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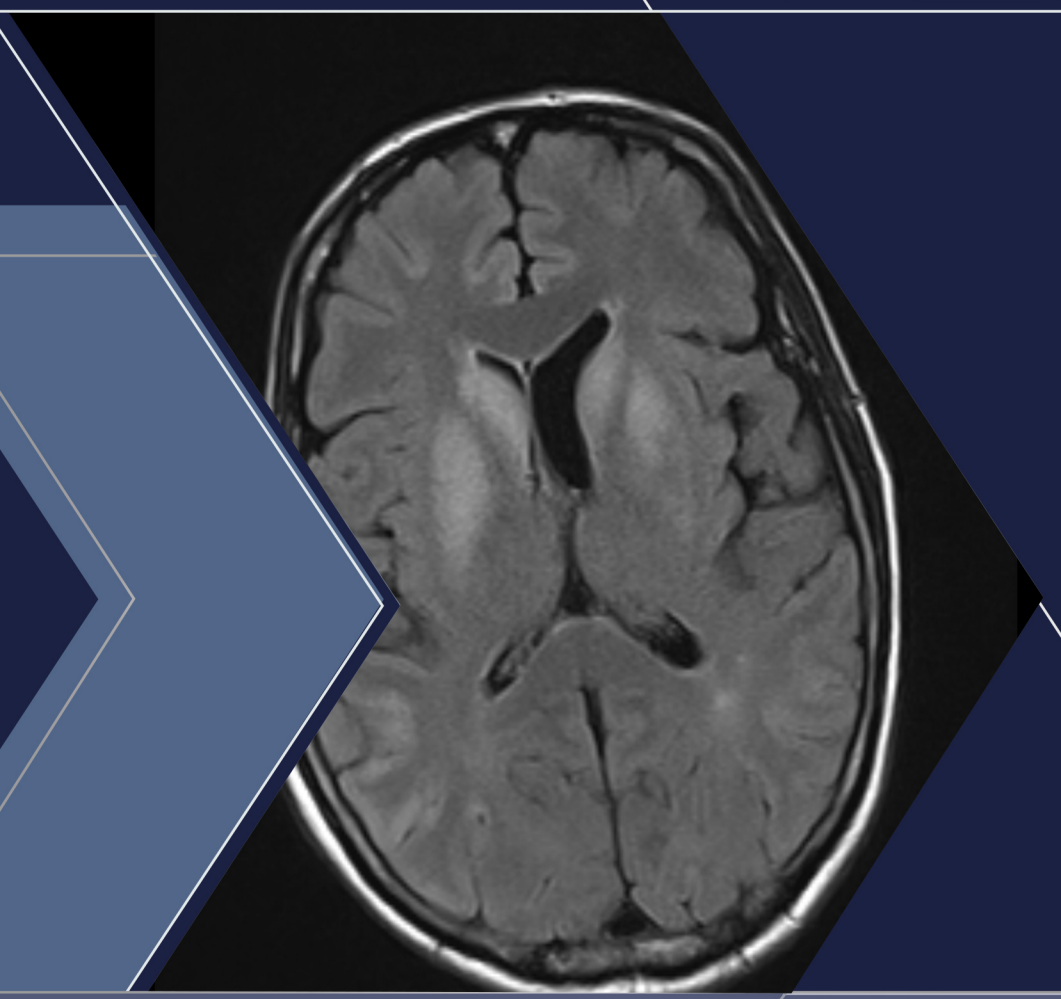

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İÇİNDEKİLER

Aksaray Üniversitesi Tıp Bilimleri Dergisi
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Araştırma Makalesi

Serotoninin Adipoz Doku Kökenli Mezenkimal Kök Hücrelerin Proliferasyonuna Etkisinin Wnt-β Sinyal Yolağı Üzerinden İncelenmesi

Investigation of the Effect of Serotonin on Proliferation of Adipose Tissue-Derived Mesenchymal Stem Cells via Wnt-β Signaling Pathway

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ÖZET

Amaç: Hücresel tedaviler açısından mezenkimal kök hücreler (MKH'ler), sahip oldukları özellikler nedeniyle en çok çalışılan hücrelerdir. Özellikle klinik çalışmalarda MKH'lerin devamlılığı önemlidir. Wnt sinyali, MKH'lerin çoğalması ve farklılaşmasının düzenlenmesinde hayati bir rol oynar.

Materyal ve Metot: Bu çalışmada adipoz doku kökenli MKH'lerin (AD-MKH'lerin) proliferatif özelliği üzerine Serotoninin (5-hydroxytryptophan [5-HT]) etkisinin Wnt-β sinyal yolağı üzerinden araştırılması amaçlanmıştır. Çalışmada AD-MKH'ler kullanıldı. İlk olarak, Serotoninin 1-100 µM arasında değişen konsantrasyonlarının AD-MKH'lere etkisi MTT testi ile analiz edildi. Hücreler üzerine apoptotik etkisi Annexin V/PI ve analizi ile belirlendi. WNT2, AXIN ve CTNNB1 genlerinin ekspresyon düzeyleri moleküler düzeyde qPCR ile analiz edildi.

Bulgular: MTT analizi sonucu 48. saatte 75 µM serotoninin proliferasyonu azalttığı gözlendi. 48 saatlik 75 µM serotonin uygulaması sonrası apoptotik hücre oranı %2.05'e çıkarken, erken apoptoz evresindeki hücre oranı %0.77 olarak tespit edildi. WNT2, AXIN ve CTNNB1 gen ekspresyonlarının kontrol grubu ile karşılaştırıldığında, WNT2 ve AXIN up-regüle olurken ($p<0.001$) CTNNB1 ekspresyonunun ise serotonin uygulanmış hücrelerde down-regüle olduğu belirlendi.

Sonuç: Sonuçlar serotoninin mezenkimal kök hücrelerin proliferatif etkisini Wnt sinyal yolağı üzerinden artırabildiğini göstermektedir. Ancak in vivo ve ileri moleküler düzeyde çalışmalarla desteklenmesi gerekmektedir.

Anahtar Kelimeler: Mezenkimal kök hücre, serotonin, Wnt-β sinyal yolağı.

ABSTRACT

Aim: Mesenchymal stem cells (MSCs) are the most studied cells due to their properties in terms of cellular therapies. In particular, the continuity of MSCs is essential in clinical studies. The Wnt signal plays a vital role in regulating the proliferation and differentiation of MSCs. In the present study, the effect of serotonin (5-hydroxytryptophan [5-HT]) on the proliferative properties of human adipose tissue-derived MSCs (hAT-MSCs) was investigated through the Wnt-β signaling pathway.

Materials and Methods: First, the effect of serotonin concentrations ranging from 1-100 µM on AD-MSCs were analyzed by MTT test. Annexin V/PI analysis was performed to determine the apoptotic effect on the cells. Finally, the expression levels of WNT2, AXIN, and CTNNB1 genes were analyzed at the molecular level by qPCR.

Results: The MTT analysis revealed that 75 µM serotonin reduced proliferation at 48 hours. After 48 hours of treatment with 75 µM serotonin, the apoptotic cell rate increased to 2.05%, while the early apoptotic cell rate was determined as 0.77%. Compared with the control group, WNT2 and AXIN gene expressions were up-regulated ($p<0.001$), while the CTNNB1 expression was down-regulated in the cells treated with serotonin.

Conclusion: The results show that serotonin can increase the proliferative effect of mesenchymal stem cells via the Wnt signaling pathway. However, further in vivo and advanced molecular studies are required to support these findings.

Keywords: Mesenchymal stem cell, serotonin, Wnt -β signaling pathway.

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INTRODUCTION

Mesenchymal Stem Cells (MSCs) are self-renewing and multipotent cells that can differentiate into various mesenchymal cell types such as chondrocytes, osteoblasts, adipocytes, myocytes, and neurons (1). Various molecular factors, including bone morphogenetic proteins, Wnt proteins, and severe transcription factors, are responsible for the sustainability and differentiation of MSCs (2). MSCs have been extensively studied for the past 30 years due to their exciting cell biology, broad clinical potential, and rapidly growing "central building block" in tissue engineering. In addition, MSCs have unique properties such as easy growth in a culture dish, internal differentiation potential not found in other cells, and abundant production of beneficial growth factors and cytokines (3).

Serotonin, or 5-hydroxytryptamine (5-HT), is a neurotransmitter and a hormone. Serotonin is made from an essential amino acid called tryptophan via the enzymes tryptophan hydroxylase and dopa decarboxylase (4). Serotonin acts on its receptors or small GTPases in target cells to exert its effects (5). Serotonin's physiological and pathological importance is well known in the central nervous, gastrointestinal, and cardiovascular systems. Additionally, studies have shown that serotonin is mitogenic in various standard and malignant cells, including fibroblasts, osteoblasts, and vascular endothelial cells (6, 7).

One study on the effects of serotonin on mesenchymal stem cells reported that fluoxetine, which is used as an antidepressant and a serotonin reuptake inhibitor (SSRI), affected the differentiation of mesenchymal stem cells to adipocytes and osteoblasts, and that each class of antidepressants had a varying effect on MSC differentiation (8). However, the number of studies on the proliferation or differentiation of mesenchymal stem cells for clinical use is limited. For this reason, we aimed to explore the effect of serotonin, which is known to have positive effects, on the proliferation of human adipose tissue-derived mesenchymal stem cells via the Wnt-β catenin signaling pathway. For this purpose, mesenchymal stem cells of adipose tissue origin were cultured. MTT analyzed their proliferation status, apoptosis status was analyzed by Annexin V\PI method, and Wnt-β catenin signaling pathway genes' expression was analyzed by qPCR after serotonin application.

MATERIALS AND METHODS

Cell culture

The study used hAT-MSCs (Sigma, SCC038), previously purchased commercially for another research and stored frozen. For the experiments, cells were cultured at 37°C and 5% CO^2 with a medium composed of DMEM (Gibco, 11966025), 10% fetal bovine serum FBS, (Gibco, 16000044), 0.2% Primocin (Invivogen, ant-pm-1) and 1% Glutamax (Gibco, 35050061). Cells were controlled daily and sub-cultured when the culture flask reached 70% confluency (approximately 2-3 days).

Cytotoxicity analysis

Serotonin was dissolved in 0.1% DMSO at concentrations ranging from 1 µM to 100 µM. Cells were seeded in a 96-well culture plate at $5x10^3$ cells per well in 200 µL of the medium. After cell attachment, 100 µL of the medium was removed and replaced with 100 µL of serotonin at the indicated concentrations. Cells were then incubated for 24 and 48 hours. At the end of the incubation periods, MTT solution was added to each well and further set for 3-4 hours. After removing the medium, 100 µL of DMSO was added, and the plate was kept in the dark for 15 minutes and measured at 540 nm absorbance using a microplate reader. Cell viability was calculated relative to the control group.

Annexin V/PI analysis

Cells were counted and seeded onto 6-well plates with $3x10^5$ cells per well in 2 ml of growth medium. After 24 hours of incubation, 1 ml of the medium was removed and replaced with 75 µM serotonin in 1 ml of fresh medium. Following incubation, cells were washed twice with 1x PBS and centrifuged for 5 minutes. After centrifugation, cells were resuspended in 100 µL of binding solution and pipetted. Next, cells were incubated in the dark with 5 µL of AnnexinV and 5µL of Propidium Iodide (PI). Subsequently, 400 µL of the binding solution was added and analyzed using a flow cytometer.

qPCR analysis

Total RNA extraction was performed from stem cells treated with serotonin (GeneAll® Hybrid-RTM, Seoul, Korea). The obtained RNAs were converted to complementary DNA (cDNA) using the cDNA synthesis kit (Atlas Biotechnology, Ankara, Turkey). For real-time PCR reaction, SYBR Green-containing master mix solution (RT² SYBR Green qPCR Mastermix, Qiagen, Hilden, Germany) and primers specific to WNT2, AXIN, CTNNB1, and GAPDH genes (Table 1) were used to analyze gene expression on Rotorgene Q5 plex+HRM Real-Time PCR device (Qiagen, Hilden, Germany). The evaluation was examined by the $2^{-\Delta\Delta Ct}$ method.

Table 1. Primer sequences used for qPCR analysis.

Gene Name	Primer sequence (Forward; Reverse)
GAPDH	CACCCTGTTGCTGTAGCCATATTC GACATCAAGAAGGTGGTGAAGCAG
WNT2	TTTGGCAGGGTCCTACTCC
AXIN	CCTGGTGATGGCAAATACAA
CTNNB1	ATGGAGCTCTCCGAGACAGA

Statistical Analysis

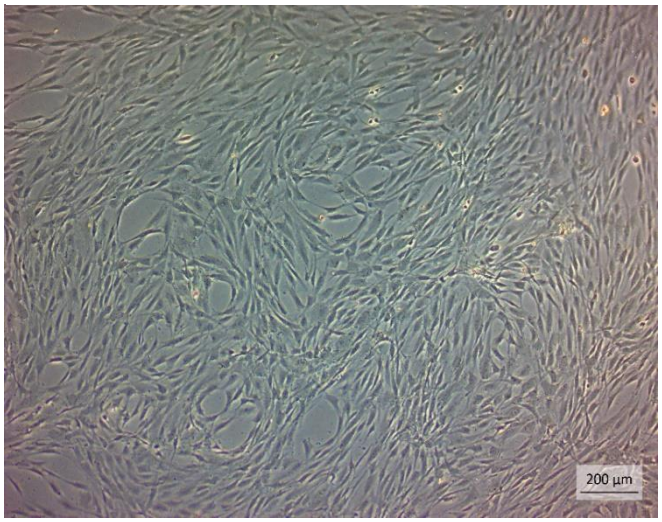
The obtained data were evaluated using one-way ANOVA with post-hoc Tukey HSD. The significance threshold values of $p<0.05$, $p<0.01$, and $p<0.001$ were used for differences between the study and control groups. All statistical analyses were performed using GraphPad Prism 7.0 software.

RESULTS

Cell Culture

During the daily examinations of cells with phase-contrast microscopy, it was observed that the cells had star-shaped or spindle fibroblast-like morphology (Figure 1).The cells were monitored daily under a microscope until the required number for the study was reached, and every three days, the culture medium was changed. When they reached 70-80% confluence, they were removed with trypsin-EDTA and passaged by dividing them into new culture dishes at a ratio of 1/3.

Figure 1. Phase-contrast microscope images of adipose tissue-derived mesenchymal stem cells adhered to the culture dish on the 3rd day after being placed into culture. The mesenchymal stem cells of adipose tissue origin were observed to have a spindle or star-shaped fibroblast-like morphology (Scale bar=200 µm).



MTT cytotoxicity analysis

Cellular cytotoxic effects of serotonin concentrations were determined at 24 and 48 hours using MTT analysis. No significant changes were observed in cell viability in the group treated with 1µM serotonin compared to the control group. However, partial reduction in cell viability was observed at 48 hours in groups treated with 75µM serotonin (Figure 2).

Annexin/PI analysis

It was observed that 1.66% of the control group cells were apoptotic, and 0.98% were in the early apoptotic stage at 48 hours. After 75 µM serotonin application for 48 hours, the rate of apoptotic cells increased to 2.05%, while the rate of cells in the early apoptotic stage was determined as 0.77%. With the application of 100 µM serotonin at 48 hours, the rate of apoptotic cells increased to 3.35%, and the rate of cells in the early apoptotic stage increased to 1.43% (Figure 3).

Figure 2. MTT analysis. % Viability values of serotonin concentrations calculated by the

MTT method at the 24th and 48th hours (ns means non-significant).and result.

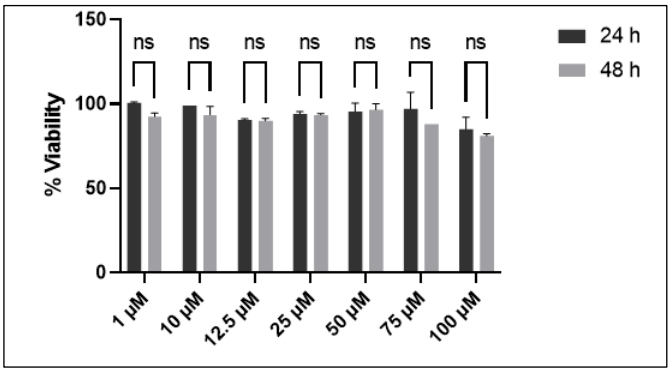
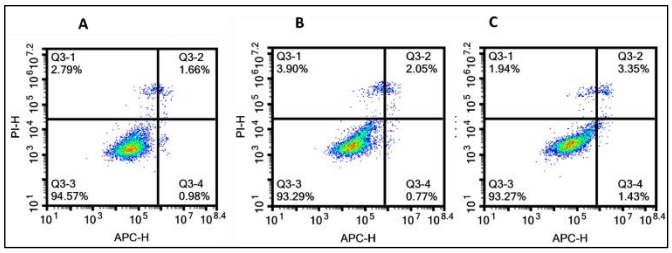


Figure 3. Annexin V/PI results of the Serotonin-treated cells. A: Untreated cells, B: 75 µM of Serotonin-treated cells, C: 100 µM of Serotonin-treated cells (Q1=Necrosis, Q2=Late apoptosis, Q3=Viability, Q4=Early apoptosis).



Results of gene expression analysis

In qPCR analysis, while WNT2 and AXIN gene expressions were up-regulated ($p<0.001$) compared to the control group, it was determined that the expression of CTNNB1 was down-regulated in cells treated with serotonin (Figure 4) (Table 2).

Figure 4. Expression profile of WNT2, AXIN, and CTNNB1 genes in mesenchymal stem cells of adipose tissue origin. Compared to the control group, it was determined that WNT2 and AXIN were up-regulated, while the expression of CTNNB1 was down-regulated (n = 3, mean ± SD, *** $p<0.001$) (Experiment was repeated three times) (ns means non-significant).

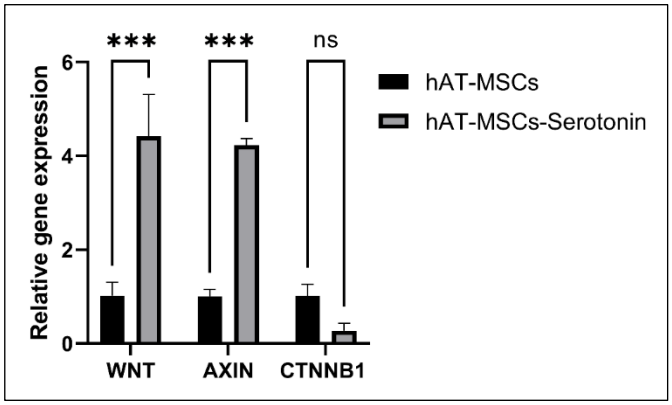


Table 2. Relative gene expression results.

Relative gene expression/cell	hAT-MSCs		hAT-MSCs-Serotonin	
	mean	sd	mean	sd
WNT	1,02	0,28	4,42***	0,89
AXIN	1,00	0,14	4,22***	0,14
CTNNB1	1,01	0,24	0,27	0,15

DISCUSSION

Subsequent studies have shown that MSCs exist in alternative tissue sources, have an adhesive, fibroblast-like population, and can differentiate into different cell types (9,10). Due to their properties and ease of isolation, they are the most preferred cell source for gene therapy and tissue engineering applications. In addition, the number of clinical studies is increasing day by day. However, the regulatory mechanisms of self-renewing and differentiation of MSCs at the molecular level, overcoming replicative senescence, and inducing desired differentiation are still significant problems awaiting solutions in the clinic (11). Therefore, our study, conducted with adipose tissue-derived MSCs that have a crucial place in cell physiology and clinical studies, will conduce to the literature in this area.

Various studies have shown the importance of Wnt signaling in the fate decisions of MSCs. Additionally, the effects of Wnt signaling are contextual (12). The functional variation of Wnt proteins depends on the specific surface receptor they interact with and the subsequent cellular signaling pathway that is activated (13). However, it is still unclear which cell types produce Wnt proteins. β-catenin is the main component of the canonical Wnt signaling pathway; in the absence of Wnt, β-catenin associates with APC (adenomatous polyposis coli) and Axin, facilitating its phosphorylation by casein kinase Iα (CKIα) and glycogen synthase kinase 3β (GSK3β), and subsequent degradation by ubiquitin/proteasome via β-TrCP (14). Therefore, we investigated the expression levels of Wnt signaling pathway genes that play an essential role in the proliferation and differentiation decisions of MSCs.

Due to the positive results in studies using hematopoietic stem cells, we conducted research on our hypothesis that serotonin, which has never been studied before, may increase the proliferation of adipose tissue-derived hematopoietic stem cells. Serotonin has been suggested to mediate the bidirectional interactions between the nervous and immune systems. It has significant activities on inflammation and immunity by affecting the actions of almost all mature blood cell types. Serotonin is an immune signal between dendritic cells and T cells and increases the ex vivo expansion of CD34+ hematopoietic stem and progenitor cells. Platelets release 5-HT in response to signals, including damaged endothelium or ischemia (16). Since most (> 90%) of the serotonin in the blood is stored in the dense granules of platelets, serotonin in the hematopoietic system is closely related to platelets and megakaryocytes. It is known that serotonin stimulates megakaryopoiesis through 5-HT2 receptors (16, 17). Most studies on serotonin are associated with Serotonin reuptake inhibitors (SSRI), the most common class of drugs for depression. The pharmacological mechanism of these drugs is related to blocking the 5-HT (serotonin) transporter, which leads to the inhibition of 5-HT reuptake and increases synaptic 5-HT levels (18). However, there are limited studies on the effect of serotonin on mesenchymal stem cell proliferation. In the present study, there is no significant decrease in the viability of AT-MSCs after applying various serotonin concentrations. After using 75 μM and 100 μM serotonin doses that partially decreased viability, the expressions of WNT2 and AXIN genes, which activate the Wnt signaling pathway, were up-regulated ($p<0.001$). In contrast, the expression of CTNNB1 was down-regulated. We believe the reason for the increased expression of WNT2 and AXIN genes is that the Wnt signaling pathway associated with proliferation induced by serotonin in AT-MSCs may be practical. The decrease in CTNNB1 expression may be due to the activation of the non-canonical pathway of this pathway.

CONCLUSION

Conclusions

The evaluation of the Wnt signal by the cell can vary depending on the microenvironment in which the stem cell is located and the influence of other signals provided by the microenvironment. Therefore, future studies should address the microenvironment of MSCs along with serotonin and the involvement of different signaling pathways.

Conflict of interest statement

The authors declared no conflict of interest

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Araştırma Makalesi

Ön Çapraz Bağ Ameliyatı Olan Futbolcularda Genetik Sakatlık Duyarlılığında COL12A1 Gen Polimorfizmi Profillerinin Araştırılması

Investigation of COL12A1 Gene Polymorphism Profile in Genetic Injury Susceptibility in Football Players Having Anterior Cruciate Ligament Surgery

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ÖZET

Amaç: Futbolda tekrarlayan travmalar, aşırı yüklenmeler, dönme, kayma hareketleri, kas zayıflıkları, aşırı antrenman yoğunluğu ve süresi, hatalı antrenman gibi risk faktörleri sporcularda adeta ön çapraz bağ yaralanmalarına davetiye çıkarır. Bu bağlamda futbolcuların performanslarını artırmak ve sakatlıklardan kaçınmak için gen profillerinin belirlenmesinin hem performans hem de sporcu sağlığı açısından sahaya ciddi katkı sağlayacağı düşünülmektedir. Moleküler mekanizmaların etiyolojisi tam olarak anlaşılamamış olsa da genetik faktörler, MMP'ler gibi onarım sürecinde yer alan genler veya apoptoz sürecinin bileşenleri dahil olmak üzere birçok risk faktörü ön çapraz bağ yırtıkları ile ilişkilidir. Bu çalışmada çapraz bağ cerrahisi geçiren futbolcularda COL12A1 gen polimorfizminin ön çapraz bağ yaralanması ile ilişkisi araştırıldı.

Materyal ve Metot: Ön çapraz bağ ameliyatı olan (ÖÇB) olan 41 hasta ve yaş-cinsiyet uyumlu 65 sağlıklı birey COL12A1 A/G polimorfizmi açısından araştırıldı. COL12A1 A/G'nin genotiplemesi, PCR-RFLP kullanılarak belirlendi. Verilerin istatistiksel analizi Epi ve Arlequin yazılım programı ile yapıldı. $p < 0,05$ değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışma bulgularımız, hasta ve kontrol grupları arasında COL12A1 polimorfizminin allel sıklığı ve genotip dağılımı açısından anlamlı bir fark olmadığını gösterdi ($p=0,880$).

Sonuç: Bu çalışmanın bulguları COL12A1 (rs970547)'in Türk toplumunda ön çapraz bağ yaralanmalarına yatkınlıkla ilişkili olmadığını ortaya koydu.

Anahtar Kelimeler: Futbolcu; kollajen; ön çapraz bağ yaralanmaları; PCR; RFLP.

ABSTRACT

Aim: Risk factors such as repetitive traumas, overloads, turning, sliding movements, muscle weakness, excessive training intensity and duration, and faulty training in football invite anterior cruciate ligament injuries in athletes. In this context, it is thought that determining the gene profiles of football players to increase their performance and avoid injuries will make a serious contribution to the field in terms of both performance and athlete health. Although the etiology of the molecular mechanisms is not fully understood, many risk factors are associated with anterior cruciate ligament tears, including genetic factors, genes involved in the repair process such as MMPs, or components of the apoptosis pathway. In this study, the relationship between COL12A1 gene polymorphism and anterior cruciate ligament injury in football players who underwent cruciate ligament surgery was investigated.

Materials and Methods: 41 patients who had Anterior cruciate ligament (ACL) surgery and 65 age-sex-matched healthy individuals were investigated for COL12A1 A/G polymorphism. Genotyping of COL12A1 A/G was determined using PCR-RFLP. Statistical analysis of the data was done with Epi Information Software and Arlequin Software. A value of $p < 0.05$ was considered statistically significant.

Results: Our study findings showed that there was no significant difference between the patient and control groups in terms of allele frequency and genotype distribution of the COL12A1 polymorphism ($p=0.880$).

Conclusion: The findings of this study suggested that COL12A1 (rs970547) was not associated with susceptibility to anterior cruciate ligament injuries in the Turkish population.

Keywords: Anterior cruciate ligament injuries; collagen; footballer; PCR; RFLP.

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INTRODUCTION

Football is the most popular sport in the world today. Football, which is a complex contact sport, is played more aggressively and faster than other branches (1). Depending on the fast game flow, the players must have high endurance in order to perform the movements such as repetitive sprinting, jumping, stealing, hitting the ball and changing direction (2). The risk of injury to the players during football matches is also high due to the physiological demands required during the performance of these movements, body contact and physical interaction during bilateral struggles (3). As a result of the studies, it is stated that the risk of injury in football is higher than in other sports branches (4, 5). When the studies on injuries in football were examined, the types of injuries, the regions where the injuries occurred, and the severity of the injuries were evaluated (6, 7). The effect of individual factors on the occurrence of injury was also examined separately (8, 9). In a study conducted on Turkish national team football players, it was stated that injuries mostly occur in the lower extremities, especially in the thighbone and knees (10). It is also supported by various studies that knee injuries are very common in football (5, 11).

It can be said that one of the most important injuries that make it difficult for football players to return to the field and prevent them from playing football for a long time is anterior cruciate ligament injuries (12). The anterior cruciate ligament (ACL), which plays a role in the stabilization of the knee joint, is the connective tissue originating from the intercondylar region (anteromedial surface) and connecting to the lateral condyle of the thigh bone, and consists of two components: anteromedial and posterolateral bundles (13-15). Anterior cruciate ligament injuries, which frequently require reconstruction, are among the most common knee ligament injuries and are also the most common soft connective tissue injury in the knee (12). Damage typically occurs during activities that involve stopping rapidly, jumping and landing abnormally, sudden changes in direction of motion, a direct blow to the side of the knee, or slowing down while running (16).

The incidence of ACL, which is the most common ligament to be damaged (teared) in the knee, is between 100,000-200,000 in the USA. Although there is no difference in terms of demographic factors (age, gender) in ACL ruptures, it is suggested that the risk of ACLs increases in women. Some studies attribute the high prevalence of the anterior cruciate ligament in women to the weakness of the posterior cruciate ligaments, and preferably to the use of the quadriceps muscle group during deceleration, to the increase in the valgus angle of the knee, and to estrogen (13). Although its etiology is not clear; many risk factors associated with anterior cruciate ligament injuries have been identified. In the formation of anterior cruciate ligament injuries, genetic factors as well as anatomical, hormonal, biomechanical and neuromuscular factors have been associated with anterior cruciate ligament rupture (17, 18). Studies of sports genetics on injuries that occur frequently in sports have become widespread, and studies in the fields of identifying genes that affect athletic performance, elucidating their mechanisms of action and determining their sensitivity to athletic performance have also become widespread (19, 20). Genomic DNA profiling for athletic performance and sports injuries is thought to lead to an understanding of genetic advantages and genetic barriers to be overcome in the future (21). Genetic risk factors include proteins such as DNA repair genes, apoptosis genes, collagen proteins and matrix metalloproteinases (22). DNA sequence variants in many genes encoding collagen, which is thought to be a genetic risk factor for anterior cruciate ligament injuries, have been associated with anterior cruciate ligament ruptures (23). Due to the multi fascicular structure of the ACL, it is thought that collagen plays a role in the tensile strength of the connective tissue and its polymorphisms are effective in ACL ruptures (24). Recent studies have emphasized the importance of COL5A1, COL1A1, COL12A1 and COL14A1 genes in Achilles tendon problems and anterior cruciate ligament injuries (25, 26).

As a result, the biological mechanisms that cause non-contact soft tissue injuries in the movement system have not been elucidated yet. There is strong evidence that genetic factors are associated with susceptibility to sports injuries and may play an important role in the healing process, and many studies have confirmed the influence of genetic factors (27). In this context, it is thought that determining the gene profiles of the football players in order to increase their performance and avoid injuries will make a serious contribution to the field in terms of both performance and athlete health. Understanding the etiology of ACL injuries, determining the mechanism and risk factors correctly are important in terms of preventing injuries. From this point of view, in this study, the possible role of COL12A1 gene polymorphism in anterior cruciate ligament injury in football players who play active football in professional leagues and have undergone anterior cruciate ligament surgery was investigated.

MATERIALS AND METHODS

Working group

The study group of the research was composed of 41 football players who were over the age of 18 and had at least one anterior cruciate ligament surgery in the 2020-2021 seasons in Turkish Professional Football Leagues (Tokatspor Football Club, Erbaaspor Football Club, Çaykur Rize Sports Club and Of Sports Club). The control group consisted of football players who actively played football in the Turkish Professional Football Leagues in the 2020-2021 seasons, were over the age of 18, had at least 5 years of football history and had not undergone surgery due to injury before. According to the power analysis, the sample size was determined as at least 40 people in each group (80% power, 5% margin of error and

0.3 effect size). The G-power 3.1.9.6 program was used for the sample size. For the study, the remaining blood from the blood samples taken during routine screenings was used with the consent and knowledge of the participants. Ethics committee approval was obtained from Tokat Gaziosmanpaşa University Clinical Research Ethics Committee with the number 21-KAEK-028. The entire study was carried out by Tokat Gaziosmanpaşa University Faculty of Medicine, Department of Medical Biology.

Methods

Genomic Analysis

In the study, blood samples were collected from football players (41 people) who had anterior cruciate ligament surgery and from the control group (65 people) who did not have cruciate ligament surgery. DNA was extracted from a peripheral blood sample using the Biobasic Genomic DNA Kit according to the manufacturer's instructions. Variation in the collagen gene COL12A1 (rs970547) was analyzed by a polymerase chain reaction (PCR) based restriction fragment length polymorphism (RFLP) method.

The reaction was carried out by preparing a PCR reaction mixture with the components and ratios given in Table 1 to be 25–50 ng of genomic DNA. PCR primers 5'-GAGAATCCAGAACAGCTCCACCAG-3' and 5'-CATGGCTAGTATGGGACAG-3' were synthesized by the commercial company. The PCR program, restriction product length and restriction enzyme applied in the study are given in Table 2.

Table 1. PCR components used in the detection of COL12A1 polymorphism.

	PCR compenents	µl/Tube
1.	distilled water	17,0 µl
2.	10X PCR buffer	2,5 µl
3.	$MgCl_2$ (25mM)	1,5 µl
4.	dNTP Mix (12,5mM)	0,3 µl
5.	Primers (F-R) (10pmol/ µl)	0,8 µl
6.	Taq DNA Polymerase (5 u/µl)	0,1 µl
7.	Genomic DNA	2 µl
	Total volume	25 µl

Table 2. The PCR program, restriction product length and restriction enzyme used in the detection of COL12A1 polymorphism.

Program	COL12A1		Restriction Enzyme
Initial Denaturation	94°C	3 minutes.	Alu I
Denaturation	94 °C	30 seconds	
Annealing	59 °C	30 seconds	
Extension	72 °C	120 seconds	
Termination	72 °C	10 minutes.	
The number of cycles	30 cycles		
Product Length	615 bp		AA =460,139,16 GG=599,16

Statistical Analysis

Statistical analysis of the data was performed using Epi Info Software version 3.2.2 (CDC, Atlanta, GA). The distribution of COL12A1 gene polymorphisms in football players who underwent anterior cruciate ligament surgery and control groups was compared with the $\chi 2$ or Fisher test. A value of $p< 0.05$ was considered statistically significant. Genotype distribution and Hardy-Weinberg equivalence were tested with the Arlequin Software 2000 (University of Geneva, Switzerland) program.

RESULTS

There was no statistically significant difference between groups in terms of COL12A1 A/G polymorphism genotype and allelic distribution. Both patients and controls were in Hardy-Weinberg equilibrium with COL12A1 A/G genotypes distribution ($p > 0.05$). Although the overall genotype distributions of COL12A1 A/G polymorphism are different from patient and control groups, these differences was not statistically significant (p=0.880). In this study the collagen gene COL12A1 variant was genotyped in football players who have had anterior cruciate ligament surgery and control groups. The genotype frequencies of COL12A1 are shown in Table 3. COL12A1 rs970547 polymorphism gel image is given in Figure1.

Figure 1. Agarose gel image of the COL12A1 (rs970547) polymorphism. The 615 bp PCR product was digested with the AluI restriction enzyme.Well 1=GG, well 2=AA, well 4=AG, well 6=Marker

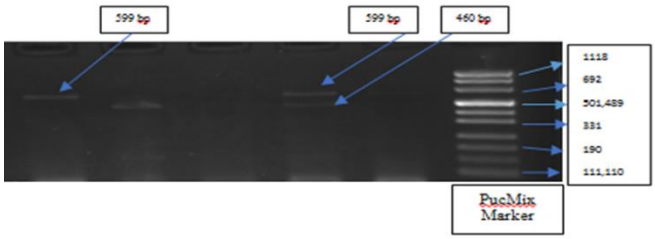

Table 3. COL12A1 polymorphism statistical analysis results.

COL12A1 polymorphism	Patient n=41	Control n=65	p
Genotype (rs970547)			
AA	19 [% 46	28 [% 43]	0.880
AG	14 [% 34]	25 [% 38,5]	
GG	8 [% 20]	12 [% 18,5]	
Allele frequency			
A	52 [% 63,5]	81 [% 62,3]	0.828
G	30 [% 36,5]	49 [% 37,7]	

DISCUSSION

ACL is a feared condition that is most commonly observed in young people, especially in players playing sports that require sudden movement and has negative physical and psychological effects in the long term. This is important in

terms of negatively affecting the long-term active sports lives of athletes (28). Many risk factors for ACL injuries have been identified, including BMI (Body Mass Index), female gender, decreased lower extremity strength, increased joint laxity, genetics, family history, and altered trunk and knee biomechanics (29). The main treatment option for ACL injuries is surgery and the healing process is time-consuming. However, recurrent ruptures and degenerative joint injuries such as osteoarthritis and meniscal tears are common after surgery (24). ACL injuries continue to be an important burden and problem for both sports clubs and athletes. To determine the treatment and prevention interventions for ACL injuries, the effect of factors such as gender, anatomical, genetic, hormonal, and neuromuscular should be better understood (30, 31, 32).

Many studies have been conducted on the role of genetic polymorphisms in ACL tears and its effectiveness has been proven. One of the genes thought to play a role in ACL injuries is collagen (24). For example; Beckley et al. reported that the COL3A1 polymorphism was not significantly associated with knee laxity measurements in a study they conducted with African professional athletes (33). However, in a study conducted with Polish skiers, it was revealed that there is a relationship between COL3A1 rs1800255 polymorphism and ACL ruptures (34). In a study, it was reported that the maximum knee extensor tendon elongation and tension measurement values of the CC genotype were higher than those of the CT or TT genotypes in individuals with the COL5A1 rs12722 polymorphism (35).

Collagen XII, a member of the collagen family, is a heterodimer located on chromosome 6 and encoded by the COL12A1 gene. Studies have shown that COL12A1 is expressed at high levels in tendons and ligaments. In addition, mutations in COL12A1 have been associated with the absence of tendon reflexes and hypermobile distal joints (36).

In this study, the possible relationship between injury exposure and COL12A1 (rs970547) gene polymorphism in professional male football players with anterior cruciate ligament injury and a history of surgery was investigated. According to our findings, there was no statistically significant difference between this polymorphism and anterior cruciate ligament injuries. There are conflicting results between populations in the literature between COL12A1 and the risk of ACL injury (36). Posthumus et al. analyzed the rs240736 and rs970547 polymorphisms of COL12A1 in their study comparing anterior cruciate ligament rupture (142 individuals) and healthy controls in a South African population and found that the AA genotype in the rs240736 polymorphism increased the risk of rupture by 2.4 times in female participants with anterior cruciate ligament injury. It has been reported that it has no effect on men (37). In the Caucasian population, O'Connell et al. and Ficek et al. found similar results to that of Posthumus et al. It was stated that the AA genotype of COL12A1 (rs970547) increased the risk of ACL injury in women, but there was no such relationship in men (38, 39). However, in the study of John et al., and Kang et al., they were shown that both the AA genotype and the frequency of the A allele were associated with a significantly higher risk of ACL injury in the entire population (19, 40). In addition, the COL12A1 gene rs970547 and rs240736 are associated with ACL on Chinese men. According to these results, AA genotype may cause an increased risk of ACL (41).

Our study results suggest that COL12A1 gene polymorphism is not an effective factor in susceptibility to anterior cruciate ligament injuries in the Turkish population. However, since our study is the first to investigate the relationship between COL12A1 polymorphism and anterior cruciate ligament injuries in the Turkish population, and our relatively low number of patients and controls, our results need to be confirmed by other studies.

Authors' Contributions

All authors contributed to the design and design of the study to review, read, and approve the final version of the manuscript. Material preparation and analysis were done by Kubra SAHIN, Nihan BOZKURT, Sadegul SAVKIN. The first version of the manuscript was written by Kubra SAHIN.

Compliance with Ethical Standards

All authors have no conflicts of interest with the submission. Our study was approved by the local Ethics Committee of Gaziosmanpasa University, Turkey (Number: 21-KAEK-028), conducted in line with the principles of the Declaration of Helsinki. All patients were obtained full written informed consent for this research.

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Araştırma Makalesi

En Az İki Doz COVID-19 Aşısı Olan Sağlık Çalışanlarında SARS-CoV-2 Omicron Varyantı Pozitifliği Sonrası COVID-19 Aşı Tutumu

COVID-19 Vaccination Behavior After SARS-CoV-2 Omicron Variant Positivity in Healthcare Workers with at Least Two Doses of COVID-19 Vaccine

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ÖZET

Amaç: Sağlık çalışanları birinci basamak sağlık hizmetlerinde görev almalarına bağlı olarak bulaşıcı hastalıklar ve pandemiler açısından oldukça yüksek risk altında olan öncelikli bir gruptur. Toplumda rol model olan sağlık çalışanlarının aşı ve tedavilere yönelik davranışları, toplumsal olarak bir hastalıkla mücadele etme veya bir pandemiyi kontrol altına alma ve sonlandırma çabaları açısından önemli ölçüde insanları etkileyebilmektedir.

Materyal ve Metot: Bu çalışmada, en az 2 doz aşı sonrası SARS-CoV-2 omikron varyantı pozitif çıkan sağlık çalışanlarının COVID-19 aşı tutumlarının belirlenmesi amaçlanmıştır. Bu tanımlayıcı çalışma, en az 2 doz aşı yaptırdıktan sonra SARS-CoV-2 pozitif çıkan ve çalışmaya katılmaya gönüllü olan sağlık çalışanlarını kapsamaktadır. 15-28 Ekim 2022 tarihleri arasında gerçekleştirilen çalışmada 532 sağlık çalışanına ulaşılmış ve çevrimiçi anket şeklinde kesitsel bir çalışma gerçekleştirilmiştir.

Bulgular: Çalışmada 340 (%63,91) kadın, 192 (%36,09) erkek katılımcı bulunmaktadır. Katılımcıların 224 (%42,11)'ü laboratuvar teknisyeni, 198 (%37,22)'i diğer sağlık meslek mensubu,78 (%14,66)'i biyolog ve 32 (%6,02)'si doktor idi. 364(%68,42)'ünün kronik hastalığı yoktu ve kronik hastalığı olanların %35,71'inde hipertansiyon vardı. COVID-19 pozitif olan 32 (%6,02) hastada SARS-CoV-2 varyantı tespit edilmedi. Katılımcıların 508'i (%95,49) 3 doz COVID-19 aşısı olurken, 400'ü (%75,19) üçüncü doz için BioNTech aşısını tercih etti.

Sonuç: Sağlık çalışanları arasında aşının teşvik edilmesinde destekleyici ve bilgilendirici yaklaşım içeren çok yönlü veri derlemesinin önemli olduğu belirlenmiştir. Aşıların etkinliğini değerlendirmek için sağlık çalışanlarına doğru ve güncel bilimsel bilgiler sağlanmalıdır.

Anahtar Kelimeler: Sars-CoV-2, omikron varyantı, COVID-19, sağlık çalışanı, aşı davranışı.

ABSTRACT

Aim: Healthcare workers are a priority group that is at very high risk of infectious diseases and pandemics due to their work in primary healthcare services. The behavior of healthcare professionals who are role models in society towards vaccines and treatments can significantly affect people with respect to their efforts to combat a disease or control and end a pandemic.

Materials and Methods: This study aimed to determine healthcare workers' COVID-19 vaccine attitude who had positive Sars-CoV-2 omicron variant after receiving at least 2 vaccine doses. This descriptive study includes healthcare workers who tested positive for SARS-CoV-2 after receiving at least 2 doses of vaccine and volunteered to participate in the study. The study reached 532 healthcare professionals and a cross-sectional study was conducted as an online questionnaire between 15-28 October 2022.

Results: It was determined that 340 (63.91%) of them were female and 192 (36.09%) were male. 224 (42.11%) were laboratory technicians, 198 (37.22%) were other healthcare professionals,78 (14.66%) were biologists and 32 (6.02%) were physicians. 364 (68.42%) of them did not have chronic disease and 35.71 % of those with chronic disease had hypertension. Sars-CoV-2 variant was not detected for the 32 (6.02%) who were COVID-19 positive. 508 (95.49%) of the participants received 3 doses of COVID-19 vaccine and 400 (75.19%) preferred BioNTech vaccine for the third dose.

Conclusion: It has been determined that a multifaceted data compilation with a supportive and informative approach is important in promoting vaccination among healthcare professionals. Healthcare workers should be provided with accurate and up-to-date scientific information to evaluate effectiveness of vaccines.

Keywords: SARS-CoV-2, omicron variant, COVID-19, healthcare worker, vaccine behavior.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) was first discovered in Wuhan city of China's Hubei province in 2019 and has spread worldwide causing a pandemic (1). COVID-19 has become a rapidly growing major public health crisis with disquieting variants of Sars-CoV-2 that have increased contagiousness those can cause severe disease and significant adverse effects in the COVID-19 epidemiology (2). Approximately 762 million people have been affected by this virus since the pandemic was declared by the World Health Organization (WHO) on March 11, 2020 and approximately 6.5 million deaths have been reported by February 2023 (3). It is clearly seen that the number of deaths may increase with the effects of variants along with the ongoing mutations in Sars-CoV-2 virus genome and the already threatening consequences of the epidemic may become more serious (4). It is known that there is an urgent need for effective and safe COVID-19 vaccines to control the pandemic and reduce the burden of COVID-19 worldwide in addition to effective public health measures. Hundreds of research and development institutions around the world are working at an unprecedented pace to develop vaccines to end the COVID-19 pandemic (5). A total of 13.339.265.403 COVID-19 vaccine doses have been administered as of February 11, 2023 according to WHO data (3). The first emergency use approval for the inactivated Sars-CoV-2 vaccine CoronaVac (Sinovac Life Sciences, Beijing, China) was issued on January 13, 2021 in Türkiye (6). The adoption and implementation of the COVID-19 vaccine play an important role to fight against the pandemic. Health workers (HW) are priority individuals because they take part in primary health care services, exposed to COVID-19 and have a high risk of severe disease among the high-risk groups accepted as candidates for early vaccination in Türkiye (7).

However, it has been reported that some HW in Türkiye, as well as in the world, were infected with COVID-19 with Sars-CoV-2 Omicron variant positive after at least 2 doses of vaccines (8). It is important to consider the attitudes of healthcare professionals towards the developed COVID-19 vaccines to better identify the barriers against widespread vaccination. Overall acceptance of the vaccine by healthcare professionals will also affect society's attitude. Therefore, healthcare professionals become particularly important through role modeling as well as advising patients and communities (9). WHO recognizes vaccine-acquired immunization as one of the most cost-effective methods in preventing vaccine-preventable diseases and deaths from these diseases (10). In this study, it is aimed to evaluate the attitudes of laboratory HWs for these vaccines after they have been vaccinated against COVID-19 at least 2 doses but relapsed with the omicron variant.

MATERIALS AND METHODS

This study was approved by the Clinical Research Ethics Committee of Yıldırım Beyazıt University Yenimahalle Training and Research Hospital with decision number 2022-58. Research data was collected digitally from employees who were positive for Sars-CoV-2 RT-PCR at least 20 days after receiving at least 2 doses of COVID-19 vaccine in order to determine their attitudes towards COVID-19 vaccines between October 15, 2022 and October 25, 2022 in Ankara Provincial Health Directorate Public Health Molecular Diagnosis Laboratory. The population of this study consisted of individuals over the age of 18, working in the Molecular Diagnosis Laboratory of Ankara Provincial Health Directorate those volunteered for the study. It is a single-center study. The number of HWs included were 532 in the laboratory between 15 and 25 October 2022 with a written questionnaire using the snowball sampling method with Scale of Attitudes Towards COVID-19 Vaccine developed by Geniş et al and presented in "Attitudes Towards COVID-19 Vaccine Scale Scoring: In 2020". The scale was prepared as a five-point Likert type and consists of 9 questions. The questionnaire consists of 3 main parts (11).

The first part of the questionnaire consists of sociodemographic characteristics of the respondents such as age, gender, education level; the second part covers health status of the participants, their COVID-19 and vaccination history and the third part collected information about the attitude of HWs towards the COVID-19 vaccine. The scoring of the abovementioned scale" consists of 2 subsections containing 9 items. Positive attitude items are as follows: "I want my family to get the vaccine developed for this disease", "I would like to have the vaccine developed for this disease at the first opportunity", "I think everyone should have the vaccine developed for this disease", "I trust the explanations about the vaccine developed". Negative attitude items are as follows: "The vaccine developed may cause the transmission of the disease", "I think that the vaccine developed does not have a protective effect", "The vaccine developed is dangerous", "I think that the effectiveness of the developed vaccine has not been adequately tested". The statements in the scale were evaluated as "I totally disagree. (1)", "I disagree. (2)", "I am undecided. (3)", "I agree. (4)" and "I totally agree. (5)" Items in the negative attitude sub-section (5, 6, 7, 8 and 9th items) are scored inversely. A value between 1 and 5 is obtained by dividing the total score obtained by summing the item scores in the scale sub-section by the number of items in that sub-section. High scores obtained from the positive attitude sub-section (items 1, 2, 3 and 4) indicate that the attitude towards the vaccine is positive. It is calculated after the items in the negative attitude sub-section are reversed and the high scores in this sub-dimension indicate that the negative attitude towards the vaccine is less. Inverse items are coded as 1→5; 2→4; 3→3; 4→2;5→1 (11).

Statistical Analysis

Statistical analyzes were carried out with SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) Frequency tables and descriptive statistics were used to interpret the findings. Non-parametric methods were utilized for measurement values without normal distribution. “Mann-Whitney U" test (Z-table value) was used to compare the measurement values of two independent groups and the "Kruskal-Wallis H" test ($\chi 2$ -table value) method was used to compare the measurement values of three or more independent groups in accordance with non-parametric methods. Bonferroni-Dunn post hoc test was applied for pairwise comparisons of variables with significant differences for three or more groups. “Spearman” correlation coefficient was used to examine the relationships of two quantitative variables that do not have a normal distribution. The statistical significance level was accepted as $p < 0.05$.

RESULTS

340 HWs (63.91%) were women, 238 (44.73%) were in the 30-39 age group and 158 (29.7%) were undergraduates in this study. 224 (42.11%) employees were laboratory technicians, 364 (68.42%) did not have a chronic disease and 35.71% of those with chronic diseases had hypertension (Table 1).

Table 1. Sociodemographic characteristics of healthcare workers.

Variable (N=532)	n	%
Gender		
Female	340	63.9
Male	192	36.1
Age Distribution		
18-29	80	15.03
30-39	238	44.74
40-49	154	28.95
50-59	55	10.34
=> 60	5	0.93
Education Level		
Primary School	8	1.5
Middle School	30	5.64
High School	60	11.28
Associate degree	224	42.11
Bachelor	158	29.7
Graduate	52	9.77
Occupation		
Physician/Doctor	32	6.01
Biologist	78	14.66
Laboratory Technician	224	42.11
Other Healthcare Professionals	198	37.22
Chronic Disease		
Yes*	168	31.58
No	364	68.42
Name of Disease*		
Asthma	12	7.14
Diabetes mellitus	38	22.62
Hypertension	60	35.71
Cardiovascular disease	13	7.74
Hypothyroidism	10	5.95
Other	35	20.84

Viral variant could not be determined in the Sars-CoV-2 RT-PCR test positivity that occurred at least 20 days after at least two doses of vaccination of 32 HW (6.02%). 508 (95.49%) had 3 doses of COVID-19 vaccine and 400 (75.19%) of them was 3 doses of BioNTech while 52 HWs (9.77%) were regularly vaccinated against influenza every year (Table 2).

Table 2. Sars-Cov-2 omicron variant 19 transmission status and vaccination history of healthcare workers.

Variable (N=532)	n	%
Sars-CoV-2 omicron variant		
Yes	500	93.98
Variant not determined	32	6.02
Covid-19 Vaccination		
2 Doses	24	4.51
3 Doses	508	95.49
If you had a choice in the COVID-19 vaccination before you had any vaccinations yet		
wouldn't consider getting the vaccine and will never get another dose.	48	9.02
Sinovac®	152	28.57
BioNTech®	304	57.14
Turkovac®	27	5.07
Moderna®	0	0
Sputnik V®	1	0.2
Regular Annual Influenza Vaccine		
Annual	52	9.77
Some Years	184	34.59
No Vaccination	296	55.64

It was found that the difference between the scale of attitudes towards COVID-19 vaccine according to healthcare workers’ age class (p=0,296), gender (p=0,831), and chronic disease status (p=0.061) of was not significant in statistical evaluation.

The scale of attitudes towards COVID-19 vaccine was statistically significant in terms of positive attitudes (p=0.010) according to the professions and education levels of healthcare professionals. It was determined that the positive attitude scores of undergraduate and graduates compared to high school degrees and doctors/biologists compared to other health personnel were significant and higher (p=0.005) towards COVID-19 vaccine according to this significant difference (Table 3). The attitudes towards COVID-19 vaccine obtained in this study in which HWs who had a positive Sars-CoV-2 omicron variant at least 20 days after receiving at least 2 doses of Covid-19 vaccine are given in Table 4.

Positive attitude scores of those who want to have Sinovac®, BioNTech and Turkovac are significantly higher when compared with HWs who have tested positive for the omicron variant at least 20 days after receiving at least 2 doses of COVID-19 vaccine and no longer choose to receive a new dose of COVID-19 vaccine (p=0.008). A statistically significant difference was found in attitudes towards COVID-19 vaccine among HWs compared to those who do not have

influenza vaccination and those who receive regular influenza vaccination every year and some years (p=0.002). It has been determined that those who had regular influenza vaccination every year and some years and had 2nd dose or 3rd dose of COVID-19 vaccine may want to have a new dose vaccine. Their negative attitude towards the vaccine was less when compared to HWs who had positive omicron variant at least 20 days after receiving at least 2 doses of COVID-19 vaccine and no longer preferred to receive a new dose of COVID-19 vaccine. The percentage of responses given to the positive/negative attitude scale is given in Table 5.

Table 3. Comparison of attitudes towards COVID-19 vaccine according to sociodemographic characteristics of healthcare workers.

		Scale of attitudes towards the Covid-19 vaccine			
Variable (N=532)	**n**	**Positive Attitude**		**Negative Attitude**	
		$\bar{x}$ ± . SD	Median (IQR)	$\bar{x}$ ± SD	Median (IQR)
Gender					
Female	340	3.50±1.36	4.0 (2.8)	4.02±0.76	4.2 (1.0)
Male	192	3.44±1.39	4.0 (2.6)	4.12±0.66	4.2 (0.8)
Statistical Analysis		Z=-0.213		Z=-0.968	
p-value		p=0.831		p=0.333	
Age Distribution					
18-29	80	3.19±1.53	3.8 (2.9)	4.15±0.79	4.2 (1.0)
30-39	238	3.51±1.39	4.0 (2.8)	4.13±0.68	4.2 (0.8)
40-49	154	3.40±1.35	3.8 (2.0)	3.99±0.69	4.0 (0.8)
50-60	60	3.90±0.99	4.0 (1.3)	3.82±0.90	4.1 (1.6)
Statistical Analysis		$\chi2$ =3.695		$\chi2$ =4.697	
p-value		p=0.296		p=0.195	
Education Level					
Primary/Middle School	38	3.72±1.10	3.8 (1.4)	3.89±0.51	4.0 (0.5)
High School	60	3.65±1.39	4.0 (2.1)	4.12±0.62	4.2 (0.5)
Associate degree	224	3.69±1.29	4.0 (1.8)	4.04±0.77	4.2 (1.0)
Bachelor	158	2.86±1.47	2.8 (2.6)	4.14±0.73	4.2 (1.0)
Graduate	52	3.28±1.32	3.8 (2.0)	3.99±0.82	4.2 (1.2)
Statistical Analysis		$\chi2$ =13.231		$\chi2$ =3.524	
p-value		p=0.010		p=0.474	
Differentiation		(2-4.5)			
Occupation					
Physician/Biologist	110	3.75±1.43	4.5 (1.8)	4.27±0.48	4.2 (0.6)
Laboratory Technician	224	3.63±1.28	4.0 (1.9)	4.01±0.82	4.2 (1.0)
Other Healthcare Professionals	198	3.15±1.37	3.5 (2.0)	4.00±0.73	4.0 (1.0)
Statistical Analysis		$\chi2$ =10.491		$\chi2$ =3.806	
p-value		p=0.005		p=0.149	

*"Mann-Whitney U" test (Z-table value) for comparison of measurement values of two independent groups was used for data without normal distribution; "Kruskall-Wallis H" test statistics ($\chi2$ -table value) were used to compare three or more independent groups.

The attitudes towards COVID-19 vaccine obtained in this study in which HWs who had a positive Sars-CoV-2 omicron variant at least 20 days after receiving at least 2 doses of Covid-19 vaccine are given in Table 4.

Table 4. Comparison of healthcare professionals' attitudes towards COVID-19 vaccine preference according to health status and flu vaccine history.

		Scale of attitudes towards COVID-19 vaccine			
Variable (N=532)	**n**	**Positive Attitude**		**Negative Attitude**	
		$\bar{x}$ ± S.S.	Median (IQR)	$\bar{x}$ ± S.S.	Median (IQR)
Chronic Disease					
No	364	3.61±1.29	4.0 (2.0)	4.02±0.74	4.0 (1.0)
Yes	168	3.20±1.48	3.8 (2.5)	4.14±0.70	4.2 (0.6)
Statistical Analysis		Z=-1.873		Z=-1.454	
p-value		p=0.061		p=0.146	
Covid-19 Vaccination					
2 doses	24	2.38±1.14	2.3 (1.4)	4.10±0.69	4.2 (0.8)
3 doses	508	3.53±1.36	4.0 (2.3)	3.21±1.10	3.2 (1.7)
		Z=-2.671		Z=-2.967	
p-value		p=0.008		p=0.003	
Choice for a new dose of Covid-19 vaccine					
I wouldn't consider getting vaccinated, I won't do it again.	48	2.57±1.14	2.5 (1.9)	3.09±0.83	3.1 (1.3)
Sinovac®	152	3.51±1.33	4.0 (2.4)	3.96±0.71	4.0 (1.3)
BioNTech®	304	3.61±1.38	4.0 (1.8)	4.21±0.60	4.2 (0.6)
Turkovac®	27	3.63±1.32	4.0 (2.4)	4.19±0.65	4.3 (1.0)
Statistical Analysis		$\chi2$ =14.327		$\chi2$ =37.27	
p-value		p=0.002		p<0.001	
Differentiation		(1-2.3.4)		(1-2.3.4)	
Regular Annual Influenza Vaccine					
Annual	52	3.70±1.39	4.0 (1.7)	4.45±0.49	4.4 (0.7)
Some Years	184	3.59±1.44	4.0 (2.5)	4.22±0.59	4.3 (0.6)
No Vaccination	296	3.40±1.34	3.8 (2.5)	3.93±0.78	4.0 (1.0)
Statistical Analysis		$\chi2$ =3.442		$\chi2$ =15.251	
p-value		p=0.179		p<0.001	
Differentiation				(1.2-3)	

**"Mann-Whitney U" test (Z-table value) for comparison of measurement values of two independent groups was used for data without normal distribution; "Kruskall-Wallis H" test statistics ($\chi2$ -table value) were used to compare three or more independent groups.

Table 5. Distribution of frequencies obtained from the scale of attitudes of healthcare workers towards COVID-19 vaccine.

Statement	**I strongly disagree. n (%)**	**I disagree. n (%)**	**I'm undecided n (%)**	**I agree. n (%)**	**Strongly Agree n (%)**
I would like my family to have the vaccine developed for this disease.	57 (10.71)	30 (5.64)	38 (7.14)	141 (26.51)	266 (50)
I would like to have the vaccine (a new dose) developed for this disease at the first opportunity.	46 (8.65)	50 (9.4)	38 (7.14)	88 (16.54)	310 (58.27)

I think everyone should have the vaccine developed for this disease.	48 (9.02)	51 (9.59)	16 (3.01)	202 (37.97)	215 (40.41)
I trust the statements about the vaccine developed	110 (20.68)	86 (16.17)	82 (15.41)	140 (26.31)	114 (21.43)
Developed vaccine can cause disease transmission	391 (73.5)	102 (19.17)	29 (5.45)	7 (1.32)	3 (0.56)
I think that the developed vaccine has no protective effect	364 (68.42)	148 (27.82)	10 (1.88)	9 (1.69)	1 (0.19)
Developed vaccine is dangerous	256 (48.12)	174 (32.71)	94 (17.67)	6 (1.13)	2 (0.37)
I think the effectiveness of the developed vaccine has not been sufficiently tested.	219 (41.16)	180 (33.83)	60 (11.28)	46 (8.65)	27 (5.08)
I think I can survive the epidemic without a vaccine.	400 (75.19)	108 (20.30)	16 (3.01)	6 (1.13)	2 (0.37)

DISCUSSION

Vaccination is considered as one of the greatest achievements in public health and a life-saving invention capable of controlling and eradicating infectious diseases in many parts of the world (12). Total doses of COVID-19 vaccines applied in Türkiye is 152.718.197 as of May,2023 and the rate of second dose administration at age 18 and over is 85.70%. The number of vaccinated HWs is over one million (13). This study is one of the first studies to evaluate the attitudes of healthcare professionals towards COVID-19 vaccines who had positive omicron variant after at least two doses of vaccination while public debate on vaccination necessity and vaccine safety continues. The aim of the study was to obtain subjective evaluation of health professionals about receiving another COVID-19 vaccine dose after receiving at least two doses of COVID-19 vaccines at least 20 days after being positive with the omicron variant those work at the Ankara Public Health Molecular Diagnosis Laboratory. It is one of the laboratories with the highest test capacity authorized for the diagnosis of Sars-CoV-2 in Türkiye. The data obtained at the end of the study is in line with the positive attitude of the participants towards their own vaccine who believe that the pandemic will end in this way. This attitude coincides with the results of the study conducted in Greece in 2022 which reported Sars-Cov-2 positivity despite full-dose vaccination and the study conducted in Italy in 2021 which showed that the Sars-CoV-2 COVID-19 vaccine could be the only way to end the pandemic (8,13).

A positive attitude towards vaccines is expected from health professionals considering their scientific and medical training. Positive behaviors of healthcare professionals towards vaccination can positively affect the rate of vaccination in the public as revealed in a study (14). A study carried out in Israel observed a difference in COVID-19 vaccine acceptance rates between doctors and nurses. Differences in vaccine acceptance rates among occupational categories (doctors vs. nurses) have been observed for seasonal influenza and COVID-19 vaccines. Nurses were found to accept fewer vaccines than doctors with 92% and 69% for influenza and 78% and 61% respectively ($p<0.1$) (15). It was determined that other healthcare professionals (administrative staff, technicians, cleaners, and security guards) had a more negative attitude towards the COVID-19 vaccine compared to doctors/nurses in studies reported from Israel, Congo, Belgium, France, Nepal and Slovenia and as consistent with our study (16-17).

A study from the United Arab Emirates revealed the lowest willingness or negative attitude towards the vaccine among doctors contrary to other data (18). Approximately 93.37% of the population of age 18 and over received a dose of COVID-19 vaccine in Türkiye, as of October 2021. Studies have shown that vaccination of HWs with influenza vaccine reduces patient deaths and staff shortages (19). It would be reasonable to expect a similar benefit from COVID-19 vaccination. It was found that participants who had the flu vaccine were more willing to be vaccinated against COVID-19 in a study conducted in Italy (20).

It is possible to express that 28.19% of the healthcare professionals who participated in our study had influenza vaccine every year or some years and this situation created a positive perception of vaccination in general. It was determined that the negative attitude of those who have regular influenza vaccine every year and some years are less than those who are not vaccinated according to this result (9). Although sociodemographic characteristics such as age, education level and income status can affect people's attitudes about a subject positively or negatively, the gender and age classes of HWs did not affect their attitudes towards the COVID-19 vaccine in our study. It was identified that increasing age and education level in the USA positively affected attitudes towards the COVID-19 vaccine and the acceptance of these vaccines increased contrary to our study (21). Several studies reported that the vulnerability to environmental factors will increase with increasing age and positive attitude for the vaccine will increase accordingly (22).

I Pfizer-BioNTech® s the most preferred vaccine with a rate of 75.19% by Ankara Public Health Molecular Diagnostics Laboratory healthcare professionals. The choices were 20.68% "Strongly Disagree" and 16.17% "I do not agree." for the statement "I trust the explanations made about the developed vaccine". Our research results support studies conducted in other countries. Healthcare workers' absence of fear about vaccine safety, useful information about the vaccine provided by them and having their relatives get these vaccines

will affect the rate of vaccination in the community (23). It was determined that the physicians' knowledge level about the vaccine is high (75.3%) and a significant relationship was found between the vaccination rate and the level of knowledge in a study evaluating physicians in Türkiye about influenza vaccine in which doctors who regularly vaccinate their patients and healthcare professionals every year encourage them to vaccinate (24).

More than 2/3 of healthcare professionals stated that they would recommend COVID-19 vaccine to their colleagues and immediate family members as reported in the study. More than half of the healthcare professionals reported that they would recommend the improved vaccine to their elementary family members in our study. COVID-19 disease poses a great threat especially for people with chronic diseases such as hypertension, diabetes, asthma, and obesity (25). This will affect attitude towards vaccines developed against Sars-CoV-2 infection. However, no significant difference was found between the positive and negative attitudes of HWs with chronic diseases towards re-administration of COVID-19 vaccine doses in this study. In our study, it was determined that a certain number of healthcare professionals had varying opinions about the COVID-19 vaccine. They were cautious for more than one vaccine dose and the main concern was that vague trust in the vaccine.

CONCLUSION

This study found that a multifaceted intervention consisting of a supportive and informative approach is critically important for promoting COVID-19 vaccination among healthcare professionals. It is crucial to implement vaccination programs to ensure social immunity as well as personal protective measures to control the epidemic. Lack of information among healthcare professionals shows that the leading decisive aspects are not different from the population in extraordinary conditions such as pandemics despite many scientific studies on efficacy, safety, and side effects for current COVID-19 vaccines. We determined that the appetite to have a COVID-19 vaccine among healthcare professionals varied by age, gender, and role in the laboratory with the highest acceptance rate among physicians and research scientists as a result of our study. Vaccination hesitancy and safety concerns were higher for laboratory technicians and other health personnel. Vaccine safety, possible side effects, efficacy and duration of vaccine development were identified as important factors affecting participants' concerns. The authors believe findings of this study can guide public health campaigns, particularly healthcare professionals, to increase COVID-19 vaccine acceptance. All HWs should access to accurate and up-to-date scientific information about vaccines at the same time

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Araştırma Makalesi

Göçün 10. Yılında Mülteci Anne ve Yenidoğanların Perinatal Değerlendirilmesi

Perinatal Outcomes of Refugee Mothers and Newborns in The Tenth Year of Migration to Turkey

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ÖZET

Amaç: Artan göç olaylarından sonra az gelişmiş ülkelerden milyonlarca birey mülteci olarak yaşamaktadır. 2011 yılında başlayan göçün 10. yılında mültecilerin sağlık durumlarını değerlendirerek mültecilerin doğum oranlarını ve ülkemizde doğan bebeklerin sağlığını incelemeyi amaçladık.

Materyal ve Metot: Hastanemizde 2983 doğum dosya ve hastane bilgi sistemi verileri kullanılarak retrospektif olarak incelendi. Anne yaşı, gebelik sayısı, gebelik süresi, bebeklerin antropometrik ölçümleri ve doğum şekli değerlendirildi.

Bulgular: Analiz edilen 2893 doğumdan sırasıyla 2435 ve 458 doğum Türk vatandaşları ve mülteciler tarafından yapılmıştır. Mülteciler arasında gebelik sayısı yüksekti ($p<0.001$). Geç preterm, term ve posterm doğum oranlarında istatistiksel anlamlılık saptanmamakla birlikte, mültecilerde erken preterm ve preterm doğum anlamlı olarak daha yüksek bulundu ($p<0,001$); Mültecilerde normal doğumlar daha yüksek olarak saptandı.

Sonuç: Artan mülteci sayısı ve göç olayları önemli sağlık sorunları arasındadır. Artan mülteci nüfusuna bağlı doğurganlık oranları da hem gebelik hem de erken doğum sayılarını artırmaktadır. Mültecilerin ekonomik sorunlarına eşlik eden sağlık sigortasının olmaması da mültecilere ev sahipliği yapan ülkelerde bir diğer önemli sorun olarak öne çıkmaktadır.

Anahtar Kelimeler: Bebek, anne sağlığı, göç, gebelik, mülteci.

ABSTRACT

Aim: Millions of individuals from underdeveloped countries live as refugees after increasing migration events. In the 10th anniversary of the migration commencing in 2011, we aimed to evaluate the health status of refugees and examine refugees' birth rates and babies' health born in our country.

Materials and Methods: 2983 births were examined retrospectively, using file and hospital information system data. Maternal age, number of pregnancies, duration of pregnancy, babies' anthropometric measurements, and mode of deliveries were evaluated.

Results: Of 2893 births analyzed, 2435 and 458 births were given by Turkish citizens and refugees respectively. Number of pregnancies was high among refugees ($p<0.001$). Although no statistical significance was detected in late pre-term, term, and post-term birth rates, early pre-term and pre-term births were found to be significantly higher in refugees ($p<0.001$); normal births were higher in refugees.

Conclusion: The increasing number of refugees and increasing migration events are among important health challenges. Fertility rates due to the increasing population of refugees also increase the number of pregnancies and premature births. The lack of health insurance accompanying the economic problems of refugees comes to the fore as another important problem in countries hosting refugees.

Keywords: Baby, maternal health, migration, pregnancy, refugee.

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INTRODUCTION

Based on the figures provided by the United Nations High Commissioner for Refugees (UNHCR) for 2022, more than 100 million people continue to live as refugees or asylum seekers around the world (1). Due to the ongoing civil war since 2011, Syria is now the country with the highest number of refugees (6.7 million), and the neighboring country of Syria, Turkiye is the country hosting the most refugees across the world. As of 2020, there are 3.7 million refugees in Turkiye, and under the data released by UNHCR, external migration to Turkey is mostly from Syria, Afghanistan, and Iraq (2, 3), and these refugees are mostly composed of women and children.

It is known that refugees cannot benefit from the services of maternal-children health care and family planning sufficiently; unwanted pregnancies and gynecological diseases are common; the controls of pregnancies are not performed, and the rates of maternal and perinatal mortality increase. On the other hand, in the studies conducted in Europe, a great number of refugees have been determined not to use the health services provided for them (4,5). Regarding reproductive health, refugee women have also been found to carry a higher risk in terms of having babies with low birth weight, giving premature births, malpresentation, placenta previa, amniotic fluid anomalies, fetal anomalies, antenatal mortality and congenital malformations (6). On the other hand, Turkey is one of the rare countries offering unlimited and free health services to refugees so that they can maintain their normal lives.

However, there is limited information on how the provision of free health care or the length of the time spent in target countries affects perinatal outcomes. The present study aimed to compare the perinatal outcomes of refugee mothers and their children 10 years after migration with those of host families.

MATERIALS AND METHODS

In this retrospective cross-sectional study, the records of 2893 postpartum mothers and their newborns in 2021 at a university hospital were reviewed. Based on the personal identification numbers, mothers were divided into two groups: Turkish citizens and refugees. As well as recording such factors as maternal age, gestational period, number of pregnancies, single and multiple pregnancies, the status of still or live births, management, and causes of deliveries, the sex of the newborns, age of births (week), birth weight, and whether or not the newborns were only breastfed in the first days of the delivery were also recorded. In addition, the need for hospitalization in the neonatal intensive care unit (ICU) due to any diagnosis during the first month was evaluated in terms of the length of hospitalization and the ways of discharge from neonatal ICU, and the data obtained were compared between Turkish citizens and refugees.

Statistical Analysis

Data were summarized as mean ± standard deviation and Median (Min.-Max.) for continuous variables, frequencies, and percentiles for categorical variables. Student's t-test and/or Mann Whitney U test were used for independent two-group comparisons, considering the results of the Shapiro–Wilk normality test. The chi-square test was used for proportions and its counterpart Fisher's Exact test was used when the data were sparse. A "p" value of less than 0.05 was considered statistically significant and Statistical analyses were performed using the Statistical Package for Social Sciences for Windows, version 25.0 (SPSS, IBM Corp., Armonk, NY, U.S., 2017).

Ethical Approval

In our study, written consent was obtained from all the cases participating in our study, in

accordance with the Declaration of Helsinki. Ethics Committee permission was obtained from the local Ethics Committee with the decision dated 27.10.2022 and numbered 136-SBKAEK.

RESULTS

The differences between the groups consisting of the refugees and Turkish citizens were investigated in terms of the variables considered regarding continuous measurements, and the medians of both groups were found to be statistically different only in terms of the number of pregnancies ($p<0.001$). The number of pregnancies by Turkish women was observed to be significantly lower than that of refugee women (Table 1).

Table 1. Characteristics of mothers given births, and values of newborns' measurements.

	Refugees		Turkish Citizens		p
Maternal age (years)	26.30±5.70	25 (16-57)	26.72±5.86	26 (16-45)	0.188
Number of Pregnancies	3.39±1.79	3 (1-12)	2.64±1.49	2 (1-13)	<0.001
Duration of Pregnancies	38.91±2.23	39.3 (22.3-42.6)	39.1±1.77	39.3 (22.4-46.2)	0.149
Birth weight	3286.03±560.69	3310 (555-4900)	3252.05±494.65	3275 (500-4960)	0.187*
Height	49.87±2.56	50 (28-56)	49.98±1.92	50 (28-58)	0.843
Head circumference	34.93±1.81	35 (17-48)	34.99±1.59	35 (5-51)	0.904

*The student's t-test and all others from p values were obtained through the Mann-Whitney U test. Mean±S.Dev. and Median (Min.-Max.)

Of 2893 births examined in the study, 2435 were born to the citizens of the Republic of Turkey (1233 girls vs. 1202 boys). Even so, the remaining 458 births were performed by refugee mothers (249 girls vs. 209 boys). Ten of the births by refugee mothers and 38 of the births born to the citizens of the Republic of Turkey were multiple pregnancies. Five of the refugee mothers' pregnancies and 17 of the pregnancies by Turkish citizens ended in stillbirth, and there was no statistically significant difference in terms of sex and number of babies. In addition, babies were also evaluated in terms of age of birth (weeks), and types and causes of births. While there was no significant difference between the term births of the pregnancies, the rate of <34-week births among pre-term births was found to be four times higher among refugees (p<0.001). Given the mode of deliveries, the rate of normal births was observed to be higher in refugees, and the difference was statistically significant (p<0.001) (Table 2).

Table 2. Epidemiological characteristics of newborns

		Refugees (n) (%)	**Turkish Citizens (n) (%)**	***p***
Sex	Female	249-54.37	1233-50.64	0.143
	Male	209-45.63	1202-49.36	
Exitus/Survivors	Exitus	453-98.91	2418-99.3	0.376*
	Survivors	5-1.09	17-0.7	
Single/Multiple	Single	448-97.82	2397-98.44	0.338
	Multiple	10-2.18	38-1.56	
Terms	Early Pre-term	7-1.52	3-0.12	**<0.001***
	Moderate Pre-term	7-1.52	8-0.32	
	Late Pre-term	25-5.45	189-7.76	
	Term	410-89.51	2213-90.88	
	Post-term	9-1.96	22-0.9	
Birth weight	Extremely Low	4-0.87	6-0.25	0.283*
	Very low	1-0.22	5-0.21	
	Low	22-4.8	120-4.93	
	Normal	403-87.99	2172-89.2	
	Macrosomic	28-6.11	132-5.42	
Only breastfeeding in the first days	No	80-17.47	503-20.66	0.128
	Yes	378-82.53	1932-79.34	
Mode of delivery	Normal Delivery	322-70.31	1429-58.69	**<0.001**
	Cesarean section	136-29.69	1006-41.31	
Types of Cesarean section	Normal	322-70.31	1429-58.69	**<0.001**
	Repeated cesarean section	72-15.72	598-24.56	
	Primary cesarean section	64-13.97	408-16.76	
Presentations	Cephalic	437-96.26	2347-96.58	0.612
	Breech	16-3.52	69-2.84	
	Others	1-0.22	8-0.33	

p values through the *Fisher's exact test

Of 2435 babies born to Turkish citizens and 458 babies born to refugees, 422 (17.1%) and 83 (18.1%) were followed up or hospitalized in the neonatal units of our hospital due to any complaint or diagnosis, respectively. No significant difference was detected between the two groups in terms of the rates of hospitalization in neonatal units, length of hospital stay, and ways of discharge from the hospital. In addition, two babies died in each group during the stay in the neonatal period, and although there was a percentage difference, no statistical difference was found between both groups (p=0.128) (Table 3).

Table 3. Statistical analyses of newborns admitted to neonatal intensive care units

		Turkish Citizens	**Refugees**	**p**
Stages of neonatal ICU	Primary	288-68.25	54-65.06	0.850
	Secondary	70-16.59	15-18.07	
	Tertiary	64-15.17	14-16.87	
Ways of discharge	Reference to tertiary facilities	41-9.72	10-12.05	0.240*
	Discharge for status	27-6.4	4-4.82	
	Discharge with good health	350-82.94	66-79.52	
	Treatment rejection	2-0.47	1-1.2	
	Exitus	2-0.47	2-2.41	
Exitus/Survivors	Survivors	420-99.53	81-97.59	0.128*
	Exitus	2-0.47	2-2.41	
Length of hospital stay		5.95±5.44 [5.0(1.0-38.0)]	5.72±5.87 [4.0(1.0-37.0)]	0.406#

*;p values through Fisher's exact test, and #;p values through the Mann-Whitney U test. Descriptive statistics, Mean±St. Dev.(SD) [Median (Min.-Max.)] and (n), (%)

DISCUSSION

In the present study, the prenatal and perinatal data of the refugees migrating to Turkey within the last decade were examined and compared with those of the newborns born to Turkish citizens and Turkish mothers' pregnancies taking place in our hospital in 2021. There was no significant difference between both groups in terms of the rates of hospitalization, length of hospital stay, and modes of hospital discharge.

Migration also affects the delivery preferences of women of reproductive age. For most refugee women, giving birth to children is important to preserve their traditional cultural characteristics and the continuity of their status (7). Thus, a refugee woman tries to increase her fertility. Refugees more frequently becoming pregnant have been reported to benefit less from primary health services related to maternal and children's health care and family planning (9). Regarding reproductive health, refugee women are also at higher risk in terms of having babies with low birth weight, giving premature births, antenatal mortality, and congenital malformations.

Based on the findings of a study where 949,593 births were evaluated between 1997 and 2012 in Sweden (2018), it was determined that low birth weight was 1.47 times higher, and post-term labor was 1.41 times higher in the refugee group, compared to the Swedish-born population (8). The most common reproductive health problems among refugee women in Turkiye are infectious diseases, inability to benefit from family planning services, inability to benefit from services of prenatal care, higher rate of births at home without health professionals, irregular menstruation, spontaneous abortions,

and multiple and short-term pregnancies (9). In our study, the number of pregnancies was higher in refugees than that in Turkish citizens ($p<0.001$). In addition, the rates of early and moderate pre-term births were determined to be significantly higher in refugees ($p<0.001$). The higher rates of pregnancies and premature pre-term births may suggest that the risk of perinatal morbidity and mortality may be higher in births born to refugees.

The ideal rate of cesarean sections reported by the World Health Organization (WHO) is between 10-15%; however, the rate of cesarean sections is today well above this rate (10). It has been accepted that the rates of perinatal and maternal morbidity and mortality will increase when the number of cesarean sections becomes lower or higher than the determined rate. In terms of the methods of deliveries, the rate of normal spontaneous vaginal deliveries was statistically significantly higher in refugees at 70.31%, compared to that of Turkish citizens at 58.69% in our study ($p<0.001$). It may be asserted that the high rate of cesarean sections among Turkish citizens will increase the rate of perinatal morbidity and mortality.

In another study conducted in Turkiye in 2016, it was stated that refugees have difficulties in communicating due to language barriers while receiving health care and experience many challenges in communicating with health care providers, as well as those in performing the procedures (11). In 2018, the factors affecting the reproductive health of refugee women in Geneva were reported to be economic inadequacies, language barriers, real or perceived social discrimination, lack of information, and feelings of shame (12). As a governmental policy or at institutional levels, novel strategies such as facilitating the use of interpreters, and training both healthcare providers and recipients on the coverage and eligibility of services are needed to increase refugees' quality of life in host countries (13). In addition, it has been emphasized that the programs of language and pictogram can be performed to increase the accessibility to health information and services recommended for refugees - that is, to elevate health literacy among refugees (14). In addition, an interpreter was appointed to each hospital by the Turkish Ministry of Health in 2018. The service provided by interpreters continues 24 hours a day in our hospital. This service has aimed to overcome the language barriers and contribute to the health policies put into effect for refugees in Turk. Compared with the findings reported in previous studies, it may be asserted that refugees may have been less affected by social discrimination and cultural negativities due to the similar religious and cultural structures between Syria and Turkiye, as well as spending longer time in Turkiye and resolving the language problem in hospitals.

Turkey has implemented a generous health policy towards nearly 3.5 million refugees from Syria. Syrian refugees have been integrated into the health insurance system in Turkey in the same way as Turkish citizens, and therefore have the right to free access to public primary, secondary, and tertiary health care services. Unregistered Syrian refugees can also benefit from preventive and emergency health services free of charge (15). Refugees are registered with family physicians of Turkey. The fact that refugees can apply free of charge to secondary and tertiary health facilities along with the family physicians at the primary centers and the compulsory follow-up of those with pregnancy in the system can be suggested to have positive effects on maternal and children's health status.

The retrospective nature of the study was a limitation.

CONCLUSION

In conclusion, there was no difference between refugee mothers/their newborns and Turkish mother/their newborns in terms of hospitalization rates and length of hospital stay. However, the number of pregnancies, pre-term births and the rates of vaginal delivery were higher among refugees. The similarity of perinatal mortality and morbidity rates may be related to the fact that Turkey offers free health services to refugees without separating them from its own citizens. Despite all these factors, differences in pregnancy and birth parameters may be due to sociocultural differences or other differences requiring further studies.

Ethical Approval: Ethics Committee permission was obtained from Medical Faculty Clinical Research Ethics Committee with decision number 136 on 27.10.2022.

Conflict of Interest: The authors have no conflict of interest regarding this study.

Financial Disclosure: No financial support has been received for this study.

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Aksaray Üniversitesi Tıp Bilimleri Dergisi
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Olgu Sunumu

Sekundum Atriyal Septal Defektli Bir Hastada İzole Sağ Ventrikül Miyokard Enfarktüsü: Olgu Sunumu

Isolated Right Ventricular Myocardial İnfarction in A Patient With Secundum Atrial Septal Defect: A Rare Case

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ÖZET

Sağ ventrikül miyokart infarktüsü, ani olarak gelişen sağ ventrikül sistolik işlev bozukluğu ve sağ ventrikül genişlemesinin yol açtığı hemodinamik bozukluklara neden olan acil bir durumdur. İnferiyor duvar miyokart infarktüslerinin yaklaşık %25 ile %50'sine, sağ ventrikül miyokart infarktüsü de eşlik etmektedir. Atriyal septal defekt ise; atriyumlar arasında şant oluşturan, sağ atriyum ve sağ ventrikül genişlemesine neden olabilen doğuştan bir anomalidir. Daha önceden atriyal septal defekti olan bir hastada sağ ventrikül miyokart infarktüsü nadiren bildirilmiştir. Ancak atriyal septal defekti olan bir hastada izole sağ ventrikül miyokart infarktüsü ise hiç bildirilmemiştir. Bu yazıda; 56 yaşında olan, izole sağ ventrikül miyokart infarktüsü ile başvuran ve daha önce tanı konulmamış sekundum atriyal septal defekti bulunan bir hastayı sunuyoruz.

Anahtar Kelimeler: Atriyal septal defekt, sağ ventrikül miyokart infarktüsü, sağ koroner arter

ABSTRACT

Right ventricular myocardial infarction is a serious emergency that causes hemodynamic disturbances as a result of sudden right ventricular systolic dysfunction and dilatation. 25% to 50% of inferior wall myocardial infarction cases are accompanied by right ventricular myocardial infarction. Atrial septal defect is a congenital anomaly that causes a shunt between the atria and can cause dilatation of the right atrium and ventricle. Right ventricular myocardial infarction has been rarely reported in a patient with atrial septal defect previously. In addition, isolated right ventricular myocardial infarction was not reported in a patient with atrial septal defect. In this article, we present a 56-year-old patient with a previously undiagnosed secundum atrial septal defect presenting with isolated right ventricular myocardial infarction.

Keywords: Atrial septal defect, right ventricular myocardial infarction, right coronary artery

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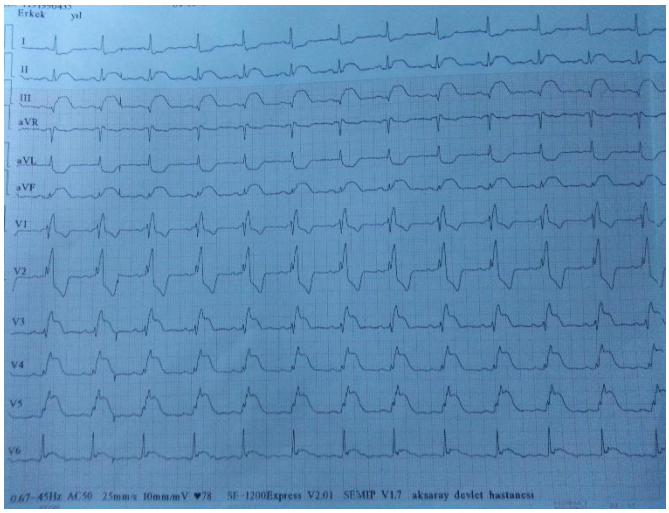
INTRODUCTION

25% to 50% of inferior wall myocardial infarction cases are accompanied by right ventricular myocardial infarction (RVMI) (1). The clinical presentations of RVMI vary widely and range from hemodynamically stable to cardiogenic shock, depending on the degree of right ventricle (RV) ischemia. Atrial septal defect (ASD) is a persistent communication between the atria and causes a shunt between systemic and pulmonary circulation. According to ASD size, it causes volume overload of the pulmonary circulation and the RV. In this article, we present an isolated RVMI in a patient with ASD.

CASE REPORT

A 56-year-old male patient with no known disease was admitted to the emergency room with a chest pain complaint that began 1 hour ago. There were ST elevations in II, III, aVF, and V3-4-5-6 leads, ST depression in I, aVL, and right bundle branch block morphology on the electrocardio¬gram (ECG) taken at the time of admission (Figure 1).

Figure 1. Admission electrocardiographyesim



Blood pressure was 160/90 mm Hg, heart rate 74/min, and oxygen saturation was 92%. Routine blood tests were normal. Portable echocardiography showed RV free-wall hypokinesis, RV dilatation, and normal left ventricle (LV) wall motion. After that, thorax computed tomography (CT) was taken to eliminate pulmonary embolism and was viewed normally. Later, the patient underwent coronary angiography. The non-dominant right coronary artery (RCA) was observed to be obstructed. Percutaneous coronary intervention (PCI) was performed on the RCA (Figure 2). After PCI, the patient's ECG findings improved and there was no chest pain (Figure 3). The patient was evaluated as isolated RVMI. Nevertheless, there were no signs of RVMI. However, another underlying disease was investigated due to clinical incompatibility. Secundum ASD was observed in detailed echocardiography (Figure 4). The patient was discharged healthily after 2 days of follow-up. In control echocardiography after one month, RV dilatation persisted, but RV wall movements were normal. Hereby, percutaneous closure of the ASD was decided.

Figure 2. Coronary angiography; right coronary artery obstruction and non-dominant right coronary artery after succesful percutaneous coronary intervention electrocardiographyesim

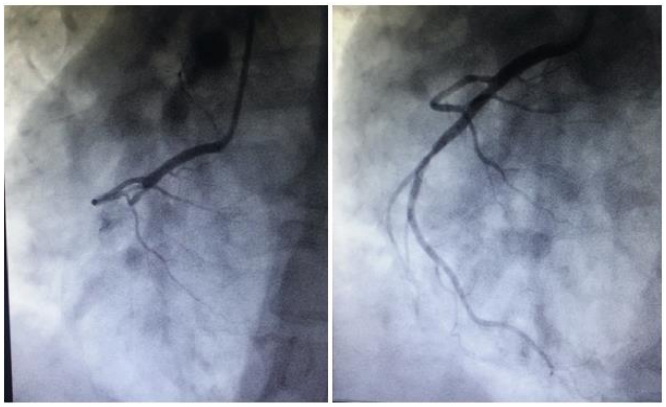


Figure 3. Electrocardiography after succesful percutaneous coronary intervention

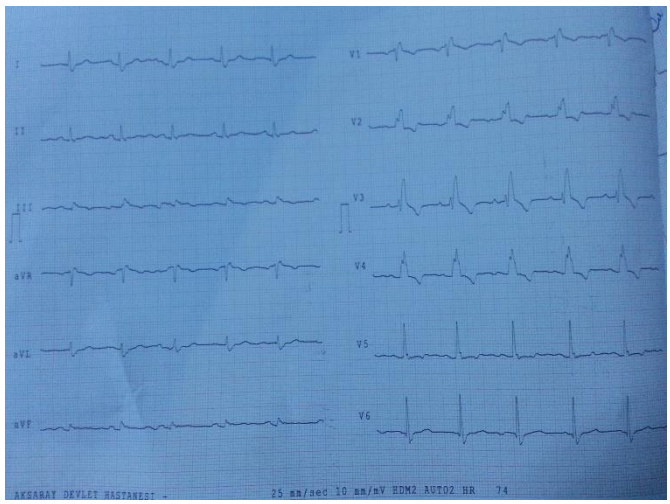
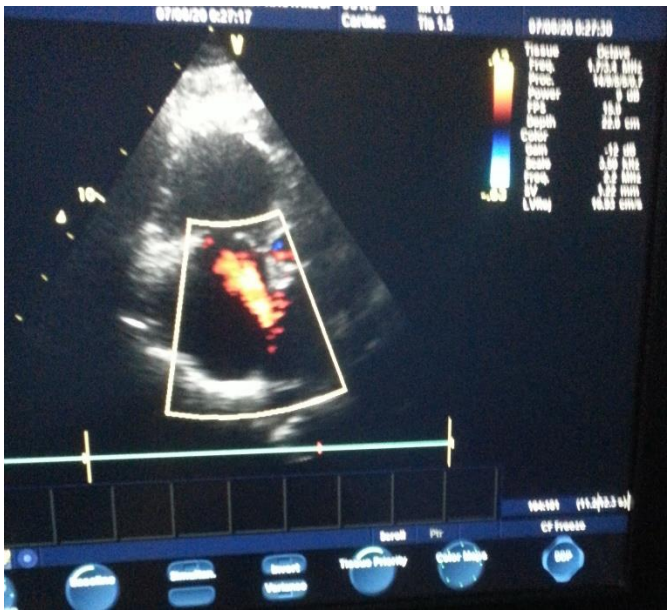


Figure 4. Secundum atrial septal defect by transthoracic echocardiography window



DISCUSSION

The primary effect of RVMI is to cause impaired RV contractility. This leads to reduced blood flow to the lungs and then to the LV. Its clinical manifestations are elevated RV pressures, and decreased LV preload (2). For this reason, RVMI is usually characterized by hypotension, increased venous pressure, and cardiogenic shock (3).

Our patient was hemodynamically stable. Blood pressure and heart rate were normal. There were no signs of RVMI. Persistent moderate or large ASDs cause left-to-right shunts, resulting in right atrial and RV volume overload. These unrepaired shunts can eventually lead to pulmonary arterial hypertension, increased pulmonary vascular resistance, and ultimately RV hypertrophy and dilatation. In our patient, chronic RV dilatation due to ASD may have prevented the reduction of preload LV due to its preconditioning effect. In short, since acute events observed in RVMI developed on a chronic basis due to ASD in our patient, signs of RVMI may not have been observed in our patient.

The ECG findings suggestive of RVMI include ST-segment elevation in leads II, III, and aVF with reciprocal ST-segment depression in the lateral leads (4). ST-segment elevation in lead V4R $\geq$ 1.0 mm is diagnostic of RVMI (5). Isolated RVMI occurs in fewer than 3% of all patients with myocardial infarction (6). Isolated RVMI has been described as acute occlusion of a non-dominant RCA or occlusion of the RV marginal branch during the PCI of the mid-RCA (7,8).

In our patient, there was ST-segment elevation in the anterior and inferior leads, ST-segment depression in I, aVL and there was also a right bundle branch block. Right-sided ECG was not performed because the patient did not have RVMI findings. However, our patient had a non-dominant RCA, normal LV wall movements, hypokinesia in the RV, and RV movements returned to normal after one month, suggesting isolated RVMI.

In some cases of pulmonary embolism, ST-segment elevations mimicking myocardial infarction are observed (9). Additionally, RV dilatation, acute signs of right heart failure, and RV ischemia can be seen.

Our patient had RV dilation, right bundle branch block, and LV wall movements were normal. Therefore, thorax CT was performed to rule out pulmonary embolism.

A rare complication of RVMI is that a pre-existing ASD causes an acute right-to-left shunt. A right-to-left shunt should be suspected in patients who develop acute cyanosis and hypoxemia unresponsive to oxygen administration (10). RVMI may increase right ventricular pressures and cause shunt reversal and hypoxia in patients with pulmonary hypertension due to ASD.

Our patient did not have the right-to-left shunt and hypoxic findings were not observed. The left-to-right shunt was present and oxygen saturation was normal. The patient was likely admitted without an increase in RV pressures, possibly due to early admission. Because our patient applied at our hospital in the first hour of chest pain. If our patient had been admitted to the hospital lately, RV pressures would gradually increase and the left-to-right shunt could have turned to right-to-left shunt.

As a result, RV enlargement due to ASD complicates the diagnosis of isolated RVMI and may affect its hemodynamic effects. The coexistence of RVMI and ASD has been reported very rarely, but isolated RVMI has not been previously reported in a patient with ASD. So, we presented a rare case of the coexistence of ASD and isolated RVMI in this article.

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Olgu Sunumu

Anaflaksi Sonrasi Gelişen Parkinsonizm Olgusu

A Case of Parkinsonism Developing After Anaphylaxis

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ÖZET

Giriş: Bazal ganglionlar perfüzyon sınır bölgesinde yer almaları nedeni ile akut ve kronik hipoksik-iskemik durumlara oldukça duyarlı bölgelerdir. Yapılan çalışmalar hipoksinin PH gibi nörodejeneratif hastalıklara yol açabildiğini göstermiştir. Anafilaksi arı sokması nedeni ile oluşabilen, birçok organın etkilendiği, ölüm ve hipoksi ile sonuçlanan hipersensitivite reaksiyonudur. Biz de arı sokması nedeni ile anafilaksi ve kardiak arrest gelişen, taburcu edildikten sonra takiplerinde parkinsonizm gelişen bir olguyu nadir görülmesi nedeni ile sunmayı planladık.

Olgu: 58 yaşında erkek hasta, arı sokması, anaflaksi sonrası kardiak arrest gelişen hasta 1 haftalık entübasyon süresinden sonra extübe edilmiş. Sonrasında hareketlerde yavaşlama, REM uyku davranış bozukluğu ve unutkanlık şikayeti olması üzerine tarafımıza konsülte edildi. Nörolojik muayenede bradimimi, solda daha belirgin bilateral bradikinezi, bilateral rijidite tespit edildi. Adım aralığının daralmış, postüral instabilitenin pozitif olduğu tespit edildi. Yapılan nöropsikolojik testte özellikle yürütücü işlevlerde bozulma olduğu görüldü. Kranial manyetik rezonans görüntülemesinde (MRG) bilateral nukleus kaudatus, putamen ve globus pallidusta T2 ve FLAIR simetrik hiperintens lezyon olduğu izlendi. Donepezil ve levodopa tedavisi başlanıldı, tedaviden kısmen fayda gören hasta poliklinik kontrolüne alındı.

Sonuç: Bazal ganglion fonksiyonunu bozan, dopaminerjik nöron işleyişine hasar veren tüm durumlar parkinsonizm tablosuna yol açabilmektedir. Tanı ve tedavi yönetimi zor olmaktadır. Gelecekte raporlanacak daha çok vaka ile tanı için kesin kriterler belirlenebilecek ve daha net tedavi planları yapılabilecektir.

Anahtar Kelimeler: Anafilaksi, hipoksi, Parkinson hastalığı.

ABSTRACT

Introduction: Basal ganglias are very sensitive regions at acute and chronic hypoxic-ischemic conditions because of their location in the border of the perfusion region. Studies have shown that hypoxia can lead to neurodegenerative diseases such as Parkinson's disease (PD). Anaphylaxis is the most severe systemic hypersensitivity reaction that can be caused by a number of triggers and conditions like bee sting and can result in cardiac arrest and death. We aimed to present a case who developed anaphylaxis and cardiac arrest due to bee sting and developed parkinsonism in the follow-up after discharge because of its rarity.

Case: A 58-year-old male patient, who developed cardiac arrest after bee sting and anaphylaxis, was extubated after a 1-week intubation period. Afterwards, the case was consulted to us since there are complaints of slowing movements, REM sleep behavior disorder and amnesia. He has bradymymia and bilateral bradykinesia and rigidity more prominent on the left was revealed in neurological examination. It was determined that the step interval was narrowed and the postural instability was positive. It was seen that especially executive functions were impaired in the neuropsychological test. Cranial magnetic resonance imaging (MRI) showed T2 and FLAIR symmetric hyperintense lesions in the bilateral nucleus caudatus, putamen and globus pallidus. Donepezil and levodopa treatment were started. The patient who has partially benefited from the treatment, was taken to the outpatient control.

Conclusion: All conditions that impair basal ganglia function and damage dopaminergic neuron functioning can lead to the parkinsonism. It is difficult to make diagnosis and to manage treatment. Precise criteria for diagnosis and more clear treatment plans will be determined with more cases to be reported in the future.

Keywords: Anaphylaxis, hypoxia, parkinson's disease.

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GİRİŞ

Parkinson hastalığı (PH) istemli motor hareketlerde yavaşlama ile giden progresif nörodejeneratif bir hastalıktır. PH yaklaşık 3/1000 sıklığında gözükmekte iken, 65 yaş üstünde görülme sıklığı %1-3'e yükselmektedir. Hastalığın altında yatan temel neden bazal ganglionun substantia nigra kısmında meydana gelen dopaminerjik nöron kayıplarıdır (1). Bazal ganglionlar perfüzyon sınır bölgesinde yer almaları nedeni ile akut ve kronik hipoksik-iskemik durumlara oldukça duyarlı bölgelerdir. Yapılan çalışmalar hipoksinin PH gibi nörodejeneratif hastalıklara yol açabildiğini göstermiştir (2).

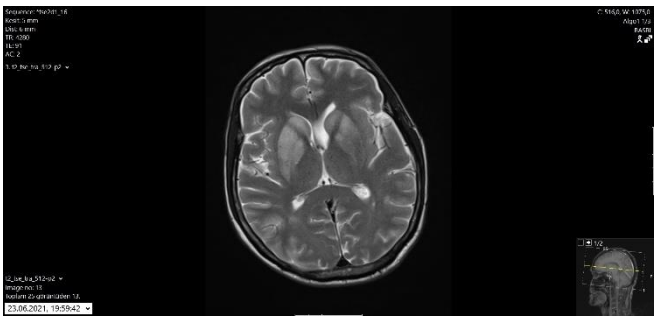
Anafilaksi birçok organın etkilenebildiği, kardiak arrest ve ölümle sonuçlanabilen, çok şiddetli bir hipersensitivite reaksiyonudur. Sebep olarak sırasıyla yiyecekler (%66), böcek zehiri (%19) ve ilaçlar gelmektedir. Literatürdeki bir derleme Avrupa'da her yıl 1,5-7.9/100.000 kişinin anafilaksi yaşadığını raporlamıştır. Arı zehiri de duyarlılığı olan insanlarda sıklıkla alerji ve anaflaksiye neden olan faktörlerden biridir (3).

Biz de arı sokması nedeni ile anafilaksi ve kardiak arrest gelişen, taburcu edildikten sonra takiplerinde parkinsonizm gelişen bir olguyu nadir görülmesi nedeni ile sunmayı planladık.

OLGU

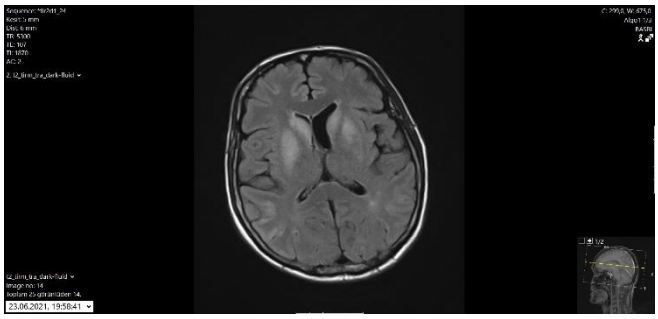
58 yaşında erkek hasta, daha öncesinde herhangi bir şikayeti olmayan hastada arı sokması sonrası anaflaksi gelişmiş ve ardından kardiak arrest ve hipoksi meydana gelmiş. Yaklaşık 1 haftalık entübasyon süresinden sonra extübe edilen hastada hareketlerde yavaşlama, Rem uyku davranış bozukluğu ve unutkanlık şikayeti olması üzerine tarafımıza konsülte edildi. Nörolojik muayenede bradimimi, solda daha belirgin bilateral bradikinezi ve rijidite tespit edildi. Adım aralığının daralmış olduğu ve postüral instabilitenin pozitif olduğu tespit edildi. Kranial manyetik rezonans görüntülemesinde (MRG) bilateral nukleus kaudatus, putamen ve globus palliduslarda T2 ve FLAIR (Fluid Attenuated Inversion Recovery) sekanslarında belirgin simetrik hiperintens lezyon olduğu izlendi (Şekil 1-2).

Şekil 1. Axial T2 Ağırlıklı MR Kesitleri



Hastada hipoksiye sekonder Parkinson hastalığının gelişmiş olduğu düşünüldü. Unutkanlık şikayeti de tarif eden hastanın ayrıntılı nöropsikolojik değerlendirmesinde özellikle yürütücü işlevlerde belirgin bir bozulmasının olduğu, muhakeme ve ikili benzerlik testinde belirgin bozulma olduğu tespit edildi. Bu nedenle hastaya levodopa tedavisi ile birlikte donepezil 5 mg başlanıldı ve takiplerinde 10 mg'a yükseltildi, tedaviden kısmen fayda gören hasta poliklinik kontrolüne alındı. Hastadan yazılı aydınlatılmış onam belgesi alınmıştır.

Şekil 2. Axial FLAIR Ağırlıklı MR Kesitleri



TARTIŞMA

Santral sinir sistemi (SSS) vücutta üretilen enerjinin çok büyük bir kısmını tüketmesi nedeni ile hipoksiye en hassas bölgedir. SSS total oksijen metabolizmasının yaklaşık %20'sini harcar. Bu enerjinin de %75-80'i nöronlar tarafından sinaptik iletim, nörotransmitter sentezi ve depolarizasyon sonrası tekrar membran potansiyeli oluşturmak için kullanılmaktadır. Ağır hipoksi ya da anoksi gibi patolojik koşullar altında nöronlarda hipoksi ile indüklenen metabolik değişiklikler meydana gelir, mitokondri yapısında ve fonksiyonlarında bozulma, oksidatif streste artış, mikroglia aktivasyonu ve en sonunda nörodejenerasyon gerçekleşir (4). Kardiak arrest sonrası uzun dönem sonuçlarda bazal ganglionları da içine alan talamo-kortikal bağlantılarda ve bilateral kortikal bölgelerde hasarlanma meydana gelir, PH, myoklonus, kore ya da tik gibi hareket bozuklukları ortaya çıkabilir. Manyetik rezonans görüntüleme (MRG) ile daha fazla fikir sahibi olunabilmektedir. Nukleus kaudatus, putamen, talamus gibi izole derin beyaz cevher hasarlanması ya da hem kortikal hem de derin beyaz cevher hasarının birarada olduğu görüntüleme bulguları tespit edilebilir (5). Bizim olgumuzda da MRG'de bilateral globus pallidusta simetrik T2 hiperintens görüntü mevcuttu.

PH de meydana gelen dopaminerjik nöron kaybı hastalığın ilk dönemlerinde substantia nigradan başlar, zamanla pons, bulbus, mezensefalon ve neokortekse doğru yayılım gösterdiği bilinmektedir. PH etyolojisi hala net olarak anlaşılamamıştır, fakat mitokondriyal disfonksiyon ve oksidatif stresin patofizyolojiye katkıda bulunduğuna dair güçlü kanıtlar vardır. PH de mitokondriya yapısında bozulma ve sayısında azalma ile birlikte mitokondriyal solunumsal zincir kompleks I aktivitesinde de azalma görülmektedir (6). Hipoksik hasarlanma ile meydana gelen değişiklikler dopaminerjik disfonksiyona kolayca neden olabilmektedir.

Diğer taraftan Hur ve ark. ile Park ve ark. yüksek irtifa çıkışlarını takiben parkinsonizm gelişen dağcılar raporlamıştır. Altta yatan mekanizmanın hipoksi nedeni ile globus pallidusta gelişen hipometabolizma olduğu öne sürülmüştür (7,8).

Swaminath ve ark. da yüksek irtifa tırmanışı sonrasında bilateral globus palliduslarda simetrik lezyon tespit edilen fakat PH gelişmeyen bir olgu tanımlamışlardır (9). Literatürdeki vakalarda nöropsikolojik testler ile kanıtlanmış kognitif disfonksiyon olduğu gösterilmiş, bu durumun medial frontal ve dorsolateral frontal lob hasarı ile ilişkili olabileceği düşünülmüştür. Frontosubkortikal bağlantılar paralel olarak yerleşmiş olup, pallidumdan aşağı doğru inerler. Pallidal lezyonların da unutkanlık ve yürütücü işlevlerde ağır bozulmaya neden olduğu raporlanmıştır. (10). Bizim vakamızda da benzer şekilde pallidal lezyonlar mevcuttu.

Verslegers ve ark kardiak arrest sonrası parkinsonizm gelişen 21 yaşında kardiak arrest gelişen, resüsitasyon ile döndürülen bir olgu tanımlamışlardır. Hastada 3. günden sonra dizartri, hipofoni,, mikrografi, jeneralize ağır rijidite ve bradikinezi ile parkinsonizm bulguları gelişmeye başlamıştır. Bu olguda da bizim vakamızda ve diğer vaka takdimlerinde olduğu gibi MRG'de bilateral globus palliduslarda simetrik enfarktlar tespit edilmiştir (3).

Biz de olgumuzda parkinsonizme yol açan mekanizmanın arı zehri ile gelişen anafilaksi ve kardiak arrest sonrası hipoksi olduğunu düşünmekteyiz.

SONUÇ

Sonuç olarak bazal ganglion fonksiyonunu bozan, dopaminerjik nöron işleyişine hasar veren tüm durumlar parkinsonizm tablosuna yol açabilir. Literatürde anafilaksi ve hipoksi nedeni ile PH gelişen çok az sayıda olgu olması nedeni ile bu tür durumlarla karşılaşıldığında tanı ve tedavi yönetimi zor olmaktadır. Gelecekte raporlanacak daha çok vaka ile tanı için kesin kriterler belirlenebilecek ve daha net tedavi planları yapılabilecektir.

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Olgu Sunumu

Akut İskemide Mezenterik Arter Trombektomisi, Balon ile Genişletme ve Stent Uygulaması Olgusu

A Case of Mesenteric Artery Thrombectomy, Balloon Inflation, and Stenting in Acute Ischemia with Collaboration

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ÖZET

Bu vaka raporu, açık ameliyatın yüksek riskli bir seçenek olduğu birden fazla komorbiditesi olan bir hasta için endovasküler yaklaşımla tedavi edilen akut mezenterik tromboz ve iskemi (AMI) vakasını tanımlamaktadır. Hastanın öncelikle USG ve CT anjiyografi ile değerlendirilmesi sonrasında, tanı doğrulandıktan sonra, trombu çıkarmak için brakiyal yaklaşım ile mezenterik anjiyografi yapıldı. Ancak, orta-distal mezenterik arterde %80 daralma ile yüksek trombus yükü hala gözlendiği için, perkütan translüminal anjiyoplasti ve stent yerleştirilmesi yapıldı. Tatmin edici sonuçlar elde edildikten sonra, hasta şikayetsiz olarak taburcu edildi.

Anahtar Kelimeler: Akut mezenterik iskemi, girişimsel tedavi, işbirliği

ABSTRACT

This case report describes the treatment of a 75-year-old female patient with acute mesenteric thrombus and ischemia (AMI) using an endovascular approach due to multiple comorbidities that made open surgery a high-risk option. The patient underwent initial evaluation with ultrasound (USG) and CT angiography, and after the diagnosis was confirmed, mesenteric angiography was performed via a brachial approach to extract the thrombus. However, a high thrombus burden with 80% narrowing in the middle-distal mesenteric artery was still observed, and therefore, percutaneous transluminal angioplasty with stenting was performed. After satisfactory results were achieved, the patient was discharged with no complaints.

Keywords: Acute mesenteric ischemia, interventional treatment, collaboration

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INTRODUCTION

Acute mesenteric thrombosis and ischemia (AMI) occur in 1-2% of all abdominal emergencies with a 50-70% mortality rate. The pathogenesis of AMI stems from inadequate blood supply, inflammation, and necrosis of the intestinal wall due to arterial embolism, arterial thrombosis, mesenteric venous thrombosis, and non-occlusive causes. Clinically, AMI usually presents with an abrupt onset of severe abdominal pain, vomiting, diarrhea, nausea, abdominal distension, fever, and rectal bleeding. Moreover, peritonitis and septicemia may develop once the ischemia and necrosis have progressed. [1,2]

Although ultrasound (USG) and computed tomography angiography (CTA) are widely used diagnostic tests, mesenteric angiography, which is recommended by the American Gastroenterological Association, is the best way to diagnose AMI. [3] After confirming the diagnosis of AMI, surgery is the most acceptable choice if there are no contraindications. However, since AMI always occurs in elderly patients with multiple comorbidities and poor nutritional status, open surgery is not the best option. [1,3]

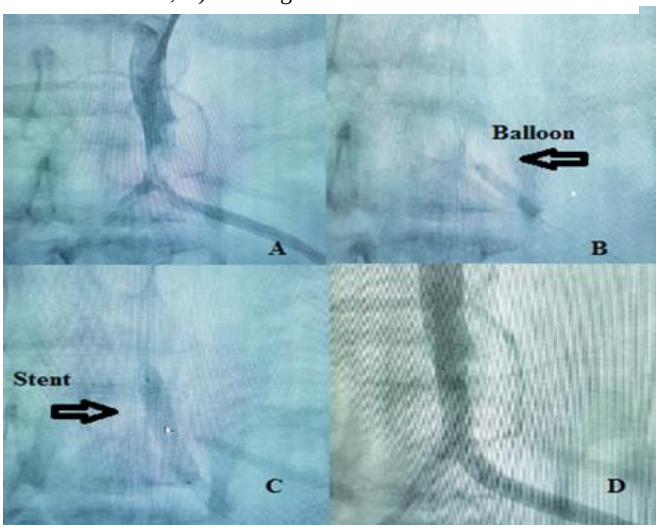
As a result of advancements in endovascular strategies such as percutaneous aspiration of thrombus, thrombolysis, balloon thrombectomy, percutaneous transluminal angioplasty, primary superior mesenteric artery (SMA) stenting, and a combination of these therapies are becoming more popular and becoming an alternative strategy to surgical interventions. Sometimes these endovascular strategies are followed by endoscopic laparotomy for the evaluation of the intestines and, if necessary, resection of the infarcted bowel segments. [4,5].

CASE REPORT

We present here a case of a 75-year-old female patient who was admitted to our general surgery department with acute mesenteric thrombus and ischemia after experiencing 2 days of abdominal pain and vomiting, as well as elevated levels of leukocytes and CRP. The patient had several comorbidities including high blood pressure, type II diabetes, and morbid obesity, making her unsuitable for open surgery. The patient was suspected to have developed acute mesenteric ischemia due to a thrombus formed on the background of chronic systemic atherosclerosis. As a result, an endovascular treatment strategy was chosen after consulting with cardiology and vascular surgery departments.

The patient underwent mesentery angiography via brachial approach with a 7F Amplatz L2 guiding catheter. A thrombosed lesion was identified and passed with a PT-2® 0.014 guide wire, followed by administration of 10,000 units of heparin. Initially, a Capturer® 6F thrombus extraction catheter was used to remove the thrombus, but high thrombus burden with 80% narrowing in the middle-distal mesentery artery was still observed. Therefore, percutaneous transluminal angioplasty (PTA) with stenting was planned. A 4.0-20 mm NC Coronary Balloon was used for debulking and a 4.5-24 mm Bare metal coronary stent was delivered. (Figure 1B, C)

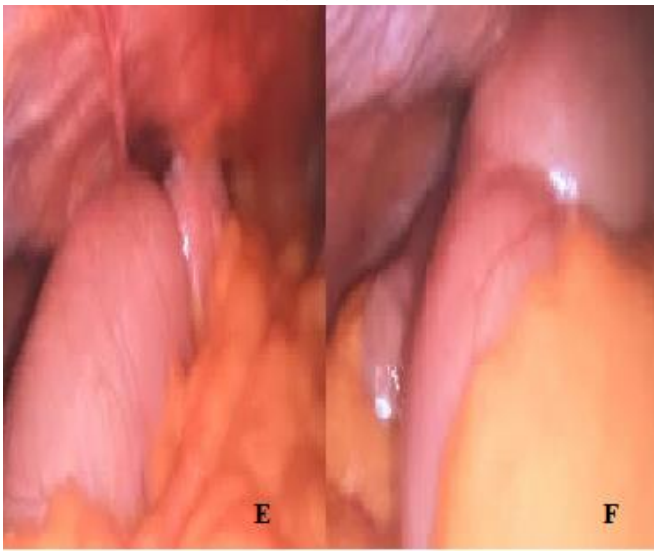
Figure 1. A) Angiography and thrombus aspiration, B) Balloon inflation, C) Stenting and result.



The procedure was completed after satisfactory results were obtained and bleeding was controlled. The patient was given 1 mg/kg Enoxaparin twice a day, tirofiban infusion calculated by weight, and crystalloid infusion during the follow-up period, as recommended by the general surgery department.

After one day of follow-up in the cardiology intensive care unit, the patient underwent an explorative laparoscopy to evaluate intestinal injury, and it was found that the intestinal segments and abdominal cavity were healthy. (Figure 2E, F)

Figure 2. E) Laparoscopic view of affected segment of intestine after intervention, F) Close view of intestine.



Gas and feces discharge were observed on the third day, and the patient was started on a daily dose of 75 mg clopidogrel and 81 mg acetylsalicylic acid after consulting with the cardiology department. The patient was discharged in good health and did not experience any complaints or symptoms during routine follow-up visits at 1 week and 1 month later.

DISCUSSION

AMI and thrombus with arteriosclerotic plaque are surgical emergencies with high mortality rates. The major finding is severe abdominal pain, which is resistant to antispasmodic agents. Physical examination may reveal little findings, accompanied by gastrointestinal emptying symptoms such as vomiting and diarrhea in AMI [1, 2]. Although abdominal radiography and ultrasonography can help with diagnosis, negative results of the USG and X-ray cannot rule out the possibility of AMI. Angiography and CT scans may provide a clear and sensitive diagnosis [2, 3].

Endovascular approaches are becoming increasingly popular in both diagnosis and treatment [4, 5], and the presence of bowel infarction and risk factors can determine a planned treatment approach [5]. Successful treatment depends on early clinical recognition based on a detailed history and physical examination along with diagnostic tests. Treatment of AMI requires close collaboration between general surgery and invasive cardiology [4, 5]. Our case highlights the importance of this collaboration, as recent studies have shown [4].

During the diagnostic period of AMI, the surgery department requested CT angiograms and USG from the radiology department based on clinical and laboratory findings, following current guidelines [1, 2]. Surgery then decided on clinical observation and IV medication because there were no signs of perforation or necrosis. However, the patient's general status deteriorated, and invasive cardiology and vascular surgery consultations were requested by the general surgery team for a joint decision.

Cardiology performed mesenteric angiography to confirm the diagnosis and plan therapy. Angiography revealed partial obstruction of the jejunal-ileal and distal terminal branch of the superior mesenteric artery by thrombus and atherosclerotic plaque. Again, rapid consultations were made with general surgery and vascular surgery due to the necessity of interventional therapy, as shown in current publications [5]. An interventional therapy was undertaken using available coronary equipment. Due to the possibility of intestinal injury, follow-up treatment was planned by surgery and cardiology, which included a low molecular weight heparin and tirofiban infusion until bowel movements resumed [1,5].

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Olgu Sunumu

Histerektomize Vajinal Cuff Prolapsusu Olan Hastaya Carter-Thomason Operasyonu: Olgu Sunumu

Carter-Thomason Operation On Patient With Hysterectomized Vaginal Cuff Prolapsus: A Case Report

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ÖZET

Günümüzde insan yaşam süresi uzamakla beraber, kadın yaşam süresi uzamaktadır. Kadınlar yaşamlarına daha etkin olarak devam etmektedir. İlerleyen yaşa bağlı pelvik doku zayıflaması ve sayısı artan histerektomi ameliyatları sonrasında vaginal cuff prolapsusu görülme ihtimali de artmaktadır. Bundan dolayı yapılan ek ameliyat gereksinimi de artmaktadır. Carter-Thomason operasyonu, round ligamentlerin eleve edildiği uterin prolapsusu ortadan kaldıran cerrahi bir yöntemdir. Yaklaşık 5 yıl önce vajinal histerektomi operasyonu yapılmış olan 80 yaşındaki kadın hastamıza kronik vajınal prolapsusu nedeniyle laparotomik olarak Carter-Thomason operasyonu uygulandı. Bizim bu metodu uygulamamızın nedeni daha önceden yapılan histerektomiye bağlı olarak douglusa ve sakruma yapışıkların gözlemlenmesi ve bu yapışıklıkların açılaması nedeniyle batın fasyasına histerektomiden kalan round ligament kalıntıları suspansiyonu işlemi yapıldı. Bizim olgu sunumumu yapmamızın nedeni ise; bu yöntemin uterin prolapsusu olan hastalarda kullanılmasına rağmen, vajinal cuff prolapsusu olanlarda Carter-Thomason operasyonu tekniğinin kullanılmadığıdır. Bu yöntemin nadir olarak uygulanmaması nedeniyle Carter-Thomason operasyonunu son literatür bilgileri eşliğinde bu olgumuzda tartışmayı planladık

Anahtar Kelimeler: Carter-Thomason operasyonu, histerektomi, round ligament, vajınal prolapsus.

ABSTRACT

Today, while human life expectancy is getting longer, the life expectancy of women is getting longer. Women continue their lives more effectively. The possibility of vaginal cuff prolapse increases with age-related weakening of the pelvic tissue and after hysterectomy operations with increasing numbers. Therefore, the need for additional surgery is also increasing. Carter-Thomason operation is a surgical method that eliminates uterine prolapse in which round ligaments are elevated. Our 80-year-old female patient, who had undergone vaginal hysterectomy about 5 years ago, underwent laparotomy Carter-Thomason operation due to chronic vaginal prolapse. The reason for our application of this method was the observation of adhesions to the pelvis and sacrum due to the previous hysterectomy, and the opening of these adhesions, so the round ligament remnants from the hysterectomy were suspended in the abdominal fascia. The reason for presenting our case report is; although this method is used in patients with uterine prolapse, the Carter-Thomason operation technique is not used in patients with vaginal cuff prolapse. Since this method is rarely used, we planned to discuss the Carter-Thomason operation in this case, in the light of the latest literatüre

Keywords: Thomason operation, hysterectomy, round ligament, vaginal prolapse.

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GİRİŞ

Uterusun vajen duvarlarını kendisiyle beraber sürükleyerek aşağıya doğru anormal şekilde sarkması uterin prolapsus olarak isimlendirilir. Genel olarak da mesane, rektum ve barsak sarkması (sistosel, rektosel ve enterosel) ile beraber görülür. Uterin prolapsus ileri yaş kadınlarda oldukça sık görülen vaka olup tedavisinde genel olarak operasyon planlanılmaktadır (1). Cerrahide amaç, prolobe olan kısımların normal anatomiye uygun şekle getirilmesi, onarılması veya çıkartılmasıdır.

Vajen duvarının tamamen dışarı çıkması, histerektomi komplikasyonu olarak vakaların %0.2-1'inde görülür. Primer risk faktörü obesite olup (2,3) tedavide çeşitli abdominal ve vajinal cerrahi yöntemler mevcuttur.

Vajen kafı prolapsuslarında usta ellerde vajinal sakrospinöz fiksasyon ve abdominal sakrokolpopeksi teknikleri ile %90 oranında başarı elde edildiği rapor edilmiştir (4,5). Pelvik rekonstrüktif cerrahi teknikleri arasında abdominal teknikler vajinal olanlara göre daha etkindir (6). Vajen kaf prolapsusu vakalarında abdominal yaklaşım tercih edildiğinde, fasyal askı tekniği, basit ve etkin olması nedeniyle tercih edilir (7).

Modifiye Carter- Thomason operasyonu laparotomik olarak round ligament suspansiyonu olup daha önceden vajınal histerektomi operasyonu geçiren kadınlarda sistosel-enterosel ve rektosel oluşumlarını engellemek için kullanılabilir (8).

Kliniğimize kronik vajinal prolapsus mevcudiyeti nedeniyle başvuran yaklaşık 5 yıl önce vajinal histerektomi operasyonu uygulanmış, 80 yaşındaki bir kadına Carter-Thomason metodu kullanılarak laparotomik olarak batın fasyasına round ligament suspansiyonu işlemi yapıldı. Bu olgu sunumunu son literatür bilgileri eşliğinde tartışmayı planladık.

OLGU

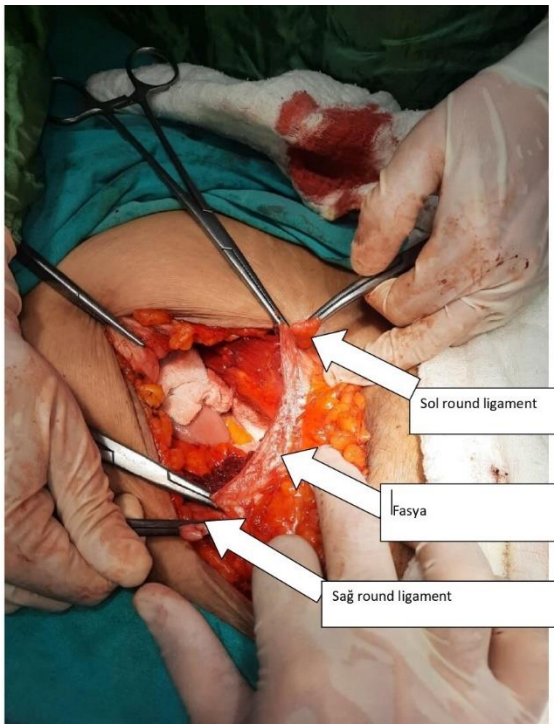
Seksen yaşında gravida 3, parite 3 olan, beş yıl önce vajınal histerektomi operasyonu olan sonucu da benign gelen hasta, mesane ve rektumunun uzun zamandır dışarı çıkması ve ağrı şikayeti ile polikliniğimize başvurdu. Hastaya daha önceki müdahalelerde vajınal pesser 6 numara takılmasına rağmen zaman zaman prolapsus şikâyetinin devam etdiğini bildirdi. Yapılan jinekolojik muayenesinde total vajınal prolapsus gözlenen hastaya vajinal cuff prolapsusu tanısıyla preop hazırlıkları tamamlanan hastaya operasyon planlandı (Resim1).

Preoparatif hazırlıkları tamamlanan, tetkikleri düzenlenen hasta ameliyata alındı. Proflaktif antibiotik verildi ve foley sonda uygulandı. Genel anestezi altında litotomi pozisyonunda batına pfannenstiel kesi yapıldı ve batına girildi. Hastanın önceki vajınal histerektomi operasyonuna bağlı mesanenin douglasa ve cuffa yapışıklıkları olduğu izlendi. Kolonun da sakruma ileri derecede yapışık olduğu izlendi.

Resim 1. Preop vajinal prolapsus

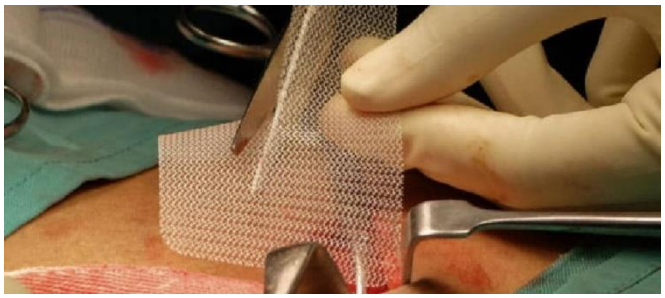
Sakrumdaki yapışıkların ileri derecede olmasından dolayı hastaya sakrokolpopeksi ve cuffın batına süspansiyonu operasyonları uygun görülmedi. Hastanın bilateral round ligamentlerinin histerektomiye rağmen sağlam olarak kaldığı izlendi. Sonrasında round ligamentler 1.0 prolen ve 1.0 PDS ile iki taraflı olarak geçilerek batın ön duvarına yaklaştırılarak, fasyaya sütüre edilip sabitlendi (Resim 2).

Resim 2. Roud ligamentlerin fasyaya süspansiyonu

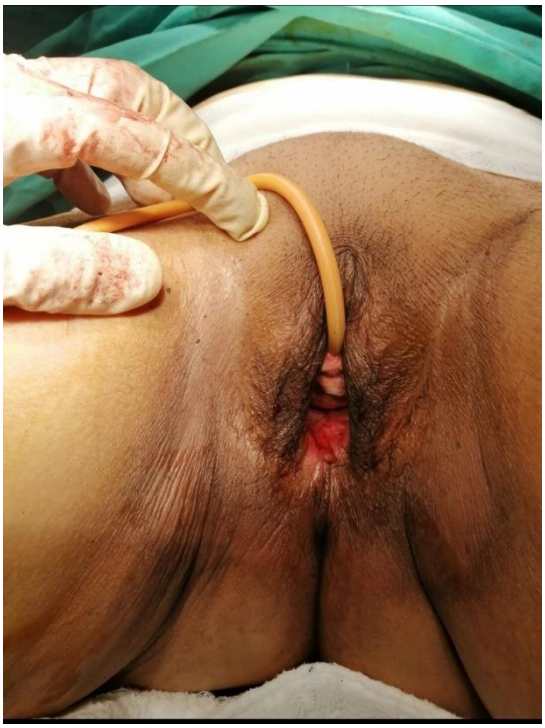


Ayrıca bu sütürler yaklaşık 5*2 cm boyutundaki mesh (Resim 3) ile yatay olarak da birbirlerine yaklaştırılarak dikildi. Hemostazı takiben batın anatomiye uygun kapatıldı. Operasyona son verildi. Operasyon sonrasında prolapsusunun olmadığı izlendi (Resim 4). Postop takiplerinde şikayetleri olmayan hasta yaklaşık 3 gün sonara taburcu edildi. 15 gün sonraki kontrollerinde şikayeti olmayan hasta 3 ay sonraki kontrolünde de prolapsus şikayetinin olmadığı izlendi.

Resim 3. Round ligamentleri birbirine yaklaştıracak mesh hazırlığı



Resim 4. R Postop vajinal prolapsus ortadan kaybolmuştur.



TARTIŞMA

Günümüzde yaşlılıkta, aktif yaşam tarzını seçen eden kadın sayısı fazladır. Çoğunun seksüel yaşamları yetmiş-seksen yaşarlına kadar devam etmektedir. Yaşlanma ve postop histerektomide vajinal güdükte yetersiz olan destek dokusu, vajinal cuff prolapsusu oluşumunda önemli iki etkenlerdendir. Ayrıca menapoz, konstipasyon, obesite ve obstrüktif akciğer hastalıkları da başlıca sebeplerdir(9). Bundan dolayı pelvik rekonstrüksiyon cerrahi gereksinimi de doğmaktadır. Operasyonu gerçekleştirecek cerrahın amacı; semptomları kaybetmek, anatomiyi tekrardan elde etmek ve fonksiyonel bütünlüğü sağlamaktır. Vajinal cuff prolapsusunu düzeltmeye yönelik cerrahi prosedürler arasında Carter-Thomason metodu yer alır (8). Carter-Thomason metodunda amaç, round ligamenti rektus kası fasyasına yaklaştırmaktır.

Round ligament kullanılarak cuff suspansiyonu yapılması tartışmalı bir yöntem olup, kısa dönemde yarar sağlamakta iken, rekürrensler operasyondan kısa bir süre sonra görülebilmektedir(10,11). Yapılan çalışmalar çoğunlukla histeropeksi tarzında olsa da sonuç olarak desensus olan dokunun süspansiyonu ana amaç olarak görülmektedir. Krauer's ve ark. 81 kadında laparoskopik olarak uterusu promontoriuma asmışlar. Yirmi aylık takipte hastaların %l2'sinde postop semptomatik prolapsus saptanmıştır(12). Yapılan diğer bir çalışmada abdominal sakrohisteropeksi yapılan 30 kadının 94 ay takibi sonucu sadece ikisinde prolapsusun tekrarı raporlanmıştır(13). Cutner ve arkadaşlarının çalışmasında ise laparoskopik olarak mesh yardımı ile bilateral olarak uterusu sakral promontoriuma süspanse edip; 8 hastadan ancak birinde rekürrens görülmüştür(14). Transvaginal olarak uterosakral süspansiyon yüksek seviyede üreter yaralanması ve nörolojik morbidite ile ilişkisi saptanmıştır(15). Başka bir çalışmada ise sakrospinoz fiksasyon yapılan 70 kadından %74'de başarı görülmüştür(16). Price ve ark. yaptıkları çalışmada uterusu polipropilen mesh ile sakrum üzerindeki longitudinal ligamente astıktan on hafta sonrasında 5l kadından yalnızca birisinde tekrar saptanmıştır(17). Wu ve ark. yaptıkları başka bit çalışmada ise laparoskopik uterosakral plikasyon yöntemi ile 7 hastanın 9-17 ay takibinde tekrar izlememişlerdir (18). Literatür taramasında baktığımızda cuff prolapsusunda daha önceden kullanıldığına dair bir çalışma saptanamamıştır. Biz vakamızda laparotomik yöntemle round ligament aracılığı ile prolabe vajen cuffının rektus fasyasına suspanse edildiği bir yöntem kullandık. Takibinde ise orta dönemde hastada rekürrens saptamadık. Tüm bunlara rağmen, özellikle round ligament kullanılarak, uterin süspansiyon ameliyatlarının uzun dönem sonuçları tartışmalı olabilir. Gerçekten de, zamanla askı amacıyla kullanılan bağların gevşeyerek askı görevlerini yerine getiremedikleri düşünülmektedir. Ayrıca biz bu vakamızda ek olarak mesh ekleyerek de ileri dönemde sarkıklığın oluşma ihtimalini de azalttığımızı düşünüyoruz.

SONUÇ

Sonuçta uterin plikasyon yöntemleriyle alakalı yeni çalışmalar sürmektedir. Bizim olgu sunumumu yapmamızın nedeni ise; vajinal cuff prolapsusunda daha önceden Carter-Thomason operasyonu tekniğinin kullanılmadığıdır. Bu konuyla alakalı farklı cerrahi tekniklerin uzun dönem sonuçlarının değerlendirileceği daha geniş çaplı araştırmalara gereksinim vardır.

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