmic or mitotic staining. There was no statistically significant difference between the diagnosis and patterns of these patients. We suggest that the ANA should be reported as "negative" in case of cytoplasmic or mitotic pattern unless the term anti-cell antibody is used. It should be noted in the description part of the report in order to distinguish significant cytoplasmic patterns and give an idea for some specific conditions.
Keywords: Anti-nuclear antibody; anti-cytoplasmic pattern; anti-mitotic pattern; autoantibody; indirect immunofluorescence assay

Özet

Sistemik otoimmün hastalıkların tanısında antinükleer antikor (ANA) incelemesi yapılır ve HEp-2 hücrelerini kullanan indirekt immünfloresan (IIF) test altın standart yöntemdir. HEp-2, çok sayıda hedef antijene yönelmiş otoantikorların saptanmasına imkân verir. "Antinükleer Antikor (ANA) Paterninde Uluslararası Uzlaşı" rehberi, paternleri üç gruba ayırır: nükleer, sitoplazmik ve mitotik. Bunların çoğu otoimmün hastalıklarla ilişkilidir, ancak bazıları otoimmün hastalıklarda nadiren görülür veya otoimmün hastalık dışındaki durumlarla ilişkili olabilir. Sitoplazmik ve mitotik paternlerin nasıl raporlanacağı konusunda- negatif veya pozitif- bir fikir birliği yoktur. IIF ile ANA değerlendirmesinde sitoplazmik veya mitotik boyanma olan hastaların özelliklerini incelemeyi amaçladık. Tıbbi Mikrobiyoloji Laboratuvarımızda 01.01.2015-31.12.2019 tarihleri arasında 16940 hastaya ait 18985 ANA testi çalışılmıştır. 385 hastaya ait 393 (%2.07) testte sitoplazmik veya mitotik patern tespit edildi. Anti-mitokondriyal antikor (AMA), anti-düz kas antikoru (ASMA), anti-Jo-1 ve anti-ribozomal P-proteini düşündüren sitoplazmik paternler çalışmaya dahil edilmedi. En sık görülen paternler anti-midbody (hücreler arası köprü), anti-spindle fibers (iğsi iplikçikler) ve anti-vimentin paternleriydi. Altmış altı romatoloji hastasında ANA negatifti ancak sitoplazmik veya mitotik boyanma saptandı. Bu hastaların tanı ve paternleri arasında istatistiksel olarak anlamlı bir fark bulunamadı. Anti-hücre antikoru terimi kullanılmadıkça, sitoplazmik veya mitotik patern olması durumunda ANA'nın "negatif" olarak rapor edilmesini öneriyoruz. Bu boyanma, önemli sitoplazmik paternleri ayırt etmek ve bazı spesifik durumlar hakkında fikir vermek için raporun açıklama kısmında belirtilmelidir.
Anahtar Kelimeler: Anti-nükleer antikor; anti-sitoplazmik patern; anti-mitotik patern; otoantikor; indirekt immünfloresan test

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1. Introduction

The indirect immunofluorescence (IIF) assay using HEp-2 cell substrate is still the gold standard method in the examination of antinuclear antibody (ANA) (1). HEp-2 is an epithelial cell line from human laryngeal carcinoma, consisting large cells with high number of mitotic cells. The high rate of mitosis provides the expression of a large number of different antigens specific to the cycle in cells, thus allowing the detection of multiple target antigen-directed autoantibodies (2). By using the HEp-2 cells, cytoplasmic and mitotic cell patterns besides nuclear patterns, can also be recognized (3). Therefore, the term "anti-cellular antibodies" has been suggested to meet the wider variety of these autoantibodies (4). In the guide referred as "The International Consensus on ANA Patterns (ICAP)", patterns are characterized into three major groups: nuclear, cytoplasmic, mitotic (5). In this guide, the patterns are numbered from AC (anti-cellular) -1 to AC-29 (6). Recently, AC-0 was added to refer the negative result. The nomenclature and representative 29 patterns are available online at the ICAP website: www.anapatterns.org.

The majority of these autoantibodies are associated with autoimmune diseases, but some of them are rarely seen in autoimmune diseases or may be associated with other conditions. Nevertheless, many autoantibodies that have not been proven to be disease-specific so far cause staining in these cells, so interpretation of them by the clinician can be confusing. There is no consensus on how to report cytoplasmic and mitotic patterns-negative or positive (7). The EASI (The European Autoimmunity Standardization Initiative) and IUIS (International Union of Immunological Societies) recommend that cytoplasmic and mitotic patterns should be reported and specified when possible (4).

In this study, patients who applied to the rheumatology clinic and were found to have only cytoplasmic or mitotic patterns were evaluated in terms of demographic characteristics, diagnoses, treatments and concomitant diseases.

2. Materials and Methods

In Medical Microbiology Department of Eskisehir Osmangazi University Faculty of Medicine, 18985 ANA tests of 16940 patients were studied between 01.01.2015-31.12.2019. ANA was tested by IIF on HEp-2 and primate liver cells with fluorescence microscopy according to the instructions of the manufacturer (Euroimmun AG, Luebeck, Germany). The patterns and titers according to the fluorescence intensity compared with the controls were recorded.

This study was approved by Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee (30.04.2019/25). This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Statistical analysis

SPSS statistics program (IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY) was used for data analysis.

3. Results

Among 18985 serum samples, 6506 (34.27%) were positive for ANA. Cytoplasmic or mitotic pattern was detected in 393 (2.07%) tests belonging to 385 patients, but these patterns are not reported as ANA positive. Patients who had cytoplasmic patterns such as anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), anti-Jo-1, anti-ribosomal P-protein specific to an autoimmune disease were not included in this group.

Of these 385 patients, 250 (64.9%) were female and 135 (35.1%) were male. The mean age of these group was 46.11 (min 1-max 88). Ninety-two (23.9%) patients were from rheumatology clinics, 242 (62.9%) were from other adult clinics except rheumatology and 51 (13.2%) were from pediatric clinics.

The number and ratio of cytoplasmic or mitotic patterns among all tests in five years are shown on Table 1.

Table 1. The number and ratio of cytoplasmic or mitotic patterns among all ANA tests

Cytoplasmic and/or mitotic patterns and AC codes	The number and ratio of patterns detected in all ANA tests n, % (n/18985)
Anti-midbody (AC-27 Intercellular bridge)	118, 0.62
Anti-spindle fibers (AC-25 Spindle-fibers)	87, 0.46
Anti-vimentin (AC-16 Cytoplasmic fibrillar filamentous)	66, 0.34
Anti-centrosome (AC-24 Centrosome)	42, 0.22
Anti-golgi-like (AC-22 Polar/Golgi-like)	35, 0.18
Rods and rings (AC-23 Rods and rings)	26, 0.14
Anti-tropomyosin-like (AC-16 Cytoplasmic fibrillar filamentous)	10, 0.05
Anti-mitotic coat (AC-28 Mitotic chromosomal)	6, 0.03
Anti-lysosome-like (AC-18 Cytoplasmic discrete dots/GW body-like)	3, 0.02
TOTAL	**393 tests**

There was no statistically significant difference between the cytoplasmic or mitotic pattern groups according to their ages. The most common cytoplasmic or mitotic pattern was anti-midbody pattern. There was no statistically significant difference between distinct patterns and the clinics of the patients ($p>0.05$). In addition, no statistically significant difference was found between gender and cytoplasmic or mitotic patterns ($p>0.05$).

Ninety-two of the patients with cytoplasmic or mitotic staining were rheumatology patients. Among them ANA was positive with different patterns and titers in 24 patients, and 2 patients were weak positive with speckled pattern. Since it was aimed to examine patients who were ANA negative but had cytoplasmic or mitotic staining, remaining 66 patients were evaluated in detail. Table 2 shows the cytoplasmic or mitotic patterns among these 66 patients.

Table 2. The number and ratios of cytoplasmic or mitotic patterns among rheumatology patients

Cytoplasmic and/or mitotic patterns (AC codes)	The number and ratio of patterns detected in rheumatology patients n, %
Anti-midbody (AC-27 Intercellular bridge)	20, 30.3
Anti-vimentin (AC-16 Cytoplasmic fibrillar filamentous)	14, 21.2
Anti-spindle fibers (AC-25 Spindle-fibers)	9, 13.6
Anti-centrosome (AC-24 Centrosome)	9, 13.6
Anti-golgi-like (AC-22 Polar/Golgi-like)	6, 9.1
Rods and rings (AC-23 Rods and rings)	4, 6.1
Anti-tropomyosin-like (AC-16 Cytoplasmic fibrillar filamentous)	3, 4.6
Anti-mitotic coat (AC-28 Mitotic chromosomal)	1, 1.5
Anti-lysosome-like (AC-18 Cytoplasmic discrete dots/GW body-like)	-
TOTAL	**66 patients, 100**

These 66 patients were evaluated in terms of the complaints at the initial referral to the clinics, the diagnoses (Table 3), the treatments they received, the course of their disease and the presence of accompanying diseases, retrospectively. There was no statistically significant difference between the diagnosis and patterns of 66 rheumatology patient.

Table 3. The diagnosis of rheumatology patients with cytoplasmic or mitotic pattern

	NRD	Fb	RA	SNRA	SS	SLE	CV	AS	BD	OA	FMF	PMR	GPA	HFA	Total
Anti-midbody	7	4	2	-	1	-	1	2	1	-	1	-	-	1	20
Anti-vimentin	7	4	1	1	-	-	-	-	-	-	-	-	1	-	14
Anti-spindle fibers	6	-	-	-	-	1	1	-	1	-	-	-	-	-	9
Anti-centrosome	5	1	-	-	1	-	-	-	-	1	1	-	-	-	9

Anti-golgi-like	1	2	-	1	-	-	1	-	-	-	-	1	-	-	6
Rods and rings	2	1	-	-	-	-	-	-	-	1	-	-	-	-	4
Anti-tropomyosin-like	-	-	1	1	-	-	-	1	-	-	-	-	-	-	3
Anti-mitotic coat	-	-	-	1	-	-	-	-	-	-	-	-	-	-	1
TOTAL	28	12	4	4	2	1	3	3	2	2	2	1	1	1	66

NRD: no rheumatologic disease, Fb: fibromyalgia, RA: rheumatoid arthritis, SNRA: seronegative rheumatoid arthritis, SS: Sjögren's syndrome, SLE: systemic lupus erythematosus, CV: cutaneous vasculitis, AS: ankylosing spondylitis, BD: Behçet's disease, OA: osteoarthritis, FMF: familial Mediterranean fever, PMR: polymyalgia rheumatica, GPA: polyangiitis with granulomatosis, HFA: hereditary familial amyloidosis

4. Discussion and Conclusion

The usage of HEp-2 cells as a substrate for ANA IIF has raised awareness that cytoplasmic and mitotic cell patterns can be recognized as well as nuclear patterns (3). The terms 'anti-nuclear antibodies' (ANA) and 'extractable nuclear antigens' (ENA) are no longer technically correct and they do not cover all of the autoantibodies targeted against mitotic spindle apparatus, cytosol or cytoplasmic organelles. (4). Therefore, ICAP actually recommends using the definition of anti-cell (AC) antibody instead of ANA. When these autoantibodies are reported as ANA negative, they can be overlooked by the physician even if additional information is stated in the explanation section (3). According to some reports, clear cytoplasmic or mitotic apparatus reactivity should be reported as ANA IIF positive (5), but some literatures opposed to report cytoplasmic or mitotic patterns as ANA positive (3,8,9). Cytoplasmic patterns have been reported as ANA positive for more than a decade in Brazil (10).

Von Mühlen et al. reported an article based on practices of 118 laboratories in 68 countries, on how to report the ANA (anti-cell antibodies) with recommendations from ICAP. Fifty-five percent of the laboratories reported cytoplasmic patterns as ANA positive (11). In fact, since cytoplasmic patterns are not exactly ANA, the Brazilian Consensus recommends using "anti-cell antibodies" to cover anticytoplasmic patterns, rather than calling them ANA, as per ICAP's recommendation. They also suggest to report the mitotic patterns (AC-24 to AC-28) as positive (12). In our laboratory, we report these patterns as ANA negative and write additional information in the explanation section.

In routine ANA tests, cytoplasmic pattern is reported in different rates as 6.4–21.8% (13-17). In a study, cytoplasmic patterns were detected in 21.8% of 670 ANA positive cases, and the frequency of cytoplasmic patterns was reported to increase with age (17). Stinton et al. reported a positivity rate of 40.5% nuclear pattern and 15% of cytoplasmic pattern out of 2724 sera (14). In our laboratory, cytoplasmic or mitotic patterns, other than significant patterns for autoimmune diseases such as AMA and Jo-1 account for about 2.07% of all ANA tests.

Anti-midbody antibody

We detected the anti-midbody pattern most frequently among cytoplasmic or mitotic patterns, with a rate of 0.62% (118/18985). In ICAP, it is defined and coded as intercellular bridge, AC-27 pattern. Betancur et al. reported anti-midbody positivity as 0.32% in 113491 sera. Among those anti-midbody positive patients, 43% had connective tissue disease (mostly Sjögren's syndrome, rheumatoid arthritis-RA and systemic lupus erythematosus-SLE) and 6% had malignancy. They reported sensorineural hearing loss in 36.6% of patients (18). Vermeersch and Bossuyt reported anti-midbody positivity rate as 0.13% in 68128 consecutive patients in a 14-year period (19). In 1980's anti-midbody antibodies were described in patients with systemic sclerosis and Raynaud's syndrome (20,21). There are case reports reporting the association of systemic sclerosis and anti-midbody antibody (22,23).

Twenty of 66 rheumatology patients were positive for anti-midbody pattern. No

rheumatological disease was considered in 7 of them while four of them were followed-up with fibromyalgia. Only one patient was diagnosed as systemic sclerosis, and the remaining 8 patients were diagnosed with different rheumatological diseases.

Anti-spindle fibers antibody

Anti-spindle fiber antibodies, one of the components of the mitotic apparatus, were the second most common cytoplasmic or mitotic pattern among all ANA tests, and were seen in 9 of 66 rheumatology patients. The two main autoantigens of the anti-mitotic spindle apparatus antibodies are nuclear mitotic apparatus protein 1 (NuMa1) and the kinesin HsEg5 (NuMa2) (19,24,25). In our study, we did not include NuMA1 patterns that are spindle fiber staining accompanied by nuclear speckled staining on interphase cells. ICAP identified spindle fiber (AC-25) and NuMA-like patterns (AC-26) under different codes. The AC-25 spindle fibers pattern is reported to have low positive predictive value for any disease and to be found infrequently in a routine serology diagnostic setting (26). Vermeersch and Bossuyt reported the prevalence of anti-spindle fiber (NuMA2) pattern as 0.06% among 9268 ANA-positive patients (19). Szalat et al. reported 13 anti-NuMA2 positive patients among 36498 sera. One of them was presented with an antiphospholipid syndrome (27).

In our study, the positivity rate of anti-spindle-fiber antibody was 0.46%. Among rheumatology patients, 9 had anti-spindle fiber pattern. No rheumatologic disease was considered in 6 of these 9 patients. One of the remaining patients was diagnosed as cutaneous vasculitis currently in remission, the other was a SLE patient, and the last one was a Behçet's disease patient with uveitis.

Anti-vimentin antibody

Autoantibodies that target vimentin, one of the cytoskeletal filaments, and other microtubules and intermediate filaments cause cytoplasmic filamentous staining. The pattern, encoded and defined as AC-16 cytoplasmic fibrillar filamentous in ICAP, was detected in 66 (0.34%) of 18985 serum samples. It is reported in various diseases but is not typical for a systemic autoimmune rheumatologic disease.

Studies have shown that anti-vimentin antibodies may indicate tissue damage (28) and it can be produced after injury from infection and/or trauma (29), but whether anti-vimentin antibodies accelerate or accentuate tissue damage is less certain (28). Anti-vimentin antibodies may be produced as a signal of chronic injury in organ transplant recipients (30-32) and can be implicated in rejection and poor outcome in solid organ transplantations (32,33). Increased vimentin levels and anti-vimentin antibodies have also been reported in patients with idiopathic pulmonary fibrosis and non-specific interstitial pneumonia, suggesting they occurred after lung injury (34,35).

Kotaska et al. studied anti-vimentin antibodies of 131 children and adolescents with neurofibromatosis type 1 and in control group of 40 individuals, and reported the anti-vimentin antibodies as relevant markers for monitoring the disease (36).

Anti-vimentin pattern was detected in 14 rheumatology patients. Only two of these patients were male. No rheumatologic disease was considered in 7 patients, one of whom was a 56-year-old woman diagnosed with interstitial lung disease. Four of the patients were fibromyalgia patients, one was RA, one was seronegative RA and the other was granulomatosis with polyangiitis (GPA).

Anti-centrosome antibody

Centrosome is major microtubule-organizing center of the cell (37) and is located in the cytoplasm usually close to the nucleus. It consists of two centrioles. Centrioles are needed to organize the assembly of microtubules in mitosis (38). In ICAP, anti-centrioles and anti-centrosome antibodies are coded as AC-24 and defined as distinct centrioles in cytoplasm of interphase and at the poles of metaphase cells. In our study, anti-centrosome antibody was detected in 42 serum samples with a ratio of 0.22%.

Betancur et al. reported anti-centrosome antibody positivity rate as 0.17% in 113491 sera, at a rate similar to ours (18). Vermeersch and Bossuyt reported anti-centrosome antibody positivity rate as 0.08% in 68128 consecutive patients in a 14-year period (19).

After being first described by Brenner et al. in 1980 (39), the antibody against centrosome or centrioles was reported in patients with Raynaud's phenomenon, localized scleroderma, systemic sclerosis, SLE and RA (40-43). In addition to these diseases, anti-centrosome antibodies are described in children with *Mycoplasma pneumonia* infection (44) and in malignancies especially in breast cancer (45).

When anti-centrosome antibody is searched in the literature, especially systemic sclerosis and breast cancer draw attention (42,43,45,46). Hamaguchi et al. reported pulmonary arterial hypertension in 4 of 5 systemic sclerosis patients with anti-centrosome antibody (42). It is stated that anti-centrosome antibody occurs early in breast carcinogenesis (46) or begins in the pre-malignant phase (45).

Anti-centrosome pattern was detected in 9 rheumatology patients that were ANA negative. No rheumatologic disease was considered in 5 of them. The other four patients were diagnosed as fibromyalgia, Sjögren's syndrome, osteoarthritis and familial Mediterranean fever. There were no patients diagnosed with systemic sclerosis. In accordance with the information stated in the literature, one of our patients, a 39-year-old female patient with no rheumatologic disease, had a metastatic breast cancer.

Seven of 9 patients with anti-centrosome were women and one of them was diagnosed with metastatic breast cancer. No information about breast cancer has been found in the records of other patients. However, since it is stated that it may occur in the early breast cancer or premalignant phase, it may be important to follow these women in terms of breast cancer.

Anti-golgi antibody

As anti-golgi antibody has a typical discontinuous speckled or granular perinuclear staining, IIF staining alone may be sufficient for morphological detection (47).

In two studies that screened patients with connective tissue or rheumatic disease, the anti-golgi antibody rate was found 0.1% (48,49). Three different studies reported anti-golgi antibody positivity rates as 0.08%, 0.2% and 0.26%, respectively (50-52). Betancur et al. reported this positivity rate very low as 0.03% (18). The anti-golgi antibody positivity rate among 18985 ANA tests in our study was 0.18% similar to the other studies.

Anti-golgi complex antibodies were first identified in the serum of a patient with Sjögren's syndrome and lymphoma (53). Then it was reported in many different situations such as Sjögren's syndrome, SLE, RA, mixed connective tissue disease, GPA, idiopathic cerebellar ataxia, paraneoplastic cerebellar degeneration, adult Still's disease, and viral infections (14,54,55). Interestingly, Bizzaro et al. reported that high titer anti-golgi antibodies may be an early indicator of systemic autoimmune diseases before significant clinical manifestations appear (56).

Vermeersch et al. identified 20 patients with anti-golgi antibodies of 51586 patients during the 10-year period. Overall, only 3 of the 20 patients had a systemic autoimmune disorder (one Sjögren's, two RA). From the other point of view, only 1 of 164 consecutive patients with Sjögren's syndrome or SLE had anti-golgi autoantibodies (52). Koh et al. reported anti-golgi antibody in 3 patients among 1173 tests, 2 of which were diagnosed as seropositive RA (15).

There are reports/case reports stating that it may be associated with autoimmune hepatitis and/or liver dysfunction (54,57-59). In addition to the aforementioned clinical cases, four women with inflammatory myopathy were reported in different literature that had anti-golgi antibody accompanied by anti-SS-A/Ro antibody (60-63).

Anti-golgi antibody was detected in 6 patients among 66 rheumatology patients. In only one patient no rheumatologic disease was considered, and the remaining patients dispersed into different disease groups. In this

group of 66 patients, there was only one polymyalgia rheumatica patient and this patient had anti-golgi antibody. No laboratory findings suggesting liver dysfunction were found in any of the patients.

Rods & Rings

In ICAP this pattern is coded as AC-23. The rod and ring structures are composed of an enzyme named as inosine monophosphate dehydrogenase type 2. As the presence of this pattern depends on the HEp-2 cell substrate used, the positivity rate in routine ANA tests is unclear. During 5-year period, we found rods and rings pattern in 26 patients which accounts for 0.14%.

When searched in the literature, the first point to notice is the relation of this pattern with HCV positive patients receiving ribavirin/IFN treatment (64,65), but it has also been reported in HCV negative patients (66,67). In addition to ribavirin treatment, patients using mycophenolic acid, azathioprine, methotrexate or acyclovir for diseases other than HCV, patients with autoimmune diseases such as SLE or healthy people can induce rods and rings pattern (17,65,66,68).

Since our study was retrospective, anti-HCV test could not be studied in 13 of 26 patients with this pattern. Anti-HCV was positive in 7 of the remaining 13 patients. This finding supported that many other reasons can trigger the formation of rods and rings pattern. This pattern was detected in four rheumatology patients with negative ANA. Unfortunately, their HCV infection status was unknown.

Anti-tropomyosin-like antibody

The anti-tropomyosin-like pattern, classified under the title AC-16 cytoplasmic fibrillar filamentous in ICAP, is reported to be found in patients with myasthenia gravis (69), ulcerative colitis (70), Crohn's disease (71) and different inflammatory reactions and infections, but exact relationship has not been proven yet. In our study, the positivity rate of anti-tropomyosin antibody was 0.05% (10/18985). This pattern was detected in 3 of 66 rheumatology patients. The diagnoses of these patients were RA, seronegative RA and ankylosing spondylitis. Interestingly, they all had a rheumatologic diagnosis.

Anti-mitotic coat antibody

Mitotic chromosomal, formerly called chromosome coat protein, dividing cell antigen or mitotic chromosome autoantigen, is classified as AC-28 in ICAP. Although this pattern is rare, it has been reported in SLE patients and patients with carcinoma (72,73). Blaschek et al. identified this antibody only in mitotic cells, and reported that it was directed against an antigen called "dividing cell antigen" as known to be histone or histone related protein. In that study, dividing cell antibody was detected in 10 of 183 SLE patients and in one of 39 patients with idiopathic Raynaud's, but not detected in any of the other connective tissue diseases (72).

In our study the positivity rate of mitotic coat pattern was 0.03%. This pattern was detected in a 50-year-old female patient with a complaint of joint pain in the rheumatology group. She was considered as RA and the treatment was initiated but she did not apply for subsequent follow-up.

Anti-lysosome-like antibody

Anti-lysosome–like antibodies are defined as small/medium sized fine-spotted and coarse droplet staining scattered throughout the cytoplasm. It is classified in AC-18 pattern as "cytoplasmic discrete dots/GW body-like" in ICAP. Autoantibodies causing staining as the AC-18 pattern have been reported in distinct systemic autoimmune rheumatologic disorders and in a variety of other diseases; and their prevalence in unselected or specified disease cohorts has not been thoroughly studied (74). While the positivity rate of this pattern was 0.02%, none of these patients were rheumatology patients.

The most important limitation of our study is that we could not identify target antigens monospecifically. Therefore, our comments are made only on IIF images. The second limitation is that the study is retrospective, so we could not reach some data of the patients.

However, our results show that the patterns do not indicate a specific disease and are also detected in the patient group without a rheumatologic disease. Another limitation is that, detailed evaluations were made only in rheumatology patients. Larger studies involving patients from other clinics may provide more valuable information.

Although these patterns constitute a low percentage among all of our ANA tests and some individual patterns are not directly associated with certain diseases; along with the negative ANA report, they should be noted in the description part in order to distinguish significant cytoplasmic patterns and give an idea for some specific conditions. If anti-cell (AC) antibody or HEp-2 indirect immunofluorescence test terms are used in the future, it would be appropriate for all patterns to be reported as positive.

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Araştırma Makalesi / Research Article

Düşük İyot Diyeti Dönemindeki Hastalarda Hemşirenin Rolü

The Role of the Nurse in Patients on Low Iodine Diet Period

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Özet

Bu çalışmada, total tiroidektomi sonrası hastaların düşük iyot diyeti sürecine uyumunda hemşirenin rolünün değerlendirilmesi amaçlanmıştır. Çalışma, randomize olmayan (ön-test son-test) vaka gruplu müdahale araştırması olup, Eskişehir Osmangazi Üniversitesi Sağlık, Uygulama ve Araştırma Hastanesi Nükleer Tıp Polikliniğinde, dahil edilme kriterlerine uyan 18 hasta ile gerçekleştirilmiştir. Verilerin toplanmasında Tanımlayıcı Özellikler Veri Formu, Hasta İzlem Formu (hastaların boy, kilo, kan basıncı değerleri) ve Baş etme-Uyum Süreci Ölçeği kullanılmıştır. Çalışmaya dahil edilen hastalara yaklaşık 30-45 dk. sürecek hemşirelik süreci uygulanmıştır. Düşük iyot diyetinin 7. ve 14. günlerinde hastaların öğrenmek istedikleri konularda açıklamalarda bulunulmuş, genel durumları hakkında bilgi alınmış ve tekrar hemşirelik süreci uygulanmıştır. Radyoaktif iyot tedavisi için nükleer tıp polikliniğine gelen hastalara düşük iyot diyeti öncesi ve sonrası Hasta İzlem Formu ve Baş etme-Uyum Süreci Ölçeği uygulanarak, hemşirelik sürecinin etkinliği değerlendirilmiştir. Normal dağılım gösteren sayısal değişkenlerin diyet öncesi ve sonrası karşılaştırılmasında Eşleştirilmiş t testi ve normal dağılmayan değişkenlerin karşılaştırılmasında Wilcoxon testi kullanılmıştır. Verilerin analizi, SPSS for Windows version 24.0 programı ile yapılmıştır. Hastalar diyet öncesi ve diyet sonrası karşılaştırıldığında; hastalarda beden kütle indeksi değerleri bakımından anlamlı fark gözlenmezken (P>0.05), hastaların sistolik ve diyastolik kan basıncı değerleri başlangıç ölçümlerine göre anlamlı düşüş göstermiştir (P<0.01). Baş etme-Uyum Süreci Ölçeği alt boyutlarında ve ölçeğin toplam puanında başlangıç değerlerine göre anlamlı düzeyde artış görülmüştür (P<0.01). Düşük iyot diyeti döneminde olan hastalara uygulanan hemşirelik sürecinin hastaların baş etme-uyum düzeylerini arttırdığı görülmüştür. Bu bağlamda söz konusu dönemindeki hastalara yönelik poliklinikte uygun ortamın düzenlenmesi, eğitim programlarının rutinleştirilmesi, hemşirelik sürecinin planlanması ve uygulanması ile ilgili çalışmaların arttırılması önerilmektedir.
Anahtar Kelimeler: Roy adaptasyon modeli; hemşirelik; düşük iyot diyeti

Abstract

In this study, it was aimed to evaluate the role of the nurse in the adaptation of patients with the low iodine diet process after total thyroidectomy. The study was a non-randomized (pre-test post-test) case group intervention study and was conducted with 18 patients who met the inclusion criteria in the Nuclear Medicine Polyclinic of Eskişehir Osmangazi University Health, Application and Research Hospital. The Descriptive Characteristics Data Form, the Patient Follow-up Form (height, weight, blood pressure values of the patients) and the Coping-Adaptation Process Scale were used to collect the data. Approximately 30-45 minutes to the patients included in the study. The ongoing nursing process was applied. On the 7th and 14th days of the low iodine diet, the patients were informed about the subjects they wanted to learn, information was obtained about their general condition, and the nursing process was applied again. The effectiveness of the nursing process was evaluated by applying the Patient Follow-up Form and the Coping-Adaptation Process Scale before and after the low iodine diet to the patients who came to the nuclear medicine outpatient clinic for radioactive iodine treatment. Paired t-test was used to compare normally distributed numerical variables before and after diet, and Wilcoxon test was used to compare non-normally distributed variables. Data analysis was done with SPSS for Windows version 24.0 program. When the patients were compared before and after the diet; While no significant difference was observed in terms of body mass index values in the patients (P>0.05), the systolic and diastolic blood pressure values of the patients showed a significant decrease compared to the initial measurements (P<0.01). A significant increase was observed in the Coping-Adaptation Process Scale sub-dimensions and the total score of the scale compared to the baseline values (P<0.01). It has been observed that the nursing process applied to patients in the low iodine diet period increased the coping-adaptation levels of the patients. In this context, it is recommended to
Keywords: Roy adaptation model; nursing; low iodine diet

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1. Giriş

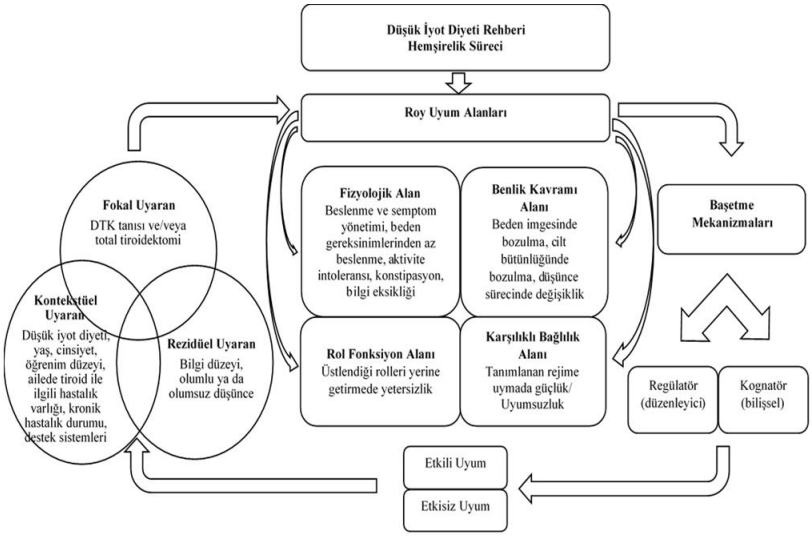
Diferansiye tiroid kanseri (DTK) hastalarının takibi ömür boyu devam eden bir süreçtir. Tiroidektomi sonrası bu takibin amacı yeterli tiroid hormonu tedavisini sürdürmek, morbidite ve mortaliteyi azaltmaktır. Bunun için ameliyat sonrası, mikroskobik rezidü dokuyu ortadan kaldırmak ve tiroid kanserinin nüksetmesini engellemek için radyoaktif iyot (RAİ) tedavisi uygulanır (1, 2). Genelde RAİ tedavisinin bir parçası olarak uygulanan izotop (I-131) rezidü tiroid dokusuna tutunur (3). I-131'in etkinliğini arttırmak için 2 temel yaklaşım vardır. İlk yaklaşım, serum tiroid stimule hormon (tirotropin-TSH) konsantrasyonunu arttırmak ve ikincisi vücuttaki tüm iyot depolarını tüketmektir (4). TSH'ın arttırılması, ameliyattan sonra ilk RAİ tedavisi öncesi hormon replasman tedavisine başlanmayarak sağlanır (5). Vücuttaki tüm iyot depolarını tüketmek için yaklaşık 1 haftadan 4 haftaya kadar değişen düşük iyotlu diyet yapılır (6). Amerikan Tiroid Birliği (American Thyroid Association-ATA) 2009 ve 2015 kılavuzlarında, I-131 uygulamasından önce 1-2 hafta boyunca <50 mg/gün iyot alımıyla tanımlanan düşük iyot diyeti yapılması önerilir (7, 8). Tiroid kanserinin yönetimine ilişkin Birleşik Krallık kılavuzları tarafından uzman görüşüne dayalı olarak, iyot açısından zengin ilaçlar veya takviyelerden kaçınılması gerektiğini ve kişilerin RAİ tedavisinden 1-2 hafta önce düşük iyotlu bir diyet izlemeleri tavsiye edilir (9). European Thyroid Cancer Taskforce tarafından ise en az 3 hafta düşük iyot diyeti yapılması önerilmektedir (10). Yayınlanan kılavuzlara baktığımızda hala standart düşük iyot diyeti protokolü bulunmamaktadır.

Çalışmayı planladığımız tıp fakültesi hastanesi nükleer tıp polikliniğine gelen DTK hastaları 3 haftalık düşük iyot diyeti uygulamaktadırlar. RAİ tedavisinin etkinliğini arttırmak için tiroid ilacının kullanımına başlanmaz ve bu sebeple hastalarda hipotiroidi semptomları görülebilir (3). Düşük iyot diyeti boyunca hastalarda görülen hiponatremi de yaşamı tehdit eden bir durum olarak ortaya çıkabilir (11,12). Bununla birlikte düşük iyot diyetinin neden olduğu hastaların günlük yaşam aktivitelerini olumsuz etkileyen psikolojik ve sosyal yönleri de bulunmaktadır. Yapılan başka bir çalışmada, diyeti sürdürmede yetersizlik, distres, izolasyon, laterji ve günlük aktivitelerin kısıtlanması gibi durumların ortaya çıktığı belirtilmiştir (3). Düşük iyot diyeti yapılan dönemde, RAİ tedavisine hazırlanan hastaların yeterli eğitim, danışmanlık ve destek almadıkları takdirde semptomlarla baş etmede yetersiz kaldıkları ve diyete uyum sağlamada zorluk yaşadıkları görülmüştür. Bu dönemde hastalar, diyetin verdiği rahatsızlık ve sevilen yiyeceklerden uzak kaldıkları için diyeti sürdürmede yetersizlik yaşamaktadırlar; hareketlerin yavaşlamasına ve ekstremitelerde ağrıya bağlı olarak günlük yaşam aktivitelerini yerine getirememektedirler; hastalarda el, yüz ve göz kapaklarında şişlik ve kilo artışına bağlı olarak da beden imajında bozulma gibi durumlar ortaya çıkmaktadır (3). Bu hastaların olası problemlerle baş etme ve diyete uyum sağlamaları ilgili bilgi ve becerilerinin arttırılmasına ihtiyaçları vardır. Bu nedenle diyet döneminde hastaların düşük iyot dönemiyle ilgili yeterli bilgiye sahip olmaları ve bu bilgilerinin pekiştirilmesiyle; olası semptomlarla baş etmeleri, diyete daha kolay uyum sağlamaları kolaylaşır ve bu diyet döneminin daha rahat geçirmesine katkı sağlar. Hastaların 3 haftalık düşük iyot diyeti dönemine uyumunu sağlamak ancak multidisipliner bir yaklaşımla gerçekleşir. Ekibin içerisinde hemşire, gerekli eğitimi vererek ve bu eğitimin devamlılığını sağlayarak hastaların diyet dönemine uyum sağlamalarına yardımcı olur ve yaşam kalitelerini arttırır. Hemşirelik yönetmeliğinin 5/1-a maddesine göre hemşire, "…Birey, aile, grup ve toplumun sağlığının geliştirilmesi, korunması, hastalık durumunda iyileştirilmesi ve yaşam kalitesinin artırılması amacıyla hemşirenin yerine getirdiği bakım verme, hekimce hazırlanan tıbbî tanı ve tedavi planının oluşturulması ve uygulanması, güvenli ve sağlıklı bir çevre oluşturma, eğitim, danışmanlık, araştırma, yönetim, kalite geliştirme, işbirliği yapma ve iletişimi sağlama rollerini…" yerine getirmektedir (13). Hemşirenin tiroidektomi sonrası RAİ tedavisi için hazırlanan, düşük iyot diyeti yapan DTK hastalarının diyet dönemine uyum sağlamalarına yönelik rolü; iyot içermeyen

besinlerle ilgili yeterli bilgiye sahip olmalarını ve olası semptomları bilip fark edebilmelerini sağlamak, bakımlarıyla ilgili yeterli düzeye gelinceye kadar danışmanlık etmektir. Bu çalışmada, total tiroidektomi sonrası hastaların düşük iyot diyeti sürecine uyumunda hemşirenin rolünün değerlendirilmesi amaçlanmıştır.

Araştırmanın kavramsal çerçevesi

Çalışmanın amacına ulaşmak için hemşirelik kuramcılarından Sister Callista Roy'un "Roy Adaptasyon Modeli (RAM)" kullanılmıştır. Bu modelin kullanılması hemşirenin genel bir çerçeve oluşturmasını sağlar. Roy'a göre insan, gereksinimlerini karşılamak ve bulunduğu çevredeki değişikliklere biyolojik, psikolojik ve sosyal uyumunu sağlamak için baş etme mekanizmalarını kullanır (14). Hemşire, insanın baş etme mekanizmalarını kullanarak fizyolojik, benlik kavramı, rol fonksiyon ve karşılıklı bağlılık alanlarında etkili uyum davranışları oluşturmasını sağlar (15). Total tiroidektomi sonrası düşük iyot diyeti sürecinde olan hastaların fizyolojik, psikolojik ve sosyal açıdan yaşadıkları sorunlar dikkate alındığında bu diyet döneminde RAM'ın kullanılmasının hastaların bütüncül yaklaşımla ele alınabilmesi açısından fayda sağlayacağı düşünülmektedir (Şekil 1).



Şekil 1. Düşük iyot diyeti sürecinde RAM'ın kullanımı

2. Gereç ve Yöntem

Araştırmanın amacı ve şekli

Bu araştırma total tiroidektomi sonrası hastaların düşük iyot diyeti sürecine uyumunda hemşirenin rolünün değerlendirilmesi amacıyla planlanan randomize olmayan (ön-test, son-test) vaka gruplu müdahale araştırmasıdır.

Araştırmanın hipotezleri

H_0: Total tiroidektomi sonrası Roy Adaptasyon Modeline göre uygulanan hemşirelik sürecinin, hastaların düşük iyot diyeti dönemine ilişkin baş etme ve uyumunu arttırmada etkisi yoktur.

H_1: Total tiroidektomi sonrası Roy Adaptasyon Modeline göre uygulanan hemşirelik sürecinin, hastaların düşük iyot diyeti dönemine ilişkin baş etme ve uyumunu arttırmada etkisi vardır.

Araştırmanın yapıldığı yer ve zamanı

Araştırma, Eskişehir Osmangazi Üniversitesi Sağlık, Uygulama ve Araştırma Hastanesi Nükleer Tıp Polikliniğinde yapıldı. Veriler, 01.04.2020-01.04.2021 tarihleri arasında toplandı.

Araştırmanın evren ve örneklemi

Araştırmanın evrenini; Eskişehir Osmangazi Üniversitesi Sağlık, Uygulama ve Araştırma Hastanesi Nükleer Tıp Polikliniğine total tirodektomi ameliyatı sonrası gelen ve radyoaktif iyot tedavisine hazırlanacak olan hastalar oluşturdu. Örneklemi ise dahil edilme kriterlerine uyan 18 hasta oluşturdu. Hastaların bu çalışmaya dahil edilebilme kriterleri:

- ✓ Diferansiye tiroid kanseri hastası olması
- ✓ Total tiroidektomi ameliyatı geçirmiş olması
- ✓ İlk defa radyoaktif iyot tedavisi alacak olması
- ✓ Düşük iyot diyetine başlamadan önceki dönemde olması
- ✓ 18 yaş ve üzerinde iletişime ve iş birliğine açık olması,
- ✓ Türkçe iletişim kurulabilmesi
- ✓ Hastanın demans, aizheimer gibi mental durumunu etkileyen herhangi bir psikiyatrik hastalığının olmaması
- ✓ Telefonun kullanılabilmesi

Çalışmanın dahil edilme kriterlerine uymayan, çalışmadan ayrılma talebi olan gönüllü ve/veya hastalar araştırmadan çıkarıldı. Hastalar araştırmadan çıktığında herhangi bir izleme alınmadı.

Post-hoc güç analizi

Toplam puandaki gözlenen değişim için cohen d değeri 3,15, bağımlı ölçümler arasındaki korelasyon ise 0,89 olarak hesaplanmıştır. 18 kişi için çalışmanın gücü %100 olarak hesaplanmıştır. Posthoc güç analizi G-power programı 3.9.1 versiyonu kullanılarak yapılmıştır.

t tests - Means: Difference between two dependent means (matched pairs)

Analysis: Post hoc: Compute achieved power

Input:	Tail(s)	=	Two
Effect size dz		=	3.1509766
α err prob		=	0.05
Total sample size		=	18

Output: Noncentrality parameter δ

	=	13.3684615
Critical t	=	2.1098156
Df	=	17
Power (1-β err prob)	=	1.0000000

Araştırmanın sınırlılıkları

Araştırmaya, etik kurul izninden sonra 01.04.2020 tarihinde başlandı. Ancak verileri alınan hastaların randevuları, covid-19 pandemisi nedeniyle iptal edildi. Yaklaşık 4 ay sonra temmuz ayında hastalara tekrar randevu verilmeye başlandı. Randevu ile beraber hasta verileri tekrar toplanmaya başlanarak ve ekim ayının sonuna kadar devam ettirilerek 21 hastaya ulaşıldı. Ekim ayının sonuna doğru pandemi nedeniyle hasta randevuları 2. kez iptal edildi. Yirmi bir hastanın 4'ü tedavisini tamamlayamadığı için araştırmadan çıkarıldı. Mart ayında hastalara tekrar randevu verilmeye başlandı. 01.04.2021 tarihine kadar 1 hastanın verisi tamamlanıp, toplamda 18 hasta ile araştırma bitirildi.

Veri toplama araçları

Araştırmanın yürütülmesi için gerekli olan verileri toplamak amacıyla 3 veri toplama formu kullanıldı. Veri toplama formları, araştırmacı tarafından literatür taranarak hazırlanan tanımlayıcı özellikler veri formu, hasta izlem formu ve Baş etme-Uyum Süreci Ölçeği (BUSÖ)'dir.

Tanımlayıcı özellikler veri formu

Araştırmacı tarafından ilgili literatür taranarak hazırlanmıştır. Bu formda, sosyo-demografik özelliklerle ilgili 3 soru, hastalığa ilişkin 3 soru olmak üzere toplamda 6 soru bulunmaktadır.

Hasta izlem formu

Formda, diyetin başında ve sonunda hastaların boy (m), kilo (kg), kan basıncı (mmHg) ölçümleri değerlendirildi. Diyetin döneminin başında ve diyetin sonunda radyoaktif iyot tedavisi öncesi hastaların vücut ağırlıkları dijital bir baskül yardımıyla ve kan basıncı

değerleri ise 10 dk dinlenme sonrası manuel tansiyon aleti ile sağ brakial arterden ölçüldü.

Baş etme-Uyum Süreci Ölçeği (BUSÖ)

Baş etme-Uyum Süreci Ölçeği, kritik ve zor durumlarda bireylerin baş etme ve uyum stratejilerinin tanımlanmasında kullanılmaktadır. Callista Roy (2004) tarafından geliştirilen ülkemizde Çatal (2015) tarafından geçerlik ve güvenirliği yapılan ölçeğin teorik temelini Roy Adaptasyon Modeli (RAM) oluşturmaktadır (16). 47 madde ve beş alt ölçekten oluşan, maddeleri 1 ile 4 arasında (1=hiçbir zaman, 2=nadiren, 3=bazen, 4=her zaman) değerlendirilen likert tipi bir ölçektir. Ölçeğin ve alt boyut maddelerinin sayısı, madde numaraları ve alınabilecek en düşük-en yüksek puanlar tablo halinde verilmiştir (Tablo 1). Ölçeğin kesme noktası ya da kritik değeri tanımlanmamıştır; ölçek ve alt boyutlarından elde edilen puanlar yükseldikçe etkili baş etme yöntemlerinin kullanımının arttığı şeklinde yorumlanmaktadır (16). Özgün ölçeğin faktör analizi sonucu ortaya konan beş faktörlü yapı, ölçekteki toplam varyansın % 45.3'ünü açıklamaktadır. Özgün ölçekte cronbach alpha güvenirlik katsayısı, toplam ölçek için .94, alt boyutları için .79-.86 arasındadır. Roy tarafından geliştirilen Baş etme-Uyum Süreci Ölçeği'nin özgün dili İngilizce'dir. Türkçe'ye uyarlanan, dil geçerliği ve içerik geçerliği sağlanan Baş etme-Uyum Süreci Ölçeği'nin faktör analizi sonrası toplam varyansın % 40.67'sinin açıklandığı, ölçeğin eş zaman geçerliğinin sağlandığı gösterilmiştir. Güvenirlik analizlerinden cronbach alpha güvenirlik katsayısı .82, alt boyutları için .65-.77 arasında bulunmuştur.

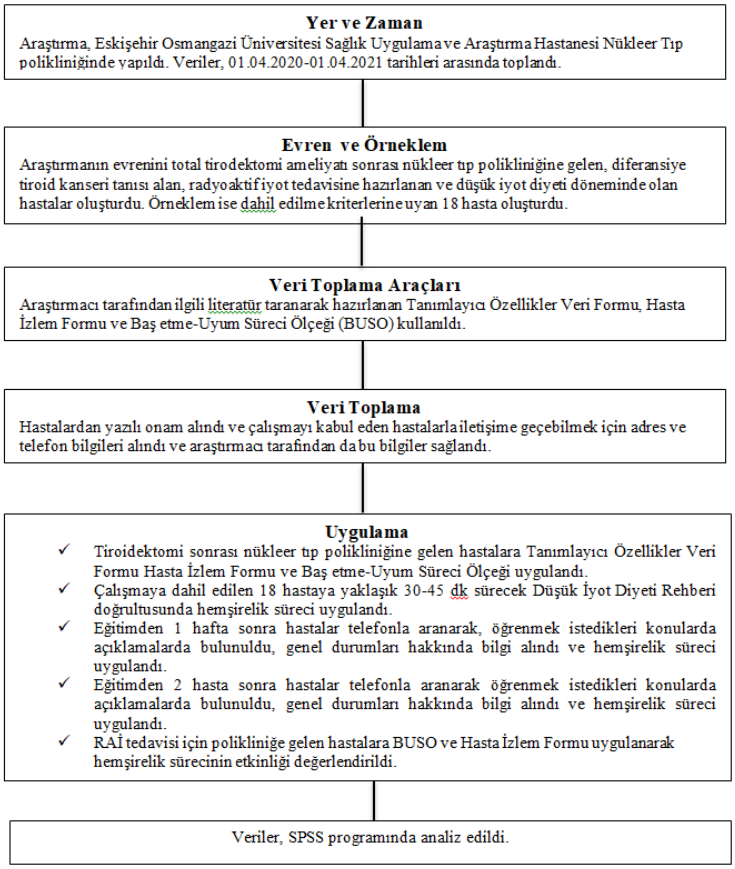
Tablo 1. Baş etme ve uyum ölçeği alt boyut maddeleri ve puanları

Alt Boyutlar	Madde Sayısı	Madde Numaraları	En Düşük ve En Yüksek Değerler
Çözüm bulma ve odaklanma	10	2,4,7,10,16,19,26,34,42,46	4-40
***Fiziksel ve karara bağlama**	14	5,8,13,15,20,23,24,29,33,35,39,43,45,47	14-56
Dikkat süreci	9	1,11,17,18,25,27,31,40,44	9-36
Sistematize etme süreci	6	3,12,14,22,30,41	6-24
Öğrenme ve ilişki kurma	8	6,9,21,28,32,36,37,38	8-32
Toplam	47		47-188

** Fiziksel ve karara bağlama alt boyutunun tüm maddeleri ters puanlanmaktadır.*

Verilerin toplanması

Radyoaktif iyot tedavisi için nükleer tıp polikliniğine gelen ve düşük iyot diyeti uygulayacak olan kadın ve erkek hastalar çalışmaya dahil edildi. Araştırmaya katılmayı kabul eden her hasta, gönüllü olur formu doldurdu. Bu aşamaya ait verilerin toplanmasına yönelik araştırmanın akış şeması verilmiştir (Şekil 2). Tüm hastalarla iletişime geçebilmek için adres ve telefon bilgileri alındı ve araştırmacı tarafından da bu bilgiler sağlandı. Ön-test verilerinin toplanmasında tiroidektomi ameliyatı sonrası nükleer tıp polikliniğine gelen hastalara Tanımlayıcı Özellikler Veri Formu, Hasta izlem Formu ve Baş etme-Uyum Süreci Ölçeği uygulandı. Çalışmaya dahil edilen hastalara yaklaşık 30-45 dk sürecek hemşirelik süreci uygulandı. Eğitimden 1 hafta ve 2 hafta sonra hastaların öğrenmek istedikleri konularda açıklamalarda bulunuldu ve genel durumları hakkında bilgi alındı ve hemşirelik süreci uygulandı. Radyoaktif iyot tedavisi için nükleer tıp polikliniğine gelen hastalara Hasta İzlem Formu ve Baş etme-Uyum Süreci Ölçeği uygulanarak hemşirelik sürecinin etkinliği değerlendirildi.



Şekil 21. Araştırmanın akış şeması

Roy Adaptasyon Modeline Göre Hemşirelik Süreci

Hastanın gereksinimleri ve semptomları doğrultusunda Roy Adaptasyon Modeline göre; davranışın ve uyaranların değerlendirilmesi, hemşirelik tanısı (NANDA-I), hedefin belirlenmesi, tanıya uygun olarak girişimlerin yapılması ve değerlendirme şeklinde hemşirelik süreci uygulanmıştır. Hemşirelik sürecinin etkinliğine izin vererek, uygun bir şekilde hemşirelerin klinik akıl yürütmesini destekleyen, daha geniş kanıta dayalı araştırma imkânı sağlayan ve mevcut tüm hemşirelik tanı sınıflandırmaları arasında en güçlü kriterlere sahip olarak kabul edilen North American Nursing Diagnosis Association (NANDA-I) sistemi kullanılmıştır (17). NANDA-I göre hemşirelik tanısı, birey, aile, grup ya da toplum tarafından sağlık koşullarına/yaşam süreçlerine verilen insani bir tepki ya da söz konusu tepki için gösterilen hassasiyete ilişkin klinik bir değerlendirmedir (18). Araştırmamıza dahil edilen hastaların NANDA-I hemşirelik tanıları aşağıda yer almaktadır:

- ✓ Hasta 1, aktivite intoleransı, konstipasyon, bilgi eksikliği ve düşünce sürecinde değişiklik
- ✓ Hasta 2, beslenmede dengesizlik; beden gereksinimlerinden az beslenme, bilgi eksikliği, beden imgesinde bozulma, cilt bütünlüğünde bozulma ve düşünce sürecinde değişiklik
- ✓ Hasta 3, aktivite intoleransı, bilgi eksikliği ve cilt bütünlüğünde bozulma
- ✓ Hasta 4, aktivite intoleransı, bilgi eksikliği, cilt bütünlüğünde bozulma, üstlendiği rolleri yerine getirmede yetersizlik ve tanımlanan rejime uymada güçlük/uyumsuzluk
- ✓ Hasta 5, beslenmede dengesizlik; beden gereksinimlerinden az beslenme, aktivite intoleransı, bilgi

eksikliği ve düşünce sürecinde değişiklik
- ✓ Hasta 6, aktivite intoleransı, konstipasyon, bilgi eksikliği, cilt bütünlüğünde bozulma ve üstlendiği rolleri yerine getirmede yetersizlik
- ✓ Hasta 7, aktivite intoleransı, konstipasyon, bilgi eksikliği, beden imgesinde bozulma, cilt bütünlüğünde bozulma, düşünce sürecinde değişiklik, üstlendiği rolleri yerine getirmede yetersizlik ve tanımlanan rejime uymada güçlük/uyumsuzluk
- ✓ Hasta 8, aktivite intoleransı, bilgi eksikliği, düşünce sürecinde değişiklik ve üstlendiği rolleri yerine getirmede yetersizlik
- ✓ Hasta 9, aktivite intoleransı, konstipasyon, bilgi eksikliği, cilt bütünlüğünde bozulma ve üstlendiği rolleri yerine getirmede yetersizlik
- ✓ Hasta 10, beslenmede dengesizlik; beden gereksinimlerinden az beslenme, aktivite intoleransı, bilgi eksikliği, cilt bütünlüğünde bozulma, üstlendiği rolleri yerine getirmede yetersizlik ve tanımlanan rejime uymada güçlük/uyumsuzluk
- ✓ Hasta 11, aktivite intoleransı, bilgi eksikliği ve üstlendiği rolleri yerine getirmede yetersizlik
- ✓ Hasta 12, aktivite intoleransı, bilgi eksikliği, beden imgesinde bozulma, düşünce sürecinde değişiklik ve üstlendiği rolleri yerine getirmede yetersizlik
- ✓ Hasta 13, aktivite intoleransı, konstipasyon, bilgi eksikliği, beden imgesinde bozulma, cilt bütünlüğünde bozulma, düşünce sürecinde değişiklik, üstlendiği rolleri yerine getirmede yetersizlik ve tanımlanan rejime uymada güçlük/uyumsuzluk
- ✓ Hasta 14, aktivite intoleransı, konstipasyon ve bilgi eksikliği
- ✓ Hasta 15, aktivite intoleransı, bilgi eksikliği, beden imgesinde bozulma, düşünce sürecinde değişiklik, üstlendiği rolleri yerine getirmede yetersizlik ve tanımlanan rejime uymada güçlük/uyumsuzluk
- ✓ Hasta 16, aktivite intoleransı, konstipasyon, bilgi eksikliği, düşünce sürecinde değişiklik, üstlendiği rolleri yerine getirmede yetersizlik ve tanımlanan rejime uymada güçlük/uyumsuzluk
- ✓ Hasta 17, aktivite intoleransı, bilgi eksikliği ve üstlendiği rolleri yerine getirmede yetersizlik
- ✓ Hasta 18, aktivite intoleransı, bilgi eksikliği, beden imgesinde bozulma, düşünce sürecinde değişiklik, cilt bütünlüğünde bozulma ve üstlendiği rolleri yerine getirmede yetersizlik

Düşük İyot Diyeti Rehberi

Araştırmacı tarafından rehberdeki diyet listesi ilgili literatür doğrultusunda hazırlandı (19-21). Hastanın düşük iyot diyeti dönemine uyum sağlamasını amaçlayan bu rehberde, iyot içeren ve içermeyen besinlerin listesi, tiroid ilacının geri çekilmesine ve iyotlu tuzun kısıtlanmasına bağlı görülen semptomlar hakkında bilgiler bulunmaktadır.

Verilerin değerlendirilmesi

Verilerin normal dağılıma uygunluğu, Shaphiro wilk testi ile test edilmiştir. Normal dağılan sayısal değişkenlerin diyet öncesi ve sonrası karşılaştırılmasında Eşleştirilmiş t testi, normal dağılmayan değişkenlerin karşılaştırılmasında ise Wilcoxon testi kullanılmıştır. Analizlerde SPSS for Windows version 24.0 programı kullanılmış ve p değerinin 0.05 den küçük olması istatistiksel olarak anlamlı kabul edilmiştir.

3. Bulgular

Araştırmaya katılan hastaların yaş ortalaması 44.17±14.42 yıl olup, genel tanımlayıcı özellikler tablo halinde verilmiştir (Tablo 2). Hastaların düşük iyot diyeti öncesi ve sonrası beden kütle indeksi (BKİ), sistolik kan basıncı (SKB) ve diyastolik kan basıncı (DKB) değerleri karşılaştırılmıştır (Tablo 3). BKİ değerleri bakımından anlamlı fark gözlenmezken ($P>0.05$), SKB ve DKB değerleri başlangıç ölçümlerine göre anlamlı düşüş göstermiştir ($P<0.01$). Diyet öncesi ve sonrası BUSÖ ve alt boyutlarına ait

tanımlayıcı istatistikler tablo halinde verilmiştir (Tablo 4). Düşük iyot diyeti öncesi ve sonrası hastaların BUSÖ ve alt boyutlarından aldıkları puan ortalamaları karşılaştırılmıştır (Tablo 5). Ölçek alt boyutları ve toplam puan başlangıç ölçümlerine göre anlamlı artış göstermiştir (P<0.01).

Tablo 2. Genel tanımlayıcı özellikler

		n	%
Cinsiyet	Kadın	15	83,3
	Erkek	3	16,7
Çalışma durumu	Çalışmıyor	13	72,2
	Çalışıyor	5	27,8
Eğitim durumu	İlkokul ve ortaokul	6	33,3
	Lise	7	38,9
	Üniversite ve üstü	5	27,8
Ailede tiroid ile ilgili hastalık varlığı	Evet	16	88,9
	Hayır	2	11,1
Başka kronik hastalık varlığı	Evet	7	38,9
	Hayır	11	61,1
İlaç almayı gerektiren hastalık varlığı	Evet	8	44,4
	Hayır	10	55,6

Tablo 3. BKİ, SKB ve DKB değerlerinin diyet öncesi ve sonrası karşılaştırılması

Değişkenler	**Ön test**	**Son test**	**Test. ist.**	**P**
	x̄ ±SS	**x̄ ±SS**		
BKİ (kg/m²)	27,02 ± 4,18	26,77 ± 4,2	T=1,009	0,327
	Medyan [% 25-% 75]	**Medyan [% 25-% 75]**		
SKB mmHg	120,5[110,0-128,0]	100[90-110]	Z=-3,036	***0,002****
DKB mmHg	80[70-80]	70[60-70]	Z=-2,693	***0,007****

**0,05 düzeyinde anlamlı; t: Eşleştirilmiş t testi, Z: Wilcoxon testi.*

Tablo 4. Ölçek puanlarına ait tanımlayıcı istatistikler

Ölçek alt boyutları	**Tanımlayıcı istatistikler (n:18)**		**Cronbach α**
	x̄ ±SS	**Medyan (Min-Max)**	
Ön test Çözüm bulma ve odaklanma	25,89 ± 4,78	25,5 (16 -33)	0,753
Ön test Fiziksel ve karara bağlama	36,72 ± 7,01	36,5 (21 -47)	0,786
Ön test Dikkat süreci	22,33 ± 3,24	21,5 (17 -29)	0,315
Ön test Sistematize etme süreci	15,22 ± 3,23	15 (10 -21)	0,742
Ön test Öğrenme ve ilişki kurma	21,33 ± 3,43	21 (16 -27)	0,637
Ön test Toplam puan	121,5 ± 17,05	125 (89 -145)	0,891
Son test Çözüm bulma ve odaklanma	33 ± 3,12	33 (27 -37)	0,547
Son test Fiziksel ve karara bağlama	42,17 ± 4,84	41,5 (34 -51)	0,751
Son test Dikkat süreci	26,83 ± 1,79	27 (24 -31)	0,369
Son test Sistematize etme süreci	20,22 ± 2,07	20 (16 -24)	0,638
Son test Öğrenme ve ilişki kurma	26,5 ± 3,03	26 (21 -31)	0,688
Son test Toplam puan	148,72 ± 11,21	151 (131 -166)	0,843

Tablo 5. Ölçek puanları için diyet öncesi ve sonrası ölçümlerin karşılaştırılması

Ölçek alt boyutları (n=18)	Ön test	Son test	t	P
	x̄ ±SS	x̄ ±SS		
Çözüm bulma ve odaklanma	25,89 ± 4,78	33 ± 3,12	-10,836	***0,001****
Fiziksel ve karara bağlama	36,72 ± 7,01	42,17 ± 4,84	-4,345	***0,001****
Dikkat süreci	22,33 ± 3,24	26,83 ± 1,79	-8,563	***0,001****
Sistematize etme süreci	15,22 ± 3,23	20,22 ± 2,07	-11,292	***0,001****
Öğrenme ve ilişki kurma	21,33 ± 3,43	26,5 ± 3,03	-8,521	***0,001****
Toplam puan	121,5 ± 17,05	148,72 ± 11,21	-13,356	***0,001****

**0,05 düzeyinde anlamlı; t: Eşleştirilmiş t testi.*

4. Tartışma

Araştırmaya katılan hastaların düşük iyot diyeti öncesi ve sonrası karşılaştırıldığında, BKİ değerlerinde diyet öncesine göre azalma olmasına rağmen fark istatistiksel açıdan anlamlı değildir (P>0.05). Tiroid ilacının geri çekilmesiyle hipotiroidiye bağlı kilo artışı görülen semptomlar arasındadır. Ancak hastaların hipotiroidi semptomları hakkında bilgilendirilmesi, hipertansiyon hastalarının ilaçlarını düzenli kullanmaya devam etmesinin öneminin anlatılması ve semptomlara yönelik hemşirelik bakımının uygulanmasından dolayı hastalar tarafından kilo artışı kontrol altında tutulmaya çalışılmıştır. Kore'de yapılan bir çalışmada, BKİ'nin iki haftalık düşük iyot diyetinden sonra önemli ölçüde azaldığı ve bu durumun normal bir diyete kıyasla düşük iyot diyeti sırasında enerji ve besin alımının azalmasından kaynaklandığı belirtilmiştir (6). Hastaların düşük iyot diyeti öncesi ve sonrası kan basıncı değerleri karşılaştırıldığında, SKB ve DKB değerleri başlangıç ölçümlerine göre anlamlı düşüş göstermiştir (P<0.01). Hastalara hiponatremiye karşı iyotsuz tuz tüketmelerinin önemi anlatılmıştır. Her ne kadar hastalar iyotsuz tuz kullanımını gerçekleştirseler de iyotlu tuz tüketim miktarı kadar olmadığını ifade etmişlerdir. Özellikle hipertansiyon hastalarına iyotsuz tuz da kullansalar iyotlu tuz miktarı kadar günlük tuz alımlarını sınırlı tutmaları gerektiği vurgulanmış olup hastalar tuz kısıtlaması ile ilgili diyetine devam etmişlerdir. İlaveten hipertansiyon hastaları diyet süresince ilaçlarını düzenli olarak kullandıklarını söylediler. RAİ tedavisine hazırlıkta, 4 hafta düşük iyot diyeti yapan hastalardan levotiroksin kesilmesinden hemen önce ve RAİ tedavisinin uygulanacağı gün, sabah saatlerinde kan basıncı ölçümleri yapılmıştır (22). Hastaların ilk SKB ölçümleri (126.0 ± 14.0) ne göre RAİ tedavisi uygulanacak günün sabahı ölçülen değerler (115.4 ± 13.4) de önemli ölçüde azalma (P<0.05) olduğu ve DKB değerlerinde ölçümler (sırasıyla 74.6 ± 14.0, 74.3 ± 10.1) arası fark olmadığı görülmüştür (22).

Araştırmada hastaların BUSÖ alt boyutları açısından karşılaştırma yapıldığında; çözüm bulma ve odaklanma, fiziksel ve karara bağlama, dikkat süreci, sistematize etme süreci, öğrenme ve ilişki kurma alt boyutlarından alınan puanlar diyet sonrası dönemde diyet öncesi döneme göre artış göstermiştir (P=0.001). Bu bulgular H1 hipotezini desteklemektedir. RAM'a göre uygulanan hemşirelik sürecinin hastaların baş etme-uyum becerisini arttırdığını söyleyebiliriz. Literatür incelendiğinde düşük iyot diyeti dönemindeki hastalarda BUSÖ kullanılarak baş etme-uyum düzeyinin belirlendiği bir çalışmaya rastlanılmamıştır. Tiroid sintigrafisi sonuçlarına bakılarak düşük iyot diyetine uyumun değerlendirildiği bir vaka çalışmasında, diyete uyum sağlayamayan bir hastanın çekilen sintigrafide ilk sonuçların negatif olduğu, hastaya diyetin uygulanmasına yönelik uygun rehberlik sağlandığında diyet rejimine bağlı kalındığına ve sintigrafi sonucunun pozitif olduğu gösterilmiştir (23). Günlük iyot alımı miktarına göre düşük iyot diyetine uyumun değerlendirildiği Kore'de yapılan bir çalışmada, yoğun beslenme eğitiminin diyete uyumu arttırmada basit bir kılavuza göre daha

etkili olduğu bulunmuştur (6). Günlük üriner iyot seviyesi ölçümüne dayanılarak hastaların düşük iyot diyetine uyumun değerlendirildiği bir çalışmada; diyet öncesi hastalar, özel eğitim almış hemşireler ve diyetisyenler tarafından 2 saat boyunca yoğun bir şekilde eğitim almış ve diyete uyumları düzenli olarak kontrol edilmiş olup, diyetin 6. gününde idrarda istenilen miktarda iyot atılımına ulaşılmış ve hastaların diyetine uyum sağladığı ifade edilmiştir (24). RAİ tedavisine hazırlığın 56 değerlendirildiği bir derlemede, düşük iyot diyeti döneminde hastalara yeterince eğitim verilirse ve diyete uyumları düzenli olarak kontrol edilirse, iyottan zengin bölgelerde bile 1 haftalık düşük iyot diyetinin yeterli olabileceği ifade edilmiştir (25).

5. Sonuçlar ve Öneriler

Sonuçlar

Bu araştırma, düşük iyot diyeti döneminde olan hastalarda RAM'a göre temellendirilmiş hemşirelik sürecinin etkisinin belirlenmesi amacı ile yapılmıştır. Araştırmanın sonuçlarına baktığımızda:

- ✓ Hastaların diyet öncesi ve sonrası karşılaştırıldığında, BKİ değerleri açısından anlamlı fark bulunmazken, SKB ve DKB değerlerinde diyet öncesine göre anlamlı düşüş görülmüştür (P<0.01).
- ✓ Hastaların diyet öncesi ve sonrası karşılaştırıldığında, çözüm bulma ve odaklanma (P<0.01), fiziksel ve karara bağlama (P<0.01), dikkat süreci (P<0.01), sistematize etme süreci (P<0.01), öğrenme ve ilişki kurma (P<0.01) ve toplam puan (P<0.01) ölçümlerinin diyet öncesine göre anlamlı düzeyde yüksek olduğu bulunmuştur. Sonuç olarak H1 hipotezi kabul edilmiştir.

Öneriler

Uygulamaya yönelik önerilere baktığımızda;

- ✓ Düşük iyot diyeti dönemindeki hastaların gereksinimlerine yönelik eğitimin hemşire tarafından verilmesi,
- ✓ Eğitimin desteklenmesi için eğitim kitapçığının kullanılması ve bu kitapçığın hastalara verilmesi,
- ✓ Diyet döneminde olan hastaların belirli zamanlarda izlemlerinin yapılması,
- ✓ Hastalar için RAM'a göre temellendirilmiş hemşirelik sürecinin uygulanması önerilir.

Araştırmacıya yönelik önerilere baktığımızda;

- ✓ Düşük iyot diyeti dönemindeki hastalara yönelik poliklinikte uygun ortamın düzenlenmesi, eğitim programlarının rutinleştirilmesi, hemşirelik sürecinin planlanması ve uygulanmasına yönelik çalışmaların arttırılması,
- ✓ Konuya yönelik nitel çalışmaların yapılması,
- ✓ Hastaların diyete uyum süreçlerini arttırmaya yönelik izlem çalışmalarının ve takiplerinin yapılması önerilir.

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Research Article / Araştırma Makalesi

Wilson Disease in Children: Analysis of 21 Patients

Çocuklarda Wilson Hastalığı: 21 Hastanın Analizi

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Abstract

Wilson disease (WD) is an autosomal recessive disorder of copper metabolism. Affected children may be asymptomatic, makes the diagnosis more difficult. In this study, we aimed to evaluate the clinical, laboratory, histopathological and genetic characteristics, and outcomes of the patients with WD. Our study includes patients who were diagnosed with WD between January 2010 and December 2020. The presenting complaints, physical examination findings, consanguinity and family history, laboratory, genetic, histopathological evaluation results, treatment and outcomes were all recorded. A total of 21 patients from 18 families [median age 9.5 (1-14) years, 10 girls] were included. Kayser-Fleischer ring was detected in 11 (52.4%) patients. Serum ceruloplasmin (<20 mg/dl) was low in 15 patients. Urinary copper excretion was >100 µg/day in 17 patients. Copper was positively stained with rhodanine in 9 of the18 liver biopsies. Liver copper content was >50 µg/g dry weight in all patients, 50-250 µg/g in 3 patients and >250 µg/g in 15 patients. Genetic evaluation was available in 18 patients and revealed heterozygous mutations in the ATP7B gene in 4 patients, combined heterozygous mutations in 6, and homozygous mutations in 8. Except for two patients with neurological findings and three asymptomatic patients who were diagnosed by family screening, all were presented with liver findings. Neurological involvement was also detected in 2 patients during follow up. D-Penicillamine and zinc sulfate combined treatments were used in 16 patients, zinc sulfate monotherapy was given to a presymptomatic patient diagnosed with family screening, and trientine and zinc sulfate combined therapies were used in four patients with neurological involvement. Transaminase values returned to normal in a median of 8.3 (4-23) months in 15 patients. The Kayser-Fleischer ring disappeared in a median of 32.8 months (10-81) in seven out of eleven patients. While liver transplantation was performed in one of the two patients who presented with fulminant hepatic failure at admission, the other was followed up with plasmapheresis and chelation therapy without the need for transplantation. Wilson disease should be considered in the differential diagnosis of all kinds of liver diseases ranging from asymptomatic elevation of transaminases to acute liver failure. Since early diagnosis and treatment are very important, family screening should definitely be recommended in diagnosed patients.

Keywords: Ceruloplasmin; Copper; Kayser-Fleischer ring; Wilson disease

Özet

Wilson hastalığı (WH), bakır metabolizmasının otozomal resesif geçişli bir bozukluğudur. Etkilenen çocuklar asemptomatik olabilir ve bu tanı koymayı zorlaştırır. Bu çalışmada WH'li hastaların klinik, laboratuvar, histopatolojik ve genetik özellikleri ve izlem sonuçlarını değerlendirmeyi amaçladık. Çalışmamıza Ocak 2010-Aralık 2020 tarihleri arasında WH tanısı konulan hastalar dahil edilmiştir. Başvuru şikayetleri, fizik muayene bulguları, akrabalık ve aile öyküsü, laboratuvar, genetik, histopatolojik değerlendirme sonuçları, tedavi ve izlem sonuçları kayıt altına alındı.18 aileden toplam 21 hasta [ortanca yaş 9,5 (1-14) yıl, 10 kız] dahil edildi. 11 (%52,4) hastada Kayser-Fleischer halkası tespit edildi. 15 hastada serum seruloplazmin (<20 mg/dl) düşüktü. 17 hastada üriner bakır atılımı >100 µg/gün idi. Bakır, 18 karaciğer biyopsisinin 9'unda rhodanin ile pozitif olarak boyandı. Karaciğer bakır içeriği tüm hastalarda >50 µg/g olup, 3 hastada 50-250 µg/g ve 15 hastada > 250 µg/g idi. 18 hastada genetik değerlendirme yapıldı ve 4 hastada ATP7B geninde heterozigot mutasyonlar, 6 hastada kombine heterozigot mutasyonlar ve 8 hastada homozigot mutasyonlar saptandı. Nörolojik bulguları olan iki hasta ve aile taraması ile tanı konulan üç asemptomatik hasta dışında, tümü karaciğer bulguları ile başvurdu. Takiplerde 2 hastada nörolojik tutulum saptandı. 16 hastada D-penisilamin ve çinko sülfat kombine tedavileri, aile taraması ile tanı konan presemptomatik bir hastaya çinko sülfat monoterapisi, nörolojik tutulumu olan dört hastada trientin ve çinko sülfat kombine tedavileri uygulandı. 15 hastada ortalama 8,3 (4-23) ayda transaminaz değerleri normale döndü. Kayser-Fleischer halkası, on bir hastanın yedisinde medyan 32,8 ayda (10-81) kayboldu. Başvuru anında fulminan karaciğer yetmezliği ile başvuran iki hastadan birine karaciğer nakli yapılırken, diğerine transplantasyona gerek kalmadan plazmaferez ve şelasyon tedavisi uygulandı. Asemptomatik transaminaz yükselmesinden akut karaciğer yetmezliğine kadar her türlü karaciğer hastalığının ayırıcı tanısında Wilson hastalığı düşünülmelidir. Erken tanı ve tedavi çok önemli olduğundan tanı konulan hastalarda aile taraması mutlaka önerilmelidir.

Anahtar Kelimeler: Bakır; Kayser-Fleischer halkası; Seruloplazmin; Wilson hastalığı

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1. Introduction

Wilson disease (WD) is an autosomal recessive disorder of copper metabolism caused by mutations in the ATP7B gene encoded in the long arm of the 13th (13q14.3) chromosome (1). As a result of the inability of copper to bind to ceruloplasmin and not be excreted in the bile, it accumulates first in the liver and then in other organs, especially in the cornea, brain and kidneys (2).

While the prevalence of the disease is 1/30,000 worldwide, the carrier frequency is 1/90 (3). Patients are frequently diagnosed between the ages of 5-35 (4). Patients may show a variety of clinical signs and symptoms, or they may be asymptomatic. While most of the cases present with hepatic findings in the first decade, 75% present with neuropsychiatric findings and 25% with hepatic and neuropsychiatric findings after the second decade (5).

Liver involvement may vary from asymptomatic liver enzyme elevation to acute hepatitis, chronic hepatitis, cirrhosis, and fulminant liver failure (6). Neurological involvement is manifested by movement disorders such as tremor, dystonia or parkinsonism (bradykinesia, rigidity, and resting tremor) and accompanying dysarthria, hypersalivation, and dysphagia (7). Common neuropsychiatric findings in children are decreased school success, inappropriate behaviors, and mood disorders (8).

There is no single diagnostic test that can exclude or confirm WD with certainty. Therefore, diagnosis is made by evaluating clinical, laboratory and genetic tests together (9). In addition, clinical symptoms may be absent and the Kayser-Fleischer (KF) ring can not be detected during early childhood and this makes the diagnosis even more difficult. It is one of the few genetic diseases which can be successfully treated with early diagnosis.

In this study, we aimed to evaluate the demographic, clinical, laboratory, histopathological and genetic characteristics and treatment responses of 21 pediatric WD patients.

2. Material and Methods

The study was conducted at Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatric Gastroenterology and Hepatology. Patients who were followed up with a diagnosis of WD between January 2010 and December 2020 were included in the study.

The patients' presenting complaints, consanguinity and family history, physical examination findings, laboratory results and liver histopathological evaluation were recorded.

The serum ceruloplasmin level, the amount of 24-hour urinary copper excretion, the D-Penicillamine challenge test results, the presence of KF ring, the amount of liver copper content and the results of genetic analysis were recorded. The Ferenci score was calculated for all patients, and those who scored 4 and above were accepted as Wilson disease (10). Renal involvement was evaluated by complete urine analysis, urine amino acid study, and 24-hour urine calcium, phosphorus and protein excretion. Routine laboratory tests were measured by standard methods, serum ceruloplasmin level analized by nephelometric method and the 24-hour urine copper and liver copper content were measured by atomic absorption spectrophotometer method.

Portal system color Doppler ultrasonography (USG) and esophagogastroduodenoscopy (EGD) were used to evaluate the presence of portal hypertension and varicose veins. Complete neurological examination and cranial magnetic resonance imaging (MRI) data were used to determine the presence of neurological involvement. The dose, duration and adverse effects of drugs used for WD treatment, time to remission and liver transplantation requirements were also recorded.

3. Results

Four patients were excluded from the study due to lack of follow-up. A total of 21 patients from 18 families [median age 9.5 (1-14)

years, 10 girls, 11 boys] were included in the study. Six of the patients were siblings, and the parents of seven were consanguineous (Table 1).

The presenting manifestations of the disease were as follows: fatigue in 9 (42.9%) patients, jaundice in 4 (19%), epistaxis in 2 (9.5%), tremor in 1 (4.8%), and bradykinesia in 1 (4.8%). Two patients presented with fulminant hepatic failure. Seven of the patients were referred because of raised transaminases. Hepatomegaly was the most common clinical finding, in 11 (52.4%) patients, followed by splenomegaly in 8 (38.1%), jaundice in 6 (28.6%), ascites in 3 (14.3%), clubbing in 2 (9.5%), epistaxis in 2 (9.5%), fine tremor in 1 (4.8%), and bradykinesia in 1 (4.8%) (Table 1).

While the transaminase levels were high in 20 (90.5%) patients, one patient who was early diagnosed by family screening, had normal liver function tests. High international normalized ratio (INR) values were detected in 10 (47.6%) patients, hyperbilirubinemia in eight (38.1%), anemia in eight (38.1%), hypoalbuminemia in four (19%), and Coombs negative hemolytic anemia in one patient (4.8%) (Table 1). Renal involvement was present in three (14.3%) patients on admission. Two patients had proteinuria, impaired tubular phosphorus reabsorption, and mild to moderate amino aciduria, while one patient had hypercalciuria.

Table 1. Demographic features, physical examination findings and laboratory results of the patients

Patient characteristics	
Age at diagnosis, median (25-75p)	8.4 (6-11.1)
Sex (Girl/Boy)	10/11
Consanguinity, n (%)	7 (33.3)
Positive family history, n (%)	3 (14.2)
Hepatomegaly, n (%)	11 (52.4)
Splenomegaly, n (%)	8 (38.1)
Jaundice, n (%)	6 (28.6)
Aspartate aminotransferase, IU/L, median (25-75p)	126.5 (95.3-176.1)
Alanine aminotransferase, IU/L, median (25-75p)	136.1 (79.5-274.5)
γ-Glutamyltransferase, IU/L, median (25-75p)	116 (49-212)
Alkaline phosphatase, IU/L, median (25-75p)	322 (278-354)
Total protein, g/dL, median (25-75p)	7.1 (6.3-7.9)
Albumin, g/dL, median (25-75p)	3.8 (2.4-4.1)
Total bilirubin, mg/dL, median (25-75p)	0.58 (0.31-1.82)
Direct bilirubin, mg/dL, median (25-75p)	0.22 (0.083-0.81)
International normalized ratio, median (25-75p)	1.21 (1.16-2.01)

Hepatobiliary USG revealed hepatomegaly in 11 patients, splenomegaly in nine, liver parenchymal heterogeneity in eight, hepatosteatosis in six and, irregular liver contours and nodularity in three patients. Portal hypertension was detected in six patients on portal system color Doppler USG examination.

Kayser-Fleischer ring was present in 11 (52.4%) patients. The youngest patient with KF ring was 4 years old, and the others were older than 6 years old. Serum ceruloplasmin was low (<20 mg/dl) in 15 (71.4%) patients and lower than 10 mg/dl in eight (38.1%) of them. Urinary copper excretion was >100 µg/day in 17 patients. D-Penicillamine challenge test was performed in 2 patients with urinary copper excretion between 40 and 100 µg/day and more than fivefold increase was observed in both patients (Table 2). Eighteen (85.7%) patients underwent USG-guided tru-cut liver biopsy. Liver biopsies of nine (42.9%) patients were positively stained with rhodanine. According to the Ishak fibrosis staging, three patients had stage 1, two had stage 2, three had stage 3, two had stage 5 (precirrhosis), and eight had stage 6 fibrosis (cirrhosis). Steatosis was present histopathologically in eight (38.1%) patients. Liver copper content was >50 µg/g dry weight in all patients, 50-250 µg/g in 3 patients and > 250 µg/g in 15 patients. (Table 2).

Table 2. Specific laboratory finding of the patients with Wilson disease

Diagnostic tests	
Kayser-Fleischer ring, n (%)	11 (52,4)
Serum ceruloplasmin, mg/dl, median (25-75p)	14.1 (6.5-21.12)
<20 mg/dl, n (%)	15 (71.4)
Urinary copper excretion µg/day, median (25-75p)	262.5 (151.3-578)
>100 µg/day, n (%)	17 (81)
40-100 µg/day, n (%)	2 (10.5)
D-Penicillamine challenge test	
>fivefold increase, n (%)	2 (10.5)
Liver dry copper content, µg/g, median (25-75p)	538 (260-844.5)
>250 µg/g, n (%)	15 (71.4)
50-250 µg/g, n (%)	3 (14.2)
Histopathological findings	
Steatosis, n (%)	8 (38.1)
Chronic active hepatitis, n (%)	10 (47.6)
Cirrhosis, n (%)	8 (38.1)

In the ATP7B gene, heterozygous mutations were found in four patients, mixed heterozygous mutations in six patients, and homozygous mutations in eight patients. The most common mutation was p.H1069Q and its frequency was 19.1%.

Ferenci score was 4 and above in all patients.

Except for two patients with neurological findings and three asymptomatic patients who were diagnosed by family screening, all were presented with liver findings. Ten of the patients (47.6%) had chronic liver disease, two (9.5%) had findings of fulminant hepatic failure, and seven (26.3%) had elevated transaminases. Of the nine patients who underwent EGD for portal hypertension, stage 1 esophageal varices were found in three, stage 2 in two, and stage 3 in one. Endoscopic band ligation was performed in three patients for varice eradication.

Neurological involvement was detected in four (19%) patients. Two patients who presented with neurological findings had headache, amnesia, dysmetria, right bradykinesia in one, and dysarthria, hypersalivation and tremor in the other. Two patients with no neurological symptoms showed minor abnormalities on MRI at the time of diagnosis, and progress was detected in follow-up due to noncompliance with therapy. Kayser-Fleischer ring was present in all four patients with neurological involvement.

D-Penicillamine and zinc sulfate combined treatments were used in 16 patients, zinc sulfate monotherapy was given to a presymptomatic patient diagnosed with family screening, and trientine and zinc sulfate combined therapies were used in four patients with neurological involvement. No adverse drug reactions were observed in any of the patients. Penicillamine treatment was replaced by trientine in two patients due to the lack of improvement in transaminase values.

Transaminase values returned to normal in a median of 8.3 (4-23) months in 15 patients. D-Bilirubin levels returned to normal in a median of 2.5 (0.01-12) months, and the INR in a median of 8.5 (2-48) months. One of the two patients who were moved from D-penicillamine to Trientine owing to transaminase levels not normalized recovered to normal, while the other remained slightly higher. The Kayser-Fleischer ring disappeared in a median of 32.8 months (10-81) in seven patients. While liver transplantation was performed in one of the two patients who presented with fulminant hepatic failure on admission, the other was followed up with plasmapheresis and chelation therapy without the need for a liver transplant. Two of the patients with chronic liver disease also underwent liver transplant during follow-up.

4. Discussion

Because of its autosomal recessive inheritance and our country's high rate of consanguineous

marriage, taking a family history and performing family screening in WD is critical. In support of this, the consanguinity rate between the parents was 33% in our study, and three of our patients with a family history of WD were diagnosed with screening and started early treatment.

Although the presence of a KF ring and low ceruloplasmin together with clinical findings are sufficient for the diagnosis, this association is not always present especially in small children. The Kayser-Fleischer ring is found in practically all patients with neurological involvement, whereas only 40-50 percent of patients with hepatic involvement and 20-30% of presymptomatic individuals have it. (8). Since most of the pediatric patients present with hepatic involvement, the diagnostic power of the KF ring is low in children. In our study, KF ring was present in 11 (52.4%) patients, and this incidence in our hepatic presentation-weighted cohort was compatible with the literature.

Ceruloplasmin is a copper transport protein that binds 90% of circulating copper. Even in the case of genetically proven disease, ceruloplasmin levels can be in normal range approximately in 20% of patients. Its levels may increase in chronic active hepatitis and as an acute phase reactant. Furthermore, depending on the nephelometric approach, misleading highs may arise because it analyzes both ceruloplasmin and physiologically inactive apoform. (11,12). In our study, ceruloplasmin was found to be normal in five (23.8%) patients. This can be explained by the use of nephelometric method in the measurement of ceruloplasmin and the presence of chronic active hepatitis in histopathological evaluation in three of our patients. Low ceruloplasmin levels concurrent with KF ring was observed in nine (42.8%) patients, and only less than half of the pediatric cases could be detected with the positivity of these two tests.

The conventionally accepted diagnostic level for 24-hour urinary copper excretion in Wilson's disease is above 100 µg/day. However, it may be below 100 µg/day in 16-23% of children and in asymptomatic patients (8,13). In a study, the cut off value of 40 µg/g was shown to have a sensitivity of 78.9% and a specificity of 87.9% for the diagnosis of WD (14). In individuals with readings below 100 µg/day but who are clinically compatible with WD, a D-penicillamine challenge test is indicated. After the D-penicillamine challenge test, an increase of more than fivefold from the basal value is significant (15). Urine copper was below 100 µg/day in two of our 19 patients. In these two patients, a 5-fold increase in urinary copper from the basal values were obtained with the challenge test. On the other hand, there are also publications stating that there is no need for D-Penicillamine challenge test if the limit is taken as 40 µg/day (15). When the limit for urinary copper excretion was taken as 40 µg/day, it was observed that the patients in our study did not require the D-Penicillamine challenge test.

When the diagnosis cannot be confirmed with clinical findings and laboratory tests, liver biopsy is performed for histopathological evaluation and parenchymal copper concentration quantification. Histopathological findings are not pathognomonic for WD, and micro-macrovesicular steatosis, portal fibrosis and inflammation, fibrous bridging between portal areas and cirrhosis can be seen. Negative staining may occur because parenchymal copper accumulation is cytosolic in the early period and copper dyes can stain lysosomal copper (16). In our study, nine patients had positive staining with Rhodanin. Parenchymal copper concentration >250 µg/g in non-cholestatic patients has been shown to be diagnostic for WD. Lower values have been reported in about 20% of Wilson patients, but it has been reported that it may also be due to sampling error due to the inhomogeneous distribution of copper in the liver (8,17,18). In one of the few studies conducted with children, 28 of 30 WD patients were found to have a liver copper concentration of >250 µg/g, while two patients had a liver copper concetration less than 75 µg/g (15). In our study, tissue copper was measured above the normal value (50 µg/g) in all patients, and it was above 250 µg/g in 15 of them.

More than 700 mutations associated with WD have been reported so far (19). Although most

genetic studies begin with screening for common mutations in specific populations, gene sequencing is frequently required because no specific mutation is responsible for the majority of cases in our country. (20-22). With the new generation sequencing, 95% of the mutations can be detected in the affected person. However, this technique is not diagnostic in molecular defects outside the coding regions, intron-exon junctions, and deletions greater than 200 kd (23). In our study, 4 patients had heterozygous mutations. These patients, on the other hand, were diagnosed with WD according to the Ferenci score along with other laboratory and clinical findings. The most common mutation was p.H1069Q with a frequency of 19.1%, and it was found at similar rates (17.39%) with a previous study from our country (22).

The Ferenci scoring system was developed to solve the diagnostic confusion in WD (10). In a study evaluating its use in children, its sensitivity was found to be 98.14%, and its specificity was 96.59% (24). The absence of diagnostic methods such as “relative exchangeable copper, nonseruloplasmin bound copper”, electron microscopy evaluation and radioactive copper study, as well as the discussions about the thresholds of 24-hour urine copper excretion and liver parenchymal copper concentration can be considered as disadvantages of Ferenci scoring system. In addition, patients with idiopathic copper toxicosis and MDR3 deficiency can score 4 and above from the Ferenci score.

The treatment is based on the principle of removing excess copper from the body with chelators such as D-Penicillamine and trientine, and preventing its absorption from the intestine with zinc salts. All treatments have been shown to be effective in asymptomatic or mild hepatic involvement (25-27). In symptomatic patients, the use of chelators is recommended (8). D-Penicillamine was suggested to be used as the first choice in WD patients. Trientine was recommended as the second choice for those who developed adverse effects with D-penicillamine, but later it was also suggested to be used as the first choice in neurological involvement. However, Weiss et al. evaluated neurological deterioration after treatment and found the risk to be similar for all drugs (9.1% for D-Penicillamine, 8.8% for Trientine, and 7.3% for zinc) (28). In our center, trientine was given as first choice in patients with neurological involvement, zinc therapy was started in presymptomatic patients, and D-Penicillamine and zinc were given in other patients.

In the literature, early-stage side effects such as D-Penicillamine-induced hypersensitivity reactions and mid-late-term side effects such as nephrotoxicity and lupus-like syndrome have been reported up to 30% (8). However, interestingly, D-Penicillamine-related side effects were not observed in our patients. This may be due to the relatively small patient size in our study.

Follow-up should be done weekly in order to detect drug side effects at the beginning of the treatment, and then at intervals of 1-3 months until remission is achieved. Recovery of liver enzymes takes approximately 3-12 months, while recovery of INR takes approximately 3-12 months, with 1 month at the earliest (29). In our patients, transaminase values returned to normal in a median of 8.3 (4-23) months in 15 patients after medical treatment. Transaminase elevation continued throughout the follow-up period in two patients whose treatment compliance was not good. Kayser-Fleischer ring disappeared in seven patients in a median of 32.8 months (10-81).

Transplantation can be prevented with various supportive treatments in children with decompensated cirrhosis who have liver failure but do not have encephalopathy. It is recommended to use "King's Wilson Index" (KWI) to predict transplantation-free mortality in the follow-up of these patients (30). (31). One of the two patients in our study who presented with fulminant hepatic failure at admission received a liver transplant, while the other patient recovered without transplantation with plasmapheresis and chelation therapy, although the KWI was above 11. Liver transplantation was performed in another two patients with decompensated chronic liver disease during follow-up.

In conclusion, WD should be considered in the differential diagnosis of all liver diseases ranging from asymptomatic transaminases to acute liver failure. When the results of ceruloplasmin, KF ring and copper excretion in 24-hour urine are not sufficient for diagnosis, liver biopsy should be performed and histopathological evaluation of liver dry copper weight should be measured and the Ferenci score should be calculated with genetic testing to confirm the diagnosis. Family screening should be done in diagnosed patients because early diagnosis and treatment are critical.

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Olgu Sunumu / Case Report

Covid-19 Enfeksiyonu Sonrası İmmün Trombositopeni Tanısı Alan Hastaların Retrospektif Analizi ve Literatür Özeti

Retrospective Analysis of Patients Diagnosed with Immune Thrombocytopenia After Covid-19 Infection and Review of the Literature

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Özet

İmmün trombositopenik purpura (ITP) olarak bilinen immün trombositopeni, COVID-19'un önemli bir komplikasyonu olarak ortaya çıkabilmektedir. COVID-19 ile ilişkili ITP'yi teşhis etmek için kapsamlı bir yaklaşım gereklidir. Bu çalışmada COVID-19 PCR pozitifliği sonrası ilk 60 gün içinde ITP tanısı alan 7 hasta sunulmuştur. Hastaların tanıdaki medyan trombosit sayısı 16x109/L'dir. Şiddetli hayatı tehdit eden kanama yoktu. COVID-19 semptomlarının başlangıcından ITP tanısına kadar geçen medyan gün sayısı 21 gün olarak bulundu. Kemik iliği baskılanması, mikrovasküler trombüs nedeniyle trombosit tüketimi veya trombositlerin otoimmün yıkımı gibi çeşitli mekanizmalar COVID-19 ilişkili trombositopeni nedeni olabilir. IVIG tedavisine yanıt alınmıştır ancak IVIG sonrası medyan 13 günde relaps gelişmiştir. Relaps olan hastalarda kortikosteroid kullanılabilir. COVID-19 sonrası hastalarda trombositopeni gelişimi açısından dikkatli olunmalıdır. Yeni tanı ITP'li hastalarda COVID-19 testi yapılmalıdır.
Anahtar Kelimeler: COVID-19, immun trombositopeni, tedavi

Abstract

Immune thrombocytopenia, known as immune thrombocytopenic purpura (ITP), has emerged as a major complication of COVID-19. A comprehensive approach is required to diagnose ITP associated with COVID-19. In this study, 7 patients who were diagnosed with ITP in the first 60 days after COVID-19 PCR positivity were presented. The median platelet count of the patients at diagnosis is 16x109/L. There was no severe life-threatening bleeding. The median day from the onset of COVID-19 symptoms to the diagnosis of ITP was 21 days. Various mechanisms such as bone marrow suppression, platelet consumption due to microvascular thrombus, or autoimmune destruction of platelets may be the cause of COVID-19-associated thrombocytopenia. Response to IVIG treatment was achieved, but relapse developed in a median of 13 days after IVIG. Corticosteroids can be used in patients with relapse. Care should be taken in terms of the development of thrombocytopenia in patients after COVID-19. Patients with newly diagnosed ITP should be tested for COVID-19.
Keywords: COVID-19, immune thrombocytopenia, treatment

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1. Giriş

SARS-CoV-2 başta pnömoni olmak üzere geniş bir hastalık spektrumuna neden olmaktadır. [1] COVID-19 hastalarında yapılan çalışmalarda trombositopeni oranı %12-36 arasında bulunmuştur. [2-3] Hastalık seyri esnasında trombosit sayısının 100-150x10^9/L arasında olduğu orta derecede trombositopeni görülebilir ancak ağır trombositopeni nadirdir. [4] Kemik iliği baskılanması, dissemine intravasküler koagülasyon (DIK), mikrovasküler trombüs nedeniyle trombosit tüketimi veya trombositlerin otoimmün yıkımı COVID-19 ilişkili trombositopeni nedeni olabilir. [5] Virüs bileşenleri ile trombosit glikoproteinleri arasındaki moleküler benzerlik otoimmün bir süreci tetikleyebilir. Bu etkileşim trombosit yıkımına neden olan otoantikorların üretimini başlatabilir. [6,7] SARS-CoV-2 enfeksiyonu sırasında artan sitokinler megakaryopoezi inhibe edebilir. Kemik iliği hücrelerinin veya trombositlerin virüs tarafından (muhtemelen CD-13 reseptörleri yoluyla) doğrudan enfeksiyonu ve işlevsiz kemik iliği mikro-ortamı nedeniyle trombosit sentezinin inhibisyonu trombositopeniye neden olabilir.[8]

İmmün trombositopeni (İTP), trombosit sayısı 100x10^9/L'nin altında ve başka bir nedenle açıklanamayan izole trombositopeni ile karakterize bir otoimmün hastalıktır. Klinik prezentasyon, asemptomatik hastadan hafif mukokutanöz kanamaya ve hatta yaşamı tehdit eden ciddi kanamalara kadar heterojen olabilir. [9] ITP, primer bir durum olabilir veya diğer hastalıklara, özellikle Hepatit B virüs (HBV), Hepatit C virüs (HCV), sitomegalovirüs (CMV), Epstein-Barr virüs (EBV), insan immun yetmezlik virüsü (HIV) gibi viral enfeksiyonlara sekonder olabilir. SARS-Cov-2'ye bağlı ITP tanımlanan vakalar vardır. Bu vakalarda ITP, COVID-19 enfeksiyonu seyri sırasında gelişmiştir. [10,11] Bizim sunduğumuz vakalar ise COVID-19 enfeksiyonu geçirdikten sonra asemptomatik oldukları dönemde takiplerinde ITP tanısı almışlardır. İmmün trombositopeni genellikle trombositopeninin diğer olası nedenlerinin dışlanmasına ve tedaviye yanıtın değerlendirilmesine dayanan geriye dönük bir tanıdır. Orta-şiddetli COVID-19 hastalarında ITP teşhisi, Hemafagostik Lenfohistiyositoz (HLH), DIK, sepsis, antibiyotik kullanımı, heparin profilaksisi ve tromboembolik olaylar dahil olmak üzere birden fazla eşzamanlı durumun varlığı nedeniyle klinisyenler için önemli bir tanısal ve terapötik zorluk teşkil etmektedir.

Bu vaka serisinde yeni başlangıçlı ITP ile başvuran ve öyküde yakın tarihte geçirilmiş COVID-19 enfeksiyonu öyküsü olan hastalarının klinik özellikleri, tanı çalışmaları, kan sayımı parametreleri, tedavi stratejileri ve sonuçları analiz edilmiştir. Asemptomatik COVID-19 hastalarında da takiplerinde immün trombositopeni gelişebileceğine dikkat çekilmesi amaçlanmıştır.

2. Gereç ve Yöntem

Nisan 2021-Ağustos 2021 arasında İTP tanısı alan hastaların öykülerinde geçirilmiş COVID-19 enfeksiyonu olan olgular çalışmaya alındı. COVID-19 enfeksiyonu, nazal ve faringeal sürüntü örneklerinin gerçek zamanlı ters transkriptaz polimeraz zincir reaksiyonu (RT-PCR) analizinde pozitif sonuç olarak tanımlandı. ITP tanısından önceki 60 gün içerinde COVID-19 PCR pozitifliği saptanan hastalar çalışmaya dahil edildi. COVID-19 PCR pozitifliği devam eden hastalar ve COVID-19 aşısı sonrası trombositopeni gelişen hastalar çalışmaya dahil edilmedi. Hastalar dışlandıktan sonra ITP tanısı alan 7 hasta bulundu. Trombosit sayısı <30x10^9/L olan hastalara tedavi verildi. Hastalardan bilgilendirilmiş olur formu alındı.

3. Bulgular

Hastaların hepsi Favipravir tedavisi almıştı. Yoğun bakım yatışı gerektiren ağır COVID-19 pnömonisi olan hasta yoktu. Hiçbir hastanın COVID enfeksiyonu esnasında trombositopenisi olmamıştı. ITP tanısı esnasında tüm hastaların COVID-19 PCR testi negatifti. Hiçbir hastada mikroanjiopatik hemoliz saptanmadı ve tanı esnasında ve öncesinde tromboz kliniği yoktu. Hastaların ITP tanısındaki fibrinojen değerleri normaldi. Olgu 2, 6 ve 7'de hafif D-dimer yüksekliği saptandı (Sırasıyla 1,33, 1,1 ve 2.0 mg/L). Merkezimizde D-dimer normal aralığı 0-0,5 mg/L'dir.

Vaka serimizde 6 kadın 1 erkek hasta vardı. Medyan yaş 56 (37-82)'ydı. Medyan trombosit sayısı $16x10^9$/L ($2x10^9$/L-$69x10^9$/L) olarak bulundu. Sadece bir hastada tanıda trombosit sayısı >$30x10^9$/L'ydi. COVİD-19 tanısıyla trombositopeni saptanması arasındaki medyan gün sayısı 21 gündü. Hastalardan biri 52. günde tanı almıştı. intravenöz immunglobulin (IVIG) tedavisi alan 4 hasta oldu. IVIG tedavisine medyan 4.5 günde tüm hastalarda yanıt alındı ancak 4 hasta da 30 gün içinde relaps oldu. IVIG tedavisi sonrası medyan relaps süresi 13 gün olarak bulundu. Relaps olan hastalarda steroid tedavisi verildi. Yedi hastanın 5'i metilprednizolon sonrası remisyonda, 1 hasta ise eltrombopag tedavisi ile remisyondadır. Hastalardan 1'i (olgu 3) tedavisiz izlenmiştir. Hastaların medyan takip süresi 12 aydır. Tablo-1'de hastaların klinik özellikleri görülmektedir.

Tablo 1. Hastaların klinik özellikleri

Hasta No:	Yaş	Cinsiyet	COVID tanısıyla trombositopeni saptanması arasındaki gün sayısı	Tanıda trombosit sayısı ($x10^9$/L)	IVIG Tedavi başlangıcından sonraki yanıt günü	IVIG sonrası relaps zamanı	Metilprednizolon tedavi başlangıcından sonraki yanıt günü	Son trombosit sayımı ($x10^9$/L)	Son takibi ile COVID tanısı arasında geçen süre (ay)
1	38	K	21	3	+ / 3	10. gün	+ / 5	144	3
2	61	K	20	2	+ / 3	25.gün	+ / 5	272	6
3	82	E	24	69	-		-	95	12
4	58	K	52	16	-		+ / 4	58	13
5*	37	K	10	22	+ / 6	5. gün	+ / 9	98	13
6*	58	K	15	9	+ / 6	7.gün	+ / 3	327	12
7	56	K	30	19	-		+ / 3	187	3

** Eski ITP (immün trombositopeni) tanılı hastalar*

IVIg dozu: 400 mg/kg/gün/5 gün, metil prednizolon dozu: 1mg/kg/gün

Olgu 1

38 yaşında kadın hasta, bacaklarda peteşi ve ekimozlar ile acil servise başvurdu. Bilinen sistemik hastalığı olmayan hastanın fizik muayenesinde peteşi ve ekimozlar dışında özellik yoktu. Tetkiklerinde izole trombositopeni saptandı ($3x10^9$/L). 21 gün önce COVID-19 PCR pozitifliği saptanan hasta tedavi almış ve 15 gün önce normal trombosit sayımı ile taburcu olmuştu. Hastaya immun trombositopeni (ITP) tanısı ile IVIG 400mg/kg/gün, 5 gün verildi. Viral ve otoimmün belirteçlerde özellik yoktu. IVIG sonrası trombosit sayısı $114x10^9$/L olan hasta taburcu edildi. 10 gün sonra trombosit $28x10^9$/L olan hastaya kemik iliği biyopsisi yapıldı. Metilprednizolon 32 mg başlandı. Aspirasyonda ve biyopside patoloji saptanmadı. Takiplerinde 4 hafta sonra trombosit sayısı $103x10^9$/L olan hastanın steroid tedavisi azaltılarak kesildi.

Olgu 2

61 yaşında kadın hasta, COVID-19 PCR pozitifliğinin 20. gününde trombosit $2x10^9$/L saptanması üzerine tarafımıza yönlendirildi. Bilinen sistemik hastalığı yoktu. Fizik muayenede bacaklarda peteşiler dışında özellik saptanmadı. Viral ve otoimmun belirteçlerde özellik yoktu. Hastaya ITP tanısı ile IVIG 400mg/kg/gün/5 gün verildi. IVIG sonrası trombosit sayısı $85x10^9$/L oldu. 25 gün sonra trombosit sayısı $21x10^9$/L olan hastaya metilprednizolon 32 mg başlandı. 2 hafta sonra trombosit $15X10^9$/L olunca metilprednizolon 1 mg/kg/gün'e çıkıldı. Kemik iliği biyopsisinde patoloji saptanmadı. 1 ay sonra trombosit $136x10^9$/L olan hastanın tedavisi azaltılarak kesildi.

Olgu 3

82 yaş erkek hasta, diyabet, hipertansiyon, koroner arter hastalığı, benign prostat hiperplazisi tanıları olan hasta. COVID-19 PCR pozitifliği ile tedavi başlanmasından 24 gün sonra trombosit $69x10^9$/L saptandı. Fizik muayenede özellik yoktu. Viral belirteçler negatif saptandı. İlaçsız takip edilen hastanın 10 gün sonraki takiplerinde trombosit sayısı $150x10^9$/L saptandı. 1 ay sonraki takiplerinde trombosit sayısı $64x10^9$/L olan hasta ilaçsız olarak takip ediliyor.

Olgu 4

58 yaş kadın hasta, COVID-19 PCR pozitifliğinden 52 gün sonra bacaklarda peteşiler ile geldi. Trombosit sayısı $16x10^9$/L saptandı. HT dışında sistemik hastalık yoktu. Fizik muayenede peteşiler dışında özellik yoktu. Viral ve otoimmun belirteçlerde özellik yoktu. Hastaya ITP tanısıyla metilprednizolon 1mg/kg/gün başlandı. 4 gün sonra trombosit sayısı $145x10^9$/L'e yükseldi. Takiplerinde metilprednizolon dozu azaltılarak kesildi.

Olgu 5

37 kadın hasta, geçirilmiş ITP, pulmoner tromboemboli, sinüs ven trombozu tanıları ile varfarin tedavisi alıyordu. COVID-19 PCR pozitifliği saptandığında alınan kan sayımındaki trombosit sayımı $350x10^9$/L idi. Enfeksiyondan 10 gün sonra burun kanaması ile başvurdu. Trombosit $22x10^9$/L saptandı. Fizik muayenede bacaklarda peteşiler dışında özellik yoktu. IVIG 400 mg/kg/gün/5 gün verildi. Tedavi sonrası trombosit sayısı $40x10^9$/L olan hasta taburcu edildi. 5 gün sonra göğüste ve ekstremitelerde peteşiler ile tekrar yatırıldı. Trombosit $4x10^9$/L olan hastaya metilprednizolon 1 mg/kg/gün ve eltrombopag 1x50 mg başlandı. Yatışının 9. gününde trombosit $29x10^9$/L ile taburcu edildi. Takiplerinde prednizolon azaltılarak kesildi. Eltrombopag 1x25 mg/gün ile tedaviye devam edilmektedir.

Olgu 6

58 yaş kadın hasta, ITP ve JAK-2 negatif polisitemi ile takipliydi. COVID-19 PCR pozitifliği sırasında alınan hemogramdaki trombosit sayımı normaldi. 15 gün sonra ekstremitelerde ve ağız mukozasında peteşiler, sağ bacakta ekimoz şikayetleri ile başvurdu. Trombosit sayısı $9x10^9$/L olması üzerine ITP relaps düşünülerek IVIG 400 mg/kg/gün/ 5 gün verildi. IVIG sonrası trombosit $50x10^9$/L olan hasta taburcu edildi. 1 hafta sonra trombosit sayısı $1X10^9$/L ile gelen hastaya 1 mg/ kg/gün dozunda metilprednizolon başlandı. Viral belirteçler negatif saptandı. Kemik ilği aspirasyon ve biyopsisinde özellik saptanmadı. Anti nükleer antikor (ANA) 3+ nükleer boyanması olması nedeniyle romatolojiye danışılan hastaya sitemik lupus eritematozus (SLE) tanısı konularak hidroksiklorokin tedavisi başlandı. Takiplerinde steroid dozu azaltılarak kesildi.

Olgu 7

56 yaşında atriyal fibrilasyon tanılı kadın hasta COVID-19 PCR pozitifliğinden 30 gün sonra bacaklarda peteşiler ile acile başvurdu. Trombosit sayısı $19x10^9$/L saptandı. Viral ve otoimmun belirteçlerde özellik yoktu. Hastaya ITP tanısıyla metilprednizolon 1 mg/kg/gün başlandı. 3 gün sonra trombosit sayısı $49x10^9$/L oldu. Takiplerinde metilprednizolon dozu azaltılarak kesildi.

4. Tartışma ve Sonuç

COVID-19 seyrinde trombositopeni insidansı bir çalışmada %11,8 olarak bulunmuştur ve ağır trombositopeni kötü prognostik faktör olarak bilinmektedir. [12] Mikrovasküler trombüs ağır vakalarda trombosit tüketiminden sorumlu olabilir. ITP tüketim trombositopenisinden farklı bir antite olarak hastalığın farklı evrelerinde gelişebilir. Bugüne kadar sık bildirilmemesine rağmen, SARS-CoV-2 enfeksiyonu sekonder ITP ile ilişkilendirilebilir. SARS-CoV-2'nin otoreaktif B hücrelerini uyarması ve ardından trombosit glikoproteinlerine karşı otoantikor gelişmesi ITP gelişimine neden olabilir. [13] Literatürdeki COVID-19 ilişkili trombositopeni vakalarının çoğunda trombositopeni; COVID-19 PCR pozitifliği saptandıktan sonraki ilk 10 günde veya ağır COVİD-19 enfeksiyonu seyrinde görülmüştür. [14] COVID-19 PCR testinin negatifleşmesi sonrası ITP gelişen çok az vaka vardır. [15] S Bhattacharjee ve arkadaşları literatürde COVID-19 sonrası ITP geliştiği bildirilen 39 hastanın verilerini incelemişlerdir. COVID-19 semptomlarının

başlangıcından ITP tanısına kadar geçen medyan gün 13 gün bulunmuştur ve çoğunluğu ikinci ve üçüncü haftada rapor edilmiştir. Medyan en düşük trombosit sayısı $5x10^9$/L idi; sadece 7 hastada (%15,5) en düşük sayı $20x10^9$/L'den fazlaydı. ITP tanısı alanların %71'i 50 yaş üstüydü ve %75 orta-ağır COVID-19 enfeksiyonu geçirmişti. [16] Glukokortikoid ve IVIG tedavilerine iyi yanıt alındığı görülmüştür. Tanı anında vakaların %31'inde herhangi bir kanama belirtisi bildirilmemiştir. Hastaların 4'ünde 60 günlük takipte relaps gelişmiştir.

Bizim hastalarımızda medyan trombosit sayısı $16x10^9$/L olarak bulunmuştur. COVID-19 semptomlarının başlangıcından ITP tanısına kadar geçen medyan gün 21 gün bulunmuştur. Literatürdeki vakalar ile uyumludur. IVIG tedavisine yanıt alınmıştır ancak IVIG sonrası medyan 13 günde relaps gelişmiştir. Relaps olan hastalarda kortikosteroid kullanılmıştır. IVIG, hızlı yanıt alınmak istenen vakalarda ilk tedavi seçeneği olarak kullanılabilir. Yanıt alınamayan vakalarda kortikosteroidler ve trombopoetin reseptör agonistleri kullanılabilir. Literatürdeki vakalarda yalnızca ağır trombositopenisi olan vakalar bildirildiğinden orta derecede trombositopenisi olan ITP hastalarının oranı yeterince temsil edilmemektedir. Bizim 7 hastamızın birinde hafif trombositopeni görülmüştür. Tüm vakaların takip süresi, tedavi yanıtının devamlılığı hakkında yorum yapmak için yeterli değildir. Bu nedenle, tekrarlama/relaps verileri gerçek verileri tam olarak yansıtmayabilir.

Hastaların trombositopeniye neden olabilecek komorbid hastalıkları açısından dikkatlice değerlendirilmesi gereklidir. COVID-19 tedavisinde kullanılan ilaçlara bağlı trombositopeni gelişebileceği göz önünde bulundurulmalıdır. COVID-19 sonrası gelişen ITP ile ilgili veriler sınırlıdır. Hastaların takiplerinde trombositopeni gelişimi açısından dikkatli olunmalıdır. ITP ile takipli hastalarda relaps gelişebileceği akılda bulundurulmalıdır. Asemptomatik COVID-19 hastalarında bildirilen ITP vakaları, pandemi sırasında COVID-19 semptomlarından bağımsız olarak yeni tanı almış ITP'li hastalarda COVID-19 testi ihtiyacının altını çizmektedir. COVID-19 sonrası trombositopeni ile ilgili hafif trombositopeni gelişen hastaların da değerlendirildiği daha fazla çalışmaya ihtiyaç vardır.

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Olgu Sunumu / Case Report

Multiple Myeloma Case with Pericardial Involvement

Perikard Tutulumu olan Multiple Myelom Olgusu

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Abstract

Multiple myeloma (MM) is an atypical plasma cell dyscrasia in the bone marrow (BM) which accounts for about 10% of all hematological malignancies. While extramedullary disease (EMD) is reported at a ratio of 6-20% in MM, cardiac and pericardial involvement is rare. In the event of cardiac or pericardiac involvement, on the other hand, progression into cardiac tamponade takes place in 60% of the patients. We will present a very rare case of recurrence with pericardial involvement after autologous stem cell transplantation
Keywords: Multiple myeloma, relapse, pericardial involvement

Özet

Multipl miyelom (MM), tüm hematolojik kanserlerin yaklaşık %10'unu oluşturan kemik iliğinin atipik plazma hücre bozukluğudur. MM'da ekstramedüller hastalık %6-20 oranında görülürken kardiyak ve perikardiyal tutulum varlığı ise nadirdir. Kardiyak veya perikardiyal tutulum meydana geldiğinde, kalp tamponadına ilerleme hastaların %60'ında gerçekleşir. Biz de otolog kök hücre nakli sonrası çok nadir görülen perikard tutulumu ile nüks olan olguyu sunacağız.
Anahtar Kelimeler: Multiple myelom, relaps, perikardiyal tutulum

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1. Introduction

Multiple myeloma (MM) is an atypical plasma cell dyscrasia in the bone marrow (BM) which accounts for about 10% of all hematological malignancies (1). While extramedullary disease is reported at a ratio of 6-20% in MM, cardiac and pericardial involvement is rare (2). In the event of cardiac or pericardiac involvement, on the other hand, progression into cardiac tamponade takes place in 60% of the patients (3-4).

2. Case Report

A 56-year-old female patient who had been during her workup, immunoglobulin G (IgG) level was 9,840 mg/dL and monoclonal gammopathy was determined through serum protein electrophoresis. BM biopsy revealed CD138 positive diffuse plasmacytoid cell infiltration with a cytogenetic analysis of 70-72, XXXX, + der(1) del(1) (p36) x 4, + der(1) del(1)(q25), -1, +2, -4,+5,+5,+6,-7,-8,der(9)(q?), -10, -13, -14, +15, +20, -21, -22[cp3]/46 XX[8]. PET-CT scan demonstrated increased enhancement in the lesion of 4 x 2.5 cm located at corpus pancreatis (SUV Max:10). Tru-cut biopsy was performed on the lesion identified at the pancreas, results of which were consistent with plasmacytoma. The patient was initiated on bortezomib, cyclophosphamide, dexamethasone chemotherapy. Concomitant with the second cycle, radiotherapy targeting her pancreatic plasmacytoma was administered. As the patient was unresponsive subsequent to the 4th cycle, she was shifted to bortezomib, lenalidomide, dexamethasone (VRd) treatment. After 3 cycles of VRd, she underwent autologous stem cell transplantation (ASCT). On Day 98 of ASCT, whole-body MRI scan revealed masses with irregular boundaries, one at the L3-S1 level and at a size of 88x40x38 mm. The patient was initiated on radiotherapy and carfilzomib, lenalidomide, dexamethasone treatment concomitantly. During her follow-ups, a total of 5 nodular immobile masses at a size of 2-3 cm were detected; located on her chest. Upon the pre-diagnosis of skin involvement, skin biopsy was planned but could not be performed due to thrombocytopenia. In further follow-ups, the patient developed hypotension and decreased electrocardiography voltage and shortness of breath. As pericardial effusion was noted on her thoracic tomography (Figure 1a). Therefore an echocardiogram was taken which indicated pericardial effusion of 22 mm surrounding the anterior wall, 12 mm at the posterior, 27 mm at the apex, and 35 mm adjacent to the right ventricle. Thus, pericardiocentesis was applied to drain out 650 cc of hemorrhagic fluid. A peripheral smear was prepared from her pericardiocentesis sample which included atypical plasma cells, and results from the flow cytometric analysis was consistent with MM involvement (Figure 1b and 1c). Radiotherapy was administered for her plasmacytomas, followed by cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD) chemotherapy. (Informed consent was obtained from the patient).

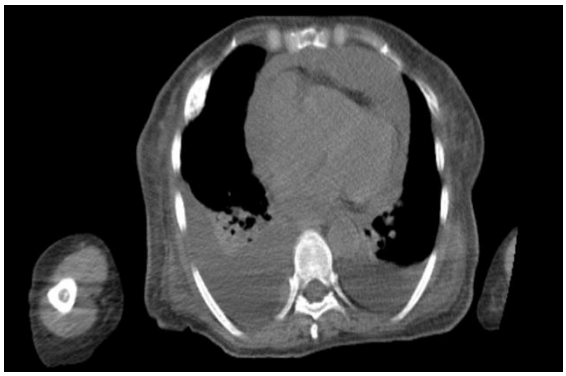

Figure 1a. Appearance of pericardial fluid on thoracic tomography

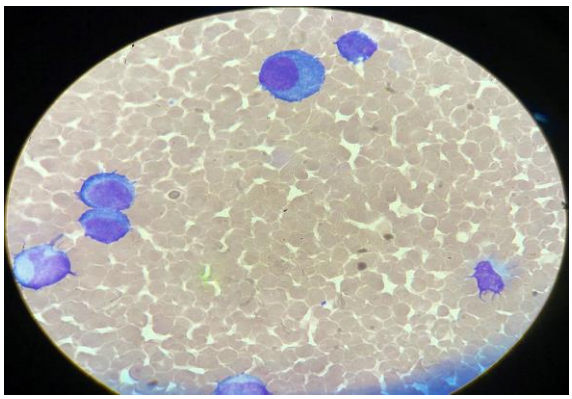

Figure 1b. Peripheral smear from pericardial fluid sample.

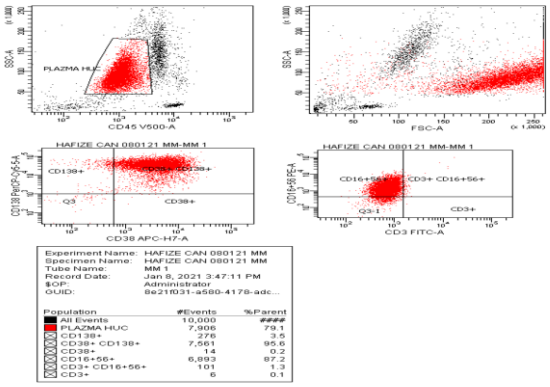

Figure 1c. Flow cytometric analysis of pericardial fluid sample.

3. Discussion

Among all MM cases, cardiac involvement occurs in less than 1% and cardiac tamponade is even more infrequent (5). By now, there have been approximately 29 documented cases of this complication. Our case is one of those rare occasions. In new case series it has been reported that 57.5% of the patients were lost within the 15 months of first admission (4). Likewise, our case was also lost in about 17 months after her diagnosis. The treatment options beyond the fluid drainage includes chemotherapy and steroid combinations, pericardial radiation therapy, and intrapericardial injection of sclerosing/chemotherapeutic agents (5). Our patient had only partially responded to pericardiocentesis, radiotheraphy, and systemic chemotherapy, and then was lost to sepsis and disease progression.

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Olgu Sunumu / Case Report

Hypophosphatemia Associated with Tumor-Induced Osteomalacia Caused by A Third Primary Tumor: A Case Report.

Üçüncü Primer Tümör Nedeniyle Gelişen, Tümör İlişkili Osteomalaziye Bağlı Bir Hipofosfatemi Olgusu.

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Abstract

Tumor-induced osteomalacia (TIO) is a paraneoplastic condition in which a tumor, usually of mesenchymal origin, causes osteomalacia often by producing Fibroblast Growth Factor-23 (FGF-23). FGF-23 induces hypophosphatemia through its phosphaturic action. Case Presentation: A 65-year-old male patient presented with complaints of muscle weakness, difficulty walking and severe bone pain. His medical history included distal gastrectomy for a moderate-risk gastrointestinal stromal tumor (GIST) of 4 cm in diameter, Billroth II antecholic gastroenterostomy and subsequently total thyroidectomy for Stage 1 multicentric micropapillary carcinoma (CA). Widespread lesions detected on bone scintigraphy were considered as bone metastases of GIST. Laboratory investigations revealed the following results: calcium (Ca): 8.3 mg/dL; phosphate (P): 1.5 mg/dL; Parathormone (PTH): 75 pg/mL; 25-OH vit D3: 31 ng/mL; 1-25-(OH)2 vit D3: 36 pg/mL; creatinine: 0.75 mg/dL; ALP: 109 IU/L, urine phosphate: 2.54 g/day. His hypophosphatemia was considered to be most probably due to TIO induced by bone metastases of GIST. Since it was not possible to remove the metastases, the patient was started on oral phosphate and calcitriol therapy. However, despite an improvement in Ca levels after the initiation of the treatment, P levels persisted around 2 mg/dL. After one year of treatment, an ulcer developed on his right first toe, which was excised and identified as "extraskeletal myxoid chondrosarcoma" on pathological examination. Following excision of the tumor, the patient's Ca and P values returned to normal range. The development of TIO in the presence of a GIST and thyroid CA is an unusual occurrence. As a matter of fact, the cause of hypophosphatemia was TIO which induced by a third primary tumor in this patient. To the best of our knowledge, TIO due to a third primary tumor is the first and only case in the literature. Another primary tumor focus should be suspected and carefully investigated if the patient already has a primary tumor and that tumor is not among those frequently inducing TIO.
Keywords: Third primary tumor, tumor-induced osteomalacia, hypophosphatemia, hypophosphatemic osteomalacia

Özet

Tümörle ilişkili osteomalazi (TİO), genellikle mezenkimal kaynaklı bir tümörün sıklıkla Fibroblast Büyüme Faktörü- 23 (FGF-23) üreterek osteomalaziye neden olduğu paraneoplastik bir durumdur. FGF-23, fosfatürik etki ile hipofosfatemiye neden olur.Olgu: Altmışbeş yaşında erkek hasta, kas güçsüzlüğü, zor yürüme ve şiddetli kemik ağrıları şikayetleri ile başvurdu. Tıbbi öyküsünde: 4 cm çapta orta riskli gastrointestinal sistem stromal tümör (GİST) sebebiyle distal gastrektomi, Billroth 2 antekolik gastroenterostomi ve sonrasında Evre 1 multisentrik mikropapiller karsinom (CA) sebebiyle total tiroidektomi operasyonları mevcuttu. Kemik sintigrafisindeki yaygın lezyonları GİST'in kemik metastazı olarak kabul edilmişti.Laboratuvar tetkiklerinde: Kalsiyum (Ca):8.3 mg/dL, fosfor (P): 1.5 mg/dL, parathormon (PTH): 75 pg/mL, 25-OH vit D3: 31 ng/mL, 1-25-(OH)2 vit D3: 36 pg/mL, kreatinin: 0.75 mg/dL ALP: 109 IU/L, idrar fosforu: 2.54 gr/gün idi. Hastanın hipofosfatemisinin olası sebebi GIST kemik metastazlarına bağlı olarak gelişmiş TİO'ye bağlı olduğu düşünüldü. Metastazların cerrahi olarak çıkartılması mümkün olmadığından, hastaya oral fosfat ve kalsitriol tedavisi başlandı. Ancak tedavi başlandıktan sonra Ca düzeyleri düzelmesine rağmen, P düzeyleri yaklaşık 2 mg/dl düzeylerinde seyretti. Tedavi başlandıktan bir yıl sonra sağ ayak birinci parmağında ülser gelişmesi üzerine, bu lezyon eksize edildi ve patoloji sonucu "ekstraskeletal miksoid kondrosarkom" olarak raporlandı. Tümörün eksizyonu sonrasında Ca ve P değerleri tamamen normale geldi. GIST ve tiroid CA ile TİO gözlenmesi genellikle beklenilen bir durum değildir. Nitekim hipofosfatemi sebebi olarak, hastamızda üçüncü primer tümöre bağlı olarak gelişmiş bir TİO tespit edildi. Üçüncü primer tümöre bağlı olarak gelişen TİO bildiğimiz kadarıyla literatürde ilk ve tek olgudur. Eğer hastada halihazırda primer bir tümör var ve bu tümör TİO'ye sık neden olan tümörlerden değilse, başka bir primer tümör odağının olup olmadığı dikkatle araştırılmalıdır.
Anahtar Kelimeler: Üçüncü primer tümör, tümör ilişkili osteomalazi, hipofosfatemi, hipofosfatemik osteomalazi

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1. Introduction

Oncogenic osteomalacia, also known as tumor-induced osteomalacia (TIO), is a paraneoplastic disorder often caused by a bone or soft tissue tumor that secretes fibroblast growth factor-23 (FGF-23), a phosphaturic protein, leading to the signs and symptoms of osteomalacia (or rickets)1. The mean age of onset is 40 to 45 years. Phosphaturic mesenchymal tumor, mixed connective type (PMT-MCT) is a rare mesenchymal tumor which is most frequently associated with TIO. The majority of PMT-MCTs are benign, slowly growing polymorphic neoplasms and the time from onset of symptoms to definitive diagnosis usually is longer than 2.5 years1,2. It has been reported that about 56% of these tumors are located in the lower extremities and 31% in the head region3. Colon, prostate, ovarian, lung cancers, osteosarcoma and spindle cell sarcoma are other tumors that can rarely cause TIO4,5.

Hypophosphatemia, phosphaturia, and low or inappropriately normal serum calcitriol levels are observed in TIO2,6. FGF-23 reduces reabsorption of phosphate from renal tubules and production of 1,25-dihydroxyvitamin D3 in the kidney via FGF receptor-1 (FGFR-1) signaling7. The resulting hypophosphatemia leads to bone pain, muscle weakness, rickets/osteomalacia and fractures. Pathological fractures have been reported to occur most commonly in vertebrae, ribs, femur and pelvis8.

As patients with X-linked hypophosphatemia (XLH), autosomal dominant hypophosphatemic rickets (ADHR) and autosomal recessive hypophosphatemic rickets (ARHR) also have increased serum FGF-23 levels, these diseases need to be differentiated from TIO9,10. Compared to patients with XLH, clinical manifestations of patients with TIO are usually more severe, which may be related to more severe drops in serum phosphate and calcitriol levels. The presence of a previously normal serum phosphate level in an affected patient often supports the diagnosis of TIO11. If the diagnosis remains uncertain, genetic testing may be done for XLH, ARHR and ADHR. Until the underlying tumor is identified, other disorders causing renal phosphate wasting should also be considered in the differential diagnosis12.

The only definitive treatment of TIO is the resection of the tumor. Since the tumors are typically small in size and can be anywhere in the body, locating them on X-ray images is challenging. Therefore, whole body magnetic resonance imaging (MRI), 111indium-pentetreotide scintigraphy, 18F-Fluoro-2-deoxy-glucose positron emission tomography/computed tomography (FDG-PET/CT) and Gallium-68 (Ga68)-DOTA-TATE PET/CT may be used when necessary1,3,8. Despite the availability of various diagnostic tools, localization of the culprit tumor can only be achieved in 65-80% of patients. In general, serum levels of FGF-23 decrease to normal, biochemical abnormalities improve rapidly and bone disease resolves within a period of 6 to 12 weeks following tumor resection2,6,13.

However, pharmacological therapy is required when the tumor cannot be localized. The goals of treatment are to try to achieve normal serum phosphate, alkaline phosphatase (ALP) and parathormone (PTH), manage bone pain, address mobility limitations and treat fractures. Oral calcitriol and oral phosphate have been traditionally used for the treatment of TIO. Calcitriol is usually administered as 0.5 to 1 mcg/day (15–60 ng/kg/day) in two divided doses and phosphate is given as 1 to 2 g daily (15–60 mg/kg/day) elemental phosphate in three to four divided doses. Since abdominal pain and diarrhea commonly occur with phosphate treatment, doses should be increased by up-titration. Serum phosphate, calcium, creatinine, bone-specific ALP, 24-hour urinary calcium, and PTH levels should be assessed at least every six months in patients receiving treatment with phosphate and calcitriol. Patients should be followed on a regular basis since toxicity manifested by hypercalcemia and hyperphosphatemia may occur suddenly in a patient who has been stable for many years11.

If the tumor cannot be identified or removed, medical therapy is continued indefinitely. It

would be appropriate to repeat tumor localization investigations at different intervals after starting drug therapy.

The best of our knowledge, this case is that it was the first TIO case developed due to the third primary tumor in the literature. For this reason, we wanted to publish this case to draw attention to this rare condition.

2. Case Presentation

A 65-year-old patient was referred to our clinic from the oncology department in 2015 because of hypophosphatemia. His complaints were muscle weakness, difficulty walking and bone pain. The patient was taking Levothyroxine 150 mcg/day for hypothyroidism due to thyroidectomy and alendronate 70 mg weekly orally for osteoporosis. He had a history of distal gastrectomy and Billroth II antecholic gastroenterostomy in 2011, with a pathology report of a moderate-risk gastrointestinal stromal tumor (GIST) of 4 cm in diameter. He also had a history of total thyroidectomy in 2013 due to FDG uptake by the thyroid gland on PET-CT scan which was requested by the oncology department for staging and follow-up purposes, and Stage 1 multicentric micropapillary carcinoma (CA) was reported by the pathologist. The patient has been experiencing bone pain since 2013 when extensive lesions were detected on bone scintigraphy, which were considered by the oncology department to be consistent with metastasis. During that period, he was followed by oncologists for metastatic GIST and started on alendronate therapy because of established osteoporosis. A PET-CT scan in 2015 showed diffuse FDG uptake in the middle portion of the right clavicle and on the right side of the ribs and a mass (16x12 mm) showing increased FDG uptake in the right adrenal gland was also considered as metastasis by the oncologists. On bone scintigraphy from 2015, minimally increased activity was observed as multiple foci in the left frontoorbital, occipital and parietal bones in the cranium; the medial segment of the right clavicle; in both hemithorax ribs; left lateral segment of the sacrum, the tarsal bones of the right foot and first metatarsophalangeal joint. These findings were first considered to be consistent with bone metastasis and despite the disappearance of some foci compared to bone scintigraphy from 2014, they were identified as progression due to the presence of new foci in both hemithoraxes.

At the time of his initial presentation in January 2015, physical examination showed that his general condition was fair, his blood pressure was 110/70 mmHg, pulse was 80 beats/minute and rhythmic and lung sounds were normal, and he was walking with assistance. An incision scar over the abdomen and a thyroidectomy scar on the neck were observed. Biochemistry results were as follows: Ca: 8.3 mg/dL (ref. range: 8.5-10.5 mg/dL), P: 1.5 mg/dL (ref. range: 2.5-4.5 mg/dL), PTH: 75 pg/mL (ref. range: 15-65 pg/mL), 25-OH vit D3: 31 ng/mL (ref. range: 20-50 ng/mL) 1-25 (OH)2- vit D3: 36 pg/mL (ref. range: 18-64 pg/mL), urea: 32 mg/dL (20-40 mg/dL), creatinine: 0.75 mg/dL (ref. range: 0.6-1.2 mg/dL), sodium: 145 mmol/L (ref. range: 135-145 mmol/L), potassium: 4.3 mmol/L (ref. range: 3.5-5 mmol/L), AST: 14 IU/L (ref. range: 5-34 IU/L), ALT: 10 IU/L (ref. range: 3-42 IU/L), ALP: 109 IU/L (ref. range: 40-129 IU/L), TSH: 0.71 mIU/mL (ref. range: 0.27-4.2 mIU/mL), free T4: 1.22 ng/dL (ref. range: 0.93-1.7ng/dL), Thyroglobulin: <0.2 ng/mL (ref. range: 0.2-0.3 ng/mL), Anti-Tg:<10 ng/mL (ref. range: :<10 ng/mL) .

While the 24-hour urinary phosphate excretion measured in 2018 and 2019 was low, tubular phosphate reabsorption was found to be high (Table 1).

Serum metanephrine and normetanephrine and basal cortisol levels and aldosterone/renin ratio were in normal range. His adrenal mass was classified as a non-functioning incidentaloma. Celiac tests (tissue transglutaminase IgA, IgG, anti-endomysial antibodies IgA and IgG) were negative. A L1-L4 T-score of -2.3 (consistent with osteopenia) was found on a DXA scan obtained while he was receiving alendronate therapy, which was initiated by an external center. The patient was started on treatment with oral phosphate, calcium and 25-OH vit D3. Bisphosphonate therapy was discontinued and the patient was asked to return for follow--up every month. His symptoms started to

improve with this treatment. At 6 months after starting treatment, he had virtually no complaints with improvement of clinical symptoms and he was able to walk without help. However, his phosphate levels did not exhibit a significant improvement. At 12 months of treatment, 25-OH vitamin D3 was stopped and calcitriol was started on 30.03.2016 due to persistently low phosphate levels despite oral phosphate and 25-OH vitamin D3 treatment. In 2019, the patient presented to the orthopedics clinic for an ulcer on his right toe. An MRI scan showed an iso-hyperintense well-defined lesion area (approximately 2.5x4 cm in size) on the T2A sequence at the sole of the right foot, located under the first metatarsal bone (Figures a, b, c).

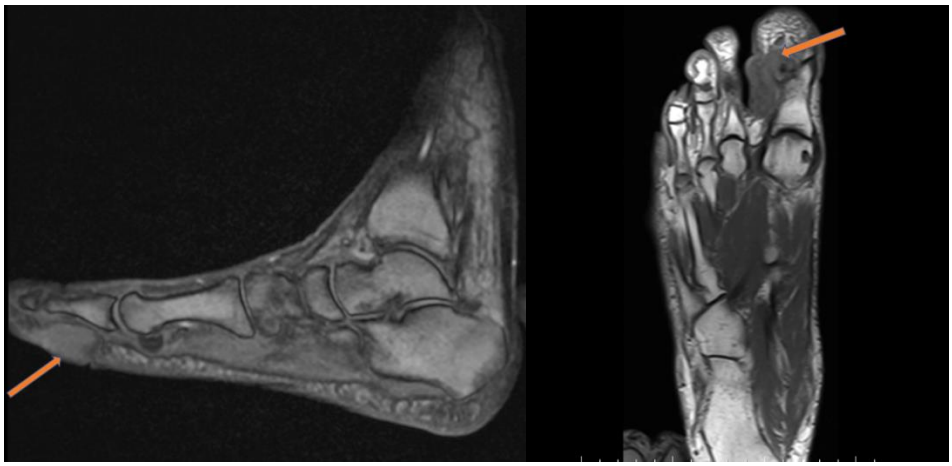

Figure 1a **Figure 1b**

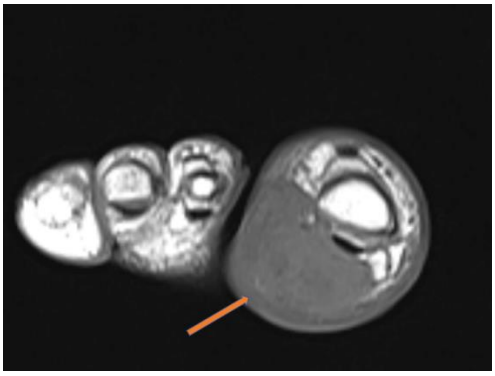

Figure 1c

An iso-hyperintense well-defined lesion on MRI T2A sequence at the sole of the right foot, located under the first metatarsal bone area (approximately 2.5x4 cm in size).

Table 1. Follow-up laboratory investigations for Ca and P metabolism

Parameter Reference range	Ca (mg/dL)* (8.5-10.5 mg/dL)	P (mg/dL) (2.5-4.5mg/dl)	25-OH-Vit D3 (ng/L) (20-50 ng/mL)	PTH (pg/mL) (15-65 pg/mL)	24-h urinary Ca (mg/day) (100-320 mg/day)	24-h urinary P (g/day) (0.4-1.30 g/day)	Tubular P reabsorption (%) (% 82-95)
23.06.2015	6.6	2.8	56.1	113	198	0.71	
01.06.2016	7.3	2.4	3.7	70			
14.02.2017	8.2	2.1	27.5		164		
01.11.2018	9	2	34.6	92.6		2.54	% 17
31.10.2019	8.6	2.15	45.5	114	242	2.23	% 26.5
28.11.2019		Tumor resection					
19.08.2020	8.9	3.05	34				
22.01.2021	9	2.6				1.11	% 82.5
06.09.2021	9.3	2.67		67			

*Abbreviations: *Ca: Serum calcium levels adjusted for serum albumin levels, P: Serum phosphate levels, PTH: Serum intact parathormone, 24-h urinary Ca: 24-hour urinary calcium excretion, 24-h urinary P: 24-hour urinary phosphate excretion, tubular P reabsorption: Renal tubular phosphate reabsorption.*

On 26.11.2019, PET scans showed increased FDG uptake (max. SUV: 3.8) in a soft tissue lesion adjacent to the proximal phalangeal and metotarsophalangeal joint of the right first toe, FDG-negative lesions in the liver and a FDG-positive (max. SUV: 5.3) lesion in the right adrenal gland. Preliminary diagnoses of acral metastasis and osteomyelitis were considered by the orthopedists. This lesion in the right toe which also showed activity on 2014 bone scans was not excised because it was evaluated as metastasis. However, the patient was operated on 28.11.2019 with the decision of the hospital council since osteomyelitis and GIST tumor metastasis were deemed unlikely based on his laboratory and clinical findings and the mass lesion located in his right toe was excised. Pathological examination revealed extraskeletal myxoid carcinoma with a tumor size of 3x1.7x4 cm.

A postoperative whole body bone scan showed increased osteoblastic activity in the cranium, which was focal and most prominent in the left occipital region as well as focal, moderately increased activity in the superolateral segment of the left orbit and slightly increased, diffuse osteoblastic activity in the upper neighborhood of the right orbit, slightly increased osteoblastic activity in all costae, increased osteoblastic activity in the sacroiliac joint bilaterally, increased osteoblastic activity in the thoracic (T)11, L1 and L3 vertebrae, increased osteoblastic activity in the lateral portion of the right scapular spine, inferior segment of the left humeral head, superior segment of the left trochanter minor and right femoral neck, slight-to-moderate increase in osteoblastic activity in the maxillary region, and moderately increased osteoblastic activity in the lateral segment of the anterior tubercle of the right tibia. These findings were evaluated by the radiologist as bone metastases of the primary disease most probably and changes secondary to oncogenic osteomalacia were considered less likely (Figures-2a and 2b).

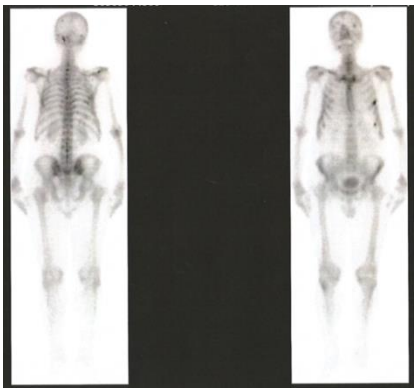

Figure 2a

Increased osteoblastic activity in the T11, L1 and L3 vertebrae; lateral portion of the right scapular bone; inferior segment of the left humeral head; superior segment of the left trochanter minor and right femoral neck; slight-to-moderate increase in osteoblastic activity in the maxillary region and moderately increased osteoblastic activity in the lateral segment of the anterior tubercle of the right tibia.

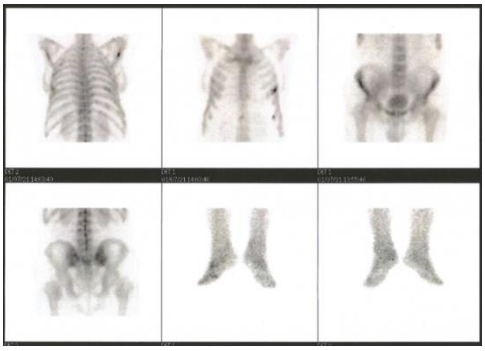

Figure 2b

Multiple foci of increased osteoblastic activity uptake: in the left frontoorbital, occipital and parietal bones in the skull; medial segment of the right clavicle; on both hemithorax ribs; left lateral part of the sacrum; in the tarsal bones of the right foot and the first metatarsophalangeal joints.

During postoperative follow-up, oral phosphate therapy was discontinued since the patient's serum phosphate level was increased up to 3.9 mg/dL two months after the surgery. Treatment with oral calcium and calcitriol was stopped due to elevation of calcium level up to 10.2 mg/dL eight months after the operation. Currently, the patient is followed routinely free of medication and his calcium and phosphate levels are normal.

3. Discussion

At the time of our patient's first presentation to our clinic with severe signs of osteomalacia, he had a history of two primary tumors including a differentiated thyroid tumor and a GIST. Assuming the risk of bone metastasis was very low due to the fact that thyroid CA was a stage 1 tumor with low risk, the appearances in the bone were considered to be consistent with bone metastasis of GIST. Initially, TIO was considered in this patient since he had clinical manifestations of new-onset hypophosphatemia and osteomalacia without prior history and clinical symptoms thereof. TIO associated with thyroid CA and GIST has not been previously reported in the literature. However, the patient was kept under observation due to the presence of these two tumors and failure to locate any other tumor keeping in mind the clinical suspicion of another possible tumor.

Elevated FGF-23 is detected in XLH, ADHR, ARHR, McCune-Albright Syndrome, Epidermal Nevus Syndrome and Type 1 Neurofibromatosis Syndrome, all associated with hypophosphatemia. All of these conditions are included in the differential diagnosis of TIO but further investigations for these disorders were not deemed necessary for two reasons: firstly, because of recent development of hypophosphatemia with no previous laboratory data indicating hypophosphatemia and secondly, other clinical components suggestive of McCune-Albright Syndrome, Epidermal Nevus Syndrome and Type 1 Neurofibromatosis Syndrome were absent. Ultimately, improvement of his signs and symptoms and laboratory tests following tumor excision led us to exclude these hereditary conditions in the differential diagnosis.

Fanconi syndrome is a condition that should be considered in the differential diagnosis of TIO because it can cause chronic phosphaturia. Isolated hypophosphatemia is uncommon and other electrolytes are also lost in Fanconi syndrome. This diagnosis was ruled out due to the absence of phosphaturia and other electrolyte disturbances in our patient.

FGF-23 testing is unavailable in our hospital. As a matter of fact, TIO was considered right from the start in our patient but no tumor focus could be identified which could then be removed. Since FGF-23 testing would not help tumor localization except for confirming the diagnosis of TIO and would provide no additional benefit for the follow-up of the patient, no attempt has been made to send for FGF-23 testing at an external center.

At the initial presentation, our patient had intolerable bone pain and was unable to walk without assistance. Shortly after starting conventional osteomalacia treatment (oral phosphate and calcitriol), his clinical symptoms improved dramatically but his phosphate levels did not improve completely and persisted around 2 mg/dL.

Our patient has been started on oral bisphosphonate (alendronate) treatment before presenting to our clinic. It was thought that this treatment was prescribed because of osteoporosis detected on DXA (dual-energy X-ray absorptiometry) scan. Bisphosphonates are the first-line agents for the treatment of male osteoporosis and among them, alendronate is the most commonly used bisphosphonate14. At our hospital, osteopenia was detected on DXA scan. Bisphosphonates are frequently used for bone pain associated with metastatic tumors. However, parenteral bisphosphonates such as pamidronate and zoledronate are mostly used for this indication15,16. Bisphosphonates can also be used to reduce bone pain from metastatic GIST but zoledronic acid is the recommended bisphosphonate for this condition16,17.

Bisphosphonate therapy has no place in the treatment osteomalacia. Upon the diagnosis of TIO, no progression of bone loss was detected during follow-up bone densitometry after discontinuation of alendronate therapy and initiation of conventional osteolamacia.

A new treatment option for TIO is burosumab, an anti-FGF-23 monoclonal antibody, which has been to be used as monotherapy in this indication. As of June 2020, burosumab has been approved by the US Food and Drug Administration (FDA) for use in patients diagnosed with TIO induced by curatively unresectable tumors18. Burosumab is not associated with potential side effects that occur with oral phosphate and calcitriol use which were previously first-line treatment10,19. Since burosumab is a newly approved agent with no sufficient experience in this indication and it is currently not readily accessible, we still need to follow traditional treatment methods for the management of TIO.

When a non-healing ulcer newly developed on our patient's foot, the mass in that area was excised and identified as extraskeletal myxoid chondrosarcoma. As in our patient, tumors causing TIO are usually of mesenchymal origin and almost all of them are benign, slowly growing tumors with an indolent course1,2.

In this patient, the cause of hypophosphatemia was identified as TIO that developed as a result of a third primary tumor. He also had two other primary tumors which were not demonstrated to be associated with TIO. After removal of the last detected tumor, his clinical symptoms improved which was reflected by an improvement in quality of life, as observed by reduced bone pain and walking without help. At the same time, he no longer needed to continue treatment with oral phosphate and calcitriol he has been receiving, further improving his quality of life. This highlights the importance of investigating a newly developed tumor focus even when there are two primary tumors at hand. Our patient has become able to live his remaining years more comfortably.

This case underscores the challenging and often difficult diagnosis of TIO. In our opinion, the take home message from this case is that in a patient with TIO, another primary tumor focus tumor should be carefully investigated in the presence of a primary tumor that is not the associated with TIO.

Note

This case was presented as a poster (Poster No: 27) by Hünkar AĞGÜL, MD at the Postgraduate Training Course (Endokurs-5) held in Antalya/Turkey between November 10 and 14, 2021.

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Written informed consent was obtained from the patient for the use of his medical data, laboratory tests and imaging details to publish his case anonymously. We thank him for his contribution

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Derleme / Review

Cilt Mikrobiyotası ve Yara Tedavisine Etkisi

Skin Microbiota and Effect on Wound Treament

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Özet

Mikrobiyota, günümüzde insan vücudunda yaşamsal fonksiyonların hemen hemen tamamında etkisi olduğu düşünülen mikroorganizma topluluğudur. Vücutta bağırsak mikrobiyotası gerek sayısal olarak gerek ise çeşitlilik açısından mikroorganizmaların en yoğun bulunduğu bölgedir. Bu nedenle de çalışmaların büyük bir bölümü bağırsak mikrobiyotası üzerine yapılmıştır. Cilt mikrobiyotası da tıpkı bağırsak gibi dış çevreden direkt olarak etkilenmektedir. Derinin fiziksel bariyer fonksiyonunda ve deri immunitesinde önemli bir rol oynamaktadır. Mikrobiyotada çeşitli faktörlerin etkisiyle olan değişim disbiyozis olarak adlandırılmakta ve bazı hastalıklarla ilişkisi olduğu düşünülmektedir. Kronik yara, normal iyileşme fazları ve süresinde iyileşmeyen ve tedaviye yanıtı kötü olan yaradır. Kronik yaralar sisteme ciddi bir yük oluşturmakta, morbidite ve mortaliteyi arttırmaktadır. Yara tedavisi sağlık bakımının bir parçasıdır ve hasta, yakınları, hekim, sağlık çalışanları ve sağlık sistemini maddi ve manevi zorlamaktadır. Kronik yaraların etkin tedavisine yönelik arayışlar devam etmektedir. Tedavide yaranın kronikleşmesinin önüne geçilmesi için iyileşmeyi hızlandıracak ve komplikasyonsuz kapanmasına faydası olabilecek yöntemler kullanılmaktadır. Çok sayıda çalışmada disbiyozisin düzeltilmesini hedefleyen tedavilerin iyileştirici rolü tartışılmaktadır. Bu tartışmalar kronik yara tedavisiyle de ilişkili olarak sürmektedir. Bu derlemede cilt miktobiyotası, yara iyileşmesindeki fonksiyonu ve kronik yara tedavisindeki rolü güncel literatür ışığında değerlendirilmiştir.
Anahtar Kelimeler: Yara iyileşmesi, Mikrobiyota, Cilt Mikrobiyotası, Bağırsak Mikrobiyotası

Abstract

Today, microbiota is a community of microorganisms that are thought to have an effect on almost all vital functions in the human body. In the body, the intestinal microbiota is the region where microorganisms are most concentrated in terms of both amount and diversity. For this reason, most of the studies have been conducted on the intestinal microbiota. The skin microbiota is directly affected by the external environment as much as the gut, and plays an important role in the physical barrier function of the skin and skin immunity. The change in the microbiota due to various factors is called dysbiosis, and is thought to be associated with some diseases. A chronic wound has a poor response to treatment, as a result of which the healing process takes longer than expected, and the recovery is not always a success. Chronic wounds are a serious burden on the health system, and increase morbidity and mortality. Wound treatment is a part of healthcare, and it encumbers the patient and their next of kin as much as physicians, health workers and the health system both financially and emotionally. Research on effective treatment of chronic wounds has been continuing. In this treatment, various methods are used to accelerate the healing process and to promote the closure of the wound without intractability so that the chronicity of the wound can be prevented. Many studies discuss the curative role of treatments aimed at correcting dysbiosis. The applicability of the same treatment in relation to chronic wound is still a matter for debate. In this review, the skin microbiota, its function in wound healing and its role in chronic wound treatment have been evaluated in the light of current literature.
Keywords: Wound healing, Microbiota, Skin Microbiota, Gut Microbiota

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1. Cilt Mikrobiyotası ve İşlevleri

Mikrobiyota, insan vücudunda yer alan mikroorganizma popülasyonun tümüne verilen genel isimdir. Mikrobiyom ise, bu mikrobiyotanın genetik materyalini ve bulunduğu ekosistemi de dahil eden bir terimdir (1). Tüm bu ekosistem bir denge halinde yaşamaktadır. Mikrobiyota içeriği, insanın yaşamda varlığını sürdürmeye başladığı anne karnındaki ilk günden son güne kadar dinamik olarak değişir ve bu değişkenliği doğum şekli, genetik, beslenme, yaşam tarzı, çevre, stres, alışkanlıklar, hayvan teması başta olmak üzere çok sayıda etken tarafından belirlenmektedir (2, 3). Vücudun her bölgesinde mikrobiyota kompozisyonu, ayrı sayı ve içerikte mikroorganizma ve sayıca insan hücrelerinin yaklaşık 1.3 katıdır. (4). Bu mikroorganizmaların konakçıya yararlı ve zararlı potansiyel etkileri sağlık için olumlu ve olumsuz etkilere neden olabilmektedir.

Cilt, insan vücudunun en büyük organı olarak kabul edilmektedir ve en önemli fonksiyonu fiziksel ve kimyasal bariyer özelliği ile kişinin dış etkenlerden korunmasının sağlanmasıdır. İnsan vücudunda hem bireysel hem de anatomik farklı bölgelerde cilt mikrobiyotası farklı sayı ve çeşitlilikte mikroorganizma içermektedir. Deride yaklaşık cm2 başına 1 milyonun üzerinde bakteri bulunmaktadır. Bunun yanında daha az sayıda olmakla birlikte mantar ve parazitler de bulunabilmektedir. Cilt mikrobiyotasının %90 kadarını *Actinobacteria, Firmicutes, Proteobacteria* ve *Bacteriodes* oluşturmaktadır. Deride en çok bulunan ve kültürde en çok üreyen tür Firmicutes filumundan *Staphylococcus epidermidis*'tir. Cilt mikrobiyotasın de en sık olan mantar cinsi *Malassezia*. olup *Cryptococcus* ve *Candida* en baskın diğer mantarlardır. Cilt hastalıklarında, bakteri ve mantar kompozisyonunda değişimler olabildiği gösterilmiştir. Her bir mikroorganizmanın ayrı işlevi vardır ve cilt pH dengesi, cildin hidrasyonu, cidin nem dengesi ile mikrobiyota kompozisyonu arasında ilişki bulunmaktadır ve cilt-immün sistemn arasında da bir ilişki olduğu gösterilmiştir. (5).

Cilt mikrobiyotası kompozisyonunu içerik ve sayısal olarak etkileyen konak ile ilgili olan ve çevresel faktörler bulunmaktadır. Yaş ve yaşlanma, cinsiyet, genetik, altta yatan hastalık öyküsü konak ile ilgili faktörlerdir (5). Cilt mikrobiyoytasında bireysel farklılıklar 'parmak izi' tanımı kullanılacak kadar özgün olabilmektedir. Yaşam alanı, meslek, yaşam tarzı, alışkanlıklar, ilaçlar, kozmetik ürünler de başlıca dışsal etkenlerdir. Bunun yanında vücudun farklı bölgelerinde derinin nem, kıl dağılımı ve yüzey özelliklerine göre mikrobiyota kompozisyonu değişmektedir (6). Mikrobiyota, keratinositler başta olmak üzere ilişkili diğer hücreleri de etkileyerek hücresel immun cevap ve sitokin yanıtında rol oynar. Mikrobiyota kompozisyonu direkt olarak antimikrobiyal peptit ve bakteriosin salgılayarak patojen mikroorganizmaların kolonizasyonunu da önler. Özellikle *S. epidermidis'in S. aureus* gibi patojenlerin kolonizasyonunu önlediği bilinmektedir (7). Diğer taraftan cilt mikrobiyotası regülatör T hücreleri aracılı proinflamatuar immün cevaba da katkı sağlar (5). Derideki kıl folikülleri, sebase bezler ve ter bezlerinin kendi mikroçevrelerine özgü mikrobiyotaları ile lokal ve sistemik immunite üzerine etki gösterdiği debildirilmiştir (8).

Mikrobiyota dengesinin konakçıya ait ve/veya çevresel faktörler bağlı bozulması disbiyozis olarak tanımlanmaktadır. Disbiyozis bir çok hastalıkta (inflamatur bağırsak hastalıkları, otizm spektrum bozuklukları, otoimmun hastalıklar, obezite, kanser ve metabolik sendrom) olarak tanımlanmış olup, henüz neden sonuç ilişkisi aydınlatılamamıştır. sayılabilir. Cilt mikrobiyotasında disbiyozis ile ilişkili olarak tanımalan hastalıklar ise seboreik dermatit, akne, psöriazis, atopik dermatit, yara ve yara enfeksiyonlarıdır(9). Bu hastalıkların oluşmasında mikroorganizma çeşitliliğinin değişmesi, bazı yerleşik mikroorganizmaların baskın hale gelmesi ve hatta patojenlerle yer değiştirmesinin rolü olduğu düşünülmektedir. Diğer taraftan bağırsaktaki disbiyozis de bağırsak- beyin-deri aksı üzerinden sistemik etkide bulunur ve cilt hastalıklarının oluşumunda önemi büyüktür.

Yara İyileşmesinde Cilt Mikrobiyotasının Rolü

Kronik yaralar günümüzde ciddi bir halk sağlığı sorunu oluşturmaktadır. Kronik yaralar ile ilişkili mortalite hızı %20 ila %50 arasında değişmekte olup gerek mortalitesi gerek ise sağlık sistemindeki mali yükü önemini her geçen gün artmaktadır. Klinik pratikte en sık karşılaşılan kronik yaralar diyabetik ayak, bası ülserleri, venöz bacak ülserleri ve iyileşmeyen cerrahi yaralardır (10).

Yara iyileşmesi çoklu basamaklardan oluşur. Büyüme hormonu, sitokinler ve kemokinler ile yakın ilişki içindedir (11). Son dönemde gerek yerleşik cilt mikrobiyotasını oluşturan mikroorganizmaların gerek ise patolojik olanlarının yara iyileşme sürecine etkisi bilimin ilgi alanına girmiş ve yara tedavisine katkısı araştırılmaktadır. Cilt mikrobiyotasının yara iyileşme sürecini modüle etmede faydalı olduğu diğer yandan patojen mikroorganizmaların iyileşmeyi geciktirdiği ve normal süreci bozduğu düşünülmektedir (12). Kronik yarada mikrobiyotanın sağlıklı ciltten farklı olduğu, kalıcı mikroorganizmaların azaldığı patojenik mikroorganizmaların arttığı, özellikle yaranın tipine göre değişmekle birlikte anaerobik enfeksiyonların gelişmesinin iyileşmeyi bozduğu bilinmektedir. Cildin normal mikrobiyotası özellikle patojen bakterilerin invazyonunu önlemeye yönelik bakteriyosin salgılar. *S. epidermidis*'in salgıladığı sekretom, lipopeptit LP01, lipoteikoik asit ve IL-10'un aktivasyonuna neden olmaktadır. Bu da keratinositler tarafından AMP'nin (insan beta defensin, HBd-2, katelisidinler ve LL-37) salgılanmasını arttırmaktadır. Bu mekanizmalar Toll like reseptör (TLR)-2 sinyal yolunu aktive eder. Ve patojenik bakterilerin yok edilmesini ile yara iyileşmesinde önemli rol oynamaktadır. S. epidermidis, epidermal bariyeri güçlendirmek ve patojen invazyonunu sınırlandırmak için IL-17A veya IFN-y ile birlikte CD8 T hücrelerinin sıklığını arttırabilmektedir (13). Özellikle yara iyileşmesinde keratinositlerden salgılanan perforin-2 (P-2) anahtar role sahiptir. Kronik yaralarda *S. aureus* prevalansındaki artış, S. aureus'un P-2'yi baskılaması, yara bölgesinde bulunan invaziv patojenlerin kalıcılığını teşvik ederek sürecin kronikleşmesine neden olur. Tersine, yerleşik bakterilerin varlığı, bakteriyel yara enfeksiyonlarını önlemeye yönelik deriyi ve yara ortamını değiştirebilir (13).

Yara iyileşmesinde mikroorganizma davranışında biyofilm formasyonu da rol oynamaktadır. Biyofilm, yüzeylere tutunarak ekstra sellüler matriks içinde birlikte yaşayan mikroorganizma topluluğudur. Özellikle yarada gelişen biyofilmler, bir nevi yaranın yeni mikrobiyota yapılanmasını oluşturur. Çok farklı sayı ve yapıda, her yara için değişken içeriklere sahiptir (14). Özellikle mikroorganizmaların daha uzun yaşamasında ve anaerob mikroorganizmaların invazyonunda daha elverişli ortam sağlar, antimikrobiyal etkiye direnç ve tolerans gelişmesi, kültür üremelerinde azalma ve tedavi başarısızlığı ve kronikleşmeye sebep olur. Kronik yarada en etkin tedavi basamaklardan biri olan debridman, özellikle bu biyofilm tabakanın bozulmasını da hedeflemektedir. Debridman mikrobiyal yükü azaltabilir ve bu sayede de iyileşmeyi hızlandırabilir. Bu hipoteze dayalı farklı yara modelleriyle yapılan çalışmalarda debridman öncesi ve sonrasındaki yara örneklerinde mikrobiyal dizilimlerle ilgili olarak farklı sonuçlar göstermektedir (15). Bu da biyofilm ve disbiyozis süreçlerine sadece lokal debritmanın yetmeyeceğini, sistemik nedenlerin de etkili olduğunu ve yaradaki mikroorganizma yükünün ve çeşitliliğinin çok fazla faktörden etkilendiğini düşündürmektedir.

Deri Mikrobiyotasının Yara Tedavisinde Yeri Olabilir mi?

Yara iyileşmesi sürecine mikrobiyotanın etkisini değerlendiren çok sayıda girişim çalışması vardır. Özellikle deride yara dokusu üzerine topikal olarak ve/veya oral yoldan bağırsak mikrobiyotası üzerinden sistemik etkilerinden faydalanmak amaçlı kullanılan probiyotiklerin inflamatuar yanıtı modüle edici etkisi ve patojen kolonizasyonu sınırlayarak yara iyileşmesini düzelttiği farklı çalışmalarda gösterilmiştir (16).

Oral probiyotikler, bağırsak, beyin ve deri aksı üzerinden etki gösterir. Bağırsak mikrobiyotasının düzenlenmesi ciltte de

olumlu sonuçlara yol açar. Pek çok farklı kronik yara tipinde oral probiyotikler kullanılmıştır. Bunun yanında bazı spesifik cilt hastalıklarında da probiyotik çalışmaları mevcuttur. En iyi bilinen ve en çok araştırılan cilt hastalıklarından atopik dermatit etyopatogenezinde ve tedavisinde mikrobiyota çalışılmış ve mikrobiyotaya yönelik değişikliği hedefleyen klinik uygulamalarda, patojen mikroorganizmaların kolonizasyonunu azaltmak amaçlı yapılan girişimlerin yanında probiyotik uygulamaların faydaları gösterilmiştir. Atopik dermatit hastalarının dahil edildiği bir çalışmada oral olarak 12 haftalık çoklu suş içeren probiyotik kullanımı sonrası atopik dermatit skorlarının azaldığı gösterilmiştir. Topikal probiyotiklerin kullanımından sonra lokal inflamasyonun azaldığı, skorların düzeldiği gösterilmiştir (16). Yara iyileşmesini değerlendiren hayvan çalışmalarında topikal kullanılan *Lactobacillus brevis (L. brevis), L. plantarum, L. fermentum* yarada inflamasyonu azalttığı ve yara iyileşmesini hızlandırdığı bildirilmiştir (17). Yanık ve cerrahi alan yaralarının iyileşmesine yönelik kullanılan probiyotiklerin de yara iyileşmesini hızlandırdığı ve antibiyotiklerle birlikte kullanılmasını destekleyen çalışmalar da mevcuttur. Yanık tedavisinde kullanılan *L. plantarum* içeren topikal kremin *Pseudomonas aeruginosa* enfeksiyonlarını azalttığı, *L. plantarum*'un gümüş sülfadiazin kadar etkili olduğu, granülasyon dokusu ve yara iyileşmesini düzenlediği bildirilmiştir (18,19). Yine postoperatif cerrahi alan yaralarında oral ve topikal probiyotiklerin enfeksiyon gelişimi ve antibiyotik kullanım sürelerini azalttığı bildirilmiştir (20). Probiyotiklerin diyabetik ayak enfeksiyonlarında kullanımı ile ilgili çalışmalar da bulıunmaktadır. Redel ve ark. (21) diyabetik/nondiyabetik hastaların mikrobiyota kompozisyonlarını değerlendirdikleri bir çalışmada diyabetik hastaların plantar bölge mikroorganizma yapısının nondiyabetiklere göre farklı olduğu, *Acinetobacter* ve *S. aureus'*un belirgin yüksek seviyede olduğunu belirtmişler ve bu farklılığın diyabetik ayak enfeksiyonun gelişmesinde rol oynayabileceğini bildirmişlerdir (21). Bu amaçla planlanmış bir çalışmada evre 3 diyabetik ayak yarası ile takip edilen 60 hasta değerlendirilmiş, 12 haftanın sonunda oral probiyotik tedavisi alan grupta metabolik parametrelerin düzeldiği ve yara genişliğinde kontrol grubuna göre anlamlı küçülme görüldüğü bildirilmiştir (22). Bu da bizlere probiyotiklerin yarada inflamasyonu düzenleyici rollerinin yanında metabolik parametreleri de etkileyerek yara tedavisine katkı sunabileceğini düşündürmektedir.

Kronik yarada polimikrobiyal ortam içinde gelişen yeni yara mikrobiyotası, farklı türler arasındaki etkileşimlerin dinamik olduğu ve mikroorganizmaların davranışını değiştirdiği bir ortamdır. Bu durum artan virülans, direç ve gecikmiş yara iyileşmesi ile sonuçlanmaktadır. Yara mikrobiyotasını hedefleyen potansiyel tedavileri belirlemek için mikroorganizma-konak ve mikroorganizmalar arası etkileşimleri daha fazla araştırmak gerekmektedir.

Sonuç olarak; deride yara iyileşme sürecinin karmaşıklığı ve kendine has dinamikleri nedeniyle hem konakçıyı hem de mikrobiyomu hedefleyen kombinasyon tedavilerinin geliştirilmesi, iyileşmeyi artırmak ve yaralarda, deride ve yumuşak dokulardaki enfeksiyonları önlemek ve tedavi etmek için uygun olabilir. Literatürdeki olumlu sonuçlar ve mevcut mikrobiyota araştırmalarında önemli ilerlemeler kaydedilmesine rağmen, temkinli yaklaşmak ve mikrobiyotanın yara iyileşmesini nasıl etkilediğini ve tedavide kullanımını aydınlatabilmek için daha geniş ölçekli randomize kontrollü çalışmaların sonuçlarını çok yönlü değerlendirmek gerekmektedir.

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