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Address: Selçuk Üniversitesi, Tıp Fakültesi Çocuk Yoğun Bakım Bilim Dalı Alaeddin Keykubat Yerleşkesi Selçuklu/Konya 42075 Türkiye
Phone: +90 (332) 241 50 00-44513
Fax: +90 (332) 241 21 84
e-mail: cagdastipdergisi @gmail.com
web: http://www.jcontempmed.com

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Journal article on the Internet

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Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

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The source of financial grants and the contribution of colleagues or institutions should be acknowledged.

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Prof. Dr. Resul YILMAZ
Selçuk Üniversitesi, Tıp Fakültesi
Çocuk Yoğun Bakım Bilim Dalı
Alaeddin Keykubat Yerleşkesi Selçuklu/Konya 42075 Türkiye
Phone: +90 (332) 241 50 00-44513
Faks: +90 (332) 241 21 84

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Orjinal Araştırma / Original Article

Chest Pain and Its Recurrence in Pediatric Population: A Large Cohort Study

Çocukluk Çağında Göğüs Ağrısı ve Tekrarlama Sıklığı: Geniş Bir Toplum Çalışması

Esma Keleş Alp[1], Hayrullah Alp[2]

[1]Dr. Ali Kemal Belviranlı Obstetrics and Children's Hospital, Department of Pediatrics, Konya, Turkey
[2]KTO Karatay University, Medical Faculty, Department of Pediatrics, Konya, Turkey

Abstract

Introduction: Chest pain is a common complaint in children. In this retrospective study we investigated the clinical and etiological characteristics and the recurrence rates of chest pain in a large cohort of patients.

Material and Method: This study enrolled children under the age of 18 years who admitted to our pediatrics and pediatric cardiology departments with the chief complaint of chest pain. The medical files and laboratory data of patients with chest pain were retrospectively reviewed.

Results: Among 503 patients with chest pain, 346 (68.7%) cases were referred to pediatric cardiology department because of a suspicious of a cardiac chest pain. Non-cardiac chest pain accounted for 95.2% (478 patients) and cardiac chest pain accounted for 4.8% (25 patients). A total of 23 (92%) patients in cardiac chest pain group and 212 (44.3%) patients in non-cardiac group had recurrent chest pain. Recurrent chest pain was commonly detected in cardiac chest pain, respiratory, gastrointestinal and psychological disorders.

Discussion and Conclusion: In this study, the most common etiologies of chest pain in children were idiopathic chest pain and musculoskeletal disorders. Also, our results showed that chest pain is commonly recurrent and cardiac causes of chest pain are very rare in children. Unnecessary referrals should be reduced with a careful history and physical examination.

Keywords: Chest pain, children, recurrence, cardiac related, referrals

Öz

Amaç: Göğüs ağrısı çocuklarda yaygın görülen bir şikâyettir. Bu retrospektif çalışmada pediatri bölümüne başvuran ve pediatrik kardiyoloji bölümüne sevk edilen geniş bir hasta grubunda göğüs ağrısının klinik ve etiyolojik özellikleri ile tekrarlama oranlarını araştırdık.

Gereç ve Yöntem: Bu çalışmaya pediatri bölümümüze başvuran ve göğüs ağrısı şikayeti ile pediatrik kardiyoloji bölümüne sevk edilen 18 yaşın altındaki çocuklar dâhil edildi. Göğüs ağrısı olan hastaların tıbbi dosyaları ve laboratuar verileri retrospektif olarak incelendi.

Bulgular: Göğüs ağrısı olan 503 hastadan 346'sı (%68.7) kardiyak göğüs ağrısı şüphesi nedeniyle pediatrik kardiyoloji bölümüne sevk edilmişti. Kardiyak nedenlerle ilişkili olmayan göğüs ağrısı %95.2 (478 hasta), kardiyak nedenlerle ilişkili göğüs ağrısı %4.8 (25 hasta) oranlarında idi. Kardiyak nedenlerle ilişkili göğüs ağrısı grubunda 23 hasta (%92) ve kardiyak olmayan grupta 212 hastada (% 44.3) tekrarlayan göğüs ağrısı vardı. Tekrarlayan göğüs ağrısı, kardiyak nedenlerle ilişkili göğüs ağrısı, solunum, gastrointestinal ve psikolojik bozukluklarda yaygın olarak saptandı.

Sonuç ve Tartışma: Bu çalışmada, çocuklarda göğüs ağrısının en sık etiyolojik nedeni idiyopatik göğüs ağrısı ve kas-iskelet sistemi hastalıkları olarak bulunmuştur. Ayrıca, bizim sonuçlarımız çocuklarda göğüs ağrısının sık tekrarladığını ve göğüs ağrısının kardiyak nedenlerinin çocuklarda çok nadir olduğunu göstermiştir. Sonuç olarak, dikkatli bir öykü ve fizik muayene ile gereksiz sevk ve yönlendirmeler azaltılabilir.

Anahtar kelimeler: Göğüs ağrısı, çocuklar, tekrarlama, kalple ilişkili, sevkler

Corresponding *(İletişim)*: Esma Keleş Alp, Dr. Ali Kemal Belviranlı Obstetrics and Children's Hospital, Department of Pediatrics, Division of Pediatric Cardiology, 42285, Konya, Turkey
E-mail *(E-posta)*: esmaalp@hotmail.com
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INTRODUCTION

Chest pain is a common complaint in children admitted to the pediatrics, pediatric cardiology and pediatric emergency departments.[1] Also; it threatens life and has an effect on daily life with accounts for 0.3–0.6% of all chest pain accesses.[2] On the other hand, it is one of the most common reasons for referral to the pediatric cardiologist being second only to heart murmur.[3] Unlike children, chest pain in the adult population is commonly associated with cardiac disorders and sudden death. Dramatic media accounts of sudden deaths in young athletes have focused attention on chest pain as a sign of severe heart disease. However, fatal heart disease is extremely rare in the pediatric population and families seek reassurance when they bring their child to the pediatrics and pediatric cardiology departments or a specialist with a complaint of chest pain.[4,5]

Although cardiac disease rarely presents as chest pain in pediatric population, every patient should be evaluated to rule out significant underlying disease with history and physical examination being the first steps in diagnosing the cause of such pain in most cases.

Definitively ruling out cardiac disease in children can be more challenging because most young children are not able to accurately describe or localize their pain. Also, follow-up studies revealed that 43% of patients still experienced chest pain at 6 months and 16% of children with chest pain had more than one visit to the emergency department with the same complaint.[1,6] This may prompt further testing, leading to high resource utilization for chest pain evaluation. However, a cardiac etiology is found only in a small minority of cases, reported from 0 to 10% in most of the previous studies.[1-8] Because of the potential association with several complex anatomic malformations that may be life threatening and high costs associated with chest pain, there is wide practice variation in the outpatient evaluation of these patients, stimulating efforts to create standardized assessment algorithms.[9-11]

The primary objective of this study was to investigate the clinical and etiological characteristics and the recurrence of chest pain in a large cohort of patients admitted to pediatrics department and that referred to pediatric cardiology department. The secondary aim was to examine the occurrence of significant cardiac disease in this population.

MATERIAL AND METHOD

Study population

This study enrolled children under the age of 18 years who admitted to our pediatrics department and that referred to pediatric cardiology department with the chief complaint of chest pain over a period of 2.5 years (January, 2017–August, 2019). Information to determine general demographics (ages, sex, weight, height, body mass index, family history), clinical presentation, recurrence of chest pain, associated symptoms, disposition, hospital course, medications and final diagnoses were retrospectively reviewed.

All children underwent complete physical examination, including weight and height measurements. The body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. Children were defined as obese if they had a body mass index greater than or equal to 95th percentile, and overweight if they had a body mass index between 85th and 94th percentile for age and gender based on the standards of the Centers for Disease Control and Prevention.[12] Blood pressure was measured with a standard mercury sphygmomanometer after a 10-minute rest. Abnormalities detected on physical examination, which were considered pertinent positives, included tenderness on palpation over the chondrosternal or costochondral junction, swelling at the chondrosternal junction, murmur, click, gallop, pericardial rub, abnormal second heart sound, distant heart sounds, hepatomegaly, decreased femoral or peripheral pulses, peripheral edema, painful or swollen extremities, and tachypnea. Also, the following studies were performed by a pediatrist and pediatric cardiologist: complete blood count in all patients; fasting total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides levels in overweight and obese children and children with a family history of premature cardiovascular disease; electrocardiogram, chest X-ray. Additionally, if necessary 24-hour electrocardiogram monitoring and/or exercise stress tests were performed by the pediatric cardiologist. Electrocardiograms were performed on all the patients with chest pain while echocardiograms were performed on the patients who were referred to pediatric cardiology department. Also, if necessary the patients were referred to pediatric gastroenterology, endocrinology and psychiatry departments for final diagnoses. The recurrence time course was defined as more than one attack during a day period or more than one attack during a week period or more than one attack during a month period.

All the medical records were reviewed by a pediatrician and by a pediatric cardiologist, and children were categorized as affected by cardiac or non-cardiac chest pain. The study was approved by the local ethics committee. (T.C. Ministry Health Konya Provincial Health Directorate Dr. Ali Kemal Belviranli Obstetrics And Pediatrics Hospital date 2020 numbered 99980113-903.99)

Echocardiographic study

Echocardiographic investigations were performed using Philips Affiniti 50 (Philips Healthcare, Andover, Netherlands) with 5.0 MHz transducers in our pediatric cardiology echocardiography laboratory by the same observer. A full echocardiography including conventional Doppler, color images, and M-mode measurements was performed. Echocardiograms were recorded on a flash drive for repeated evaluation. All measurements were performed according to the American Society of Echocardiography.[13]

Statistical analyses

Descriptive statistics were calculated using counts, frequencies, medians, and interquartile ranges for patient demographics and sedation procedure characteristics. Categorical data were presented as frequencies (%) and analyzed using Chi-square test. Statistical significance was inferred at $p<0.05$. Statistical analyses were done using SPSS for Windows Version 17.0 software (Chicago, IL, USA).

RESULTS

During the study period, a total of 13,741 patients admitted to pediatrics department and among them 503 patients had a complaint of chest pain. Among these 503 patients with chest pain, 346 (68.7%) cases were referred to pediatric cardiology department because of a suspicious of a cardiac chest pain (**Figure 1**). The mean age of the cases was 11.1±3.5 years (4-17 years) and 225 (45%) were girls while 278 (55%) patients were boys in the study population. The mean age of the girls was 10.5±2.7 years with a median of 11 years and a range of 4–17 years and the mean age of the boys was 11.3±2.1 years with a median of 11 years and a range of 4–16 years. Also, recurrent chest pain was determined in a total of 235 (46.7%) patients.

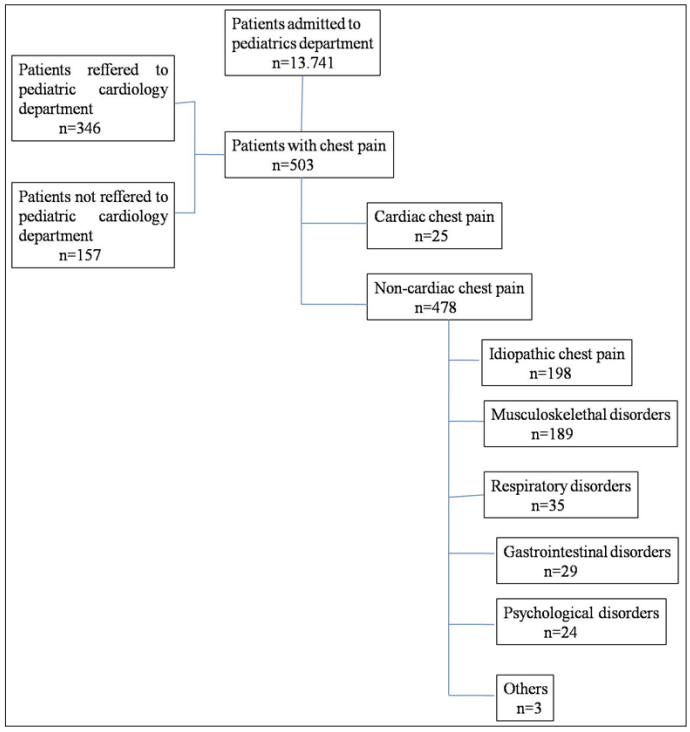

Figure 1. The number of referred patients from pediatric department to pediatric cardiology department and diagnoses for patients with cardiac and non-cardiac chest pain.

Non-cardiac chest pain accounted for 95.2% (478 patients) and cardiac chest pain accounted for 4.8% (25 patients). The diagnoses for patients with cardiac and non-cardiac chest pain and related demographic parameters are illustrated in **Table 1**. There was no statistical difference for mean age (11.68±4.05 vs. 11.04±3.47, p>0.05), gender (p>0.05), weight (38.3±11.2 vs. 35.6±9.2, p>0.05), height (137.5±14.3 vs. 139.1±13.9, p>0.05), body mass index (15.23±3.2 vs. 16.35±3.8, p>0.05), systolic blood pressure (95.5±7.8 vs. 97.1±5.6 mmHg, p>0.05), chest pain recurrence with effort (p>0.05) or at rest (p>0.05) and hospitalization (p=0.06) between the patients with cardiac and non-cardiac chest pains. On the other hand, non-cardiac chest pain group had the higher percentages (55.6%, 266 patients) for chest pain without recurrence (p<0.001). Also, 48% of patients in cardiac chest pain group and 21.1% of patients in non-cardiac chest pain group had more than one visit to our pediatrics and pediatric cardiology departments with the same complaint and this achieved statistical significance (p=0.03). Additionally, non-steroidal anti-inflammatory drug therapy was required for one patient with viral pericarditis in cardiac chest pain group while 149 patients were given non-steroidal anti-inflammatory drugs in non-cardiac chest pain group (p=0.02).

Table 1. Demographic data of patients with cardiac and non-cardiac chest pain

	Cardiac chest pain N:25	Non-cardiac chest pain N:478	P value
Median age	11.68±4.05	11.04±3.47	>0.05
Gender Male Female	 11 (44%) 14 (56%)	 267 (55.9%) 211 (44.1%)	>0.05
Weight (kg)	38.3±11.2	35.6±9.2	>0.05
Height (cm)	137.5±14.3	139.1±13.9	>0.05
Body mass index (kg/m^2)	15.23±3.2	16.35±3.8	>0.05
Systolic blood pressure	95.5±7.8	97.1±5.6	>0.05
Recurrence With exercise At rest	 4 (17.4%) 19 (82.6%)	 35 (16.5%) 177 (83.5%)	>0.05
Without recurrence	2 (8%)	266 (55.6%)	<0.001
Recurrent visits	12 (48%)	101 (21.1%)	0.03
Hospitalization	1 (4%)	31 (6.4%)	0.06
Medical therapy	1 (4%)	149 (31.1%)	0.02

In all the patients, 37 patients (7.3%) in non-cardiac chest pain group had obesity and 21 patients (4.1%) were overweight. However, no patient was diagnosed as obese or overweight in cardiac chest pain group.

Table 2 shows the etiology of chest pain in patients. Mitral valve prolapse, hypertrophic cardiomyopathy, bicuspid aortic valve and aortic stenosis, pulmonary artery hypertension and pericarditis were the causes of cardiac chest pain. Idiopathic chest pain and musculoskeletal disorders were the most common diagnosis (39.4% and 37.6%) in the study population. Respiratory, gastrointestinal and psychological disorders are rare causes (7%, 5.8% and 4.8%, respectively). Also, among all the patients with psychological disorders, generalised

anxiety disorders (32.3%) were the most common form and diagnosed in 11 boy patients which was more common than girls. Of the 189 patients who had musculoskeletal disorders, chostochondritis was the major etiology and was most common in boys. Additionally, severe cough and gastroesophageal reflux were the most common reasons for respiratory and gastrointestinal disorders, respectively. On the other hand, girls had severe cough than the boys in non-cardiac chest pain group. Owing to breast pain, two patients had chest pain due to gynaecomastia. Also, one patient was diagnosed Familial Mediterranean Fever and he was treated with colchicine. Additionally, cardiac-related chest pain was more common in girls, whereas non-cardiac related chest pain was more common in boys.

Table 3 shows the recurrence in chest pain. A total of 23 (92%) patients in cardiac chest pain group and 212 (44.3%) patients in non-cardiac group had recurrent chest pain. Recurrent chest pain was commonly detected in cardiac chest pain, respiratory, gastrointestinal and psychological disorders. Also, recurrent chest pain was more common in girls in the cardiac chest pain group. On the other hand, recurrence was more common in boys who had idiopathic chest pain, musculoskeletal, gastrointestinal and psychological disorders.

DISCUSSION

Chest pain is a common referral complaint in children and in some patients can become recurrent and severe, interfering significantly with the daily life activities. In recent years, news and media reports on sudden deaths in athletes have created concern among both families and physicians. Primary care and emergency department physicians may be fearful of missing cardiac pathology and assuming responsibility for clearing athletes to participate in sports. In this retrospective study, we reported demographic and clinical characteristics, as well as causes of chest pain and its recurrence in children referred to our pediatric and pediatric cardiology departments. Also, our study is one of the largest studies that has evaluated chest pain in children.

The serious and rare cardiac causes of pediatric chest pain, including anomalous coronary origins, cardiomyopathy, pulmonary hypertension, myocarditis, and pericarditis, can be diagnosed by history, cardiac examination, electrocardiogram, and echocardiogram.[1-8] Previous retrospective[8,14,15] and prospective[1-7] studies reported a prevalence of cardiac abnormalities from 0 to 10%. Similarly, our results emphasize the findings of previous reports showing that cardiac etiologies of pediatric chest pain are rare. The incidence of cardiac causes

Table 2. The etiology of chest pain in study population.

	Gender		Total	
	Boys N (%)	**Girls N (%)**	**N**	**%**
Cardiac chest pain	11 (4)	14 (6.2)	25	
Mitral valve prolapse	3	12	15	
Hypertrophic cardiomyopathy	1	1	2	
Bicuspid aortic valve and aortic stenosis	4	1	5	4.8
Pulmonary artery hypertension	2	-	2	
Pericarditis	1	-	1	
Non-cardiac chest pain	267 (96)	211 (93.8)	478	
Idiopathic chest pain	107 (38.5)	91 (40.4)	198	95.2
Musculoskeletal disorders	114 (41)	75 (33.3)	189	39,4
Costochondritis	101	66	167	37,6
Chest wall strain	11	8	19	
Trauma	2	1	3	
Respiratory disorders	15 (5.4)	20 (8.9)	35	
Cough	7	15	22	7
Pneumonia	5	4	9	
Asthma	3	1	4	
Gastrointestinal disorders	14 (5)	15 (6.7)	29	
Gastroesophageal reflux	11	10	21	5,8
Gastritis	3	5	8	
Psychological disorders	14 (5)	10 (4.4)	24	
Others	3 (1.1)	-	3	4,8
Familial Mediterranean Fever	1	-	1	0,6
Gynaecomastia	2	-	2	

Table 3. The etiology of recurrent chest pain in study population.

	Chest pain without recurrence		Recurrent chest pain	
	Boy N(%)	Girl N(%)	Boy N(%)	Girl N(%)
Cardiac chest pain	1 (0.7)	1 (0.8)	10 (7.6)	13 (12.6)
Non-cardiac chest pain				
Idiopathic chest pain	78 (53.4)	68 (55,7)	29 (22)	23 (22.3)
Musculoskeletal disorders	57 (39)	39 (32)	57 (43.2)	36 (35)
Respiratory disorders	5 (3.4)	6 (4.9)	10 (7.6)	14 (13.6)
Gastrointestinal disorders	1 (0.7)	5 (4.1)	13 (9.8)	10 (9.7)
Psychological disorders	4 (2.7)	3 (2.5)	10 (7.6)	7 (6.8)
Others	-	-	3 (2.3)	-

of chest pain was 4.8% in our study. Also, we found that mitral valve prolapse was the most common etiology in cardiac chest pain group and it was diagnosed in girls more than boys. It is known that, mitral valve prolapsed may cause chest pain by papillary muscle or left ventricular endocardial ischemia.[2,3]

A follow-up study of 149 children presenting with chest pain showed recurrence with 43% and the majority of these cases were diagnosed as idiopathic chest pain.[6] In another study, 16% of children with chest pain had more than one visit to the emergency department with the same complaint and 8% of them had chest pain for more than 1 year.[14] Similarly, Sert et al. [5] reported that, in their series chest pain had lasted for more than 6 months in 32.9% of the children and approximately 5% of children with chest pain had more than one visit.In our study, we reported that, 92% of patients with cardiac chest pain and 44.3% of patients with non-cardiac chest pain had recurrences. So, recurrent chest pain was found to be higher in cardiac chest pain group in our study population. Also, 48% of patients in cardiac chest pain group and 21.1% of patients in non-cardiac chest pain group had more than one visit to our pediatrics and pediatric cardiology departments with the same complaint.

As in previous studies, idiopathic chest pain and musculoskeletal disorders are the main cause of non-cardiac chest pain in the pediatric age.[1-8,14-17] Idiopathic chest pain is diagnosed when no clear etiology can be found. In some studies, it was suggested that in 20–45% of cases with pediatric chest pain, no clear etiology can be found.[1,5,17] On the other hand, musculoskeletal disorders are also common causes of chest pain in children and careful physical examination reveals chest wall tenderness or pain with movement of the torso or upper extremities.[1-8] Costochondritis, chest wall strain and trauma are common causes of musculoskeletal disorders in children.[3-5] Similarly in our study, we reported the incidence of chest pain related with idiopathic and musculoskeletal system disorders as 39.4% and 37.6%, respectively. Also, we found that costochondritis was the major causes of musculoskeletal disorders in non-cardiac chest pain group.

Obesity is a growing problem around the world and it became an important etiology for chest pain on its own or in combination with other conditions in children and adults. [18] So, another potential reason that more children with chest pain are being referred to pediatric cardiology is the increased number of overweight and obese children. It is possible that with increasing concern for premature coronary disease in overweight children. Also, their effort capacity is lower than the healthy population. In our study, 37 patients (7.3%) in non-cardiac chest pain group had obesity and 21 patients (4.1%) were overweight.

School absenteeism is a specific marker of psychological distress and should always be investigated and emphasized with studies showing that it is a specific feature of children affected by somatic symptom disorders or other psychopathologies.[19] It should also be considered that in such a frequent non-severe disease, as chest pain is, parental concerns more than child's fear may influence the quality of life of the child. Moreover, parents' catastrophist and hyper-protective attitudes are also a well-known risk factor for the development of children's somatic symptom disorder. Such studies revealed the incidence of psychogenic disturbances as 10.7%-74%.[5,7] In our study, we reported the incidence of psychological disorders as 4.8% (and it was more common in boys.

In our study, we found the referral incidence of patients with chest pain from the pediatrics departments to pediatric cardiology department as higher as 68.7%. This may be because of parental concerns that are more than child's fear, dramatic media news about sudden deaths in young athletes and adolescents, family history of cardiac diseases and families' own wills for referral to pediatric cardiology departments. However, despite all these reasons, high referral rates increase the unnecessary inspection rate and increase the cost.

CONCLUSION

Chest pain is a common referral complaint in children. In this study, the most common etiologies of chest pain in children were idiopathic chest pain and musculoskeletal disorders. Although, our results showed that chest pain is commonly recurrent and cardiac causes of chest pain are very rare in children. So, unnecessary referrals should be reduced with a careful history and physical examination. We suggest that echocardiography may not be necessary for the routine evaluation of children with chest pain with a weighted use of the resources to contain the health costs.

ETHICAL DECLARATIONS

Ethics Committee Approval: This is a retrospective study. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation of Turkish Ethical Guidelines and with the Helsinki Declaration of 1975, as revised in 2008. Also, to screen the files retrospectively, written consent was obtained from the head physician of the hospital's committee. (T.C. Ministry Health Konya Provincial Health Directorate Dr. Ali Kemal Belviranli Obstetrics And Pediatrics Hospital date 2020 numbered 99980113-903.99).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Orjinal Araştırma / Original Article

The Impact of Fibromyalgia in Disease Activity Assessment and Treatment Response in Axial Spondyloarthritis

Aksiyal Spondiloartritte Fibromiyaljinin Hastalık Aktivitesi Değerlendirilmesine ve Tedavi Yanıtına Etkisi

Orhan Zengin[1]

[1] Dr. Ersin Aslan Research Hospital, Department of Rheumatology, Gaziantep, Turkey

Abstract

Aim: Spondyloarthritis represents a group of diseases with common clinical features. When axial symptoms are predominant, the disease is called axial SpA (axSpA). Fibromyalgia frequently accompanies rheumatological diseases and affects the evaluation of disease activity measurements and treatment responses. In this study, we aimed to compare axSpA patients with and without accompanying fibromyalgia syndrome (FS).

Material and Method: The patients with axSpA were retrospectively reviewed according to the Assessment of Spondyloarthritis international Society classification criteria. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), erythrocyte sedimentation rate, and C-reactive protein data were used to evaluate disease activity. The Bath Ankylosing Spondylitis Functional Index (BASFI) was used to evaluate the functional status of the patients.

Results: The study included a total of 300 patients, including 162 (54%) males and 138 (46%) females. The median age of the patients (25%-75% IQR) was 35 (30-46) years. In the comparison of the two axSpA groups with and without FS, age, BASFI, ESR and CRP levels, and the rate of receiving biological therapy were similar. In the FS group, female gender was dominant (n=46, 92%; p=0.000) and the rates of peripheral arthritis and BASDAI were significantly higher (p=0.024 and p=0.004, respectively).

Conclusion: AxSpA is frequently accompanied by FS, especially in women. The symptoms of FS cause an increase in disease activity scores. Therefore, it is evaluated as low treatment response. The disease activity of FS and axSpA should be carefully evaluated to lower treatment costs and apply more accurate treatment.

Keywords: Axial spondyloarthritis, fibromyalgia, disease activity, treatment response

Öz

Amaç: Spondiloartritler, ortak klinik özellikleri olan bir grup hastalığı temsil eder. Aksiyal semptomların baskın olduğu aksiyal SpA (axSpA) olarak tanımlanır. Fibromiyalji sıklıkla romatolojik hastalıklara eşlik eder ve hastalık aktivitesi ölçümleri ve tedavi yanıtlarının değerlendirilmesini etkiler. Bu çalışmada, axSpA'da eşlik eden fibromiyalji sendromu olan hastaları, axSpA hastaları ile karşılaştırmayı amaçladık.

Gereç ve Yöntem: Aksiyel spondiloartritli hastalar, Assessment of Spondylo Artritis International Society sınıflandırma kriterlerine göre geriye dönük olarak incelendi. Bath AS Hastalık Aktivite Endeksi (BASDAI), eritrosit sedimantasyon hızı ve c-reaktif protein verileri hastalık aktivitesine erişmek için kullanıldı. Hastaların fonksiyonel durumlarını değerlendirmek için Bath AS Fonksiyonel İndeks (BASFI) kullanıldı.

Bulgular: Çalışmaya 162 (% 54) erkek ve 138 (% 46) kadın olmak üzere toplam 300 hasta dahil edildi. Hastaların ortanca yaşı (25-75 IQR) 35 (30-46) idi. İki grubun karşılaştırılmasında: axSpA ve FM+axSpA; yaş, BASFI, ESR ve CRP seviyeleri ve biyolojik tedavi alan hastaların oranı benzerdi. AxSPA+FM grubunda kadın cinsiyet dominant 46 (% 92) (p=0.000), periferik artrit ve BASDAI anlamlı olarak yüksekti (p=0.024, p=0.004).

Sonuç: AxSpA'ya özellikle kadınlarda sıklıkla FM eşlik eder. FM semptomları hastalık aktivite skorlarında artışa neden olur. Bu nedenle düşük tedavi yanıtı olarak değerlendirilir. FM ve axSpA'nın hastalık aktiviteleri, daha düşük tedavi maliyetleri ve daha doğru tedavi için dikkatlice değerlendirilmelidir.

Anahtar Kelimeler: Aksiyel spondiloartrit, fibromiyalji, hastalık aktivitesi, tedavi yanıtı

Corresponding *(İletişim)*: Orhan Zengin, Dr. Ersin Aslan Research Hospital, Department of Rheumatology, Gaziantep, Turkey
E-mail *(E-posta)*: drorhanzengin@gmail.com
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INTRODUCTION

Spondyloarthritis (SpA) refers to a group of inflammatory arthritis diseases with spinal involvement, which generally present with chronic inflammatory back pain. Ankylosing spondylitis is a prototype of SpA. Undifferentiated SpA, psoriatic arthritis, reactive arthritis, and inflammatory bowel disease-related SpA are all considered to be among this group of diseases.[1] SpA can be clinically classified into two subgroups as axial SpA (axSpA) in which the signs and symptoms of sacroiliac joint involvement (sacroiliitis) and spinal involvement (spondylitis) are predominant, and peripheral SpA, in which peripheral joint involvement is prominent.[2] If sacroiliitis is detected on x-ray, the disease is described as radiographic axSpA and if detected on MRI, it is referred to as non-radiographic axSpA. However, it remains unclear whether these concepts represent two distinct entities or a single spectrum of different chronologies and disease severities.[3,4]

Fibromyalgia syndrome (FS) is the most common cause of chronic musculoskeletal pain with an unclear pathophysiology and etiology. Pain, fatigue, psychiatric symptoms, somatic symptoms and cognitive disorders are the clinical features of disease.[5,6] FS frequently accompanies rheumatological diseases, such as rheumatoid arthritis, Sjogren's syndrome, and SpA. This association affects the evaluation of disease activity measurements and treatment responses due to the effect of this syndrome on patient symptoms.[7] Therefore, FS in rheumatologic diseases is an important factor in terms of disease and treatment management.

In this study, we aimed to compare axSpA patients with and without accompanying FS in terms of demographic characteristics, clinical characteristics, disease activity assessment, and treatment response.

MATERIAL AND METHOD

This cross-sectional study included 300 patients diagnosed with axSpA according to the following criteria of the Assessment of the Spondyloarthritis International Society (ASAS): 1) sacroiliitis detected in the radiological evaluation the presence of at least one SpA feature or 2) two SpA features in patients with a positive HLA-B27 gene test. The SpA features are inflammatory low back pain, high C-reactive protein (CRP), good response to non-steroidal anti-inflammatory drugs (NSAIDs), HLA-B27 positivity, enthesitis, arthritis, dactylitis, uveitis, psoriasis, inflammatory bowel disease, and a family history of SpA.[8]

The American College of Rheumatology (ACR) 2010 criteria were used in the diagnosis of FS.[9] Patients with an inflammatory joint disease other than SPA, history of cancer, uncontrolled diabetes, and active inflammatory bowel disease were excluded from the study. Peripheral involvement, HLA-B27 positivity, uveitis, family history, drugs, treatment responses, and demographic data of the patients were analyzed. Disease activity was determined using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[10] erythrocyte sedimentation rate (ESR), and CRP. Functional status was evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI).[11] The two groups, namely the patients with axSpA alone and those with axSpA+FS were compared.

Ethics committee approval was obtained from the Clinical Studies Ethics Committee of Adıyaman University with the decision numbered 2018/8-1 and conducted in accordance with the principles of the Declaration of Helsinki. Statistical data were analyzed with SPSS version 20. In statistical analyses, categorical variables were given as numbers (%) and continuous variables as median (25-75 IQR) values. The two groups were compared with the Mann-Whitney U test, and the categorical variables were compared with the chi-square and Fisher's tests. A p value of <0.05 was considered significant.

RESULTS

A total of 300 patients, 162 (54%) male and 138 (46%) female, were included in the study. The median age of the patients (25-75 IQR) was 35 (30-46) years. The median (25-75 IQR) delay in diagnosis (time from the first symptom to diagnosis) was 4.5 (3-6.5) years. The median (25-75 IQR) age at diagnosis was 32 (26-41) years. HLA-B27 was positive in 130 patients (43.3%). Among the parameters used in the evaluation of the disease, the median (25-75 IQR) BASDAI was 4.1 (3.1-5.6) and BASFI was 3.6 (3.1-5.3). The median (25-75 IQR) ESR was 13 (11-17) mm/hr, and the median (25-75 IQR) CRP was 3.0 (2.0-6.0) mg/dl (**Table 1**). A total of 101 (33.6%) patients were under antitumor necrosis factor (anti-TNF) or secukinumab (biological therapy) treatment, and 199 (66.4%) patients were using NSAIDs and/or sulfasalazine.

Table 1. Demographic and clinical characteristics of the patients

	Patients (n=300)
Age	35 (30-46)
Age at diagnosis	32 (26-41)
Delay in diagnosis (years)	4.5 (3-6.5)
Gender	
Male	162 (54%)
Female	138 (46%)
HLA-B27 positivity	130 (43.3%)
BASDAI	4.1 (3.1-5.6)
BASFI	3.6 (3.1-5.3)
ESR (mm/h)	13 (11-17)
CRP (mg/dl)	3 (2-6)

Values are given as median (25-75% IQR) or number (%). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

In the comparison of two axSpA and axSpA+FS groups, current age, age at diagnosis, delay in diagnosis, enthesitis, uveitis, BASFI, ESR and CRP levels, the rate of patients receiving biological therapy, and the rate of radiographic axSpA were

similar (p=0.079, p=0.075, p=0.880, p=0.540, p=0.086, p=0.174, p=0.452, p=0.221, p=0.181, and p=0.494, respectively). The number of male patients was significantly higher in the axSpA group (63.2%) while female gender was dominant in the axSpA+FS group (n=46, 92%) (p=0.000). Peripheral arthritis and BASDAI were significantly higher in the axSpA+FS group (p=0.024 and p=0.004, respectively). HLA-B27 positivity was found to be higher in the axSpA group (46%), but this was not statistically significant (p=0.337) (**Table 2**).

Table 2. Comparison of the clinical characteristics of the groups

	Axial SpA+Fibromyalgia (n=50)	Axial SpA (n=250)	p value
Age	38 (34.5-48)	35.5 (31-45)	0.079
Age at diagnosis	35 (31.5-40.5)	31 (27-40)	0075
Delay in diagnosis (years)	3.5 (3-8)	4 (3-6.5)	0.880
Gender			0.000*
Male	4 (8%)	158 (63.2%)	
Female	46 (92%)	92 (36.8%)	
Peripheral arthritis	6 (12%)	14 (5.6%)	0.024*
Enthesitis	12 (24%)	50 (20%)	0.540
Uveitis	6 (12%)	15 (6%)	0.086
HLA-B27 positivity	15 (30%)	115 (46%)	0.337
BASDAI	6.1 (4.1-7.1)	4.2 (3.3-5.4)	0.004*
BASFI	4.1 (3.3-5.2)	3.6 (3-5.2)	0.174
ESR (mm/h)	12 (8.5-14.5)	13 (11-17)	0.452
CRP (mg/dl)	3 (2-4.6)	3 (2-6)	0.221
Biological therapy	16 (32%)	75 (30.0%)	0.181
Radiographic sacroiliitis	10 (20%)	75 (30.0%)	0.494

Values are given as median (25-75% IQR) or number (%). * $p < 0.05$ was considered statistically significant. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

DISCUSSION

The clinical features of SpA include axial system involvement, peripheral arthritis, enthesitis, uveitis, dactylitis, and HLA-B27 positivity.[12] The ASAS diagnostic criteria defined in 2009 have high diagnostic sensitivity and specificity.[13] However, the ASAS criteria may also cause misdiagnosis or overdiagnosis in cases where there is no objective evidence of inflammation or structural damage, and especially in the presence of other diseases that may cause pain, such as FS.[14] The similar clinical features of FS and axSpA (chronic low back pain, sleep disorder, fatigue, and mood disorders) is an important reason for the difficulty in the diagnosis and differentiation of these two diseases. In addition, this situation leads to an incorrect evaluation of SPA treatment response.[15]

FS frequently accompanies rheumatological diseases. In a previous study, the frequency of FM in axSpA was reported between 4% and 17.2%, and significantly higher in women.[16] The female-male ratio of FS was found to be 3.8/1 in ankylosing spondylitis patients and 5.6/1 in axSpA.[15,16] Consistent with previous studies, in our study, female gender was significantly predominant in patients with axSpA accompanied by FS (92%, p=0.000). The clinical features of enthesitis, uveitis and HLA-B27 positivity were similar in the two groups (p=0.540, 0.086, and 0.337, respectively), but peripheral arthritis was more common in the axSpA+FS group (p=0.024). As a result, there was no significant difference in clinical features between the axSpA+FS group compared to the axSpA group.

In SPA, BASDAI is frequently used in evaluating disease activity and BASFI for measuring functional status. In a previous study, it was found that if AS and FM coexist, higher BASDAI and BASFI values were observed in these patients compared to them alone.[17] In a Spanish study of 462 patients, it was observed that the presence of FM in AS patients significantly affected the BASDAI and BASFI scores and caused deviations in the results.[18] In our study, BASFI values of the groups were similar (p=0.174). Among the disease activity parameters, ESR and CRP values were similar between the groups. However, BASDAI was found to be significantly higher in the axSpA+FM group (p=0.004). Since BASDAI is a subjective, inquiry-based index, it can result in an increase in the score of patients with coexisting FS while the ESR and CRP tests did not support high scores in BASDAI and high disease activity. Based on these results, we consider that more objective methods, such as acute phase response and radiological imaging methods should also be used to evaluate disease activity in patients with axSpA accompanied by FM. This would help prevent unnecessary treatments, high treatment costs, and side effects of drugs. However, in a previous study, when the SpA groups with and without FM were compared, the anti-TNF initiation rates were found to be similar.[19] Similarly, in our study, the use of biological therapy did not differ between the two groups. These results suggest that rheumatologists should consider the negative effects of FS in the management of SpA treatment.

CONCLUSION

According to the results of our study, axSpA is frequently accompanied by FS, especially in women. Symptoms of FS, such as widespread pain and morning stiffness can cause an increase in disease activity scores, which are misinterpreted as low treatment response. These factors should be carefully considered to lower treatment costs and provide more accurate treatment. The first limitation of our study is the low number of patients. Second, we reported short-term patient data. Further studies with a long-term follow-up can provide more valuable information in evaluating treatment response.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Medical Ethics Committee of Adıyaman University (Permission granted: 20.11.2020, Decision no: 2018/8-1).

Informed Consent: Due to the retrospective design of the study, informed consent of the patients was not necessary.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflict of interest to declare.

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Author Contributions: The authors declare that they have all participated in the design, execution and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Corneal Aberrations in Keratoconus: A Pentacam Scheimpflug Imaging Study

Keratokonus ile Korneal Aberasyonların İlişkisinin Değerlendirilmesi

Murat Kaşıkcı[1], Özgür Eroğul[2], Leyla Eryiğit Eroğul[3], Hamıdu Hamısı Gobeka[4]

[1]Muğla Sıtkı Koçman University Education and Research Hospital, Department of Ophthalmology, Muğla, Turkey
[2]Afyonkarahisar Health Sciences University Department of Ophthalmology, Afyonkarahisar, Turkey
[3]Afyonkarahisar State Hospital, Department of Ophthalmology, Afyonkarahisar, Turkey
[4]Ağrı İbrahim Çeçen Universitye Faculty of Medicine, Department of Ophthalmology, Ağrı, Turkey

Abstract

Objective: To investigate high-order corneal aberration alterations at different keratoconus (KC) stages using a Pentacam Scheimpflug camera (OCULUS, Wetzlar, Germany), and to compare data with healthy eyes

Material and Method: This retrospective comparative study investigated clinical data of 50 patients (100 eyes) with KC and 59 healthy individuals (118 eyes) who underwent corneal topography using the Pentacam Scheimpflug camera in our clinic. Demographic characteristics, total aberrations, HOAs, coma and spherical aberrations of all participants were extracted and recorded.

Results: Mean age in the KC group was 29.7±10.3 years and 32.1±12.4 years in the control group. These two groups were compatible in terms of age and sex (p=0.11; p=0.76, respectively,). Sixty-three eyes had mild, 23 had moderate, and 14 had sever KC. Differences in low-order astigmatism, trefoil, coma, tetra-foil, high-order astigmatism, high-order spherical aberration, and root mean square values between eyes with KC and healthy eyes were statistically significant (p<0.05). Additionally, there were statistically significant differences in the corneal aberrations between the keratometric classification groups.

Conclusions: There is direct proportionality between the KC stage and corneal HOA changes, which may be helpful for staging and improving the safety of refractive surgery.

Keywords: Corneal aberrations, corneal topography, irregular corneal astigmatism, keratoconus, pentacam scheimpflug camera

Öz

Amaç: Farklı keratokonus evrelerindeki yüksek dereceli kornea aberasyon değişikliklerini Pentacam Scheimpflug kamera ile araştırmak ve verileri sağlıklı gözlerle karşılaştırmak.

Gereç ve Yöntem: Bu retrospektif karşılaştırmalı çalışmada, kliniğimizde Pentacam Scheimpflug kamera kullanılarak kornea topografisi yapılan keratokonuslu 50 hasta (100 göz) ve 59 sağlıklı bireyin (118 göz) klinik verileri araştırıldı. Çalışmaya dahil edilen tüm katılımcıların demografik özellikleri, toplam aberasyonları, yüksek dereceli korneal aberasyonları, koma ve küresel aberasyonları kaydedilip analize edildi.

Bulgular: Keratokonus grubunda ortalama yaş 29.7±10.3 yıl ve kontrol grubunda 32.1±12.4 yıl idi. İki grupta yaş ve cinsiyet açısından uyumlu idi (sırasıyla p=0.11; p=0.76). Keratometrik sınıflandırmaya göre 63 gözde hafif, 23 gözde orta ve 14 gözde şiddetli keratoconus var idi. Düşük dereceli astigmatizma, yonca (trefoil), koma, tetra-folyo, yüksek dereceli astigmatizma, yüksek dereceli sferik aberasyon ve kök ortalama kare (root mean square) değerleri keratokonuslu gözler ile sağlıklı gözler arasındaki farklılıklar istatistiksel olarak anlamlı idi (P <0.05). Ayrıca keratometrik sınıflandırma grupları arasında kornea aberasyonlarında istatistiksel olarak anlamlı farklılıklar var idi.

Sonuç/Tartışma: Keratokonus evresi yüksek dereceli korneal aberasyon değişiklikleri ile ilişkilendirlmektedir. Bu ilişki özellikle refraktif cerrahinin evrelendirilmesi ve güvenliğinin iyileştirilmesinde yardımcı olabilir.

Anahtar Sözcükler: Korneal aberasyonlar, korneal topografi, düzensiz korneal astigmatizma, keratokonus, pentacam scheimpflug kamera

Corresponding *(İletişim)*: Özgür Eroğul, Afyonkarahisar Health Sciences University Department of Ophthalmology, Ali Çetinkaya Kampusü Dörtyol mah. 2078 sok. No. 3/4 Afyonkarahisar, Turkey
E-mail *(E-posta)*: ozgurerogul0342@gmail.com
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INTRODUCTION

Keratoconus (KC) is a non-inflammatory or semi-inflammatory corneal disorder that generally shows bilateral and asymmetrical involvement. While its exact source has yet to be revealed, genetic, environmental and biomechanical factors are believed to be responsible.[1] Tear films of eyes with KC have been reported to have higher levels of inflammatory indicators that may support an inflammatory etiology.[2] Keratoconus, gradually leads to stromal thinning of the cornea and ectasia, irregular astigmatism and, subsequently, impaired vision.[3,4] Visual impairment deteriorates parallel to KC progression, which is characterized by high-order aberrations (HOAs).[5]

Keratoconus commonly begins during adolescence and gradually increases until the 3rd to 4th decade of life. Corneal topography along with slit-lamp biomicroscopic examination, retinoscopy, and pachymetry are used in the diagnosis of different forms of KC, including mild, moderate and advanced forms.[6] Scheimpflug imaging devices (OCULUS, Wetzlar, Germany) are also used to assess corneal height maps on both anterior or posterior corneal surfaces.[7,8]

Earlier studies in which investigation as to whether or not different ocular and corneal aberrations have distinguishing values, and if these parameters can be evaluated as almost identical or distinctive tools among KC relative to forme fruste KC and normal eyes, revealed an association between significantly higher ocular and corneal aberrations and KC.[9] Further, Jafri et al.[9] reported that the HOA vertical coma may be better data than videokeratoscopic inferior-superior asymmetry data in distinguishing early and suspected KC from normal eyes. In addition, it has been reported that HOAs in eye with KC were approximately 5.5 times higher than normal population levels, and approximately 53% of different HOA types alone were responsible for vertical coma in patients with KC.[10] Some researchers have therefore proposed that aberration data be used in the categorization of KC subtypes, which may be used during the selection of general optical corrections that are necessary for the correction of common HOA characteristics.[11-13] Gordon-Shag et al.[14] correspondingly emphasized that HOAs, particularly ocular ones, are very powerful tools in differentiating between eyes with KC and normal eyes.

As far as the current study is concerned, the authors posit parallel alterations of HOAs with respect to the progression of KC and whether or not these alterations will have any clinical consequences for the day-to-day activities of the patients concerned. The purpose of the current study was therefore to investigate HOA alterations in the eyes with different clinical stages of KC using the Pentacam Scheimpflug imaging system and to compare findings between study groups.

MATERIAL AND METHOD

Participants

In this retrospective comparative case-control study, the data of 100 eyes of 50 patients with KC and 118 normal eyes of 59 healthy individuals who applied to the Clinic of Ophthalmology at Training and Research Hospital between December 2018 and October 2019 were examined. The study protocol abided to ethical principles of the Declaration of Helsinki and was approved by the institutional review board of Muğla Sıtkı Koçman University Ethics Committee (no.2020/02-VII). Written informed consent was obtained from each participant.

Eyes with KC were classified into three groups based on the Amsler–Krumeich keratoconus classification system[12] that is, the average keratometry values: <47 D as mild; 47-52 D as medium; and >52 D as severe KC. Demographic characteristics, total aberrations, HOAs, coma and spherical aberrations of all participants were extracted and recorded. Patients with KC who were ≥18 years of age and without any systemic diseases were enrolled in the study. Exclusion criteria comprised of: presence of corneal scar and corneal dystrophies; prior corneal and/or anterior segment surgeries; usage of any systemic drugs; presence of collagen vascular diseases; usage of the contact lens; and pregnancy or lactation.

Ocular Examination and Anterior Segment Imaging

All participants underwent a comprehensive ophthalmologic examination, including measurements of the best-corrected visual acuity and Goldmann applanation tonometry and slit-lamp biomicroscopy of anterior and posterior segments before and after full pupil dilation.

In the meantime, corneal topographic imaging and aberrometry was performed using Pentacam Scheimpflug imaging device. The procedure was conducted between 9:00 am and 12:00 am in order to circumvent any feasible diurnal fluctuations. In addition, the use of contact lens was stopped at least two weeks before the study. Imaging procedures were taken at optimal compliance conditions along the visual axis, allowing the patients to look carefully at the central fixation light. Blinking was encouraged during the procedure to keep tear film layer intact. The eye movements of each patient were frequently monitored by the system, and the quality factor was automatically evaluated. The procedure was successfully carried out three times following two minutes of dark adaptation under dark scrutiny (2.2 Lux) and the resultant mean values were recorded.

Pentacam® HR device is a rotating Scheimpflug camera. Rotational imaging by Scheimpflug camera creates images in three-dimensional model. Creation of a complete view of the anterior segment of the eye takes no more than two seconds. The device's second camera was used to identify any possible ocular movements. Three-dimensional model of the anterior segment of the eye from 138.000 distinct heights was determined by Pentacam. Topography and pachymetry of the entire corneal front and back surfaces from limbus to limbus were also determined.

Analysis of the anterior segment of the eye included determination of the anterior chamber angle, anterior chamber volume, anterior chamber height, and measurement of the

function that can be applied manually anywhere in the anterior segment. Images of the corneal anterior and posterior surfaces, iris, and anterior and posterior surfaces of the lens were produced in a moving virtual eye. Lens and corneal densitometry values were automatically determined. Root mean square (RMS), coma, RMS trefoil, RMS total HOA, RMS astigmatism and global RMS aberrations were among the data collected.

Diagnosis

During diagnosis of KC, the corneal topography map, inferior-superior asymmetry, focal or inferior steepening, asymmetric bow tie with a skewed radial axis, anterior-posterior elevation pattern, and presence of more than one of the diagnostic signs essentially clinical manifestation of the Fleischer ring and Vogt's striae were considered.[15] The ocular, corneal and inner wave aberrations were measured by 6th row Zernike polynomial decomposition for a 6 mm diameter region with a central corneal peak. Further information on the Zernike polynomials has been analyzed in earlier publications.[16,17] The RMS of corneal, ocular, and internal aberrations was determined to measure amount of the HOAs. The lower the RMS value, the lower was the aberration of the optical system. In addition, groups that included low-order astigmatism, total trefoil, vertical coma, total coma, total tetra-foil, high-order astigmatism as well as total high-order spherical aberration were determined.

Statistics

The IBM SPSS Statistics software (Version 22; IBM Inc., New York, USA) was used in the statistical analysis. Data were expressed as mean±standard deviation. Chi-square test was used to compare categorical variables. Quantitative data were defined as mean±standard deviation. Kruskal-Wallis and Mann-Whitney tests were used accordingly. Spearman's correlation analysis was used to analyze association among values of the mean keratometry, posterior elevation, and RMS. P values <0.05 were considered to be statistically significant.

RESULTS

Participants were categorized into two groups: KC eyes with mean age of 29.7±10.3 years (females, 21; males, 29); and healthy eyes with mean age of 32.1±12.4 years (females, 26; males, 33). These groups were compatible regarding the age and sex parameters, respectively (p=0.11; p=0.76). The level of KC was mild in 63, moderate in 23, and severe in 14 eyes, based on the Amsler–Krumeich keratoconus classification system.

Keratometry values detected in the respective study groups are demonstrated in **Table 1**. There were statistically significant differences between eyes with KC and healthy eye in terms of low-order astigmatism, trefoil, coma, tetra-foil, HOA, high-order spherical aberration and RMS (p<0.05) There were also statistically significant differences in terms of corneal aberration among KC groups.

With regards statistical analysis of the corneal HOAs at various stages of KC, there was a general positive correlation between mean keratometry and RMS values. Specifically, the positive correlation between RMS total and mean keratometry values was statistically significant in all groups. There was also statistically significant positive correlation between RMS total coma and mean keratometry values in all groups (p<0.0001). The correlation between RMS trefoil and mean keratometry, however, was statistically significant in the medium KC group (p=0.04), and significant relative to that of all three groups (p<0.0001). The correlation between RMS astigmatism and mean keratometry was significant in all KC groups (p=0.02), and all RMS values had statistically significant positive correlation with mean keratometry in general (p<0.0001). There was also statistically significant correlation between spherical aberrations and mean keratometry in the moderate and severe KC groups (p<0.0001;p<0.001, respectively), and in comparison to the three groups (p<0.0001).

Table 1. Keratometry values detected in keratoconus and control groups

	KC; n=100	Group 1; n=63	Group 2; n=23	Group 3; n=14	Control; n=118	P1	P2
K1 (Diopter)	46.1±3.7	43.8±1.3	47.6±1.7	52.9±1.9	42.8±1.5	<0.001	<0.001
K2 (Diopter)	49.5±4.6	46.6±1.6	51.8±2.1	58.1±2.5	43.9±1.6	<0.001	<0.001
Km (Diopter)	47.6±4.1	45.1±1.2	49.7±1.7	55.5±1.9	43.4±1.5	<0.001	<0.001
LOA (µm)	-2.18±2.13	-1.74±1.83	-2.50±2.05	-3.58±2.86	-0.59±0.73	<0.001	0.041
Total trefoil (µm)	0.38±3.51	-0.011±0.14	0.21±1.08	2.39±9.15	-0.004±0.06	0.968	0.441
Total coma (µm)	0.15±0.27	0.13±0.15	0.31±0.33	0.006±0.43	-0.0001±0.05	<0.001	0.001
Total tetra-foil (µm)	0.027±0.55	-0.03±0.04	0.18±0.42	0.33±1.36	-0.03±0.04	0.808	0.280
HOA (µm)	0.18±1.38	-0.01±0.10	0.35±1.74	0.77±2.89	0.001±0.17	0.784	0.155
High-order spheric aberration (µm)	-0.19±0.78	0.06±0.38	-0.41±0.90	-0.95±1.21	0.21±0.11	<0.001	<0.001
Total high-order RMS (µm)	1.94±1.53	1.25±0.90	2.95±1.68	3.18±1.84	0.44±0.25	<0.001	<0.001

KC: Keratoconus, K1: Horizontal K, K2: Vertical K, Km: Average Keratometry, K1 post: Posterior Horizontal K, K2 post: Posterior Vertical K, Km Post: Average Posterior Keratometry, LOA: Low-Order Astigmatism, HOA: High-Order Astigmatism, RMS: Root Mean Square; P1=Comparison of Patients with Keratoconus and Controls, P2=Comparison of Patients with Keratoconus Patients Among Themselves (Group1-Group2-Group3), µm: Micrometer

DISCUSSION

This retrospective comparative study revealed correlation of ocular and corneal aberrations with KC versus healthy eyes. Nevertheless, the values of some aberration parameters, including vertical and total coma, total tetra-foil, and high-grade astigmatism were significantly different between the two groups. Similar to the study by Schlegel et al.[18] in which aberrometry was measured by OPD-Scan II, the current study revealed significantly higher optical aberrations, that is, ocular, corneal, and internal abnormalities in eyes with KC relative to normal eyes. Furthermore, in the current study, eyes with KC were more effectively differentiated from normal eye thanks to the use of the ocular HOA data, by which total HOAs, total coma and high-order astigmatism were significantly higher in eyes with KC. In the study published by Reddy et al.[19] the corneal aberrations, coma Z3-1 and Z31 extended to the uppermost viable specificity (100%, 63%, respectively) and sensitivity, while none of the topographic parameters did not reach this level of characteristic. In the presents study, however, sensitivity of almost all the ocular aberration parameters was obviously significant in differentiating eyes with KC from normal eyes. Therefore, some corneal aberrations such as vertical and total coma, and total trefoil considered to be highly potent aberration tools that can be used to differentiate eyes with KC from normal eyes.

There is currently a challenge in diagnosing cases of moderate and subclinical KC types. This is particularly important for eyes with a forme fruste KC that have not displayed any clinical signs of KC for a long time, as topographical indices and corneal curvature patterns may not be worthwhile in the diagnosis of disorder.[20] Gordon-Shaag et al.[14] and Hashemi et al.[21] suggested evaluation of the aberration parameters such as vertical asymmetry along with corneal topography in the assessment of patients with mild and subclinical KC forms. Correspondingly, the current study observed substantial differences between eyes with KC and normal eyes in terms of low-order astigmatism, trefoil, vertical and total coma, tetra-foil, HOA, high-order spherical aberration, and RMS values.

The aberrations parameters, including coma, trefoil, astigmatism, and global aberrations generally exacerbate in progressive KC. In one study published by Çolak et al.[22] following measurement of the corneal topographic parameters using Scheimpflug-Placido topography, statistically significant correlation between increased corneal curvature and total aberrations revealed during comparison of the corneal anterior surface aberrations between eyes with KC and normal eyes. Another study by Maeda et al.[17] which collated the wave-front aberrations of eyes with KC to normal eyes and assessed the properties of HOAs measured by the Hartmann-Shack sensor in eyes with KC, reported that increase in the ocular HOAs in eyes with KC was due to a resultant increase in the corneal HOAs. In the current study, during intra-group comparison of posterior height in eyes with different KC sub-groups, statistically significant differences were revealed in all HOA variables. Despite that, posterior height and RMS values in the mild, moderate, and severe KC sub-groups were positively correlated, the fact which can be explained by both the obvious differences in the HOA alterations and presence of high posterior heights. In addition, the current study observed correlation between the corneal HOAs and degree of KC using Scheimpflug camera, similar to the study published by Delgado et al.[23] Unlike earlier reports in the literature, the current study also revealed significant correlation between severity of coma aberration and RMS trefoil values in eyes with advanced KC. In consistent with the prior reports, a Pentacam study by Nakagawa et al.[24] reported higher corneal HOAs in eyes with KC relative to healthy eyes. All of these findings indicate that corneal HOAs can be used as a method for KC staging. In view of this, Alio et al.[12] also demonstrated that HOAs of the anterior corneal surface can be applied to diagnose stages of KC using videokeratoscopy and with corneal map analysis.

Optical aberrations in the eyes with KC have been studied in several clinical trials and in conjunction with the present research, increased HOAs, in particular coma and global aberrations, have been demonstrated.[9,19] Significantly increased HOAs lead to decreased visual acuity that is uncorrected with glasses or soft contact lenses.[25,26] In spite of that, intracorneal ring segments and phakic toric implantable lenses are effective methods based on the effect of reducing optical abnormalities in the patients with KC.[27]

The authors acknowledge the limitations of the present study. Due to our relatively limited sample size analysis, these observations should be considered carefully. Even more prospective trials comprising a greater number of patients would be worthwhile in order to assess the effectiveness of the ocular and corneal aberration measurements in the identification of different stages of KC and its subsequent implications in the everyday lives of the patients concerned.

CONCLUSION

Significant differences in low-order astigmatism, trefoil, coma, tetra-foil, high-order astigmatism, high-order spherical aberration, and RMS values have been identified in the current study. Significant changes in corneal aberrations among the keratometric classification categories have also been identified. In addition, corneal HOAs were consistent with corneal topographic parameters obtained from similar devices at various stages of the KC. Consequently, these changes may not just be of benefit to KC staging. They could also enhance the safety of refractive surgery.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol abided to ethical principles of the Declaration of Helsinki and was approved by the institutional review board of Muğla Sıtkı Koçman University Ethics Committee (no.2020/ 02-VII).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was **obtained from patients.**

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Evaluation of the Seropositivity of Patients with Cystic Echinococcosis in Konya, Turkey

Kistik Ekinokokkozlu Hastaların Seropozitifliğinin Değerlendirilmesi, Konya, Türkiye

Sümeyye Başer[1], Aynur İsmayıl[1], Salih Maçin[1]

[1]Selcuk University, Faculty of Medicine, Department of Medical Microbiology, Konya, Turkey

Abstract

Aim: Diagnosis of echinococcosis is based on clinical symptoms, imaging techniques and particularly on the detection of specific antibodies in serum specimens of patients. The aim of this study is retrospective evaluation of seropositivity in patients who is diagnosed as cystic echinococcosis.

Material and Method: In this study, serum samples of the patients, which were sent to the Medical Microbiology Laboratory from several clinics of the Selcuk University Medical Faculty Hospital between 01 January 2015- 01 July 2020, were evaluated in terms of cystic echinococcosis by using indirect hemaglutination test. The results were evaluated with a cut off titer ≥160 of as recommended by the manufacturer. Results were evaluated by gender and ages.

Results: Cystic hydatid (CH) was determined to be seropositive 332 (21.6%) of 1543 patient samples. Seropositivity was found in 226 (14.7%) of 933 female patients and in 106 (6.9%) of 610 male patients. Seropositivity was mostly seen in 21-40 age group.

Conclusion: While there have been a number of animal studies, little information is available about the prevalence of cystic echinococcosis in humans in Turkey. Cystic echinococcosis continues to be a major public health problem in Konya province. Large scale prevention and control programs should be implemented against this disease.

Keywords: Hydatid cyst, echinococcosis, hemagglutination tests

Öz

Amaç: Ekinokokkoz teşhisi klinik semptomlara, görüntüleme tekniklerine ve özellikle hastaların serum örneklerinde spesifik antikorların saptanmasına dayanır. Bu çalışmanın amacı, kistik ekinokokkoz tanısı alan hastaların seropozitifliğinin geriye dönük olarak değerlendirilmesidir.

Gereç ve Yöntem: Bu çalışmada 01 Ocak 2015-01 Temmuz 2020 tarihleri arasında Selçuk Üniversitesi Tıp Fakültesi Hastanesi'nin çeşitli kliniklerinden Tıbbi Mikrobiyoloji Laboratuvarı'na gönderilen hastaların serum örnekleri indirekt hemaglütinasyon testi ile kistik ekinokokkoz açısından değerlendirilmiştir. Sonuçlar, kit prospektüsü doğrultusunda ≥160 titerde olanlar pozitif şeklinde değerlendirilmiştir. Sonuçlar cinsiyet ve yaşa göre değerlendirilmiştir.

Bulgular: Kist hidatik (KH) 1543 hasta örneğinin 332'sinde (% 21.6) kistik ekinokokkoz açısından seropozitif olduğu belirlenmiştir. 933 kadın hastanın 226'sında (% 14,7) ve 610 erkek hastanın 106'sında (% 6,9) seropozitiflik saptanmıştır. Seropozitiflik en çok 21-40 yaş grubunda görülmüştür.

Sonuç: Çok sayıda hayvan çalışması yapılmış olsa da, Türkiye'de insanlarda kistik ekinokokoz prevalansı hakkında çok az bilgi mevcuttur. Konya ilinde kistik ekinokokkoz önemli bir halk sağlığı sorunu olmaya devam etmektedir. Bu hastalığa karşı büyük ölçekli önleme ve kontrol programları uygulanmalıdır.

Anahtar Kelimeler: Hidatik kist, ekinokokkoz, hemaglütinasyon testleri

Corresponding *(İletişim)*: Salih Maçin, Selcuk University School of Medicine Department of Medical Microbiology, Konya, Turkey
E-mail *(E-posta)*: salihmacin@selcuk.edu.tr
Received *(Geliş Tarihi)*: 20.08.2020 **Accepted *(Kabul Tarihi)*:** 07.12.2020

INTRODUCTION

Cystic hydatid (CH) is a zoonotic disease which is transmitted orally by taking Echinococcus eggs. The adult form of Echinococcus granulosus produces eggs by settling into the small intestine of dogs and wolves, which are the definitive hosts. Eggs in the cestode segment or in free form infect a variety of animals such as sheep, goats and cattle.[1] When these eggs are taken by mouth, they pass through the stomach to the small intestine and become larvae. The larvae penetrate the gut wall and pass through various organs through the blood and lymph. It causes cyst formation in human organs such as liver and lung and leads to hydatid disease with high mortality.[2-4]

CH is an important public health problem in developing countries, especially where animal husbandry is intense and where sheep is consumed intensively. CH is endemic in Mediterranean countries, South American countries and most of Africa.[1] It is widespread in our country and mostly found in Central Anatolia with a rate of 38.6%.[2,3]

In addition combination of serology and imaging, serological tests are also used in the diagnosis of CH. Serology is very valuable in uncertain cases.[4] In addition to being used for diagnostic purposes, serological tests are also useful in the postoperative follow-up of the disease.[5] Most tests used in serological diagnosis are in patient serum. It is based on the search for antibodies. ELISA and Indirect hemagglutination (IHA) techniques are frequently preferred due to their ease of application, low cost, high sensitivity and specificity.[4-6]

This study was carried out in order to retrospectively examine the seropositivity of patients with a preliminary diagnosis of hydatid cyst in our hospital by indirect hemagglutination test and to contribute to the knowledge about the disease in our region.

MATERIAL AND METHOD

In this study, the blood serum samples of a total of 1543 patients, which were sent to the Medical Microbiology Laboratory from several clinics of the Selcuk University Medical Faculty between 01 January 2015-31 July 2020 with the diagnosis of CH. *E. granulosus* antibodies in serum samples were determined by indirect hemagglutination (IHA) method (Fumouze Laboratoires, France). ≥1/160 serum titers were considered positive.

The study was carried out with the permission of Selcuk University Faculty of Medicine Local Ethics Committee approval was obtained (Date: 30,09,2020 number: 2020/435).

RESULTS

In our study, seropositivity was detected in 332 (21.6%) of 1543 patients who were referred with a preliminary diagnosis of CH. The highest seropositivity was detected in the 21-40 age group. **Table 1** shows the distribution of patients with seropositivity according to age groups and gender. In our study, 176 (53.01%) of 332 positive serum samples came from the general surgery, 34 (10.24%) from chest diseases, and 37 (11.1%) from other clinics (**Table 2**).

Table 1. Distribution of seropositivity rates by age and gender

Age	Male		Female		Total Positive	
	n	%	n	%	n	%
0-6 (n:55)	5	(9.1)	3	(5.4)	8	(14.5)
7-20 (n:180)	15	(8.3)	27	(15.0)	42	(23.3)
21-40 (n:389)	32	(8.2)	73	(18.8)	105	(27.0)
41-60 (n:551)	32	(5.8)	81	(14.7)	113	(20.5)
≥61 (n:368)	22	(6.3)	42	(11.4)	64	(17.7)
Total (n:1543)	106	(6.9)	226	(14.7)	332	(21.6)

Table 2. Distribution of seropositive samples by clinics

Clinics	n	%
General surgery	176	53.01
Pulmonary diseases	34	10.24
Gastroenterology	20	6.02
External Centers	28	8.43
Pediatric infection	13	3.91
Pediatric surgery	10	3.01
Infectious diseases	14	4.21
Others*	37	11,1
Total	332	100

*Brain and nerve surgery, Pediatric emergency, Pediatric gastroenterology, Hepatology, Nutrition service, Pediatrics, Dermatology, Internal Diseases, Hematology, Orthopedics, Radiology, Dermatology, Rheumatology, Medical oncology, Urology clinics.

DISCUSSION

Cystic hydatid disease is caused by larval forms of echinococcus. There are four species of echinococcus (*E. granulosus*, *E. multilocularis*, *E. vogeli*, *E. oligarthrus*). Only *E. granulosus* and *E. multilocularis* cause disease in humans. The actual incidence of echinococcus worldwide is not evident. a total of 14,789 cases have been reported in Turkey in the 2001-2015 period.[5]

Indirect hemagglutination test is important in the diagnosis and follow-up of the treatment. It is used in the postoperative period to monitor the effectiveness of surgical treatment. With the healing of the disease, titers in the serum also gradually decrease but may remain positive for years. The increase in serology after years may indicate reinfection.[7] In our country, seropositivity was found to be between 2.7% and 54.1% in ELISA, IHA and immunofluorescence studies in different regions.[8-16] In our study, seropositivity was detected in 315 patients (21.9%).

Conducted in our country, CH is higher in women than in men.[3,16,17] According to the study of Hakverdi et al.[18] according to their study, the rate of CH was found to be 53.7% in women and 46.3% in men. In a study from the Central Anatolia Region, 56% of the patients diagnosed with CH were reported as female and 44% as male.[19] However, in a study conducted in Ankara, the rate of male patients was 51.2% and the rate of female patients was 48.8%.[20] In the literature, there are studies in which parasites are found to be equal in both genders.[14,19-22] In our study, 24.3% female patients and 17.9% male patients were seropositive.

When the studies performed in our country are examined, it has been reported that the disease is mostly seen in the 41-60 age group.[14,16,21,23,24] In our study, similar to these results, the seropositivity rate was found in 113 (20.5%) between 41-60 age groups. When we evaluate the previous studies in our region, it has seen that our study has similar characteristics with other studies according to gender and age groups.

Some studies done in Turkey, liver involvement (44-73.3%) were reported as the most common.[14,16,23] Güreser et al.[24] reported that CH positivity was found in 43.8% of the samples sent from general surgery, 21.9 infectious disease and 21.9% gastroenterology clinic. Similarly, in our study, seropositivity was found mostly in the blood samples sent from general surgery (53.01%) and chest diseases (10.24%) clinics.

Since Konya and its surroundings are one of the places where agriculture and animal husbandry are common, this disease is an important public health problem in our region. Therefore, large scale control and protection programs should be implemented.

CONCLUSION

While there have been a number of animal studies, little information is available about the prevalence of cystic echinococcosis in humans in Turkey. Cystic echinococcosis continues to be a major public health problem in Konya province. Large scale prevention and control programs should be implemented against this disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: For this research; Selcuk University Faculty of Medicine Local Ethics Committee approval was obtained (Date: 30,09,2020 number: 2020/435).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

The combination of *Demodex folliculorum* and Aerobic Bacteria in the Etiopathogenesis of Chronic Blepharitis

Kronik Blefarit Etyopatogenezinde *Demodex folliculorum* ve Aerop Bakterilerin Birlikteliği

Murat Cakmakliogullari[1], Ahmet Ozbilgin[2]

[1]Karabük University Training and Research Hospital Ophthalmology Department, Karabük, Turkey
[2]Celal Bayar University School of Medicine Medical Parasitology Department, Manisa, Turkey

Abstract

Aim: This study was conducted to investigate the presence of thecombination of *Demodex folliculorum* and aerobic bacteria in patients with chronic blepharitis.

Material and Method: Seventy-one patients diagnosed with chronic blepharitis were evaluated for the presence of *D. folliculorum* by light microscope examination of samples prepared from eyelashes collected by eyelash epilation. Culture samples were also obtained from patients' eyelid margins. Bacterial strainsamong the predominant bacterial colonies grown in cultures were identified using the BD Phoenix identification system (BD Diagnostic Systems, Sparks, USA). Patients were divided into two groups, Demodex-positive and Demodex-negative,and compared according to bacterial production and bacterial strains produced.

Results: *D. folliculorum* was identified in 42 (59.1%) patients. Comparison between Demodex-positive and -negative groups revealeda statistically significant increase in Demodex positivity with age. There was no significant relationship between gender and Demodex positivity. The Demodex-positive group showed a statistically significantly higher bacterial growth in the culture samples than the Demodex-negative group. Both groups exhibited a predominance of *Staphylococcus epidermidis*. *S. epidermidis* (38.1% vs. 31.0%), *Staphylococcus aureus* (19.0% vs. 10.3%), and *Corynebacterium spp.* (16.7% vs. 6.9%) were detected at higher rates in the Demodex-positive group than in the Demodex-negative group. There was no statistically significant difference between both groups regarding the presence of these bacterial species.

Conclusions: Patients with chronic blepharitis could have a mixedinfection site with the combination of *D. folliculorum* and aerobic bacteria found in the normal eyelid flora.

Keywords: Chronic blepharitis, *Demodex folliculorum*, aerobic bacteria, etiopathogenesis

Öz

Amaç: Bu çalışmada kronik blefarit tanısı almış hastalarda *D. folliculorum* ile aerop bakteri birlikteliğini araştırmayı amaçladık.

Gereç ve Yöntem: Kronik blefarit tanısı alan 71 hastada, kirpik epilasyonu ile alınan kirpiklerden hazırlanan preparatlar ışık mikroskobunda *D. folliculorum* varlığı açısından değerlendirildi. Aynı zamanda bu hastaların kapak marjından kültür örnekleri alındı. Kültürde üreyen baskın bakteri kolonilerinin tür tayinleri, BD Phoenix (BD Diagnostic Systems, Sparks, USA) tanımlama sistemi kullanılarak yapıldı. Hastalar, *D. folliculorum* saptananlar Demodex pozitif saptanmayanlar ise Demodex negatif olmak üzere iki gruba ayrıldı. Gruplar bakteri üremesi ve üreyen bakteri türlerine göre karşılaştırıldı.

Bulgular: Hastaların 42'sinde (%59,1) *D. folliculorum* varlığı saptandı. Demodex pozitif grupla Demodex negatif grup karşılaştırıldığında yaş arttıkça Demodex pozitifliğinin de istatistiksel olarak arttığı saptandı. Cinsiyet ile Demodex pozitifliği arasında anlamlı bir ilişki bulunmadı. Demodex pozitif grupta alınan kültür örneklerinde bakteri üremesi Demodex negatif gruba göre anlamlı yüksek bulundu. Her iki grupta en sık *S. epidermidis* üremesi olduğu saptandı. Demodex pozitif hastalarda Demodex negatif olanlara göre daha yüksek oranda görülen bakteri türlerinin *S. epidermidis* (%38,1; %31,0), *S. aureus* (%19,0; %10,3) ve *Corinobacterium spp.* (%16,7; %6,9) olduğu saptandı. Demodex pozitif ve Demodex negatif gruplarda üreyen bakteri türleri karşılaştırıldığında türler arasında anlamlı bir fark bulunmadı.

Sonuç: Kronik blefaritli hastalarda sıklıkla *D. folliculorum* ile normal kapak florasında bulunan aerop bakterilerin birlikte mix enfeksiyon alanı oluşturabileceği düşüncesindeyiz.

Anahtar Kelimeler: Kronik blefarit, *D. folliculorum*, aerop bakteriler, etyopatogenez

Corresponding *(İletişim)*: Murat Cakmakliogullari, Karabük University Training and Research Hospital Ophthalmology Department, Karabük, Turkey
E-mail *(E-posta)*: drmurat3545@gmail.com
Received *(Geliş Tarihi)*: 07.09.2020 **Accepted *(Kabul Tarihi)*:** 17.12.2020

INTRODUCTION

Demodex folliculorum and *D. brevis* are two strains of *Demodex mites* found in humans. They are most commonly found as ectoparasites on the human skin and are also present in the eyelid flora.[1] The majority of *D. folliculorum* species are located in the infundibular section of hair follicles, whereas *D. brevis* are located more deeply in the sebaceous gland and ductus.[2]

These mites can cause ocular disorders like blepharitis, conjunctivitis and keratitis.[3-5] Blepharitis is a frequently observed clinical condition, generally accompanied by a chronic course. Symptoms primarily include itching, burning, redness, feeling of a foreign body in the eye, and flaking at the eyelash roots. It is generally diagnosed from the clinical appearance of the eyelid and the accompanying symptoms.[6] Mites cause reactive hyperkeratinisation and epithelial hyperplasia by obstructing the sebaceous gland outlets and eyelash root follicles and play a role as a mechanical vector for the spread of bacteria.[7]

The most common aerobic bacterial agents causing blepharitis are *Staphylococcus epidermidis*, *S. aureus*, and *Corynebacterium spp.*, and the most common parasitic agent is *D. folliculorum*.[8] This widespread parasite is accepted as a saprophytic organism on the skin, and it is currently accepted as the pathogenic agent of chronic blepharitis; hence, when the parasite is determined, antiparasitic treatment is recommended.[9]

We conducted this study to investigate the presence of the combination of *D. folliculorum* and aerobic bacteria in patients diagnosed with chronic blepharitis.

MATERIAL AND METHOD

Patients

This study included 71 patients who presented at the Ophthalmology Polyclinic of Karabük University Training and Research Hospital between September 2016 and June 2017 and were diagnosed with chronic blepharitis. Patients were excluded if they had previously undergone eyelid surgery, had a structural disorder of the eyelid, or were using topical or systemic antibiotic treatment. The presence of *D. folliculorum* was determined in the eyelashes obtained by eyelash epilation from patients with chronic blepharitis. The patients were divided into two groups, i.e., those determined as positive and those found as negative for the presence of *D. folliculorum*. Both groups were compared in terms of bacterial production in the culture samples collected from the eyelash margins and the bacterial strains produced.

This study was approved by the Clinical Research Ethics Committee of Karabük University Medical Faculty (no: 13, dated:31/08/2016).

Bacterial Culture and Identification

Culture samples were obtained from the upper and lower eyelidsusing a sterile swab dampened with sterile saline and were sent to the microbiology laboratory in transport media. The swab samples were inoculated onto 5% sheepblood agar (Becton Dickinson, USA), eosin methylene blue agar (Becton Dickinson, USA), and chocolate agar (Becton Dickinson, USA) and then incubated at 35°C for 24–48h. The strains found among the predominant bacterial colonies grown in the culture media were identified using a fully automated BD Phoenix bacterial identification system (BD Diagnostic Systems, Sparks, USA).

Demodex Examination

Under biomicroscopy, six eyelashes were collected from the upper and lower eyelids of the patients by epilation. The eyelashes were sent to the microbiology laboratory in a sterile petri dish. The eyelash sampleswere mounted on slides and prepared using saline according to the procedure described by English et al.[10] after which they were evaluated under a light microscope at 10× and 40× magnification to detect the presence of *D. folliculorum*.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS version 24.0 software (IBM Corporation, Armonk, NY, USA). Continuous variables were represented as mean±standard deviation, and categorical data were represented as number (n) and percentage (%). In the analyses between groups of continuous variables, conformity of the data to normal distribution was assessed using the Kolmogorov–Smirnov test. Comparisons of two groups of data with normal distribution were conducted using the t-test.The chi-square test was applied for comparisons of categorical data. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Among the 71 patients diagnosed with chronic blepharitis, *D. folliculorum* was detected in 42 (59.1%) patients. An adult *D. folliculorum* detected in the eyelash sample is shown in **Figure 1**. The mean age of Demodex-negative patients was 52.34±10.65 years (range, 32–72 years), and that of Demodex-positive patient was 63.52±10.88 years (range, 35–83 years). There was a statistically significant increase in Demodex positivity with an increase in age ($p<0.001$). However, there was no statistically significant difference between the groups with respect of gender ($p>0.05$) (**Table 1**).

Table 1. Comparisons between Demodex-positive and -negative patients according to age and gender

	Demodex-Negative (n=29)		Demodex-Positive (n=42)		Total (n=71)		p
	n	%	n	%	n	%	
Age (years)							
30-39	3	10.3	1	2.4	4	5.6	
40-49	10	34.5	4	9.5	14	19.7	
50-59	9	31.0	10	23.8	19	26.8	<0.001*
60-69	6	20.7	16	38.1	22	31.0	
70+	1	3.4	11	26.2	12	16.9	
Gender							
Female	16	55.2	22	52.4	38	53.5	0.817**
Male	13	44.8	20	47.6	33	46.5	

* Chi-square test (Linear by linear association)
** Chi-square test

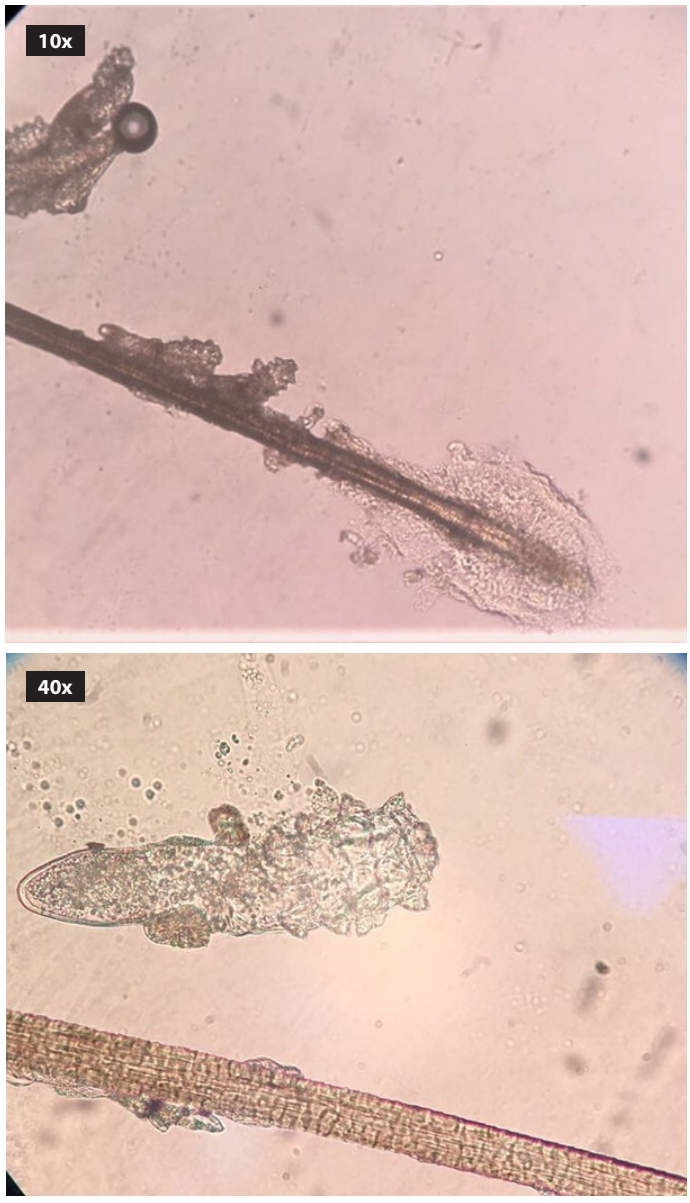

Figure 1. Microscopic eyelash examination of *D. folliculorum* at 10× and 40×

Regarding bacterial growth, 90.5% of patients in the Demodex-positive group and 72.4% of those in the Demodex-negative group had bacterial growth in the cultures. The difference between the two groups with respect to bacterial growth was statistically significant (p=0.048) (**Table 2**).

Table 2. Comparisons between Demodex-positive and -negative patients with respect to bacterial growth

	Demodex-Negative (n=29)		Demodex-Positive (n=42)		Total (n=71)		p
	n	%	n	%	n	%	
Bacterial growth (-)	8	27.6	4	9.5	12	16.9	0.048*
Bacterial growth (+)	21	72.4	38	90.5	59	83.1	

* Chi-square test (Fisher's exact test)

In the culture samples obtained from the 71 patients with chronic blepharitis, aerobic bacterial growth was detected in 59 (83.1%) patients and no bacterial growth was detected in 12 (16.9%) patients. According to the frequency of the bacterial growth, *S. epidermidis* (35.2%), *S. aureus* (15.5%), *S. epidermidis* other coagulase-negative Staphylococcus (CNS) (15.5%), *Corynebacterium spp.* (12.7%), and *Streptococcus spp.* (5.6%) were identified.

Regarding the distribution of bacterial species, *S. epidermidis* (38.1% vs. 31.0%), *S. aureus* (19.0% vs.10.3%), and *Corynebacterium spp.*(16.7% vs. 6.9%) were observed at higher rates in the Demodex-positive group than in the Demodex-negative group. *Streptococcus spp.* (6.9% vs. 4.8%) and other CNS (20.7% vs.11.9%) were detected at higher rates in the Demodex-negative group than in the Demodex-positive group. However, there was no statistically significant difference between the patient groups withrespect to the bacterial species(p>0.05) (**Table 3**).

Table 3. Comparisons between Demodex-positive and -negative groups with respect to bacterial species

	Demodex-Negative (n=29)		Demodex-Positive (n=42)		Total (n=71)		p
	n	%	n	%	n	%	
S. epidermidis	9	31.0	16	38.1	25	35.2	0.618*
S. aureus	3	10.3	8	19.0	11	15.5	0.506*
Corynebacterium spp.	2	6.9	7	16.7	9	12.7	0.239*
Streptococcus spp.	2	6.9	2	4.8	4	5.6	1.000*
Other CNS	6	20.7	5	11.9	11	15.5	0.338*

* Chi-square test (Fisher's exact test)

DISCUSSION

Blepharitis is a clinical condition frequently observed in the community and generally has a chronic course. Despite the presence of inflammation in the eyelash roots, the aetiology of blepharitis is still not completely understood.[6] It is believed that bacterial infections and inflammatory skin lesions such as atopic dermatitis together with *D. folliculorum* infestations play a role in the etiopathogenesis.[11]

The results of several studies support the relationship between Demodex and blepharitis.[12-18] In a study conducted by Lee et al.[13] to determine the prevalence of Demodex, positivity was determined at 70%, and a strong correlation was reported between the number of Demodex and the severity of the ocular disorder. In a case-controlled study, Biernat et al.[14] reported Demodex frequencies of 62.4% in patients with chronic blepharitis and 24.3% in the control group, with the difference being statistically significant. In another meta-analysis, the probability of developing symptomatic blepharitis was reported to be 4.7-fold greater in patients with Demodex in the eyelashes.[15] Consistent with these findings in the literature, our study determined a Demodex positivity of 59.1% in 42 of 71 patients with chronic blepharitis.

Although previous studies did not find a significant difference in the frequency of *D. folliculorum* according to gender, it has been found to increase with age.[13,14,19] Arici et al.[20] reported that the presence of Demodex was not related to age and gender. Demirmizrak et al.[21] found that there was a statistically significant increase in male gender and the frequency of *D. folliculorum* with increasing age. In the current study as well, although there was no change in the frequency of *D. folliculorum* according to gender, a positive correlation was found between the frequency of Demodex and age.

The eyelid margin is known to host normal bacterial flora consisting of *S. epidermidis*, *S. aureus*, and, to a lesser degree, *Corynebacterium spp.* (22). In a study conducted by Groden et al.[8] the commonly isolated bacteria in patients with chronic blepharitis were *S. epidermidis* (95.8%), *Corynebacterium spp.* (76.8%), Acinetobacter spp. (11.4%), and *S. aureus* (10.5%). Compared with the control group, the detection rates of *S. epidermidis* and *Corynebacterium spp.* were significantly higher in patients with chronic blepharitis. Demler et al.[23] reported a 52% *D. folliculorum* positivity rate in patients with chronic blepharitis and an increase in both Gram-negative and Gram-positive bacteria in the Demodex-positive patients. In a recent study conducted by Zhu et al.[24] *D. folliculorum* frequency (76.7%) was found to be significantly higher in patients with chronic blepharitis than in the control group (41.3%). Moreover, the authors found no statistically significant increase in the density of the aerobic bacteria *S. epidermidis* and *S. aureus* in the presence of *Demodex mites* in the culture samples obtained from the eyelid margin and eyelashes. In the present study, *S. epidermidis*, other CNS, *S. aureus*, *Corynebacterium spp.*, and *Streptococcus spp.* were detected in patients with chronic blepharitis. Although bacterial growth was significantly higher in Demodex-positive patients, no significant difference was observed between the bacterial strains. The most frequently isolated bacterium in patients with blepharitis patients has been reported to be *S. epidermidis*.[7,23] Consistent with this finding in the literature, there was a predominance of *S. epidermidis* in patients with chronic blepharitis in the present study.

Mites function as vectors, especially for Staphylococcus species (25). In the current study, *S. epidermidis* (38.1% vs. 31.0%), *S. aureus* (19.0% vs.10.3%), and *Corynebacterium spp.*(16.7% vs. 6.9%) were determined at higher rates in Demodex-positive patients than in Demodex-negative patients, but the difference was not statistically significant. This suggests that these bacteria, which are frequently found in the normal eyelid flora, settle more in the eyelash follicles through the mediation of *Demodex mites* and lead to the formation of a mixed infection. *Staphylococci* are found in the normal eyelid flora and just like mites, there is an increase in colonisation with age. The biofilm layer formed by *S. epidermidis* in particular provides a suitable living and nutritional environment for *Demodex mites*. If the cylindrical layer that forms with the accumulation of the biofilm layer around the eyelash is accepted as a pathognomic finding for *Demodex mites*, there may be an association between *S. epidermidis* and *Demodex mites*.[22,26]

D. folliculorum causes direct damage to the follicular epithelium within the eyelash follicles in the eyelid and eyelid margin. The development of blepharitis due to the bacteria carried on the surface of *Demodex mites* triggers the host immune response. The resulting mechanical blockage and the delayed oversensitivity reaction cause inflammation in the eyelid margin.[1] In a study conducted by Kim et al.[27] the levels of IL-17, causing inflammation of the eyelid and ocular surface, weredetected at a significantly higher rate in patients with Demodex-infected blepharitis, indicating inflammatory events (27).

Due to the uncertainty in etiopathogenesis, the treatment for blepharitis is confusing and ineffective, and the majority of cases become chronic. In blepharitis cases, bacterial infections and allergies are considered initially, due to which antibacterial and steroid drops are generally used in empirical treatment. If the cause of blepharitis is *D. folliculorum* infestation, the patient would not benefit from this treatment and the condition could become chronic. Pretreatment detection of the parasite may be beneficial, especially in treatment-resistant chronic blepharitis patients.[28] As found in the present study, *D. folliculorum* and bacterial agents are often detected together in patients with chronic blepharitis and it must be remembered that this creates a complicated infection site, which must not be ignored in the treatment process. Therefore, the use of tea tree oil is predominant in the treatment as it has been proven to have antiparasitic, antibacterial and anti-inflammatory effects in previous studies.[29,30] In invivo and invitro studies conducted by Goa et al.[31] it was observed that *Demodex mites* were effectively eliminated by treatment with tea tree oil.

A limitation of the present study was that the patients were not followed up after treatment. In future studies, changes in the combination of bacterial strains and *D. folliculorum* should be investigated after the application of various treatments, which would helpin determining the treatment efficacy in more detail.

CONCLUSION

The results of this study suggest that in patients with chronic blepharitis, a mixed infection area is formed by the combination of *D. folliculorum* and aerobic bacteria found in the normal eyelid flora. It is beneficial to consider these results during the initiation ofempirical treatment in patients with chronic blepharitis.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Karabük University Medical Faculty (no: 13, dated:31/08/2016)

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Orjinal Araştırma / Original Article

Gaucher Disease Type 1, A Rare Disease: A Single Center Experience

Gaucher Hastalığı Tip 1, Nadir Bir Hastalık: Tek Merkez Deneyimi

Fatma İlknur Varol[1], Mukadder Ayşe Selimoğlu[1], Şükrü Güngör[1], Bengü Macit[2]

1Departments of Pediatric Gastroenterology, Hepatology, and Nutrition, İnönü University, Faculty of Medicine, Malatya, Turkey
[2]İnönü University, Faculty of Medicine, Departments of Pediatrics, Malatya, Turkey

Abstract

Aim: Gaucher disease is a rare lysosomal storage disease. Enzyme replacement therapy has proven to be very effective in reversing the risk of hepato-splenomegaly, cytopenia, osteopenia and reducing the risk of avasculer osteo necrosis, especially in children and young adults. The aim of this study is to draw attention to this rare disease and increase awareness.

Material and Method: All medical records of 8 patients diagnosed with Gaucher disease between 2008 and 2020 in our clinic were reviewed.

Result: Five of the cases were female (62.5%), average age at diagnosis; was 7.9 years. When complaints at the time of admission are examined, we found that, 3 patients admitted with swelling in the abdomen, one admitted with abdominal pain, and 4 patients had been referred to our center due to organomegaly detected during the examination. In physical examination 8 patient had splenomegaly. The mean level of glucocerebrosidase enzyme of the patients was found to be 0.61 mmol/l/h (normal range of glucocerebrosidase >3.2mmol/l/h). Considering the genetic analysis of the patients, 5 patients had homozygous and 3 patients had heterozygous mutations. One patient with portal hypertension who did not respond to enzyme replacement therapy at the time of admission underwent liver transplant.

Conclusion: Early diagnosis and treatment are important to live with in mind that this disease, which is rare in societies where consanguineous marriage is common and can result in serious morbidity and early death, can be seen more frequently.

Keywords: Rare diseases, lLysosomal storage disease, Gaucher disease, glucocerebrosidase

Öz

Amaç: Gaucher hastalığı, nadir görülen bir lizozomal depo hastalığıdır. Enzim replasman tedavisinin özellikle çocuklarda ve genç yetişkinlerde hepato-splenomegali, sitopeni, osteopeni riskini tersine çevirmede ve avaskular osteo nekroz riskini azaltmada çok etkili olduğu kanıtlanmıştır. Bu çalışmanın amacı, nadir görülen bu hastalığa dikkat çekmek ve farkındalığı artırmaktır.

Gereç ve Yöntem: Kliniğimizde 2008-2020 yılları arasında Gaucher hastalığı tanısı alan 8 hastanın tüm tıbbi kayıtları gözden geçirildi.

Bulgular: Olguların beşi kadın (%62,5), ortalama tanı yaşı; 7,9 yıldı. Başvuru anındaki şikayetler incelendiğinde; 3 hastanın karın bölgesinde şişlik ile başvurduğu, birinin karın ağrısı ile başvurduğu ve 4 hastanın muayene sırasında tespit edilen organomegali nedeniyle merkezimize sevk edildiği tespit edildi. Fizik muayenede 8 hastada splenomegali vardı. Hastaların ortalama glukoserebrosidaz enzim düzeyi 0.61 mmol/l/saat (normal glukoserebrosidaz aralığı >3.2 mmol/l/saat) olarak bulundu. Hastaların genetik analizine bakıldığında 5 hastada homozigot, 3 hastada heterozigot mutasyon vardı. Başvuru sırasında enzim replasman tedavisine yanıt vermeyen portal hipertansiyonlu bir hastaya karaciğer nakli yapıldı.

Sonuç: Ciddi morbidite ve erken ölümle bile sonuçlanabilen ve akraba evliliğinin sık olduğu toplumlarda nadir görülen bu hastalığın daha sık görülebileceği akla getirmek hastaların yaşam kalitesini arttırmak için erken tanı ve tedavi önem arz etmektedir.

Anahtar Kelimeler: Nadir hastalıklar, lizozomal depo hastalığı, Gaucher hastalığı, glukoserebrosidaz

Corresponding *(İletişim)*: Fatma İlknur Varol, İnönü University, Faculty of Medicine, Departments of Pediatrics, Malatya, Turkey
E-mail *(E-posta)*: drivarol@yahoo.com
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INTRODUCTION

Gaucher disease (GD) is a rare and chronic autosomal recessive lysosomal storage disease caused by GBA1 mutations characterized by glucocerebrosidase enzyme deficiency and accumulation of glucoceramide in the reticuloendothelial system. More than 400 mutations have been reported in the GBA1 gene.[1,2] The incidence of GD varies between 1:50,000 and 1: 100,000, and the frequency in Ashkenazi Jews is about 1: 855.[3] It was first described by Gaucher in 1882 and Braddy et al. determined that this disease was due to deficiency of a lysosomal enzyme called "β-glucocerebrosidase", in 1965. Hepatosplenomegaly, and bone fractures due to pancytopenia are common clinical findings in GD.

Although the diagnosis of the disease is based on the appearance of "Gaucher cells" (lipid-loaded macrophages in the bone marrow) in liver, spleen and bone marrow biopsies, since false gaucher cells can also be seen, the most reliable method is to show glucocerebrosidase activity in peripheral blood leukocytes.[4] It is classified under three types according to the degree, age of the patient, and findings: type 1 (chronic non-neuropathic type), type 2 (acute neuronopathic or infantile type), type 3 (subacute neuronopathic or juvenile type). In Type 1, hepatosplenomegaly, hypersplenism and skeletal pathologies are observed, whereas nervous system involvement is not observed. In Type 2, hepatosplenomegaly and hypersplenism are observed, but unlike Type 1, nervous system involvement occurs while bone fractures are not seen. In Type 3, hepatomegaly, hypersplenism, bone fractures and nervous system involvement are seen.[5] Type 1 is the most common form of the disease and constitutes 94% of all recorded GSD cases.[6] GD type 1 is a progressive disease that can result in damage, decreased quality of life, severe morbidity and even premature death. Especially in children and young adults, Enzyme Replacement Therapy (ERT) has proven to be highly effective in reversing hepatosplenomegaly, cytopenia, osteopenia and reducing the risk of avascular osteonecrosis.[7] Since Gaucher disease is a rare disease, the lack of consideration in the first evslustion may lead to diagnostic delays. The aim of this study is to draw attention to this rare disease and to increase awareness.

MATERIAL AND METHOD

This study was designed as an observational retrospective cohort and all medical records of 8 patients diagnosed with Gaucher disease between 2008 and 2020 at İnönü University Turgut Özal Medical Center Pediatric Gastroenterology, Hepatology and Nutrition Clinic were reviewed. Clinical and laboratory findings and the results of genetic analysis were collected. The study was approved by İnönü University Clinical Research Ethics Committee with protocol code 2020/978. Informed consent was obtained from the families of the patients.

Statistical Analysis

All data were summarized descriptively and statistical testing was not performed. Descriptive statistics for the categorical variables are presented by using mean and standard deviation (SD) and for continuous variables as percentage (%) and intervals.

RESULTS

Five of the evaluated cases were males (62.5%) and three were females (37.5%) and the mean age at diagnosis was calculated as 7.9 years. According to the complaints at the time of admission, 3 cases had abdominal swelling, one case had abdominal pain, and the other four cases were referred to our center after organomegaly was detected during the examination. Regarding the anthropometric measurements of the cases, the mean body weight Z score of the patients was -1.92, height Z score was 2.23, and body mass index Z score was -0.65. In the physical examination, 7 patients had hepatosplenomegaly and 1 patient had splenomegaly, in one of the patients with hepatosplenomegaly migratory spleen was present. The patient with a migratory spleen had admitted with abdominal pain. In 5 (62.5%) of the cases, there was cytopenia in the complete blood count at the time of admission. In the family history of the cases, 5 patients were inbred of consanguineous marriage. Gaucher cells were observed in bone marrow aspiration in 4 of the patients. in one of these patients who was 8-month-old, liver biopsy was performed and in addition to the appearance of Gaucher cells in bone marrow aspiration, sinusoidal and portal area histiocytic cell groups compatible with Gaucher disease were observed in liver biopsy. When the glucocerebrosidase enzyme levels of the patients were examined, it was seen that the enzyme level was zero in 3 patients and the enzyme levels were significantly below normal in other 5 patients. The mean glucocerebrosidase enzyme level of 8 patients was found to be 0.61 mmol/l/h (normal range is >3.2 mmol/l/h). When the genetic analyzes of the patients were examined, it was seen that 5 patients had homozygous mutations and the other 3 patients had heterozygous mutations. DEXA (dual energy X-Ray absorptiometry) evaluation was performed in 5 patients at the time of admission to see bone mineral density and ranged between -2 and -5. The clinical characteristics of the patients were shown in **Table1**.

In 6 patients diagnosed with Gaucher disease, enzyme replacement therapy (imigluserase) was initiated at a dose of 30 IU/kg/dose depending on the clinical findings and in two patients at a dose of 60 IU/kg, because platelet was 50000/mm3 and Hb was less than 8 g/dl.

Enzyme replacement therapy dose was revised according to the status of the patients in the follow-up. In the follow-up, it was observed that organomegaly improved in 3 patients in 1 year and in 1 patient in 4 years. One of the patients underwent liver transplantation because the signs of portal hypertension detected at the time of admission did not regress during the follow-up despite enzyme replacement therapy. In addition, in 3 of 5 cases whose bone mineral density was evaluated by DEXA method at the time of first admission, significant improvement was observed after enzyme replacement therapy.

Table 1. Clinical propeties of the patien

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age of diagnosis	15 months	14 years	23 months	6 years 9 months		10 years 6 months	8 months	14 years 10 months
Gender	F	F	M	M	F	F	M	F
Subcostal liver measurement at admission	6 cm	4 cm	5 cm	2 cm	4 cm	6-7 cm	2 cm	NP
Subcostal spleen measurement at admission	16 cm	13 cm	10 cm	6 cm	12 cm	9 cm	10 cm	5-6 cm
History of consanguinity	+	+	-	-	+	+	+	-
Cytopenia at admission	+	-	-	-	+	+	-	+
Storage cell in bone marrow	+	-	+	+	-	-	+	-
Liver biopsy	-	-	-	-	-	-	Compatible with Gaucher Disease	-
Enzym level mmol/l/h (>3,2 mmol/l/h)	0	1,9	0	0	1,54	0,2	0,1	1,2
DEXA (Z score)	-5	-	-2	-	-3	-2	-	-4
Genetics	Homozygote c.[1193G>T]; 1193G>T]	Heterozygote c.[1265_1219del]; [1342G>C]	Homozygote c.[148T>C]; c[148T>C]	Heterozygote c.[1226A>G];. [1448T>C; 1497G>C]	Homozygote c.[1193G>T]; 1193G>T]	Homozygote c.[1214G>C]; [1214G>C]	Homozygote c[148T>C]; c[148T>C]	Heterozygote [1448T>C; 1497G>C]
Treatment	30 unit/kg	30 unit/kg	30 unit/kg	30 unit/kg	60 unit/kg	30 unit/kg	30 unit/kg	60 unit/kg
Duration of treatment (years)	5	5	5	8	12	3	5	4
Subcustal liver measurement after treatment	4 cm	NP*	NP*	NP*	NP*	2 cm	NP*	Liver transplantation
Subcustal spleen measurement after treatment	10 cm	Splenectomy	NP*	NP*	NP*	NP*	NP*	Liver transplantation
DEXA after treatment	-2,2	-	-1.1	-	-2	-1	-	-4

*:Non palpabl

DISCUSSION

Gaucher disease is the most common lysosomal storage disease and affects many systems. Splenomegaly, hepatomegaly, skeletal pathology, growth retardation and pulmonary disease develop in Type 1 GD is non-neuronopathic and leads to a decrease in quality of life. Anemia and thrombocytopenia are seen due to hypersplenism. Glucoceramide accumulation in the bone marrow is associated with osteopenia, pathological fractures, lytic lesions, chronic bone pain (bone crisis) and osteonecrosis. Although anemia and thrombocytopenia can be severe, the greatest cause of morbidity is often bone disease resulting in long-term disability.

ERT should be initiated immediately after diagnosis of type 1 Gaucher disease in children and should be continued to improve the severity of the disease and to prevent complications, particularly the development of irreversible bone disease.[8] For this reason, in patients admitted to pediatric hepatology, pediatric hematology, pediatric pulmonary diseases, and orthopedics outpatient clinics, GD, which is rarely seen should be considered in the diagnosis. Early diagnosis of the disease is important for reducing morbidity and improving quality of life.

Hepatomegaly; defined as a liver, which is in excess of 2.5% of body weight and is 1.25 times larger than the normal volume of the liver.[9] Hepatomegaly is one of the most common symptoms in GD and often causes abdominal pain and a slight increase in transaminases.[10] In addition, patients with cholelithiasis, hemosiderosis steatosis, focal fibrosis, portal hypertension, cirrhosis, and hepatocellular carcinoma (HCC) have been reported.[11] Patlas et al.[12] reported a 100% prevalence of hepatomegaly in a cohort of 103 pediatric patients, by ultrasound. In three of our cases, there was abdominal distension at the first presentation and one case had abdominal pain. The other four cases had been referred to our center due to the detection of organomegaly during the examination. Seven of our patients had hepatomegaly on physical examination, and only splenomegaly was present in one patient with portal hypertension. In Gaucher disease liver fibrosis has rarely been reported.[13] In a series of 53 patients, portal hypertension complications have been reported only in

two patients.[14] In patients with hepatic parenchymal disease, ERT may be insufficient to prevent progression to hepatic decompensation.[15] In our series 1 patient underwent liver transplantation because of symptoms of portal hypertension and his findings did not regress in the follow-up despite enzyme replacement therapy. Pathological analysis of the explanted liver showed that it was compatible with cirrhosis. Liver transplant is a life-saving treatment for end-stage liver disease in patients with Gaucher disease. Ayto et al. in their report of the results of liver transplantation in four patients with GD and end-stage liver disease, reported that all patients had excellent results after liver transplantation up to 10 years post-procedure, without evidence of Gaucher-associated pathology in the graft.[15] Our patient has been followed up for 5 years, after the transplantation, without any problem.

In the assessment of bone mineral density at the time of first admission, the DEXA Z score of 5 patients was between -2 and -5. After ERT, the DEXA Z score of 3 patients returned to normal and a significant improvement was observed in 2 cases.

CONCLUSION

Gaucher disease develops as a result of glucocerobrosidase enzyme deficiency. It is a rare, autosomal recessively inherited lipid storage disease that is characterized by the accumulation of glucocerobroside in reticuloendothelial system cells. This rare disease is seen more frequently in societies where consanguineous marriage is common and can cause serious morbidity and early death. Early diagnosis and treatment are important in order to improve the quality of life of patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Local Ethics Committee of Inonu University (approval number: 2020/978).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Nursing Care Perception and Satisfaction Levels of Surgical Patients

Cerrahi Hastalarının Hemşirelik Bakımını Algılayışı ve Memnuniyet Düzeyleri

Esma Özşaker[1], Hüda Sevilmiş[2], Yasemin Özcan[3], Merve Samast[4]

[1] Ege University Faculty of Nursing, Izmir, Turkey
[2] Giresun University Prof. Dr. A. İlhan Özdemir Training and Research Hospital, Giresun, Turkey
[3] Bozyaka Izmir Training and Research Hospital, Izmir, Turkey
[4] Ege University Medical Faculty Hospital, Izmir, Turkey

Abstract

Objective: This study was conducted to examine the Nursing Care Perception and Satisfaction Levels of Surgical Patients.

Material and Method: The sample of this descriptive and cross-sectional study consisted of 300 patients aged 18 and over, who accepted to participate in the study, who were hospitalized at a university hospital surgical clinics between 17 December 2018 and 15 March 2019. Data were collected with the "Patient Information Form" created by the researchers, and "Newcastle Satisfaction with Nursing Care Scale" and "The Scale of Patient Perception of Hospital Experience With Nursing". Percentage, mean, t test, analysis of variance, and Pearson's correlation analysis were used to evaluate the data.

Results: Newcastle Satisfaction with Nursing Care Scale mean score of the surgical patients was 79.86±19.31 and the mean score of The Scale of Patient Perception of Hospital Experience With Nursing was 68.03±9.87. It was found that there was a statistically significant relationship between the score of Newcastle Satisfaction with Nursing Care Scale and the score of The Scale of Patient Perception of Hospital Experience With Nursing (r =0.665; p =0.001). A statistically significant difference was found between the average point of Newcastle Satisfaction with Nursing Care Scale and education level, chronic illness, type of hospitalization, number of patients in the room (p <0.05).

Conclusion: It was found that surgical patients' perception level of nursing care and satisfaction levels with nursing care were high. It was found that patients' perception of nursing care positively affected the nursing care satisfaction level of patients.

Keywords: Surgery, patient, nursing care, satisfaction level

Öz

Amaç: Bu çalışma, cerrahi hastalarının hemşirelik bakımını algılayışını ve memnuniyet düzeylerini incelemek amacıyla yapıldı.

Gereç ve Yöntem: Tanımlayıcı ve kesitsel türdeki bu çalışmanın örneklemini, 17 Aralık 2018- 15 Mart 2019 tarihleri arasında bir üniversite hastanesinin cerrahi kliniklerinde yatan, araştırmaya katılmayı kabul eden, 18 yaş ve üzeri, iletişim kurabilen 300 hasta oluşturdu. Veriler, araştırmacılar tarafından oluşturulan "Hasta Bilgi Formu" ve "Newcastle Hemşirelik Memnuniyet Ölçeği", "Hastaların Hemşirelik Bakımın Algılayış Ölçeği (HHBAÖ)" kullanılarak toplandı. Verilerin değerlendirilmesinde sayı, yüzde, ortalama, standart sapma, Student t testi, varyans analizi ve Pearson's Korelasyon analizi kullanıldı

Bulgular: Cerrahi kliniklerde yatan hastaların; hemşirelik bakımından memnuniyet puan ortalaması 79,86±19,31 ve hemşirelik bakımını algılayışı puan ortalaması 68,03±9,87 olarak bulundu. Hastaların Newcastle hemşirelik bakımından memnuniyet ölçeği toplam puan ortalaması ile hemşirelik bakımını algılayışı ölçeği toplam puan ortalaması arasında pozitif yönde istatistiksel olarak anlamlı bir ilişki saptandı (r=0,665; p=0,001). Eğitim düzeyi, kronik hastalık durumu, hastaneye yatış şekli, odada bulunan hasta sayısı ile hemşirelik bakımından memnuniyet puan ortalamaları arasındaki fark istatistiksel açıdan anlamlı bulundu (p<0,05).

Sonuç: Cerrahi hastalarının hemşirelik bakımını algılama düzeylerinin ve hemşirelik bakımından memnuniyet düzeylerinin yüksek olduğu bulundu. Hastaların hemşirelik bakımına ilişkin algılarının, hemşirelik bakımından memnuniyet düzeylerini olumlu etkilediği belirlendi.

Anahtar Kelimeler: Cerrahi, hasta, hemşirelik bakımı, memnuniyet düzeyi

Corresponding *(İletişim)*: Esma ÖZŞAKER, Ege Üniversitesi Hemşirelik Fakültesi, Cerrahi Hastalıkları Hemşireliği Anabilim Dalı, Izmir, Türkiye
E-mail *(E-posta)*: esmaozseker@yahoo.com
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INTRODUCTION

Nurses are members of the health team that play an active role in the management of health care, which also have a vital function of maintaining, improving, and rehabilitating the people's health, and providing uninterrupted services during the patient's stay in the hospital.[1] Nursing care is a professional service that includes the determination, planning, implementation, and evaluation of the care requirements of people with existing or potential health problems by the nurses and includes mutual trust, empathy, privacy, ethical and moral values throughout the entire process of care. Care is an important factor not only in meeting biological needs but also in meeting psychological, social and cultural needs.[2]

Surgical interventions cause many physiological and psychological changes in the human body (homeostatic balance, fear, predisposition to infection, pain, etc.). Patients need high-quality nursing care to cope with these changes in the postoperative period.[3] Nurses are the healthcare workers whom surgical patients need most before and after surgery.[4] The quality of nursing care is directly related to how the given care service is perceived by the service recipients.[5-8] Besides the individual characteristics of the patients, the support they receive from the nurse, the respect and courtesy shown by the nurse, the ability to reach the nurse when needed, and being informed clearly and satisfactorily are also very effective in terms of care perception.[7,9,10] One of the most important indicators in evaluating the service and care quality offered by healthcare professionals is the patient's satisfaction with the care service.[11-13] Patient satisfaction is determined by the level of perception of the care given in line with the expectations of the patients.[14-16] In the emergence of the perception concerning health service quality in patients, the patients' evaluation of the nursing services is important. According to the widely used definition in the field of nursing, patient satisfaction is the degree of proximity between the patient's expectation of ideal nursing care and the perception of nursing care that they actually received.[1]

It is important to systematically evaluate care within the scope of continuous improvement and quality and to share the results with healthcare professionals and managers. In this regard, it is important to periodically measure patient satisfaction, which is an important indicator of the quality of nursing services and therefore health services, and to identify situations that cause dissatisfaction, to produce proper solutions and to make necessary arrangements for nurses' patient care practices. Therefore, this study was conducted as a descriptive study to examine surgical patients' perception of nursing care and their level of satisfaction.

Research questions:

• What is the perception of surgical patients on nursing care?

• What are the satisfaction levels of surgical patients with regard to nursing care?

• Does surgical patients' perception of nursing care affect their satisfaction level?

• What are the factors affecting the nursing care satisfaction level of surgical patients ?

MATERIAL AND METHOD

Design

This descriptive study was conducted to determine surgical patients' perception of nursing care and their satisfaction levels.

Sample

The research population was composed of patients hospitalized in the surgical clinics of a university hospital (General Surgery, Urology, Otorhinolaryngology, Orthopedics, Plastic Surgery, Organ Transplantation, Neurosurgery, Thoracic Surgery, Cardiovascular Surgery) between 17 December 2018 and 15 March 2019. The sample of the study consisted of 300 patients who met the research criteria and agreed to participate in the study between the dates determined without using the sampling method.

Inclusion Criteria

- Agreeing to participate in research,
- Discharged from surgical clinics,
- Spent three days or more in the ward,
- No hearing or vision problems
- 18 years of age and older
- Being able to read and write,
- Patients who can communicate.

Data Collection Tools

The data were collected using the "Patient Information Form" created by the researchers, " Newcastle Satisfaction with Nursing Scales (NSNS)" and " Patient Perception of Hospital Experience with Nursing Care (PPHEN)".

Patient Information Form: This form, created by the researchers, includes the patients' socio-demographic (age, gender, educational status, marital status, occupation, employment status, place of residence, social security and income status, etc.) and hospitalization (clinic where the patients are hospitalized, their history of prior hospitalization, their application type, the number of patients he/she stayed together in the room where they were treated, the duration of their hospitalization, their operation status, the state of their staying in the intensive care unit and the state of presence of their companion, etc.) is a form consisting of 26 questions that query variables related to their properties.

Newcastle Satisfaction with Nursing Scales (NSNS): NSNCS was developed by Thomas and Bond in 1996 to determine the patient's perspective and experiences and satisfaction with nursing care. The Turkish validity and reliability study was done by Uzun in 2003[17] and then by Akın and Erdoğan

in 2007.[18] This scale is a 5-point Likert-type scale consisting of 19 items to determine satisfaction in terms of nursing. All items are scored on a five-point Likert scale (1=not at all satisfied, 2=barely satisfied, 3=quite satisfied, 4=very satisfied and 5=completely satisfied). Total score was summed and transformed to yield an overall 'satisfaction score' of 0-100, where "100" denoted complete satisfaction/highest level of satisfaction with all aspects of nursing care. Cronbach alpha was found as 0.96 in the study of Thomas et al. (1996), was found 0.94 in the study of Uzun (2003), and was found 0.96 in the study of Akın and Erdoğan (2007).

Patient Perception of Hospital Experience with Nursing Care (PPHEN): PPHEN was first developed by Dozier et al in 2001, and the validity-reliability study in Turkey was conducted by Çoban and Kaşıkçı in 2006.[19] There are 15 statements about the quality of nursing care in a Likert-type scale. The questions are assigned scores based on the responses to each statement, as follows: totally agree (5), slightly agree (4), undecided (3), disagree (2), and totally disagree (1). Any unanswered item is evaluated as zero (0). The scale results in a minimum score of 15 and a maximum score of 75. The cut-off point of the scale is 45. Higher total scores indicate high level of satisfaction with nursing care. In the study of Coban and Kasıkcı (2006), Cronbach alpha was found as 0.92. In this study Cronbach alpha was found as 0.95.

Data Collection

December March 17, 2018 - March 15, 2019, the patients who accepted to participate in the study were asked to fill out an Informed Voluntary Consent Form, Patient Information Form, NSNS and PPHEN after explaining the research to the patients who decided to be discharged at the surgical clinics of a university Hospital and who met the study criteria. Participation with the questionnaire lasted on average about 10 minutes.

Data Analysis

The SPSS 25.0 program was used to evaluate the data. Number, percentage, mean, standard deviation, Student's t test, variance analysis and Pearson's Correlation analysis were used to evaluate the data. The resulting p-value at <0.05 was considered statistically significant.

Ethical Issues

Ethics committee approval was obtained from the Clinical Research Ethics Committee of the relevant university (Protocol: 20/03/2018, 18-3.1/31), and written permission was obtained from the management of the hospital where the research was conducted (04.06.2018, E. 159252). Informed consent was read and signed by each participant. All principles of the Helsinki declaration were followed throughout the study. Permission was obtained via mail from Uzun, who conducted the Turkish validity and reliability study of the NSNS, and from Çoban, who conducted the Turkish validity-reliability study of the PPHEN.

RESULTS

Findings on Sociodemographic and Hospitalization Characteristics

When the sociodemographic and hospitalization characteristics of the patients participating in the study were examined; the average age was 52.73±13.00 (minimum 18, maximum 66), 54.7% of them were male, 74% of them were married; It was determined that 38.7% were high school graduates, 57% had previous surgery, 41.7% had a chronic disease, 86% had someone to give home care. The average hospitalization time of the patients was 13.23±18.26 days (min. 3, max.165 days), 65.3% applied to the hospital for a planned surgery, 42.7% stayed in a private room, 93.7% had a hospital attendant, 95% of them had information about surgery, 73.3% of them found the training sufficient, and 95% of them were satisfied with the clinic where they were hospitalized (**Table 1**).

Table 1. Sociodemographic and Hospitalization Characteristics of the Patients (n=300)

Characteristics	Min.-Max.	Mean±SD	
Age	18-66	52.73 ± 13.00	
Length of hospitalization	3-165	13.23 ± 18.26	
		n	%
Gender	Female	136	45.3
	Male	164	54.7
Marital status	The married	222	74
	Single	78	26
Education status	Literate	44	14.7
	High school	116	38,7
	Primary education	74	24.7
	University	66	22
Previous surgery	Yes	171	57
	No	129	43
Having a chronic illness	Yes	125	41.7
	No	175	58.3
Is there someone to care at home	Yes	258	86
	No	42	14
Type of hospitalization	Urgent	104	34.7
	Planned	196	65.3
Type of room	Private room	128	42.7
	Double	58	19.3
	Three or more people	114	38
Companion status	There is	281	93.7
	No	19	6.3
Receiving information about the operation	Yes	285	95
	No	15	5
Is the information given for the surgery sufficient?	Enough	220	73.3
	Partially enough	63	21
	Not enough	17	5.7
Are you satisfied with the surgery clinic you are in.	Yes	285	95
	No	15	5

Findings Related to Scale Scores

PPHEN items and the average scores obtained are shown in **Table 2**, while NSNS items and the mean scores obtained are shown in **Table 3**. It was determined that the patients got the lowest 23.16 and the highest 100 points in PPHEN and their mean score was 79.86±19.31. It was found that patients received the lowest score of 15 and the highest score of 75 from the scale of perception of nursing care, and the mean score was 68.03±9.87. It was found that there was a positive, highly significant relationship between the patients' mean NSNS total score and the mean PPHEN total score (r=0.665; p=0.001) (**Table 4**).

Table 2. Patients' opinions on general nursing practices in surgical clinics (n=300)

Patient Perception of Hospital Experience with Nursing Care (PPHEN)	Totally disagree	Disagree	Undecided	Slightly agree	Totally agree
	%	%	%	%	%
1. The nurses helped my outlook become more realistic	1.7	4.3	8.7	18.3	67.0
2. The nurses thought ahead about what I needed	1.7	5.3	8.7	23.0	61.3
3. My requests were promptly attended to by the nursing staff	0.3	3.7	4.0	19.7	72.3
4. The nurses gave me their undivided attention while caring for me	1.3	3.0	4.7	16.7	74.3
5. Little things were carried out for me without asking me	3.0	5.3	6.3	18.0	67.3
6. The nurses helped make me feel at ease in the hospital	0.7	2.7	4.0	18.0	74.7
7. The nurses helped me better deal with the unknowns of this hospitalisation	1.7	7.0	6.7	17.7	67.0
8. I was sure that the nurses alerted others to my needs and requests	0.7	3.0	11.7	17.0	67.7
9. I was sure that the nurses would be there when I needed them	0.7	1.3	7.3	17.0	73.7
10. I feel the nurses understood what this illness means to me	1.3	4.0	6.7	18.7	69.3
11. I know that because of the nurses' efforts, some problems were avoided.	0.7	3.3	13.0	19.0	64.0
12. The nursing staff helped me manage the fears I had about my illness	1.0	3.3	6.0	19.3	70.3
13. The nurses' explanations helped put me at ease	0.7	2.7	4.3	19.0	73.3
14. The nurses made me feel relaxed when treatments were being performed	0.7	2.0	2.3	18.0	77.0
15. The nurses' actions made me feel cared for.	1.0	2.0	3.0	16.0	78.0

Table 3. Patients' views on satisfaction with general nursing care in surgical clinics (n=300)

Newcastle Satisfaction with Nursing Scales (NSNS)	Not at all satisfied	Barely satisfied	Quite satisfied	Very satisfied	Completely satisfied
	%	%	%	%	%
1. The amount of time spent with you	2.0	10.3	20.0	29.3	38.3
2. How capable nurses were at their job	1.3	6.7	21.7	30.3	40.0
3. There always being a nurse around if you needed one	3.7	10.0	19.0	26.0	41.3
4. The amount nurses knew about your care	1.7	9.7	15.7	30.0	43.0
5. How quickly nurses came when you called for them	3.7	11.7	15.0	28.0	41.7
6. The way the nurses made you feel at home	3.7	14.7	15.3	27.7	38.7
7. The amount of information nurses gave to you about your condition and treatment	3.0	11.0	19.0	28.0	39.0
8. How often nurses checked to see if you were okay	3.3	6.7	18.7	29.3	42.0
9. Nurses' helpfulness	1.3	7.7	18.3	27.3	45.3
10. The way nurses explained things to you	0.7	8.7	18.7	27.3	44.7
11. How nurses helped put your relatives' or friends' minds at rest	2.0	14.0	17.0	27.0	40.0
12. Nurses' manner in going about their work	2.3	7.7	15.3	30.0	44.7
13. The type of information nurses gave to you about your condition and treatment	1.0	12.0	15.3	31.3	40.3
14. Nurses' treatment of you as an individual	2.3	8.3	15.3	31.3	42.7
15. How nurses listened to your worries and concerns	4.3	9.7	15.0	29.3	41.7
16. The amount of freedom you were given on the ward	3.3	6.7	18.3	28.0	43.7
17. How willing nurses were to respond to your requests	2.3	9.3	15.0	29.3	44.0
18. The amount of privacy nurses gave you	1.7	4.0	15.7	28.0	50.7
19. Nurses' awareness of your needs	1.3	10.3	16.3	28.7	43.3

Tablo 4. Distribution of PPHEN and NSNS Mean Scores and Relationship Status Between Scales (n=300)

Scale (Points that can be obtained) Min.-Maks.	Received Points			Correlation
	Mean±SD	Min.	Max.	
NSNS (0 -100)	79.86±19.31	23.16	100	r:0.665** p:0.001
PPHEN (15-75)	68.03±9.87	15	75	

PPHEN: Patient Perception of Hospital Experience with Nursing Care, NSNS: Newcastle Satisfaction with Nursing Scales, x: Arithmetic Average, SD: Standard deviation, Min: Minimum value, Max: Maximum value, ** Correlation relation is significant at p <0.01 level.

When the mean scores of the PPHEN and NSNS were examined according to the sociodemographic characteristics of the patients, there was a statistically significant difference (p<0.05) between their marital status and PPHEN mean scores, and between educational status and NSNS mean scores; it was seen that there was no statistically significant difference between them according to the patients' gender, employment status, place of residence, and social security status (p>0.05). Besides, when the relationship between chronic disease and nursing care satisfaction was examined; the average score of the nursing care satisfaction scale was found to be significantly higher in patients with chronic disease (82.56±18.89) than those without (77.93±19.43) (t: 0.059, p: 0,040). It was determined that the mean NSNS score of the university graduate patients was significantly lower than the primary school graduates (p<0.05) (**Table 5**).

The relationship between the satisfaction with the services in the surgical clinic where the patients are hospitalized and the variables related to their hospitalization status and the mean NSNS scores are shown in **Table 6**. According to the way of patients' hospitalization, their numbers in the room, their satisfaction status with the surgical clinic where they lied down and the hospital, medical services, nursing services, other health services, secretarial patient admission, cleaning/order, support, respect and courtesy, the way of getting clear answers to their questions, satisfaction status with accessibility to doctors and nurses, a significant correlation was found between the mean scores of NSNS (p <0.05). In an advanced analysis, it was seen that the satisfaction levels of those staying in a room of three or more people were lower than those who stayed in a private room and a double room.

Table 5. Distribution of PPHEN and NSNS Mean Scores According to Sociodemographic Characteristics of the Patients (n=300)

Characteristics	n	%	PPHEN		NSNS	
			Mean±SD		Mean±SD	
Gender						
Female	136	45.3	67.56±10.47	t: -0.740	78.39±19.19	t: -1.207
Male	164	54.7	68.41±9.36	p: 0.460	81.09±19.38	p: 0.228
Marital status						
Married	222	74	68.99±9.13	t: 2.892	80.35±19.27	t: 0.732
Single	78	26	65.28±11.34	**p: 0.004**	78.48±19.47	p: 0.465
Working status						
Working	65	21.7	67.96±8.49	t:-0.056	76.12±19.84	t: -1.769
Not working	235	78.3	68.04±10.24	p:0.955	80.90±19.07	p: 0.078
Place of residence						
City	172	57.3	67.40±10.45	t: -1.280	80.11±19.21	t: 0.259
Town-village	128	42.7	68.87±9.01	p: 0.202	79.53±19.51	p: 0.796
Social insurance						
There is	283	94.3	67.96±9.94	t:-0.467	79.59±19.35	t: -0.996
No	17	5.7	69.11±8.85	p: 0.641	84.39±18.53	p: 0.320
Chronic illness						
There is	125	41.7	69.16±9.49	t:1.680	82.56±18.89	t:0.059,
No	175	58.3	67.22±10.08	p:0.094	77.93±19.43	**p:0.040**
Education status						
Literate	44	14.7	68.47±9.87		78.70±19.56[a]	
Primary education	116	38.7	68.59±10.25	F:2.635	82.78±18.90[b]	F:2.825
High school	74	24.7	69.47±6.93	p:0.050	80.86±18.36[c]	**p:0.039**
University	66	22	65.12±11.50		74.38±20.09[d]	**d<b=a=c**

t: Student t testi, F:One Way ANOVA

Table 6. Mean NSNS Scores According to Variables Regarding Patients' Hospitalization Status (n=300)

Variables		n	%	Satisfaction Scores Mean ±SD	
Type of hospitalization	Urgent Planned	104 196	34.7 65.3	79.49±20.67 82.18±18.18	t: -2.890 **p: 0.004**
Type of room	Private room Double Three or more people	128 58 114	42.7 19.3 38	82.66±18.23[a] 82.99±15.45[b] 75.14±21.36[c]	F: 5.677 **p:0.004** **c<a=b**
Are you satisfied with the hospital in general	Yes No	282 18	94 6	80.73±18.46 66.19±26.68	t: 2.277 **p: 0.037**
Are you satisfied with the surgery clinic you are in.	Yes No	285 15	95 5	81.07±18.33 56.91±23.53	t: 4.901 **p: 0.001**
Satisfaction in the Surgery Clinic					
From physicians	Satisfied Not satisfied	290 10	96.7 3.3	80.91±18.29 49.36±24.08	t: 5.304 **p: 0.001**
From Nurses	Satisfied Not satisfied	293 7	97.7 2.3	80.65±18.67 47.06±18.29	t: 4.704 **p: 0.001**
From other healthcare professionals	Satisfied Not satisfied	292 8	97.3 2.7	80.64±18.76 51.31±18.60	t:4.364 **p: 0.001**
Physical structure and interior equipment	Satisfied Not satisfied	170 130	56.7 43.3	81.05±18.11 78.30±20.74	t: 1.202 p: 0.231
Secretariat / patient admission procedures	Satisfied Not satisfied	287 13	95.7 4.3	80.88±18.74 57.32±18.57	t: 4.434 **p: 0.001**
Cleanliness / order	Satisfied Not satisfied	231 69	77 23	82.15±17.84 72.21±22.05	t: 3.421 **p: 0.001**
Support, respect and courtesy	Satisfied Not satisfied	285 15	95 5	81.08±18.58 56.77±18.86	t: 4.933 **p: 0.001**
Getting clear and clear answers to your questions	Satisfied Not satisfied	273 27	91 9	82.12±17.94 56.99±18.03	t: 6.939 **p: 0.001**
Accessibility to physician and nurse	Satisfied Not satisfied	287 13	95.7 4.3	81.20±18.38 50.36±15.90	t: 5.945 **p: 0.001**

t: Student t testi, F:One Way ANOVA

DISCUSSION

Since surgical interventions cause many physiological and psychological changes in the human body, patients need quality nursing care in this process.[3] The quality of nursing care is directly related to how the given care service is perceived by the service recipients.[5,6] In this study, it was determined that the mean score of the patients' perception of nursing care scale was 68.03±9.87 and the surgical patients' perception of nursing care was high. In a study conducted by Çoban and Kaşıkçı (2006), it was found that patients received an average score of 54.44±12.31 from PPHEN.[19] In this study, it was seen that the surgical patients had a higher level of perception of nursing care. It was determined that the patients agreed with the statement "I felt well cared for thanks to the nurses" at the highest rate (78%), and they the least agreed with the statement "Nurses thought more than I needed" (61.3%). Kol et al. (2017), it was determined that the highest mean score of the PPHEN item belonged to the statement "I felt that I was well cared for thanks to the nurses" and "I am sure that the nurses will be there when I need them".[7] In the study of Şişe (2013), it was found that patients agreed with the statement "I felt well cared for thanks to the nurses" at the highest rate (72.2%), while the lowest rate was with the statement "They gave information about things I did not know about the hospital" (58%, 8)).[14] The study by Zhao and Akkadechanunt (2011) found that the patients' perceptions of nursing care were positive and that " nurses were with me when I needed them" had a high participation rate.[20] The perception of care quality such as knowing the patient with the technical skills of nurses, establishing a relationship of trust with him/her, making the patient feel his/her presence, etc. are possible by making the patient feel such care behaviours.[5] In studies with PPHEN, it can be said that patients have a positive perception in terms of their feeling well cared for thanks to nurses.

Patients ' satisfaction with nursing care is the most basic determinant of their overall satisfaction during their hospital care and the best indicator of health service quality.[11,12,21] In this study, it was defined that patients hospitalized in surgical clinics had high levels of satisfaction with nursing care. While this finding showed that the satisfaction of patients hospitalized in surgical clinics about nursing was at a high level in the studies of Kuzu and Ulus (2014)[4] , Yıldız et al. (2014)[22] and İçyeroğlu and Karabulut (2011)[23], It was found that it was at a moderate level in the study of Kayrakçı and Özşaker (2014)[24], Akgöz et al. (2017)[25] and Aldemir et al. (2018)[26] and at a low level in the study of Sayın et al. (2016) [27] Given this information, it can be said that the satisfaction of patients in surgical clinics with nursing care varies between low and high levels. This situation may be due to factors such as different nursing standards in research institutions and different number of patients for per nurse.

Patients' satisfaction with nursing is an important indicator concerning the quality of the nursing services offered.[1] Patient satisfaction is determined by the level of perception of the care given in line with the patient's expectations.[15,16] In this study, a statistically significant and positively high correlation was found between the total score average of the Newcastle Nursing Satisfaction Scale and the total score of the Perception of Nursing Care Scale (r=0.665; p=0.001). It was seen that as the patients' perception of nursing care increased, their level of satisfaction also increased. As is also understood from this result, when surgical patients have a positive perception of nursing care, their satisfaction with nursing care increases.

The perception factor varies according to the patient's expectations and individual characteristics from the institution or service.[9] The studies indicate that there is a relationship between patients' perception of nursing care and their social status, age, education level, cultural background and ethnic structure.[28-30] In this study, when the mean PPHEN scores were examined according to the sociodemographic characteristics of the patients; it was found that there was no statistically significant difference between them according to gender, education status, occupation, residence, social security status and chronic disease (p>0.05). When the mean NSNS scores were analyzed according to the sociodemographic characteristics of the patients; it was observed that there was no statistically significant difference between the mean scores of NSNS with gender, marital status, occupation, residence, social security status (p>0.05). Similarly, in the study done by Aldemir et al. (2018)[26], no significant difference was found between the patients' satisfaction with nursing in terms of sociodemographic characteristics such as age, marital status, occupation, having social security and previous hospital experience (p>0.05). In the study, it was found that there was a statistically significant difference between education level and mean scores of NSNS (p<0.05). While the satisfaction levels of the patients graduated from a university with nursing care were low, literates and primary school graduates were found to have higher satisfaction levels. As the education level increased, patients' satisfaction from nursing care decreased. Similarly, it was observed that the low educated patients were more satisfied with nursing care than the highly educated patients.[1,4,21,24,31] The increase in the education level of the society leads to the emergence of the individuals who are more knowledgeable and critical of the service provided, who become more active in their care, and the demands and/or expectations of the individuals constantly change.[13] It is emphasized that the satisfaction concerning nursing is proportional to the expectations, the expectations increase as the level of education increases, and it is stated that the satisfaction level of the patients with high education level is low.[7,26] Thereby, the expectation levels of the sick individuals about the service delivery in the field of health increase and this situation affects the perception of satisfaction. In the light of these findings, it is thought that as the level of education increases, individuals become more conscious, their expectations from the service they receive rise, and as a result, the level of satisfaction with the service received decreases.

Patients with chronic diseases, frequent visits to the hospital and hospitalized for a long time can see the educator, consultant and other roles of the nurse in the clinics where they receive service.[7] A study conducted by Dikmen and Yilmaz (2016) also found that patients with chronic diseases have a higher perception of nursing care.[30] In this study, while there was no significant relationship between having a chronic disease and the perception of nursing care (p>0.05), it was determined that the patients with chronic disease had a significantly higher level of satisfaction with nursing than those who did not (p<0.05).

When the mean scores of NSNS were examined according to the hospitalization status of the patients: the patients' satisfaction score averages were found to be statistically significantly higher (p<0.05) according to the method of hospitalization, the number of the patients in the room, the state of satisfaction with the hospital in general, the state of satisfaction with the surgical clinic in which they were admitted. It was found that those who stayed in triple rooms and above had lower levels of satisfaction with nursing care than those who stayed in a private room and double room. Similarly, some studies indicate that as the number of beds in the room where the patients are staying increases, their satisfaction scores related to nursing care decrease.[7,32] It was determined that there was no statistically significant difference between the satisfaction levels of surgical patients and their satisfaction with the physical structure and internal equipment (p>0.05). In the study of Kayrakçı and Özşaker (2014), the satisfaction score averages of the patients who were informed about the physical environment/functioning of the service and the treatment/care applied and who were satisfied with the communication established by the nurses were found to be statistically significantly higher.[24] In the research of Arslan and Kelleci (2011), the most important areas of patients were the ability of nurses to perform the service reliably and correctly, as well as the ability of nurses to establish knowledge, respect and empathy.[28] The least important service area was found to be physical facilities, and these results are similar to our study results.

CONCLUSIONS

As a result of the research, it was found that surgical patients had high levels of perception of nursing care and high levels of satisfaction with nursing care. It was determined that the patients' perceptions of nursing care positively affected their satisfaction level with nursing care. It was determined that the educational level of the patients, the status of having chronic disease, the number of patients in the room, and the status of satisfaction with the surgical clinic affected the satisfaction

with nursing care. In line with these results obtained from the study, to increase the satisfaction of the patients hospitalized in surgical clinics in terms of nursing; about ensuring the continuity of nursing services quality by regularly evaluating the perception of patient care, conceiving the factors affecting the satisfaction level while providing care, individualising the patient care considering patient characteristics, making improvements in multi-person patient rooms, in-service training on the subject and with priority in areas where satisfaction is low, in-service training programs may be recommended.

Limitations

This study results cannot be generalized to the whole of surgical patients' population in Turkey, as the study was conducted in only a university hospital.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from the Clinical Research Ethics Committee of the relevant university (Protocol: 20/03/2018, 18-3.1/31), and written permission was obtained from the management of the hospital where the research was conducted (04.06.2018, E. 159252).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Childhood Tuberculosis in a Reference Children's Hospital After Admission of Refugees

Mültecilerin Kabulünden Sonra Bir Referans Çocuk Hastanesinde Çocukluk Çağı Tüberkülozu

Özge Metin Akcan[1], Ayşe Kaman[2]

[1]Necmettin Erbakan Univercity School of Medicine, Division of Pediatric Infectious Diseases Konya, Turkey
[2]Dr. Sami Ulus Maternity and Children's Research and Training Hospital, Division of Pediatric Infectious Diseases, Ankara, Turkey

Abstract

Aim: We aimed to evaluate epidemiologic, clinical, laboratory, microbiologic features, treatment and outcomes of pediatric tuberculosis (TB) patients also to draw attention to immigrant patients.

Material and Method: We retrospectively conducted the medical records of children below 18 years of age with TB between January 2015 and September 2016.

Results: A total of 20 TB patients (35% were Syrian refugees, total 65% female) with a median age of 135.5±52.6 months were evaluated. Fourteen (70%) patients were adolescent. The history of contact with an active TB disease patient was found in seven (35%) patients. Four (20%) patients had no complaint at admission whereas the most common symptom was prolonged cough > 2 weeks. Fifteen (75%) patients had a Bacillus Calmette–Guérin scar on the left shoulder. A total of 16 (80%) patients had a positive tuberculin skin test (TST) result. Microbiological confirmation was provided in four (20%) patients totally. The most common chest X-ray findings on admission were hilar lymphadenopathy. Ten (50%) patients had normal chest X-ray and were diagosed with abnormal thorax tomography findings. All of the patients were treated succesfully except one Syrian patients with miliary TB who died.

Conclusion: Microbiological confirmation of childhood TB may be absent and the diagnosis can be confirmed in the light of contact history, positive TST reaction, compatible symtomps and radiological evidence. Particular attention might be paid to Syrian refugees, taking into epidemiological characteristics of TB disease and the density of immigrants in the place we live in.

Keywords: Children, tuberculosis, Syrian refugees

Öz

Amaç: Pediatrik tüberküloz (TB) hastalarının epidemiyolojik, klinik, laboratuvar, mikrobiyolojik özellikleri, tedavisi ve sonuçlarını değerlendirerek göçmen hastalara dikkat çekmeyi amaçladık.

Gereç ve Yöntem: Ocak 2015-Eylül 2016 tarihleri arasında 18 yaş altı TB'li çocukların tıbbi kayıtlarını geriye dönük olarak incelendi.

Bulgular: Yaş ortalaması 135,5 ± 52,6 ay olan 13'ü (%65) kadın ve 7'si (%35) erkek olmak üzere toplam 20 TB hastası (%35'i Suriyeli mülteci) değerlendirildi. On dört (%70) hasta ergendi. Yedi (%35) hastanın aktif bir TB hastası ile temas öyküsü mevcuttu. Dört (%20) hastanın başvuru anında hiçbir şikayeti yokken en sık görülen semptom 2 haftadan uzun süren inatçı öksürüktü. On beş (%75) hastanın Bacillus Calmette-Guérin skarı vardı. Onaltı (%80) hasta tüberkülin deri testi (TDT) pozitifti. Toplam dört (%20) hastada mikrobiyolojik doğrulama sağlandı. Başvuru anında en sık görülen akciğer grafisi bulgusu hiler lenfadenopatiydi. On (%50) hastanın akciğer grafisi normaldi ve anormal toraks tomografi bulguları ile tanı konulmuştu. Yalnızca miliyer tüberküloz tanısı ile izlenen bir hastada tedavi başarısızlığı olup hasta kaybedilmişti.

Sonuç: Tüberküloz önemli bir bulaşıcı hastalık olup çocuklarda mikrobiyolojik doğrulama her zaman olmayabilir. Çocukluk çağı TB tanısı, temas öyküsü, pozitif TDT reaksiyonu, uyumlu spesifik olmayan semptomlar ve radyolojik bulgularla doğrulanabilir. Tüberküloz hastalığının epidemiyolojik özellikleri ve yaşadığımız yerdeki göçmen yoğunluğu dikkate alınarak Suriyeli mültecilere özel dikkat gösterilebilir.

Anahtar Sözcükler: Çocuklar, tüberküloz, Suriyeli mülteciler

Corresponding *(İletişim)*: Ayşe Kaman, Dr. Sami Ulus Maternity and Children's Research and Training Hospital Babür street Number:44 (06080) Altındağ Ankara, Turkey
E-mail *(E-posta)*: ayse092003@yahoo.com
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INTRODUCTION

Tuberculosis (TB) is an important public health problem around the world which have been known as a communicable disease since the early era of humanity. It remains one of the top ten causes of death in all ages worldwide and the leading cause of death from a single infectious agent.[1,2] It is was reported that by World Health Organization (WHO) in the 2020 annual global TB report, the TB incidence rate is falling slowly in recent years. The annual incidence of TB in 2019 has been reported as 10 million (range, 8.9–11.0 million) and the rate of children (aged <15 years) was 12%. Most of the TB cases were reported from South-East Asia, Africa and the Western Pacific respectively. also lower ratios were determined in the Eastern Mediterranean, America and Europe.[3] In Turkey, the estimated incidence and mortality rate of TB in 2019 was 17 and 0.53 per 100.000 population, respectively. [4] After the Syrian civil war, over five million refugees, of whom more than three million have fled to Turkey to seek safety have been forced. Before the civil war in Syrian Arab Republic, the incidence of TB have been in the trend of decreasing with 21 cases per 100000 population. According to Geneva Convention Relating to the Status of Refugees, Syrian refugees are provided to access to healthcare and treatment free of charge, access to education for their children.[5] It is well known that TB is a communicable disease that may be affected by socioeconomic conditions including civil wars, disasters, poor nutrition, lack of food and poverty. Syrian refugees may be at risk of contracting TB because of overcrowding within the temporary shelters, stres an other determinants that can disrupt to acces to health services.[5,6] Given the unclear non-specific syptoms, low bacillus load in respiratory samples and the low rate of microbiologic evidence, the rates of definitive diagnosis in childhood TB cases are very low.[1] In this study, we aimed to evaluate epidemiologic, clinical, laboratory, microbiologic features, treatment and outcomes of pediatric TB patients. We also aimed to describe the characteristics of immigrant patients due to the risk of uncontrolled migration to Turkey during this period.

MATERIAL AND METHOD

We retrospectively analyzed the medical records of children under 18 years of age with TB between January 2015 and September 2016. The study protocol was approved by the Ethics Committee of the Necmettin Erbakan Univercity School of Medicine with the decision number of 2020/2871. Data regarding age, sex, contact history with an index case, clinical features, the results of tuberculin skin test (TST), microbiological and radiological findings were evaluated retrospectively. The characteristics of immigrant patients were evaluated separately. The diagnosis of TB was performed according to the guidelines of the Turkish Ministry of Health[7] in the light of symptoms, history of contact, positivity of TST and presence of appropriate radiologic findings. The positive TST results were defined as indurations of ≥15 mm, ≥10 mm and ≥5 mm for Bacillus Calmette–Guérin (BCG) vaccinated (BCG scar presence on the left shoulder), non-vaccinated and immunosuppressive cases respectively. Complete blood cell findings were defined as follows thrombocytopenia, a platelet count <150.000/mm^3, leukopenia and anemia, a level that lower than age-determined references, leukocytosis, a leukocyte count >15000/mm^3.[8] Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were defined as elevated in patients who had >20mm/hour and >15mg/L respectively.[9] All of the patients were underwent Human Immunodeficiency Virus (HIV) screening by anti-HIV serological test. All clinical samples were studied for *Mycobacterium tuberculosis* culture, Acid-fast bacillus (AFB) staining and mycobacteria polymerase chain reaction (PCR). Chest X-rays and thorax computed tomography (CT) of all patients were evaluated by a experienced radiologist. The patients were entitled as pulmonary or extrapulmonary TB. Standard anti-TB treatment was prescribed as four drugs [Isoniazid (INH), rifampicin, pyrazinamide, and ethambutol] or three drugs (INH, rifampicin and pyrazinamide) through the first two months followed by two drugs (INH and rifampicin). All of the patients were monitored for drug side effects and disease control monthly. We started contact tracing for all patients in their family and other intimate contacts to identify new cases.The Statistical Package for the Social Sciences (SPSS) 15.0 version was used for the statistical analysis. Numerical variables were summarized as mean±standard deviation or median (minimum-maximum) while quantitative variables as count and percent.

RESULTS

A total of 20 patients (35% were Syrian refugees) including 13 (65%) female and 7 (35%) male diagnosed with TB with a median age of 135.5±52.6 months were evaluated in this study. Demographic, epidemiological and microbiological features of patients were showed in **Table 1**. Characteristics of Syrian refugees patients were presented in **Table 2**. Fourteen (70%) patients were diagnosed during adolescence. A history of contact with an active TB disease patient was found in seven (35%) patients. A total of seven (35%) patients were diagnosed during contact tracing of an index case. Sixteen of the patients were presented with at least one symptom compatible with TB whereas four patients were asymptomatic at admission. The most common clinical symptoms were prolonged persistent cough longer than 2 weeks in seven (35%) patients, following with fever in five (25%), sputum discharge in five (25%), fatigue in five (25%), erythema nodosum in four (20%), night sweats in three (15%), weight loss in three (15%) and headache in one (5%) patient. Fifteen (75%) patients had a BCG scar on the left shoulder. A total of 16 (80%) patients had a TST

measurement ≥15mm (six patients had ≥20 mm). Complete blood count parameters were normal in all patients except one each patient with anemia and leukocytosis. Elevated CRP and ESH were detected in six (30%) and nine (45%) patients respectively. All of the patients had negatif anti-HIV serology. Clinical samples were inoculated for *M. tuberculosis* culture from nine (45%) patients and three of them were yielded positive. Microbiological confirmation was provided in four (20%) patients totally. *M. tuberculosis* PCR test was positive in two of the patients. Acid-fast bacillus staining was positive in 2 (10%) patients. The most common chest X-ray findings on admission were hilar lymphadenopathy in 4 (20%) patients, followed by consolidation in 3 (15%), reticulonodular infiltration in 2 (10%), cavitary lesion, pleural effusion, atelectasis, nodule in one patient each. Ten (50%) patients who had normal chest radiography were diagosed with abnormal CT findings. The most common thorax CT findings were hilar and mediastinal lymphadenopathy in 7 (35%) and 6 (30%) patients respectively. The thorax CT findings of patients are summarized in **Table 3**. A 14 years old Syrian patient who had tuberculoma on cranial imaging and pulmonary involvement was diagnosed as miliary TB. Lumbar puncture was performed in a patient younger than 1 year old, resulting as no central nervous system involvement. Eight (40%) of the patients were hospitalized before the definitive diagnosis made. Standard anti-TB protocol with three drugs (INH, rifampicin and pyrazinamide) regimen was prescribed in 15 (75%) patients and with four drugs regimen in 5 (25%) patients through the first two months followed by two drugs (INH and rifampicin). An additional steroid treatment was implemented in one patient diagnosed with miliary TB. Pyrazinamide-induced hyperuricemia was developed in seven (35%) patients during treatment course. Moreover one (5%) patient experienced eosinophilia during anti-TB treatment. All of the patients were treated succesfully except one Syrian patients with miliary TB who died.

Table 1. Demographic, epidemiological and microbiological features of patients

	Total (n=20)	Syrian (n=7)	Turkısh citizen (n=13)
Mean Age ±SD (minimum-maximum)	135.5±52.6 months (4-192 months)	100.5±70.7 months (4-172 months)	154.3±27.9 months (102-192 months)
Gender, (n) (F/M)	13/7	6/1	7/6
Diagnosis during adolesence, n(%)	14 (70%)	3 (42.8%)	11 (84.6%)
Presence of BCG scar, n(%)	15 (75%)	5 (71.4%)	10 (76.9%)
Contact with active TB patient, n(%)	7(35%)	4(35%)	3(35%)
TST ≥15 mm, n(%)	16 (80%)	6 (85.7%)	10 (76.9%)
M. tuberculosis culture Positive/ Total (n)	3/9	1/4	2/5
M. tuberculosis PCR Positive/ Total (n)	2/9	1/4	1/5
AFP staining positivity Positive/ Total (n)	2/9	1/4	1/5

BCG: Bacillus Calmette–Guérin, PCR: Polymerase chain reaction, TST: Tuberculin skin test

Table 3. Chest CT Findings of Pulmonary TB Patients

Signs	n	%
Hilar LAP	7	35
Mediastinal LAP	6	30
Nodule	5	25
Branching tree view	3	15
Effusion	3	15
Cavitation	3	15
Ghon complex	2	10
Fibrotic changes	1	5
Atelectasis	1	5
Consolidation	1	5
Miliary pattern	1	5

LAP: Lymphadenopathy

Table 2. Characteristics of Syrian refugees patients

Patient no	Age (months)	Clinic positivity	New case in family contact tracing	BCG scar	TST (mm)	Microbiological diagnosis	Chest X-ray	Thorax CT
1	43	Asymptomatic	No	Absent	20	Negative	Normal	Mediastinal LAP
2	131	Yes	No	Present	20	Positive	Normal	Hilar LAP,fibrotic changes
3	4	Asymptomatic	Yes	Present	13	Negative	Normal	Pleural based nodule
4	35	Asymptomatic	Yes	Absent	18	Negative	Normal	Mediastinal, hilar LAP
5	172	Yes	Yes		17	Positive	Cavitation	Cavitation, branching tree view
6	151	Asymptomatic	Yes	Absent	15	Negative	Normal	Ghon complex
7	168	Yes	Yes	Present	15	Positive	Reticulonoduler infiltrasion	Mediastinal LAP, nodule, branching tree view, miliary images

LAP: Lymphadenopathy, TST: Tuberculin skin test

DISCUSSION

It was reported that in 2019 National Turkey TB Report, the total TB patients were counted as 12.046 in 2017 and 4.6% of the patients were in the 0-14 age group whereas 15.4% of them were in 15-24 age group.[4] The risk for *M. tuberculosis* disease in childhood is highest younger than 2 years of age and during early adolescence. Disease risk is lower between 5-15 years of age, often known as "favored age for childhood TB".[2,10] Because of most children with TB have been infected from adults in their close contacts, childhood TB tends to be more common in the areas that adult TB could not be controlled.[2,11] For this reason the presence of contact history with an adult patient infected with *M. tuberculosis* is the milestone for keeping in mind and further investigation of TB in children. In a recent study from Turkey including ten years experience of a tertiary care university hospital, a total of 93 patients (53% male) ranged 3-205.2 months were included. Thirty-nine percent of the patients were over 10 years of age and five patients (8.1% of those with known BCG vaccination status) had no BCG scar on the left upper arm. Also 29% of the patients had a history for contact with an adult index case.[1] In an another multicenter study from Turkey, 539 (50.8% male) children with TB aged 10 days- 17 years (almost equal distribution in all age groups) from 16 different centers were evaluated over a 12 year period. The authors showed that contact with an index case was present in 39.8% of the patients and they concluded household contact screening techniques act very important role.[12] In a cross-sectional study from Ethiopia, which presents as the seventh highest TB burden country worldwide, a total of 384 children (51% male) with a mean age of 8.56±3.91 years which were evaluated. The most of the patients (39%) were in 6-10 years of age group, while 34.11% were in adolencent age group. It was indicated that 39.8% of the patients had a history for contact with active TB patients.[13] Similar to the mentioned children studies we detected a contact history with an index case in about one third of the patients. Furthermore we detected a female gender predominance with a ratio of 1.8:1 and most of the children in this study were diagnosed during adolescence.

The symptoms and physical signs of childhood pulmonary TB are usually not distinctive and not compatible with the degree of radiographic involvement even may be asymptomatic in many children. The most common reported symptoms are prolonged cough, fatigue and fever in many studies with high sensitivity and specificity for pulmonary TB.[2,11] In a study from an endemic area for TB, it was reported that all of the children had cough for more than three weeks, 61.46% of had fever, 59.64% of had loss of appetite and 43.75% of had weight loss.[13] In a large study conducted in İstanbul, it was shown that the most common symptoms were cough more than 2 weeks and fever while 8% of the patients were asymptomatic and had no abnormal physical examination finding.[14] In an another study from a tertiary care reference hospital, 144 children with active TB were included, the most common clinical complaint was cough, one-third of patients had at least one symptom while 16% of patients were asymptomatic.[11] The most common sypmtoms were cough, fever and fatigue respectively similar to previous studies. In this study including children with active pulmonary TB, 20% of children had no complaint, suggesting that absence of symptoms is not reliable to exclude the pediatric TB diagnosis.

In addition to compatible clinical and/or physical examination findings, close contact history with an active TB patient, a positive TST or interferon-gamma release assay and suggestive findings on a chest radiography might aid to diagnosis of TB in children.[2,11,14] Although the TST and/or IGRA does not provide information for having active TB disease, they are valuable for showing whether the case has been infected with the *M. tuberculosis* or not.[2,15] Evaluation of TST results in BCG vaccinated children is a diagnostic dilemma because of cross reaction with BCG antigens. Nonetheless TST continues to be the most valuable, simple and inexpensive method to diagnose new cases, the prevelance and annual risk of TB in a country. It has been reported that the TST sensitivity for culture positive TB patients vary between 75-90%.[15] Furthermore definite diagnosis rates of TB in childhood is low due to low bacillus load and insufficiency to ensure appropiate sputum specimens for diagnosis.[2,11] In a multicenter pediatric study including 20 years experience, TST was positive in 55.3% of the patients. Acid-fast bacillus staining, *M. tuberculosis* PCR and culure for *M. tuberculosis* complex were positive in 24.6%, 8% and 13.9% of the patients respectively.[12] In a study from Brasil involving 145 TB patients (60.7% had pulmonary TB and 39.3% had extrapulmonary TB) with a median age of 7 years, TST was applied in 83 patients. Microscopy, culture and TST were positive in 35.7%, 65.8% and 72.3% of the patients respectively.[16] In a study from our country, 250 children (162 patients had only pulmonary disease, 49 patients had only extrapulmonary disease, 39 patients had both pulmonary and extrapulmonary disease) with TB were enrolled. It was found that, TST was performed in 210 cases and was positive in 53.3% of them. A microbiological evaluation (direct microscopy and/or culture) was available in 48.8% of the patients. It was recorded that AFB staining and *M. tuberculosis* culture were positive in 13.1% and 18.7%, respectively.[14] It is known that bacteriological confirmation of TB is not always possible in children because of the low bacillus rate in the respiratory tract of children and the inability to spit enough sputum samples to make a sufficient microbiological confirmation at the time of the medical visit. Gastric lavage, a relatively invasive procedure, might be an alternative for children but it should be kept in mind that this procedure requires hospitalization.[14,16] In the present study a positive TST measurement was observed for a rate 80% which is slightly higher than previous reports. Clinical specimen could only be obtained from half of the patients for microbiological evaluation because of the low hospitalization chance of the patients. In seven patients who had a history for contact with an active TB patient, diagnosis was made according to compatible clinical, TST and radiological findings and treatment was prescribed according

to the culture susceptibility of index cases. Microbiological confirmation was achieved in one fifth of total patients.

The most common radiographic findings in childhood TB were reported as consolidation, hilar and/or mediastinal LAP and pleural effusion, following with at a lower rates of paratracheal LAP, miliary images, Ghon complex. Unfortunately the sensitivity and specificity of chest X-ray are low for the diagnosis of TB in children.[11] A study from Taiwan that aimed to investigate if thoracic CT will demonstrate compatible lung lesions for TB when chest X-ray is unremarkable included 26 patients. In half of the TB patients chest X-ray was normal despite the presence of LAP and/or nodule on CT.[17] In an another work, chest CT findings in immunocompetent children under 36 months of age with pulmonary TB were described. All of the patients with normal chest X-ray had lymph node enlargement and consolidations. In the half of the patients cavitation was present.[18] Half of our patients had normal chest X-ray and diagnosed with chest CT findings. The most common radiological findings were hilar and mediastinal lymphadenopathy and nodule formation similar to previous reports.

It is well known that TB is a socioeconomic disease. In Turkey, TB screening programme and treatment are free for Turkısh citizen and refugees who had identity card. Especially temporary shelters are high risk for transmission of TB. It was noted that, 26213 refugees were secreened for having TB in temporary shelters and 108 cases with active TB were diagnosed.[5,6] Before the migration of Syrian refugees, there was no Syrian born active TB case in 2011 while the ratio of the patients who were born outside of Turkey to the all patients with TB was 1.3%. In recent years the number of Syrian TB cases was increased, and in 2018; 595 cases of Syrian TB was noted. The proportion of total TB cases born in a foreign country was reported as 10.8% whereas the Syrian cases ratio was 5%. It was declared that, despite the increase in the proportion of Syrian patients, no significant increase has been detected in total TB cases for Turkey.[4,5] It is estimated that Syrian refugees are at higher risk for contracting TB because of unfavorable living conditions.[5,6] In a report from Hatay TB Dispensary (a city in Turkey which is neighboured to Syria), where a large number of Syrian refugees have migrated, it was reported that 68.7% of Syrian refugees were in the 0–5 age group and the results of this study was compatible with another studies that demonstrated the age structure of Syrian refugees seems to be young. Also more positive TST results developed in refugees in the 6–18 age group and it was concluded that the annual risk of TB infection was higher in Syrian refugees in this age group compared to Turks.[15,20] In a study from Jordan that aimed TB contact-tracing among Syrian refugees, it was found that a high prevalance of active TB and latent TB in contacts of pulmonary TB patients.[19] In the present study the proportion of Syrian TB cases was 35% of all the patients and it was higher than Turkısh National datas. In addition to this, the mean age of Syrian refugees were younger than Turkısh citizens. This might be as a result of that children are at higher risk for development of TB infection. Also younger age of Syrian population might be explained by the overcrowding, stress, food deficiency and other determinants which may increase the incidence of an infectious disease in this population escpecially affects negatively in childhood. In addition to all of this information, it is known that careful contact tracing enables to diagnose at young ages.

CONLUSION

TB is an important contagious disease and physicians should take care of TB especially during adolescence. In children microbiological confirmation may be absent. Diagnosis of childhood TB can be confirmed in the light of history contact with an active case, positive TST reaction, compatible nonspecific symptoms particularly prolonged cough and radiological evidence. Physicians should take in mind the regional differences in prevalence of an infectious disease in different races. Particular attention might be paid to symptomatic Syrian refugees, taking into epidemiological characteristics of TB disease and the density of immigrants in the place we live in.

ETHICAL DECLARATIONS

Ethics Committee Approval: For this study, ethical approval was obtained from the ethics committee of the Necmettin Erbakan Univercity School of Medicine with the decision number of 2020/2871.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Melatonin Receptors Increase Momordica's Anticancer Effects Against PC-3 and HT-29

Melatonin Reseptörleri PC-3 ve HT-29'a Karşı Momordica'nın Antikanser Etkilerini Artırır

Ali Taghizadehghalehjoughi[1], Yesim Yeni[2], Sidika Genc[2], David R Wallace[3], Ahmet Hacimuftuoglu[2], Zeynep Cakir[4]

[1]Ataturk University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, Erzurum, Turkey
[2]Ataturk University, Faculty of Medicine, Department of Medical Pharmacology, Erzurum, Turkey
[3] Oklahoma State University Center for Health Sciences, School of Biomedical Sciences, Tulsa, Oklahoma, United States
[4] Ataturk University, Faculty of Medicine, Department of Emergency Medicine, Erzurum, Turkey

Abstract

Aim: The aim of our study is to the evaluation of melatonin (MLT) and Momordica charantia (MC) combination on PC-3 and HT-29 cancer lines and to address the question of where or not MLT increases MC antitumor effect in the PC-3 and HT-29 cancer lines.

Material and Method: The PC-3 and HT-29 cell lines were grown in a manufacturer-specified culture medium. Cisplatin, MLT, increasing concentrations of MC, 40 µg/ml MLT+increasing concentrations MC were applied to PC-3 and HT-29 cell lines for 72 hours. 3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide (MTT) cell viability, Total Antioxidant Capacity (TAC), Total Oxidant Status (TOS), Cellular Migration (Wound Healing test), and Lactate Dehydrogenase (LDH) tests were done 72 hours after drug administration.

Results: The combination of MLT 40 µg/ml+MC 100 µg/ml reduced cell viability in both PC-3 and HT-29 cells. Besides, TAC and TOS levels showed a correlation with LDH and MTT assays and were found to be statistically significant (P<0.05). Also, it was observed in the migration test that the wound line widened in our combination groups from the 24th hours. However, it was observed that it only prevented migration at 72nd hours in pure groups.

Conclusion: The combination of 40 µg/ml MLT with MC increased the antitumor effect compared to MC alone and reduced the viability of cancer cells more effectively than MC alone. So, MLT+MC treatment combination can be a new resource of therapeutics.

Keywords: HT-29, LDH, Melatonin, Momordica, and PC-3

Öz

Amaç: Çalışmamızın amacı, PC-3 ve HT-29 kanser hatlarında melatonin (MLT) ve Momordica charantia (MC) kombinasyonunun değerlendirilmesi ve MLT'nin PC-3 ve HT-29 kanser hatlarında MC antitümör etkisini nerede artırdığı sorusunu ele almaktır.

Gereç ve yöntem: PC-3 ve HT-29 hücre çizgileri, üreticinin belirlediği bir kültür ortamında büyütüldü. Sisplatin, MLT, artan MC konsantrasyonları, MLT 40 µg/ml+artan konsantrasyonlar MC, PC-3 ve HT-29 hücre hatlarına 72 saat süreyle uygulandı. 3- (4,5-Dimetiltiyazol-2-Yl) -2,5-Difeniltetrazolyum Bromür (MTT) hücre canlılığı, Toplam Antioksidan Kapasitesi (TAC), Toplam Oksidan Durumu (TOS), Hücresel Göç (Yara İyileştirme testi) ve Laktat Dehidrojenaz (LDH) testleri, ilaç uygulamasından 72 saat sonra yapıldı.

Bulgular: MLT 40 ug/ml+MC 100 ug/ml kombinasyonu, hem PC-3 hem de HT-29 hücrelerinde hücre canlılığını azalttı. Ayrıca TAC ve TOS seviyeleri LDH ve MTT testleri ile korelasyon gösterdi ve istatistiksel olarak anlamlı bulundu (P <0.05). Ayrıca migrasyon testinde kombinasyon gruplarımızda 24. saatten itibaren yara hattının genişlediği gözlendi. Ancak saf gruplarda göçü sadece 72. saatte engellediği görülmüştür.

Sonuç: 40 ug/ml MLT'nin MC ile kombinasyonu, tek başına MC'ye kıyasla antitümör etkisini arttırdı ve kanser hücrelerinin canlılığını tek başına MC'den daha etkili bir şekilde azalttı. Dolayısıyla, MLT+MC tedavi kombinasyonu yeni bir terapötik kaynak olabilir.

Anahtar Sözcükler: HT-29, LDH, Melatonin, Momordica ve PC-3

Corresponding *(İletişim)*: Ali Taghizadehghalehjoughi, Ataturk University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, 25240 Erzurum, Turkey
E-mail *(E-posta)*: ali.tgzd@atauni.edu.tr
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INTRODUCTION

Cancer is one of the most important public welfare problems on earth. Prostate (PC) and colorectal cancer (CRC) have the most important roles among malignant cancer types. CRC is the third most common types of cancer in men and women, causing approximately 1.4 million new cases and more than 0.5 million deaths worldwide.[1] Located outside the prostate, PC is the second most common malignant tumor and is mostly seen in older men.[2] Approximately one in six men will be diagnosed with PC.[3] These two cancers have been associated with many risk factors, including smoking, alcohol consumption, dietary factors, lifestyle, ethnicity, and genetic changes.[4,5] Early diagnosis, chemotherapy, surgical resection, radiotherapy, or targeted therapies can increase the survival of patients.[6,7] Cisplatin has been especially interesting since it has shown anticancer activity in a variety of tumors, including those of the prostate and colon. However, the agents currently used for cancer treatment are usually cytotoxic and have serious side effects that can reduce the quality of life of cancer patients.[8]

Since ancient times, various plants have been used as medicines and vegetables worldwide. The combination of medicines and herbal uses has made Momordica types popular for thousands of years. Momordica, also known as bitter melon, bitter gourd, balsam pear, karela, and pare, is a member of the Cucurbitaceae family, which contains 800 species in 130 genera.[9] This plant has various biological activities like antioxidant, anti-inflammatory, antidiabetic, antihyperglycemic, antibacterial, antiviral, anthelmintic, antiulcer, hepatoprotective, antifertility, antilipolytic, antimutagenic, and immunomodulation.[10] Also, Momordica extracts and monomer components have shown strong anticancer activity against various tumors such as prostate, colon, lymphoid leukemia, lymphoma, melanoma, breast, skin, and pancreatic cancer.[11] It has been proven in many studies that Momordica stops the G2/M cell cycle, stimulates autophagy and apoptosis, reducing the invasion and migration ability of cancer. Besides, it raises the question of whether it can be used in cancer treatment because of its low toxicity and non-cytotoxicity.[12]

Melatonin (N-acetyl-5-methoxideriptamine) is derived from the tryptophan and produced circadian rhythm. Melatonin (MLT) is synthesized in many organs and tissues, including the gastrointestinal, reproductive, and immune tract cells and skin.[13] MLT is important in human pathology and physiology because of its role in the antioxidant scavenging system, anti-inflammation, immunomodulation, energy metabolism, and hematopoiesis.[14] It has also been found MLT receptors play an oncostatic role in the PC and HT-29 through their interaction with MT1 and MT2.[15,16] Due to its antioxidant properties, MLT has been shown to induce apoptosis in many studies and thus stop tumor creation.[17]

Although there are many separate studies in the literature related to MLT and MC, there is limited research about combined therapy and no data on the potential antitumor effects of MLT and MC. In this study, we purposed to search the antitumor effects of MLT and MC combination treatment in prostate (PC-3) and colorectal tumor (HT-29) cells for the first time. For this object, we planned the current study to consist of 13 distinct treatment groups. The antitumor study was done using MTT, LDH, TAC, TOS, and migration (Wound Healing test), and morphological observation for 72 hours (hrs).

MATERIAL AND METHOD

Plant material, Chemicals, and Reagents

MC was acquired from Sepe Natural Organic Products San.ve Tic.A.Ş. (Buca, Izmir, Turkey). MLT was acquired from Swanson Health Products (Fargo, ND, USA). All chemicals, phosphate-buffer solution (PBS), Dulbecco modified eagle medium (DMEM), fetal calf serum (FCS), trypsin–EDTA, antibiotic antimitotic solution (Penicillin/Streptomycin/Amphotericin B) (100×), and L glutamine was acquired from Sigma Aldrich (St. Louis, MO, USA). Cisplatin was obtained from Koçak Farma (Tekirdag, Turkey).

Cell Cultures

Prostate (PC-3) (ATCC® CRL-1435) and colon (HT-29) (ATCC® HTB-38) cancer cells were obtained from the department of the medical pharmacology department of Ataturk University (Erzurum, Turkey). Briefly, the cells were centrifuged at 1200 rpm for 5 min at room temperature were suspended in a fresh medium and then aliquoted into 24-well plates at a density of 105 cells/ml (DMEM, with FBS 10%, and antibiotic (Penicillin, Streptomycin and Amphotericin B; 1%) and allowed to grow in a humidified incubator with 5% CO_2, 95% moisture, at 37°C.[18]

Plant Administration

After cells reached 85% confluency, the plant extracts were added to corresponding treatment wells. MC (10, 20, 40, 60, 80 and 100 µg/ml) alone or in combination MC (10, 40, 80, 100 µg/ml) and MLT (40 µg/ml) was added to designated treatment wells, and the plates were returned to the incubator for 72 hrs.

MTT Assay

At the end of the experiment (after 72 hrs of treatment), 10 µL of MTT solution is added to each well plate (1 mM final concentration). Then the plates were incubated for 4 hours at 37°C in a CO_2 incubator. After 4 hours, 100 µL of DMSO solution was added to each well to dissolve the formazan crystals. The density of the formazan crystals was read at a wavelength of 570 nm by the Multiskan ™ GO Microplate Spectrophotometer reader.

TAC Assay

TAC capacity was investigated by using the existing kit (manufactured by Rel Assay Diagnostics® Company, Gaziantep, Turkey). The test was done according to the manufacturer's procedure. To assess is made by calculating spectrophotometrically (Multiskan™ GO Microplate Spectrophotometer reader). To assess the TAC status, 30 µl of the sample was added to each well followed by 500 µl of Reactive compound 1 (Buffer solution, Acetate Buffer), and the first absorbance was read at 660 nm (time 0). Then, 75 µl of Reagent 2 (Prochromogen Solution, ABTS) was added to the wells and incubated for 10 minutes at room temperature. After the end of the time, the secondary absorbance value was read at 660 nm. Distilled water Standard 1 (empty) was used, while Standard 2

was used as the second point to calibrate the relationship of the absorbance density to the pro-oxidants present. TAC standards were determined in Trolox Equiv/mmol L-1.

TOS Assay

TOS was investigated by using the existing kit (manufactured by Rel Assay Diagnostics ® Company, Gaziantep, Turkey). The test was done according to the manufacturer's procedure. To assess is made by calculating spectrophotometrically (Multiskan™ GO Microplate Spectrophotometer reader). To assess the TOS standard, 75 µl of the sample was added to each well followed by 500 µl of Reactive compound 1 (Buffer solution, H_2SO_4), and the first absorbance was read at 530 nm (time 0). Then, 25 µl of Reagent 2 (Substrate Solution, H_2SO_4, Ferrus ion, O-dianisidine) was added to the wells and incubated for 10 minutes at room temperature. After the end of the time, the secondary absorbance value was read at 530 nm. Distilled water Standard 1 (empty) was used, while Standard 2 was used as the second point to calibrate the relationship of the absorbance density to the pro-oxidants present. TOS standards were detected in H_2O_2 Equiv/mmol L-1.[19]

LDH Assay

LDH assay test was performed using a commercially available test kit from Cayman Chemical Co. Ltd, (Ann Arbor, MI, USA). Briefly, the cell culture medium was centrifuged at 400 g for 5 min at the room temperature 100 µl of the supernatant was added to 100 µl of the reaction solution (LDH Assay Buffer, LDH Substrate Mix) and incubated with gentle shaking on an orbital shaker for 30 min at room temperature. Finally, the absorbance was read at 490 nm wavelength.[20]

Migration Test (Wound Healing Test)

Cells were seeded in 24-well plates and incubated (37°C, 95% air, 5% CO_2) for 3 days. Cultures at ~80% confluence were scraped with a micropipette tip (100 µl), rinsed with phosphate-buffered saline (PBS), and incubated with fresh media. At 24, 48, and 72 hrs intervals, all groups of the image were taken by Leica microscope.

Statistically Analysis

The statistical analysis was done using one-way analysis of variance (ANOVA)to assess treatment effects followed by Tukey's LSD for posthoc comparisons when appropriate using the SPSS 22.0 statistical software. P<0.05 was considered to be the statistical threshold for each analysis.

RESULTS

MTT Assay

The survival rate of cancer cells after 72 hrs drug exposure was calculated by using the MTT test (**Figure 1A-B**). The vitality of the control group was defined as 100% and the other groups were rated accordingly. Our results show MLT (40 µg/ml)+MC (100 µg/ml) combinations have the lowest rate of viability in both PC-3 and HT-29 cell lines in comparison to other treatments (63 and 66% respectively). The highest viability ratio among treatment groups in both PC-3 and HT-29 cells were seen in cisplatin (2 µg/ml) (86 and 81% respectively, P>0.05). Besides, the survival rate in pure MC (10, 20, 40, 60, 80 and 100 µg/ml) groups dose-dependently decrease from 81 to 74% in the PC-3 cell line and from 78 to 71% in the HT-29 respectively. According to our data, Combinations of MLT and MC kill both PC-3 and HT-29 cells more effectively than pure MC. Also, all MLT+MC combination groups showed a statistical difference in comparison to the control group (P<0.05).

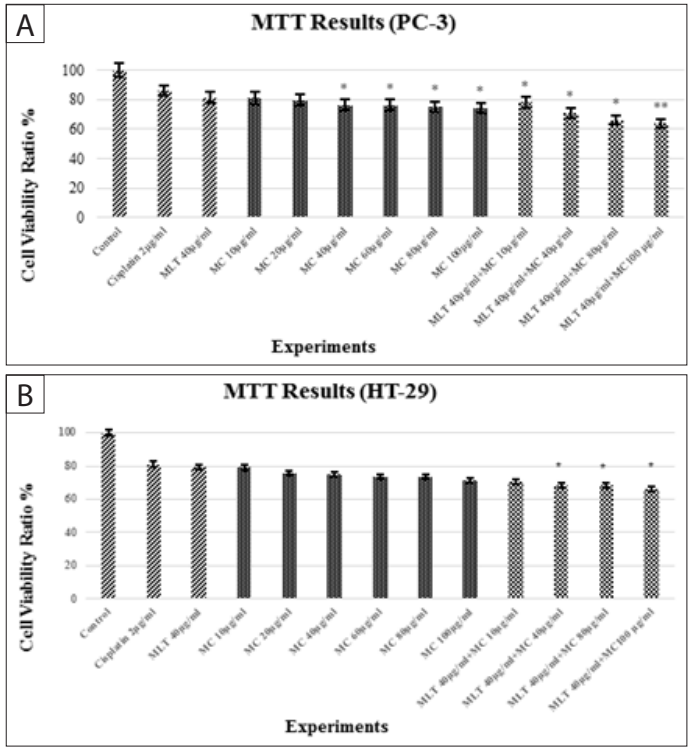

Figure 1A-B. In vitro viability ratio of MLT, MC or combination on PC-3 (A) and HT-29 (B) cells (n=6/group).

*Significant differences at P<0.05 comparedto control group; ** Significant differences at P<0.001 compared to control group.

TAC Assay

We assessed the TAC assay based on Trolox Equiv/mmol L-1 (**Figure 2A-B**). According to this test, the TAC levels of the control group were 6.22 and 6.72 Trolox Equiv/mmol L-1 in the PC-3 and HT-29, respectively. TAC levels of cisplatin (2 µg/ml) and MLT (40 µg/ml) were 6.09-5.80 Trolox Equiv/mmol L-1 in the PC-3 cell line, respectively. On the other hand, in the HT-29 cell line, TAC levels of cisplatin (2 µg/ml) and MLT (40 µg/ml) were 6.63-6.29 Trolox Equiv/mmol L-1, respectively. Also, the antioxidant capacity decreased by increasing the dose from 10 to 100 µg/ml (2.51 in the PC-3 and 2.11 in the HT-29 Trolox Equiv/mmol L-1). MLT (40 µg/ml)+MC (100 µg/ml) group was found statistically significant compared to the control group (P<0.05). Furthermore, there no statistically significant difference between the other groups (P>0.05).

TOS Assay

We assessed the TOS assay based on H_2O_2 Equiv/mmol L-1 (**Figure 3A-B**). As a result of this test, the oxidant levels of the PC-3 and

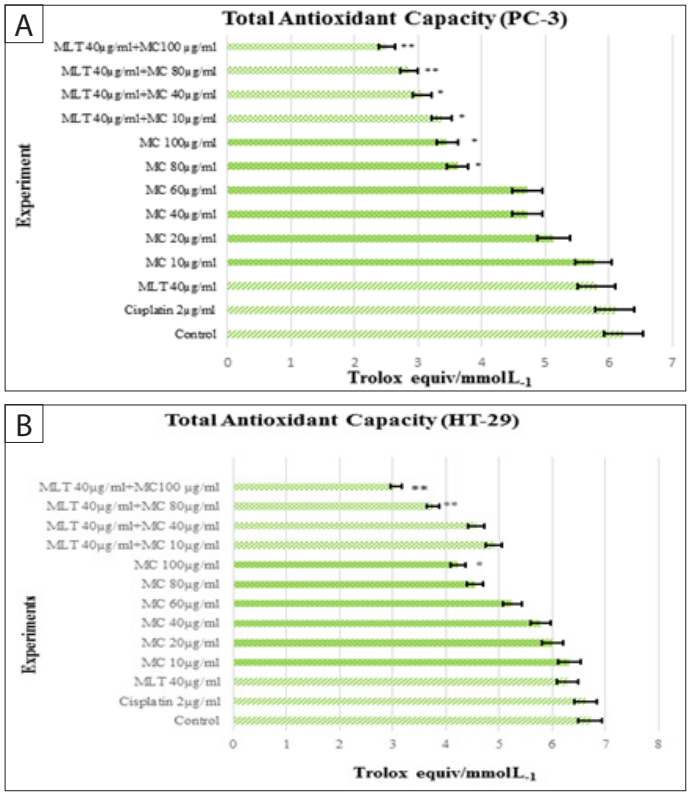

Figure 2A-B. In vitro TAC capacity of MLT, MC and combination of them on PC-3 (A) and HT-29 (B) cells (n=6/group).

*Significant differences at P<0.05 compared to control group; **Significant differences at P<0.001 compared to control group.

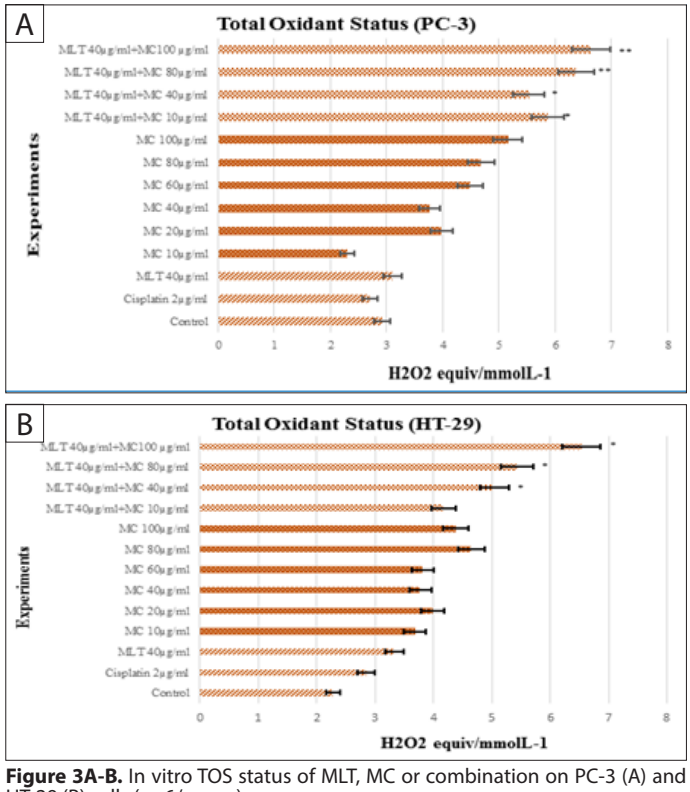

Figure 3A-B. In vitro TOS status of MLT, MC or combination on PC-3 (A) and HT-29 (B) cells (n=6/group).

*Significant differences at P<0.05 compared to control group; **Significant differences at P<0.001 compared to control group.

HT-29 control groups were 2.92 and 2.28 H_2O_2 Equiv/mmol L-1, respectively. The lowest oxidant ratio among the treatments was seen in cisplatin. On the other hand, oxidant status increased in pure MC groups and their combination with MLT both cell lines, respectively. According to these results, different combination of MLT (40 µg/ml)+MC (100 µg/ml) increased total oxidant ratio 6.64 and 6.53 H_2O_2 Equiv/mmol L-1 in the PC-3 and HT-29, respectively (P<0.05).

LDH Assay

Damage to cell membranes is reflected as elevated LDH levels in the cell medium after the cells were exposed to MLT (40 µg/ml), MC (10, 20, 40, 60, 80 and 100 µg/ml) or MLT+MC (10, 40, 80 and 100 µg/ml) combinations for 72 h. The LDH activity of the control group was defined as 100% and the other groups were rated accordingly. Our results show that the MLT (40 µg/ml)+MC (100 µg/ml) combination was most toxic as indicated by the greatest amount of LDH activity in the media from the PC-3 cell line in comparison to other treatments. When examining the HT-29 cell line, the combination of MLT (40 µg/ml)+MC (10, 40, 80, and 100 µg/ml) has the highest ratio of LDH activity compared to other treatments. **Figures 4A-4B** indicates that MLT+MC combinations induced cytotoxicity in PC-3 and HT-29 cell lines in both a time- and dose-dependent manner. Besides, all of the MLT+MC combination groups showed a statistical difference when compared to the control group (P<0.001).

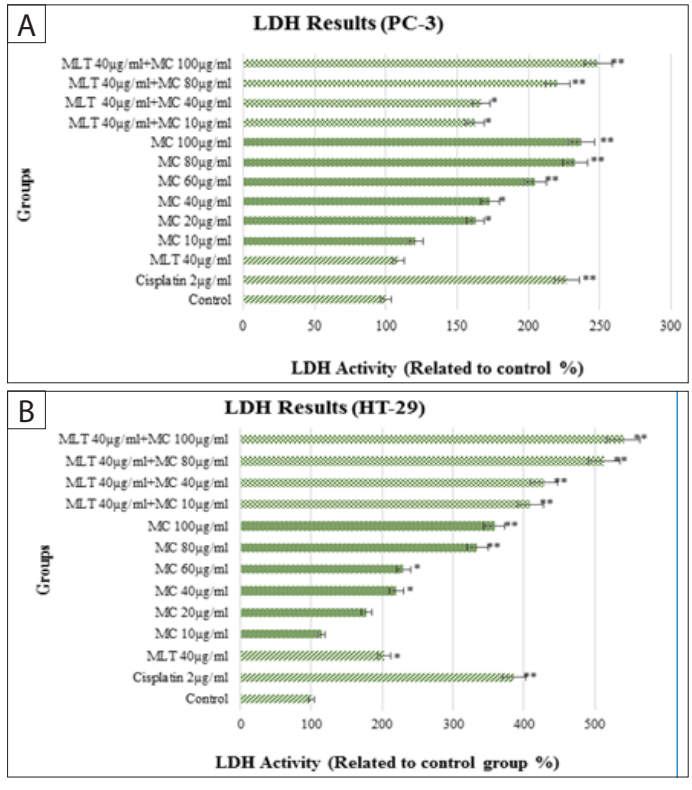

Figure 4A-B. In vitro LDH level of MLT, MC or combination on PC-3 (A) and HT-29 (B) cells (n=6/group) values read spectrophotometrically at 490 nm in cell culture.

*Significant differences at P<0.05 compared to control group; **Significant differences at P<0.001 compared to control group

Migration Test (Wound Healing Test)

The wound area was assessed through three days of the PC-3 and HT-29 cell lines. Wounds opened in HT-29 and PC-3 cultures with the help of a 100-200 µl pipette tip are shown in figure **Figure 5A-B.** In the first 24 hrs, it was observed that the cells started to close the opened regions in the control group, while no change was detected in the other groups. When the 48th hrs photos were examined, the control group progressed further and closed all wound areas. As the control group, the cisplatin group showed a large reduction in the wound area and the migrating cells bridged the wound site. Cell migration from the wound line to the middle of the wound was observed in the MLT 40 µg/ml and MC 10 µg/ml groups. However, the wound line was widened at the MC 20 to 100 µg/ml concentrations. Besides, cell deaths are seen at these concentrations. At the end of the 72nd hrs, we observed that the wound lines were completely closed in the control and cisplatin groups. But in all treatment groups, including MLT 40 µg/ml and MC 10 µg/ml, a high rate of cellular death was obvious. These cellular deaths are more apparent in the combination groups.

DISCUSSION

CRC and PC are malignant tumors with high incidence and chemotherapy is one of the most commonly used therapeutic methods for the treatment of these cancers.[21] Many studies suggest that bioactive natural compounds and their synthetic derivatives have an undeniable effect on cancer treatment procedures.[22] Also, many anticancer studies found synergy between combinations of herbs and drugs.[23] In this relation, our study showed that the combination of MLT+MC plays an important role as antioxidant and antitumor on PC-3 and HT-29 cell lines.

MLT receptor expression has been demonstrated in many cancer types and activation of MT1 and MT2 receptors are suggested to induce antiproliferative and pro-differentiating effects.[24] It has been shown that these receptors act through other regulatory effects by binding to nuclear receptors (RZR/ROR) or intracellular proteins belonging to the family of nuclear transcription factors.[25] In light of these data, our study showed that the antitumor effect of MC was increased in PC-3 and HT-29 cell lines due to the antioxidant property of MLT.

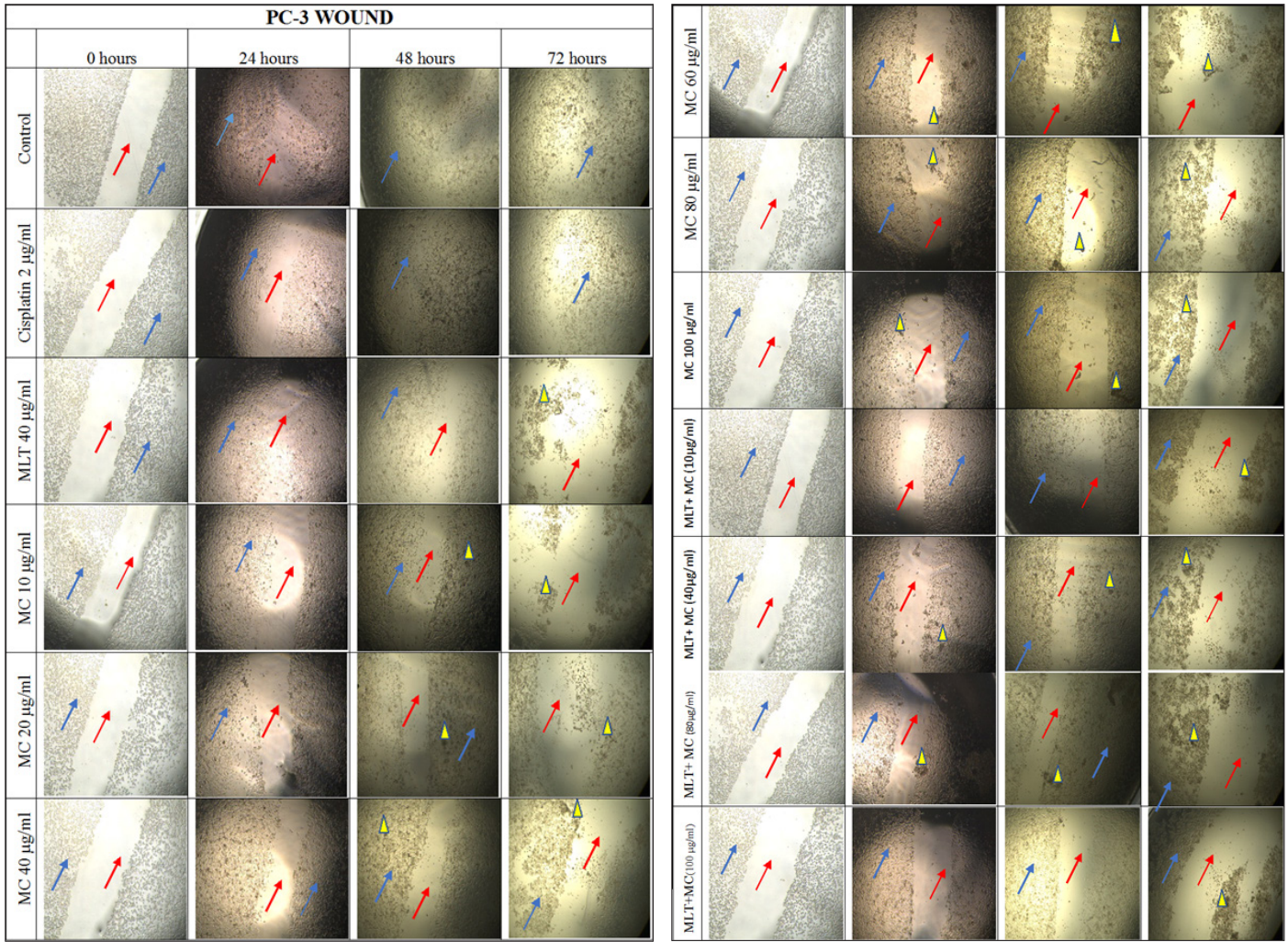

Figure 5A. Microscopic wound (migration test) view of each group after 24, 48 and 72-hrs (20×). **Blue arrow:** live cells, **Red arrow:** Empty space, **Triangle:** died cells

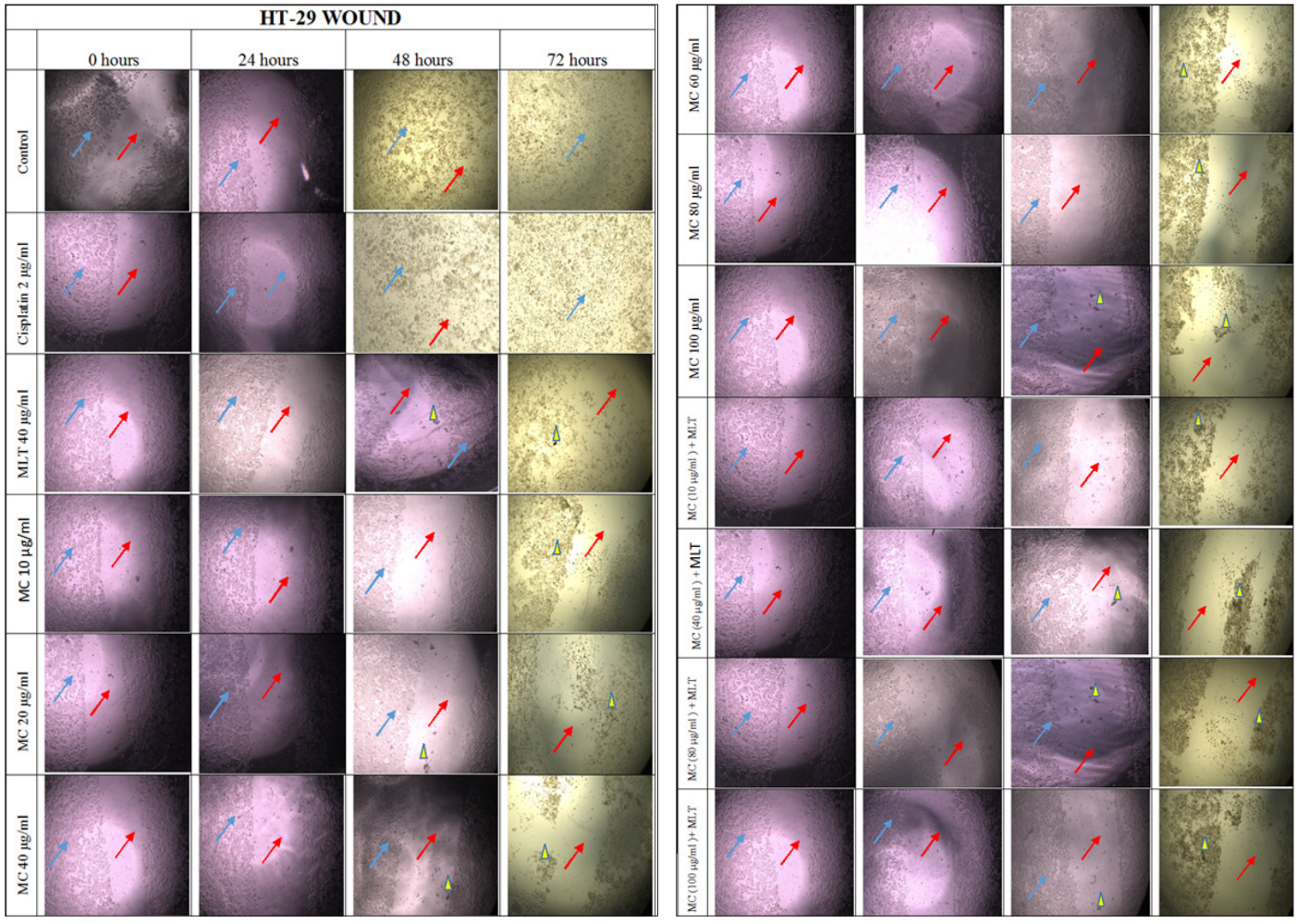

Figure 5B. Microscopic wound (migration test) view of each group after 24, 48 and 72-hrs (20×). **Blue arrow:** live cells, **Red arrow:** Empty space, **Triangle:** died cells

Calastretti et al.[14] studied the oncostatin efficiency of UCM 1037, a MLT analog, in androgen-sensitive (LNCaP and 22Rv1) and -insensitive (PC3 and DU145) PC cells. In this study, cells were exposed to UCM 1037 at 10-4 M for 24, 48, and 72 hrs and demonstrated antiproliferative and cytotoxicity effects in LNCaP and 22Rv1 cells. However, androgen-insensitive cells like PC-3 and DU145 have shown low sensitivity to UCM 1037, indicating that MLT plays a more effective role in hormone-dependent PC cells.

In a study was done by García-Navarro A et al.[26] the antiproliferative effect of MLT on human colon cancer (HT-29 cells) was investigated. After 48 hrs MLT incubation, they found that cell proliferation was reduced in a concentration-dependent and reached almost 100% inhibition in 4 mM MLT. In addition, many studies have shown similar antiproliferative effects on human OAW-42, ME-180,[27] HeLa, HT-29,[28] and CT-26[29] cells after incubation with MLT.

In the present study, we evaluated the cytotoxic effects of MLT+MC combination on PC-3 and HT-29 cell lines with LDH and MTT assays. We demonstrated that the MLT+MC combination significantly decreased the viability of the cells on both cell lines in a dose-dependent manner ($P<0.05$). A parallel finding to our findings is provided by the work of Pitchakarn et al.[30] who have found that MC treatment reduced cell growth of prostate cancer cell line concentration-dependently for 24 and 48 hrs. Dia et al.[31] showed that BG-4, a novel bioactive peptide isolated from MC, caused cytotoxicity in HCT-116 and HT-29 human colon cancer cells after 48 hours of treatment.Similarly, the findings of our study showed that the combination of MLT (40 µg/ml)+MC (10, 40, 80, and 100 µg/ml) decreased cell viability and caused further enlargement of the wound area.

The antioxidative/oxidative potential of MC+MLT combination evaluated with TAC and TOS assays. According to our results, MLT (40 µg/ml)+MC (100 µg/ml) group led to decreases in TAC level. On the other hand, TOS levels of MLT (40 µg/ml)+MC (100 µg/ml) treatment groups in both cell lines caused significant increases compared to the control value.

In our study, non-cytotoxic doses of MC, and MLT+MC combination dramatically reduced migration and invasion of human prostate and colon cancer cells. According to our data, the MLT antitumor effect increased when MC was added to both of the cell lines. Looking at the migration test, the combination group of MLT (40 µg/ml)+MC (100 µg/ml) has

shown to be more effective than cisplatin and other groups in both cell lines.

The release of LDH in all cells is generally considered a marker of membrane permeability and damage. Popovich et al showed that a triterpenoid containing MC seed extract did not increase lactate dehydrogenase release from cultured 3T3-L1 murine fibroblast cells. However, in this study, MC extract reduced LDH activity after 48 and 72 hours of treatment, indicating that MC triterpenoids were not effective on 3T3-L1 cellular membranes to improve permeability.[32] A study by conducted Lui et al.[33] showed that other plant-derived extracts containing secondary metabolites affect 3T3-L1 cells, unlike both cultured colon carcinoma and hepatocarcinoma cells. According to our data, both PC-3 and HT-29 cell lines showed an increase in LDH activity due to MC concentration after 72 hrs of treatment.

CONCLUSION

Side effects and chemotherapeutic resistance to cisplatin are significant and pose major health concerns for the patient. Especially, irreversible DNA damage, neuropathic pain, and vital organ damage have led us to find better approaches to cancer treatment that will minimize or by-pass these significant side effects. In working towards this end of better therapeutics, we utilized the plant extract \ (MC) and a hormone, MLT that has reported anticancer properties. The combination of MLT+MC shows promise to be a new anticancer agent for the treatment of colorectal or prostate cancer or adjuvant for the reduction of the side effects of chemotherapeutics. In our study, we report that the MC+MLT combination exerts inhibitory effects on the progression of cell lines PC-3 and HT-29 by inhibiting cell proliferation and viability and by suppressing cancer cell invasion. MLT and MC together augmented the anticancer effects of each compound alone, not only by inducing oxidative stress, direct or indirect apoptosis but also by a direct effect on M1 and M2 receptors. By targeting both the MLT receptors and mitochondrial function, this would be an avenue for the development of new therapies for the treatment of prostate and colorectal cancer. Also, work is being done to investigate whether the combination of these agents along with cisplatin will permit the lowering of the cisplatin dose and the resulting reduction in cisplatin -mediated side effects.

ETHICAL DECLARATIONS

Ethiccal Issue: Not required as cell line is used and no animal or indal-derived studies.

Scientific Responsibility Statement: The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the mainline, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement: No animal or human studies were carried out by the authors of this article.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Physical, Psychosocial, Occupational Problems and Protection Behaviors Experienced by Pre-Hospital Emergency Healthcare Professionals During The COVID-19 Pandemic

Hastane Öncesi Acil Sağlık Çalışanlarının COVID-19 Pandemi sürecinde Yaşadığı Fiziksel, Psikososyal, Mesleki Sorunlar ve Korunma Davranışları

Mehmet Doğan[1]

[1]Erciyes University Health Services Vocational School, Kayseri, Turkey

Abstract

Aim: COVID-19 pandemic has become one of the most critical health problems of the 21st century. Healthcare workers undoubtedly fulfil the most crucial task of combating this critical health problem all over the world. This study was carried out to determine the experiences of pre-hospital emergency healthcare workers during the COVID-19 process.

Material and Method: This descriptive and cross-sectional study was conducted on 204 healthcare workers working in Kayseri province, Turkey's pre-hospital emergency health services.

Results: 50.5% of the participants were women, 69.1% were married, and the average age was 31.7 ± 5.8. Of the participants 45.6% were working as an Emergency Medical Technician, and 85.8% were university graduates. Of the participants 99.0% stated that the workload had increased during the COVID-19 process. Of the participants 42.2% had a coronavirus test and 27.9% of those who had the test had a positive test result. During the COVID-19 process, 14.7% of participants were separated from their families, which adversely affected 90.0% psychologically. While it appears that the participants used personal protective equipment during the COVID-19 process, this increase was 98.5% in wearing a mask. Of the participants 70.6% stated an increase in violence against healthcare workers during the COVID-19 process, and 63.7% of them indicated that they experienced violence during this period.

Conclusions: During the COVID-19 process, the workload of pre-hospital emergency healthcare workers increased. As a society, support should be given to the combat against the pandemic by following precautions and to healthcare workers due to their devoted work.

Keywords: COVID-19, emergency, healthcare workers, pre-hospital

Öz

Amaç: COVID-19 pandemisi 21. yy. en önemli sağlık sorunlarından biri haline gelmiştir. Dünyanın her yerinde bu önemli sağlık sorunuyla ile mücadele en önemli görevi hiç şüphesiz sağlık çalışanları yerine getirmektedir. Bu çalışma, COVID-19 sürecinde hastane öncesi acil sağlık çalışanlarının yaşadıklarını belirlemek amacıyla yapılmıştır.

Gereç ve Yöntem: Tanımlayıcı ve kesitsel tipteki bu çalışma Türkiye'de (Kayseri ilinde) hastane öncesi acil sağlık hizmetlerinde görev yapan 204 sağlık çalışanında yapılmıştır.

Bulgular: Katılımcıların %50,5'i kadın, %69,1'i evli olup yaş ortalaması 31.7±5.8'dir. %45,6'sı ATT olarak görev yapmakta olup %85,8'i üniversite mezunudur. Katılımcıların %99,0'u COVID-19 sürecinde iş yükünün arttığını ifade etmektedir. Katılımcıların %42,2'si COVID-19 testi yaptırmış ve test yaptıranların da %27,9'unun test sonucu pozitiftir. COVID-19 sürecinde katılımcıların %14,7'si ailesinden ayrı kalmıştır. Aileden ayrı kalanların %90,0'ının psikolojisi olumsuz etkilemiştir. Katılımcıların COVID-19 sürecinde kişisel koruyucu ekipman kullanımında artış olduğu görünürken; bu artış %98,5 ile fazla en maske takmada olmuştur. Katılımcıların %70,6'sı COVID-19 sürecinde sağlık çalışanlarına yönelik şiddet olaylarında artış olduğunu ifade ederken %63,7'si bu süreçte şiddete uğradığını ifade etmiştir.

Sonuç: COVID-19 sürecinde hastane öncesi acil sağlık çalışanlarının iş yükü artmıştır. Toplum olarak bireysel önlemlere uyarak pandemiyle mücadeleye ve özverili çalışmalarından dolayı sağlık çalışanlara destek olunmalıdır.

Anahtar Kelimeler: COVID-19, acil, sağlık çalışanları, hastane öncesi

Corresponding *(İletişim)*: Mehmet Doğan, Erciyes University Health Services Vocational School, Kayseri, Turkey
E-mail *(E-posta)*: mehmetdogan@erciyes.edu.tr
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INTRODUCTION

The coronavirus epidemic, which started with cases of pneumonia with unknown cause, was defined as a new coronavirus (2019-nCoV) that was not detected in humans on January 7, 2020.[1] As in this epidemic; SARS (Severe Acute Respiratory Syndrome), which emerged in China in 2003, and MERS (Middle East Respiratory Syndrome), which emerged in Saudi Arabia in 2012, are also from the coronavirus family.[2,3] The virus was named first as SARS-CoV-2 and then as "COVID-19" due to its close similarity to SARS CoV.[4] The World Health Organization (WHO) classified the COVID-19 outbreak as an "international public health emergency" on January 30 and defined it as a global epidemic (pandemic) on March 11. Although COVID-19 is transmitted through the main droplet, it is transmitted by the droplets emitted by sick individuals by coughing, sneezing, and then touching the mucous membranes of the mouth, nose, or eyes. The virus's common symptoms, which have an incubation period of 2-14 days, include respiratory symptoms, fever, cough and dyspnea.[1]

The COVID-19 pandemic, which is spreading rapidly around the world, continues to increase day by day. As of October 29, 2020, it caused 44.5 million cases and 1 million 174 thousand deaths worldwide. Similarly, the number of cases and deaths continues to rise in Turkey. The first case was seen in Turkey on March 11, 2020. Since then, 366 thousand cases and 9 thousand 950 deaths have occurred.[5]

Pre-hospital emergency medical services (PEMS) in Turkey fulfills the first professional health services. PEMS in Turkey is implementing the Anglo-American model.[6] PEMS; it is an intervention chain that includes providing emergency care support at the scene to individuals who need urgent assistance due to disaster, accident, or illness and transporting them to the hospital safely.[7] The life-saving medical treatment and care initiated in the field continue during the transport, and the patient is delivered to the hospital emergency services for advanced emergency care. The services' main purpose is to reduce morbidity and mortality, mainly due to major trauma, chronic diseases, and acute health problems.[8]

PEMS provides routine health care services. In addition to these services, since mid-March 2020, COVID-19 suspect or positive cases have been intervened in the field and transferred to hospital emergency services. This study was conducted to determine pre-hospital emergency healthcare workers' experiences in approximately eight months since the first COVID-19 case was seen in Turkey.

MATERIAL AND METHOD

This descriptive and cross-sectional study was conducted during 1 September–20 October 2020 with healthcare professionals working in PEMS in Kayseri province, Turkey. The sample size was not selected in the study, and the whole population was included. At the end of the study, the data of 204 pre-hospital emergency healthcare workers (PEHW) were included. For the study, the ethics committee approval was obtained from the Scientific Research and Publication Ethics Board of Cappadocia University (Decision Number: 2020.31) and approved by the Ministry of Health Scientific Research Evaluation Commission. A questionnaire consisting of 40 questions related to socio-demographic characteristics, working life, working conditions, and COVID-19 of the participants was prepared. The questionnaire form prepared to eliminate the situations that would negatively affect the pre-hospital emergency healthcare workers' working conditions and the voluntary participation in the study and consider the epidemic's contagion characteristics; A link was created by transferring it to the computer environment. Information about the study was given to the volunteers on the online questionnaire page. The volunteers' informed consent was obtained by choosing the "I agree to voluntarily participate in the study" option on the same page. The data were evaluated with SPSS 15.0 (Chicago, IL, USA) software, percentage and frequency distributions, mean and standard deviation and statistical analysis.

RESULTS

50.5% of PEHW were women and 69.1% were married. 50.5% were in the 26-35 age group, and the average age was 31.7 ± 5.8. 45.6% worked as an Emergency Medical Technician (EMT) and 41.7% as a paramedic. 48.5% of the PEHW had worked for 10-20 years. While 11.3% had a chronic disease, the most common chronic disease was asthma, with 17.4%.

In the COVID-19 process, 99.0% of the PEHW stated that their workload increased, 97.1% did not see the necessary value. While 42.2% of the PEHW had the COVID-19 test, 27.9% had a positive test result. 87.7% of PEHW stated that their psychology was affected due to the possibility of being COVID-19 positive and infecting their family. During the COVID-19 process, 85.3% of PEHW continued to stay with their families, 8.3% rented another house, 3.9% sent their family to relatives and 2.5% stayed in a hotel/dormitory. The evaluation of PEHW according to some characteristics during the COVID-19 process is shown in **Table 1**.

During the COVID-19 process, the habit of wearing masks had an increased rate of 98.5% of PEHW. With an increasing rate of 77.5%, wearing gloves was the lowest increase in personal protective equipment (PPE). There was an increase in hand disinfectant use by 96.6%, protective gown with 92.6%, hand-washing with 89.7%, and goggle /face shield with 85.3%. The change in the habit of hand-washing and the use of PPE by PEHW during the COVID-19 process is shown in **Table 2**.

63.7% of PEHW were exposed to violence during the COVID-19 process. 63.2% of those who stated that they experienced a violent incident experienced verbal assault/insult, 9.3% physical violence/injury. While 73.0% of them notified about the violence experienced, most notifications were made by searching for the white code. They stated that the most violence was done by the relatives of the patients (99.0%) and the reason for using violence was the lack of education/seeing violence as a method of seeking justice with 65.2%. The evaluation of the violent events experienced by PEHW during the COVID-19 process is shown in **Table 3**.

Table 2. Changes in pre-hospital emergency health care workers' handwashing habits and personal protective equipment usage during the COVID-19 process

	n	%
Did your habit of wearing a mask increase during the COVID-19 process?		
Yes	201	98,5
No	3	1,5
Did your habit of using hand disinfectants increase during the COVID-19 process?		
Yes	197	96,6
No	7	3,4
Did your habit of wearing a protective apron increase during the COVID-19 process?		
Yes	189	92,6
No	15	7,4
Did your habit of hand-washing increase during the COVID-19 process?		
Yes	183	89,7
No	21	10,3
Did your habit of goggle /face shield increase during the COVID-19 process?		
Yes	174	85,3
No	30	14,7
Did your habit of wearing gloves increase during the COVID-19 process?		
Yes	158	77,5
No	46	22,5

Table 1. Evaluation of pre-hospital emergency healthcare workers according to some characteristics of the COVID-19 process

	n	%
Did you increase your workload in the COVID-19 process?		
Yes	202	99,0
No	2	1,0
Did you see the necessary value in the COVID-19 process?		
Yes	6	2,9
No	198	97,1
Did you take a COVID-19 test?		
Yes	86	42,2
No	118	57,8
COVID-19 test result (n=86)		
Negative (-)	62	72,1
Positive (+)	24	27,9
Are anyone of your colleagues positive (+) for COVID-19?		
Yes	153	75,0
No	51	25,0
Is anyone in your family positive (+) for COVID-19?		
Yes	36	17,6
No	168	82,4
Did the possibility of being COVID-19 and infecting your family affect your psychology?		
Yes	181	88,7
No	23	11,3
Where did you stay during the COVID-19 process?		
Continued to stay in the same house with the family	174	85,3
Rented another house	17	8,3
Sent the family to relatives	8	3,9
Hotel/ dormitory	5	2,5
Did your separation from the family affect your psychology? (n=30)		
Yes	27	90,0
No	3	10,0
Did you receive psychological support during the COVID-19 process?		
Yes	4	2,0
No	200	98,0
Did you have trouble finding personal protective equipment during the COVID-19 process?		
Yes	19	9,3
No	111	54,4
Sometimes	74	36,3
Has your sleep pattern been affected during COVID-19?		
Yes	154	75,5
No	21	10,3
Sometimes	29	14,2

DISCUSSION

Healthcare professionals are at significant risk for COVID-19 due to the nature of their work. COVID-19; healthcare workers in most countries of the world have become infected and died.[9] Although WHO has not published a systematic report on COVID-19 cases and deaths by healthcare professionals, according to the 82 Situation Report dated April 11, 2020, a total of 22 thousand 73 COVID-19 cases have been reported in 52 countries.[10] In the report titled "Epidemiological Alert COVID-19 Among Healthcare Workers," published on August 31, 2020, by the Pan American Health Organization (PAHO), approximately 570 thousand cases of COVID-19 and 2 thousand 506 deaths occurred among healthcare workers in the PAHO region.[11] In a study conducted at the Los Angeles County Department of Public Health, 5,500 healthcare workers were diagnosed with COVID-19. EMT/paramedics constituted 1.2% (61) of the diagnosed healthcare workers.[9] There is no official explanation of COVID-19 cases and deaths by healthcare workers in Turkey. According to the report of the Turkish Medical Association (TMA) dated April 1, 3474, healthcare workers have been infected with COVID-19 in Turkey.[12] In a review of Turkish studies until September 12, 85 health workers have died due to the COVID-19. 4.7% (4) of the deceased healthcare workers are PEHW.[13] In our study, 11.8% of PEHW were COVID-19 (**Table 1**). Although there are differences in our study results, WHO reports, and individual studies, healthcare workers worldwide become infected and die due to COVID-19. Also, healthcare workers being infected with COVID-19 does not only affect themselves. It also poses a risk for colleagues, family, and patients. In our study, 75.0% of the pre-hospital emergency healthcare workers' colleagues and 17.6% of their families were positive for COVID-19 tests (**Table 1**).

Since healthcare workers are faced with infection in the fight against COVID-19, the most important way for healthcare workers to protect themselves is through PPE and hand hygiene.[14] All healthcare workers involved in combating COVID-19 require adequate PPE to protect their health.[15]

Table 3. Evaluation of violence events experienced by pre-hospital emergency healthcare professionals during the COVID 19

	n	%
Did you observe an increase in violence against health workers during the COVID-19 process?		
Yes	144	70,6
No	60	29,4
Did you experience any violence during the COVID-19 process?		
Yes	130	63,7
No	74	36,3
What violence happened during the COVID-19 process? *		
Verbal assault /insult	129	63,2
Physical violence /injury	19	9,3
Sexual violence	1	0,5
Who was violent? *		
Patients' relatives	202	99,0
People on the scene	88	43,1
Patients	53	26,0
What was done about the violence? (n=159)		
Notification made	116	73,0
No notification made	43	27,0
Where were the incidents of violence reported? *		
Code white searched	92	45,1
Chief Physician / Health Directorate	55	27,0
Police/ Prosecutor's Office	40	19,6
What are the causes of violence against healthcare professionals? *		
Lack of education for those who use violence / Seeing violence as a way to seek justice	133	65,2
Inciting violence in the media (especially with anti-health worker provocative publications)	128	62,7
The perception that healthcare professionals earn a lot of money	120	58,8
Dissatisfaction with the treatment / High level of expectation	109	53,4
Desire to attract attention / Psychological problems due to the thoughts of neglect	107	52,5
The belief that the ambulance arrived late at the scene	104	51,0
Getting bad news about the patient's condition / Blame the healthcare professionals	103	50,5
Being under the influence of alcohol and drugs-substance abuse	93	45,6
Negative attitudes and behavior of healthcare professionals	37	18,1
Did you consider working in another profession or other health field due to violence?		
No	41	20,1
I thought about changing to another profession	140	68,6
I thought of moving to another healthcare field	23	11,3

* Multiple options are marked.

Especially PEHW may be exposed to COVID-19 due to patient contact or contaminated environments.[16] In our study, 54.4% of the PEHW stated that they did not have trouble finding PPE, and 45.6% (36.3% sometimes) stated that they could not find PPE in the early stages, but they have not experience such a problem throughout the working period (**Table 1**). Mask [Medical-Respirator (N95, FFP2)], gloves, gown, goggle, and face shield are the PPE of healthcare workers.[16] In the report named "COVID-19 Recommendations: Prehospital Emergency Medical Services" published by PAHO, PEHW stated which personal equipment will be used in which situations. In the report; "suspected case of COVID-19 1-meter assessment (ambulance crew)" recommended hand hygiene and wearing a surgical mask and "suspected or confirmed case of COVID-19 requiring medical transport and with aerosol-generating procedure" recommended hand hygiene, respirator mask, apron, gloves, glasses and face protection.[16] In our study, it is seen that there is an increase in healthcare workers related to the use of all PPE. During the COVID-19 process, the highest increase was observed in masks with 96.6%, the use of a protective gown with 92.2%, and protective goggle/face shield with 85.3%. Hand-washing habits increased by 89.7% (**Table 2**). Our study results, similar to a study conducted in Japan, masks became the most frequently used PPE.[17] In all countries to combat COVID-19, healthcare workers should have no trouble finding PPE. Healthcare professionals should be careful in using PPE. In this way, healthcare professionals will protect their health and their patients, colleagues, and families.

Any event or situation where a person is abused, threatened, or attacked in the workplace is considered "workplace violence."[18] Although violence is observed in all work environments healthcare workers are more exposed to violence in the workplace.[19] The risk of being exposed to violence in healthcare workers is 16 times higher than in other service sector occupational groups.[20] A systematic literature review shows that 70-80% of emergency health care workers have experienced one or more violence cases.[21] In Turkey (in Ankara), on the statistical analysis of applied violence to health workers, 13.1% of violence cases occurred in PEHW.[22] In another study in Turkey (in İstanbul), 39.8% of PEHW have been exposed to physical violence and 94.9% to verbal violence.[23] In our study, 63.7% of PEHW were exposed

to violence during the COVID-19 process. Those exposed to violence; 63.2% have been subjected to verbal assault/insult, 9.3% to physical violence/injury. According to PEHW, "the lack of education-seeing violence as a means of seeking justice" is seen as the most common cause of violence with 65.2% (**Table 3**). Our study findings are similar to the prevalence of violence exposed by pre-hospital emergency healthcare workers. The prevalence of violence, which ranged between 61.-78.1% in the studies performed, was found to be 63.7% in our study. [24-27]

CONCLUSIONS

During the COVID-19 process, the workload of PEHW has increased. During this period, two out of approximately three PEHW were exposed to violence. Among PEHW, there have been those diagnosed with COVID-19. These days when we are experiencing the COVID-19 process, the increasing workload, COVID-19 cases among healthcare workers and their exposure to violence may become a problem in the future for all healthcare workers, especially PEHW. A problem that may arise can also cause trouble in terms of combating COVID-19. To correct these situations, all healthcare professionals should be valued, and their rights should be respected. COVID-19 tests should be performed routinely for all healthcare professionals. Deterrent legal arrangements should be made to prevent violence against healthcare workers. All positive developments for the healthcare worker will result in positive developments in terms of the COVID-19 outbreak.

ETHICAL DECLARATIONS

Ethics Committee Approval: For the study, the ethics committee approval was obtained from the Scientific Research and Publication Ethics Board of Cappadocia University (Decision Number: 2020.31).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Orjinal Araştırma / Original Article

Relationship between Vitamin D Level on Pain, Functional Status and Quality of Life in Individuals with Osteoarthritis

Osteoartritli Bireylerde Vitamin D Düzeyi ile Ağrı, Fonksiyonel Durum ve Yaşam Kalitesi Arasındaki İlişki

Dilek Efe Arslan[1], Nazan Kılıç Akça[2], Sibel Şentürk[3], Murat Korkmaz[4]

[1]University Of Erciyes, Halil Bayraktar Health Services Vocational College, Kayseri, Turkey
[2]University of Bakırçay, Faculty of Health Sciences, İzmir Turkey
[3]Department of Nursing, Bucak Health School, Burdur Mehmet Akif Ersoy University, Burdur, Turkey
[4]Yozgat Bozok University, Faculty of Medicine Orthopedics Traumatology Department, Yozgat, Turkey

Abstract

Objective: This study was conducted to determine the correlation between vitamin D level and pain, functional status, and quality of life in individuals with osteoarthritis.

Material and Method: This cross-sectional and descriptive study was completed with 138 individuals. The study was carried out between April 15 and August 30, 2019. The research data were collected using the Identification Form, Visual analogue scale, The Western Ontario and McMaster University Osteoarthritis Index and Short Form-36- Quality of Life scale were used.

Results: 64.5% of the individuals had a vitamin D level of 20 ng/ml and less. It was determined that there was no significant correlation between individuals' vitamin D levels and age, VAS, WOMAC, and SF-36 subscales (p>0.05).

Conclusion: Vitamin D deficiency is very common in individuals with osteoarthritis. No relationship was found between vitamin D levels and pain, functional status and quality life of patients.

Keywords: Osteoarthritis, vitamin D, functional status, quality of life.

Öz

Amaç: Bu çalışma, Osteoartritli bireylerde vitamin D düzeyi ile ağrı, fonksiyonel durum ve yaşam kalitesi arasındaki ilişkiyi belirlemek amacıyla yapıldı.

Gereç ve Yöntem: Kesitsel ve tanımlayıcı tipte olan bu çalışma 138 kişi ile 15 Nisan - 30 Ağustos 2019 tarihleri arasında yapıldı. Veriler, tanımlayıcı bilgi formu, Görsel Kıyaslama Ölçeği, WOMAC Osteoartrit İndeksi ve Kısa Form- 36 yaşam kalitesi ölçeği kullanılarak toplandı.

Bulgular: Bireylerin % 64.5'nin D vitamini düzeyi 20 ng/ml ve daha düşüktü. Bireylerin D vitamini düzeyleri ile yaş, Görsel Kıyaslama Ölçeği, WOMAC ve SF-36 alt ölçekleri arasında anlamlı bir ilişki olmadığı belirlendi (p> 0.05).

Sonuç: D vitamini eksikliği osteoatritli bireylerde çok yaygındır. Hastaların D vitamini düzeyleri ile ağrı, fonksiyonel durum ve yaşam kalitesi arasında ilişki bulunmadı.

Anahtar Sözcükler: Osteoartrit, vitamin D, fonksiyonel durum, yaşam kalitesi.

Corresponding *(İletişim)*: Dilek Efe Arslan, University of Erciyes, Halil Bayraktar Health Services Vocational College, Kayseri, Turkey
E-mail *(E-posta)*: dilekefe_@hotmail.com
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INTRODUCTION

Osteoarthritis (OA) is a dynamic process that causes symptoms such as pain, decreased ROM and stiffness due to the breakdown of joint cartilage, progresses with mechanical and biochemical factors. Osteoarthritis is ranked as the 13th highest contributor of 310 diseases to global disability in 2015.[1] Although it is thought that genetic, metabolic, environmental, and biomechanical factors affect the pathogenesis, the pathogenesis of OA is not fully known. While cartilage fibrillation is superficial at the beginning of the disease, later the degeneration progresses to deep layers.[2,3] Osteoarthritis affects all elements of a joint such as the cartilage forming the synovial joint, capsule, subchondral bone, synovial tissue, and muscles; however, primary changes include loss of joint cartilage, reshaping of subchondral bone, and formation of osteophytes.[2] Pain, decreased physical function, stiffness, depression and sleep disturbances experienced by patients with decrease the quality of life.[4] The aim of OA treatment is to protect and improve joint functions by eliminating pain and stiffness, to prevent or recover disability, to preserve and improve muscle strength, to increase quality of life and to prevent treatment complications. Currently, there is no effective treatment for reversing or preventing structural changes developed in OA.[5]

Vitamin D is a steroid precursor that is important for bone, which undergoes 2 hydroxylations, the first converting vitamin D to 25- hydroxyvitamin D (25 (OH) D), which is an indicator of vitamin D status, and the second to the main active form, 1,25-dihydroxy vitamin D. Vitamin D deficiency (VDD) affects calcium metabolism, , articular cartilage structure, and bone density negatively.[6,7] Vitamin D can prevent OA development and progression by reducing degeneration in cartilage and bone.[8] Moreover, in VDD, proinflammatory cytokines are formed; therefore the severity of pain in the joints and bones may increase and the pain process may change. In addition, many researchers have shown the association between VDD with pain, muscle weakness and deterioration of cognitive function.[7,9] Risk of progression of OA doubled in participants with low levels of vitamin D.[10] Yu et al.[11] was found that there was low association of VDD with knee cartilage loss as evidenced by JSN (joint space narrowing). However, it showed no direct correlation with radiographic knee OA as assessed by osteophytes on plain radiograph. Thus, the association between the concentration of vitamin D and OA is controversial.[12-14] In addition, there is insufficient study showing the correlation between Vitamin D level and pain, functional status, and quality of life in OA.[6,13,14] In our study, vitamin D levels of patients were evaluated together with their quality of life, functional status and pain. In this respect, it is thought that this study will contribute to the literature.

Research questions

What are the levels of vitamin D, pain, functional status and quality of life in OA patients?

Is there a relationship between vitamin D levels and pain, functional status and quality of life in patients with osteoathritis?

MATERIAL AND METHOD

This study was conducted as a descriptive and cross-sectional. The study was carried out between April 15 and August 30, 2019, at the Orthopedics Clinic of a Research and Practice Hospital. The population of the research consisted of all patients with osteoarthritis who applied to the hospital between the specified dates. The research was completed with 138 individuals who met the inclusion criteria. At the end of the study power analysis (G*Power (v3.1.7) was performed using in order to determine the sample size. Considering VAS activity value with vitamin D obtained, the power of the study was found to be 82% at alpha=0.05. Inclusion criteria were (a) being diagnosed diagnosed with osteoarthritis for at least 6 months (b) being aged 18 years and older (c) being diagnosed with gonarthrosis (d) not having any problem that restricted daily life activities (e) being examined for vitamin D level (g) volunteering to participate in the research. Exclusion criteria were (a) being used drugs acting on the central nervous system (b) having a cancer diagnosis (c) being used vitamin D, calcium, parathyroid hormone, and antiresorptive drugs in the last year.

Data Collection

The research data were collected using the Identification Form, VAS, WOMAC and SF-36- Quality of Life scale were used. The data was collected through face to face interviews with the participants. Each interview lasted about 20-30 minutes.

The Identification form was prepared by the researchers by investigating the literature and consists of 16 questions regarding patients' socio-demographic variables, information about the disease.[6,15,16]

The Visual Analogue Scale (VAS) scale is used to determine pain severity. The most severe pain is score "10" points and the absence of pain is scored "0". The most intense pain the individual feels is marked on the scale.[17] In this study, the severity of pain was questioned separately at activity and resting periods.

Turkish validity and reliability study of the WOMAC Osteoarthritis Index (WOMAC) was performed by Tüzün, Eker, and Aytar (2005) in 72 patients (Cronbach's alpha between 0.75-0.96).[18] The index consists of 24 questions and three subscales. In the Likert-type index, the pain subscale is rated between 0-20; stiffness is rated between 0-8 for; the subscale of difficulties experienced during daily activities is rated 0-68. The highest score indicates an increase in pain and stiffness, a deterioration in physical function, and the highest level of physical limitation.[17,19] Cronbach's a values for the WOMAC pain, stiffness, and physical function subdimensions in our study were 0.95, 0.94, and 0.97

SF-36 is used scales for measuring the quality of life. It was developed (1992) by Ware et al.[20] and the Turkish validity and reliability study was conducted by Kocyigit et al. (Cronbach's alpha between 0.73-0.76).[21] The scale consists of 36 items and these items enable the measurement of 8 dimensions. The subscales evaluate health between 0 (poor health) and 100 (good health).[21] In our study Cronbach's alpha were found to range between 0.62 and 0.93.

Vitamin D levels of the patients were examined under appropriate conditions and in the same laboratory. VDD was defined as <20 ng/mL.[22-25] No additional vitamin D examination was conducted for the study. The patient, who was deemed appropriate for vitamin D by the physician, was reported after the examination. A questionnaire was applied to that patient. When the vitamin D result came out, the result was saved from the system.

Table 1. Distribution of patients with osteoarthritis according to their descriptive characteristics

Characteristics	n	%
Gender		
Female	106	76.8
Male	32	23.2
Marital status		
Married	123	89.1
Single	15	10.9
Place of residence		
Province	56	40.6
District	41	29.7
Village	41	29.7
Educational status		
Illiterate	40	29.0
Primary school	69	50.0
Secondary school	18	13.0
High school and over	11	8.0
Income status		
Income less than expenses	40	29.0
Income equal to expenses	92	66.7
Income more than expenses	6	4.3
Family type		
Nuclear	112	81.2
Extended	26	18.8
Presence of other chronic diseases*		
Yes	45	32.6
No	93	67.4
Joint deformity		
Yes	36	26.1
No	102	73.9
Use of osteoarthritis-related drugs		
Yes	119	86.2
No	19	13.8
Status of receiving training on osteoarthritis and its care		
Yes	25	18.1
No	113	81.9
Vitamin D (ng/ml)		
Vitamin D<20	89	64.5
Vitamin D≥20	49	35.5
Mean age (year)	59.00±11.66 (45-89)	
Mean disease duration (year)	5.38±4.15 (1-15)	
Mean treatment duration (year)	3.90±3.37(1-15)	
Mean vitamin D level (ng/ml)	16.37±8.33(3-39)	

** Hypertension, Myocardial Infarction, Stroke etc.*

Statistical Analysis

The research data were evaluated in SPSS 21.0 package program in a computer environment. The Kolmogorov-Smirnov test and Shapiro-Wilk test were used to assess normally distributed data. Research findings were obtained by arithmetic mean, standard deviation and student's t-test. [26] The statistical significance of the results was evaluated at $p<0.05$.

RESULTS

It was found that 76.8% (n:106) of the individuals with osteoarthritis were female; 89.1% (n:123) were married. It was determined that 67.4% (n:93) of the individuals had no other chronic disease; 73.9% (n:102) had no joint deformity; 86.2% (n:119) used drugs for osteoarthritis. 64.5% (n:89) of the individuals had a vitamin D level of 20 ng/ml and less. This finding demonstrates that most of the patients had VDD. The mean age of the individuals was 59.00±11.66 years; the mean disease duration was 5.38±4.15 years; the mean vitamin D level was 16.37±8.83 g/ml (**Table 1**).

The mean resting and activity VAS scores were 3.78±2.42 and 5.94±2.26, respectively. The mean WOMAC pain, stiffness and physical function were 10.57±5.54; 3.83±2.29 and 33.33±14.55 respectively. When the SF-36 mean subscale scores were examined, it was determined that the mean subscale score was 18.60±4.91 for physical functioning, 5.29±1.45 for role-physical, 6.43±1.91 for bodily pain, 13.48±4.17 for general health, 12.52±4.24 for Vitality (Energy), 5.54±1.72 for social functioning, 4.12±1.07 for role-emotional, and 20.91±4.59 mental health (**Table 2**).

It was determined that there was no significant correlation between individuals' vitamin D levels and age, VAS (Resting-Activity), WOMAC, and SF-36 subscales ($p>0.05$) (**Table 3**).

Table 2. Distribution of the VAS, WOMAC, and SF-36 Quality of life scale subscale scores of the individuals with osteoarthritis

Scales	Mean±SD (Min-Max)
VAS	
Resting	3.78±2.42 (0-10)
Activity	5.94±2.26 (1-10)
WOMAC	
Pain	10.57±5.54 (0-20)
Stiffness	3.83±2.29 (0-8)
Physical Function	33.33±14.55 (0-58)
SF-36 Subscales	
Physical Functioning	18.60±4.91
Role-Physical	5.29±1.45
Bodily Pain	6.43±1.91
General Health	13.48±4.17
Vitality (Energy)	12.52±4.24
Social Functioning	5.54±1.72
Role-Emotional	4.12±1.07
Mental Health	20.91±4.59

Note: Visual analogue scale (VAS); WOMAC osteoarthritis index (WOMAC); SF-36: Short Form 36; SD: Standard Deviation

Table 3. Comparison of scale scores of individuals with osteoarthritis according to their Vitamin D levels

Characteristics	Vitamin D<20 (n:89)	Vitamin D≥20 (n:49)	p*
VAS Resting	3.73±2.56	3.87±2.15	0.734
VAS Activity	6.01±2.30	5.83±2.21	0.667
WOMAC Pain	10.30±5.14	11.24±4.86	0.296
WOMAC Stiffness	3.609±2.30	4.24±2.24	0.118
WOMAC Physical Function	32.55±14.93	34.75±13.87	0.396
SF-36 Subscales			
Physical Functioning	18.76±4.79	18.32±5.14	0.618
Role-Physical	5.28±1.45	5.32±1.46	0.861
Bodily Pain	6.40±1.93	6.50±1.89	0.782
General Health	13.48±4.36	13.48±3.84	0.993
Vitality (Energy)	12.43±4.41	12.69±3.95	0.736
Social Functioning	5.57±1.75	5.48±16.8	0.787
Role-Emotional	4.19±1.18	4.06±1.04	0.523
Mental Health	20.96±4.58	20.8±14.65	0.855

Note: *Student t test used.

DISCUSSION

Vitamin D has recently found focus due to its widespread effects on the musculoskeletal system. Also, the prevalence of VDD has consistently been on the rise.[27] In our research, most of the patients were found to have VDD. Likewise, Hekimsoy et al. was found that 74.9% had vitamin D deficiency.[27] Our study finding is similar to the literature.

In our research, it was determined that there was no significant correlation between vitamin D levels of the patients and VAS and WOMAC subscales. However, the studies was found that vitamin D had a protective effect against cartilage defect progression and Vitamin D deficiency seems to be a factor contributing to pain, muscle weakness, and disability.[28,29] Similar to our study, in the studies conducted no correlation were found between vitamin D levels and osteoarthritis.[7,8,30] In a systematic review published in 2017, the effect of the use of vitamin D on the treatment of knee osteoarthritis was mainly focused on the pain parameter and it was reported that it did not affect pain.[31] The association between the concentration of vitamin D and OA is controversial. These findings determined in our study indicate that randomized controlled studies with larger sample size should be performed.

Vitamin D deficiency have been linked to poor quality of life.[9,32] In particular, pain and functional impairmentsare the primary burden of patients with OA, and taken together, they often cause a significant decrease in quality of life. According to evidence-based knee osteoarthritis treatment recommendations of the Turkish League Against Rheumatism, the first goal of the OA treatment is to control the pain, maintain and improve joint functions, provide functional independence, and improve the quality of life.[33] It was determined that there was no significant correlation between vitamin D levels and SF-36 subscales. In the study conducted by Dhesi et al., it was found that there was no significant improvement in any of the subscales of quality of life in the vitamin D loaded group.[34] In the study conducted by Alkan et al. (2012), no significant correlation was found between initial vitamin D levels and quality of life.[15] It is suggested that quality of life should be evaluated frequently by health professionals and that the quality of life should be improved by prioritizing the symptom control.

The limitations of the study include the lack of repetitive vitamin D measurements, the lack of monitoring patients after they received vitamin D supplements, the evaluation of instant status, the ignorance of the current changes in normal life of patients while only considering the severity of the disease during the examination of osteoarthritis, which has a complex structure. This is considered among the uncontrollable factors of the research.

CONCLUSION

VDD is very common in OA. Vitamin D was no correlation between pain, functional status and quality of life of patients. Health professionals may apply practices regarding the prevention of VDD in patients with osteoarthritis to prevent symptoms of the disease. We recommend that these patients be regularly evaluated for VDD. Long-term studies are needed to evaluate the effects of vitamin D.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bozok University Faculty of Medicine Non-Invasive Trial Ethics Committee (Decision Number:2017-KAEK-189_2019.04.24_14).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Determination of the Comfort Level and Self-Care Agency of the Women with Urinary Incontinence

Üriner İnkontinansı Olan Kadınların Konfor Düzeyi ve Öz Bakım Gücünün Belirlenmesi

Meltem Bozkurt[1], Evşen Nazik[2]

[1] Gaziantep Üniversitesi Şahinbey Araştırma ve Uygulama Hastanesi, Gaziantep, Türkiye
[2] Çukurova Üniversitesi Sağlık Bilimleri Fakültesi Hemşirelik Bölümü, Adana, Türkiye

Abstract

Objective: This study was carried out to determine the comfort level and self-care agency of women with urinary incontinence.

Material and Method: This descriptive and relationship seeker research was performed in a, gynecology services of a university hospital between February 2016-April 2018. A total of 124 women with urinary incontinence were included in the study The data of the study were collected by using Personal Information Form, Urinary Incontinence and Urinary Frequency Comfort Scale and Self-Care Agency Scale. Data analysis was done using SPSS windows 24.0 package program.

Results: The mean score of Urinary Incontinence and Urinary Frequency Comfort Scale of the women with urinary incontinence was 3.35±0.59, and the mean score of Self-Care Agency Scale was 88.09±14.59. A statistically significant moderate positive correlation was detected between Urinary Incontinence and Frequency Comfort Scale and Self Care Agency Scale (r=0.479 p=0.001).

Conclusion: It was determined that there is a moderate relationship between the comfort level and self-care agency of women with urinary incontinence in the study.

Keywords: Comfort, self care, urinary incontinence

Öz

Amaç: Bu çalışma, üriner inkontinansı olan kadınların konfor düzeyi ve öz bakım gücünün belirlenmesi amacıyla yapılmıştır.

Gereç ve Yöntem: Tanımlayıcı ve ilişki arayıcı olarak yapılan çalışma, Şubat 2016-Nisan 2018 tarihleri arasında, bir üniversite hastanesinin Kadın Doğum Servisinde yapılmıştır. Araştırmaya 124 üriner inkontinansı olan kadın dahil edilmiştir. Verilerin toplanmasında "Kişisel Bilgi Formu", "Üriner İnkontinans & Üriner Sıklık Konfor Skalası"ve "Öz bakım Gücü Ölçeği"kullanılmıştır. Verilerin istatistiksel analizleri SPSS Windows version 24.0 paket programında yapılmıştır.

Bulgular: Üriner inkontinansı olan kadınların Üriner İnkontinans & Sıklık Konfor Skalası toplam puan ortalaması 3,35±0,59 ve Öz Bakım Gücü Ölçeği toplam puan ortalaması 88,09±14,59 olarak saptanmıştır. Üriner İnkontinans & Üriner Sıklık Konfor Skalası ile Öz Bakım Gücü Ölçeği arasında, istatistiksel olarak pozitif yönde orta şiddette anlamlı bir ilişki bulunmuştur (r=0,479 p=0,001).

Sonuç: Araştırmada üriner inkontinansı olan kadınların konfor düzeyi ile öz bakım gücü arasında orta düzeyde ilişki olduğu belirlenmiştir.

Anahtar Kelimeler: Konfor, öz bakım, üriner inkontinans

Corresponding *(İletişim)*: Evşen Nazik, Çukurova Üniversitesi Sağlık Bilimleri Fakültesi Doğum Ve Kadın Hastalıkları Hemşireliği Anabilim Dalı, Adana, Türkiye
E-mail *(E-posta)*: eceevsen_61@hotmail.com
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INTRODUCTION

Urinary incontinence (UI), which is a medical, hygienic and social problem affecting millions of individuals in the world, is defined as involuntary release of urine. The International Continence Society explained UI as involuntary loss of urine that can be objectively observed and causes social and hygienic problems.[1,2] UI is a serious health problem that is seen 3-4 times more frequently in women than men, does not threaten life and has economic and emotional effects. The prevalence of UI in women in the literature varies based on age groups, while it is reported between 12% and 53%.[3-5] Studies conducted in Turkey have reported this prevalence to vary between 16% and 69%.[6-8] UI, which is usually observed in middle-aged and elderly women, is perceived as a normal consequence of ageing, affects the quality of life and sexual functions of women negatively, leads their physical and social lives to be limited and disrupts their comfort.[9-18] Studies have determined that women with UI hide their complaints although their comfort is disrupted, they generally do not visit health institutions, and they try to cope with this problem themselves.[16,18,19]

The primarily preferred approach in the treatment of UI is achievement of lifestyle change. Lifestyle changes consist of various self-care activities including avoiding foods and drinks that irritate the bladder, regulating fluid intake, gaining and maintaining toilet habits, achieving and sustaining an appropriate weight, quitting smoking and managing constipation.[20,21] Self-care involves individuals fulfilling their responsibilities to personally preserve their lives, health and wellbeing. Self-care agency is the capacity of the individual to start and implement health practices to maintain their life, health and wellbeing. For a healthy individual to be able to meet their basic needs and perform their daily life activities, they need to have sufficient self-care agency.[22] Self-care agency is also important in urinary incontinence, whereas a study conducted by Esparza et al. (2018) emphasized that appropriate self-care strategies need to be developed in comping with urinary incontinence.[23]

Detection of UI which affects the comfort of women negatively in the early period and performance of the appropriate interventions will provide significant contributions to improvement of women's health. Some of the most important healthcare personnel who will provide this contribution are nurses. Nurses play an active role in the diagnosis and treatment of the problem of incontinence and in increasing the quality of care.[24] It is seen that various studies have been conducted in the literature on women who had UI.[9-18] However, studies examining comfort and self-care agency have not been encountered. This study was conducted to determine the comfort levels and self-care agency of women with urinary incontinence.

Research questions:

1. What are the comfort levels of women with urinary incontinence?
2. What are the self-care agency levels of women with urinary incontinence?
3. Is there a relationship between the comfort levels and self-care agency of women with urinary incontinence?

MATERIAL AND METHOD

Type of the Study

This is a descriptive and correlational study conducted to determine the comfort levels and self-care agency of women who have UI.

Population and Sample

The study was conducted at the gynecology services of a university hospital between February 2016 and April 2018. The population of this study consisted of the inpatients of this hospital with the diagnosis of UI.

The sample of the study included women who were selected with the non-probability sampling method of random sampling, were hospitalized at the gynecology service of the aforementioned hospital with the diagnosis of UI, met the inclusion criteria of the study and agreed to participate in the study.

The inclusion criteria were as follows:

- Being at or over the age of 18,
- Not having had any surgical operation due to UI,
- Not having difficulty in communication or a diagnosed psychiatric disease,
- Being able to understand and speak Turkish.

Power analysis was conducted in the G*Power software to calculate the sample size. Based on the study by Zengin (2008), with a 95% power and a 5% error rate, it was determined that at least 105 women needed to be included.[2] By considering the possibility of the women to want to leave the study and fill out the questionnaire forms incompletely, the study was conducted with 124 women.

Data Collection

The data were collected by the researcher with the face-to-face interview method between February 2016 and April 2018 at the gynecology services of the specified hospital, and each interview lasted for about 20.

Data Collection Instruments

The data were collected using a "Personal Information Form" 1 on the descriptive characteristics of the participants, the "Urinary Incontinence and Urinary Frequency Comfort Scale" to assess comfort and the "Self-Care Agency Scale" to assess self-care.

Personal Information Form

It consisted of 25 questions on the sociodemographic (age, education status, employment status, health insurance status, income level, marital status, duration of marriage), obstetric (number of pregnancies, age of pregnancy, form of delivery, etc.) and UI diagnosis-related (type of incontinence, duration of complaints, precautions taken, etc.) characteristics, their cigarette/alcohol use status and chronic disease status.

Urinary Incontinence and Urinary Frequency Comfort Scale

It was developed by Dowd et al. (2000) to assess the comfort of the individual experiencing problems of urinary incontinence and frequent urination by utilizing the General Comfort Scale of Kolcaba.[25] Its validity and reliability in Turkey were tested by Zengin (2008).[12] The scale is a 28-item 6-point Likert-type scale with options ranging from "absolutely disagree" to "absolutely" agree. 16 of the expressions in the items are positive (1, 2, 4, 9, 11, 12, 13, 15, 16, 17, 23, 24, 25, 26, 27, 28), 12 are negative (3, 5, 6, 7, 8, 10, 14, 18, 19, 20, 21, 22), and the negative items are inversely scored in calculation of the total score. The lowest and highest possible total scores in the scale are 28 and 168. However, while assessing the scale, by dividing the total score by the number of items, an average score is obtained, and the result is evaluated in the range of 1-6. Low scores indicate poor comfort, whereas high scores indicate good comfort. The Cronbach's alpha value of the scale in its reliability study was determined as 0.77. In this study, the Cronbach's alpha value was calculated as 0.84.

Self-Care Agency Scale

The Self-Care Agency Scale developed by Kearney and Fleisher in 1979 consists of 43 items.[26] Nahcivan adapted the scale into the Turkish society by conducting a validity and reliability study on the scale with healthy young people in 1993.[27] The scale adapted to the Turkish society is a 35-item, 5-point Likert-type scale. Each item has the options of "does not define me at all", "somehow does not define me", "undecided", "somehow defines me" and "defines me a lot." In the scale translated into Turkish, items 3, 6, 9, 13, 19, 22, 26 and 31 are negatively and the other items are positively scored. The positive expressions in the scale are scored as 0, 1, 2, 3, 4 points, while the negative ones are scored as 4, 3, 2, 1, 0 points, respectively. The minimum and maximum total scores in the scale are 35 and 140. High scores indicate high levels of self-care agency. The Cronbach's alpha value of the scale was reported as 0.89. In this study, the Cronbach's alpha value of it was found as 0.81.

Data Analysis

The SPSS Windows version 24.0 package program was used for the statistical analyses. As the descriptive statistics, mean±standard deviation for the numerical variables and frequency and % for the categorical variables are presented. The relationship between the numerical variables was determined by Spearman's correlation analysis. Cronbach's alpha coefficients were calculated to test validity and reliability. $p<0.05$ was accepted as statistically significant.

Ethical Aspects

Before starting the study, the protocol was submitted to the Non-Interventional Clinical Studies Ethics Board of the School of Medicine at Çukurova University, and approval was obtained (06-11-2015/45). Additionally, written permission was also obtained from the institution where the study was conducted. To protect the rights of the women included in the study, information was provided to the participants about the purpose of the study before data collection, and those who volunteered were included. The "autonomy" principle was followed by stating that the women could leave the study whenever they wanted, while the "confidentiality and protection of privacy" principle was followed by assuring them that their individual information would be protected. By stating that the identity of the obtained information and the respondent would be kept hidden, the principle of "anonymity and security" was complied with.

RESULTS

The following findings were obtained in the study that was conducted to determine the comfort levels and self-care agency of women with urinary incontinence.

Sample Characteristics

The mean age of the participants was 48.03±7.78 (range: 18-62), 84.7% were at or over the age of 40, 38.7% were primary school graduates, and 83.9% were not working. Among the women, 88.7% had health insurance, 72.6% had moderate income levels, 78.2% were married, and the duration of marriage of 62.5% was 21 years or longer (**Table 1**).

Table 1. Distribution of the Sociodemographic Characteristics of the Women with Urinary Incontinence (N=124)

Sociodemographic Characteristics	Frequency	Percentage
Age		
39 years or younger	19	15.3
40 years or older	105	84.7
Education Level		
Illiterate	12	9.7
Literate	34	27.4
Primary School	48	38.7
Secondary School	13	10.5
High School	13	10.5
University or higher	4	3.2
Employment Status		
Working	20	16.1
Not working	104	83.9
Has Health Insurance		
Yes	110	88.7
No	14	11.3
Income Level		
Good	9	7.3
Moderate	90	72.6
Bad	25	20.1
Marital Status		
Married	97	78.2
Single	27	21.8
Duration of Marriage		
1-5 year(s)	5	5.2
6-10 years	7	7.3
11-15 years	7	7.3
16-20 years	18	17.7
21 years or longer	60	62.5

Considering the obstetric and gynecological characteristics of the participants, it was determined that the total number of pregnancies of 65.3% of the women was 4 or higher, while the total number of births of 44.9% was 4 or higher. 55.1% had their first birth at the ages of 19-24. 66.1% of the women had normal delivery, and 94.1% did not have multiple gestation. 67.7% had not had any gynecological operation before, and 57.3% had not entered menopause. Among those who had entered menopause, it was found that 37.7% entered menopause in the age range of 46-50.

Among the included women, 36.3% were overweight, 74.2% did not smoke, 54.5% of the smokers smoked 20 cigarettes a day, 92.7% never used alcohol, 51.6% did not have a chronic disease, and 41.7% of those with chronic diseases had hypertension.

Considering the UI-related findings of the participants, it was found that 36.3% of the women experienced stress urinary incontinence, 71.8% had complaints of urinary incontinence for 1-5 year(s), 46% experienced incontinence more than once a day. It was determined that 85.5% of the women took precautions about their problem of urinary incontinence. 52.8% said they went to the toilet frequently as a precaution, while 49.1% stated that they reduced their fluid intake (**Table 2**).

Table 2. Distribution of the UI-Related Characteristics of the Women with Urinary Incontinence (N=124)

Incontinence-related characteristics	n	%
Type of Incontinence		
Urge Incontinence	38	30.6
Stress Incontinence	45	36.3
Mixed type	41	33.1
Duration of Incontinence		
1-5 year(s)	89	71.8
6-10 years	25	20.1
11 years or longer	10	8.1
Frequency of Incontinence		
Once a day	30	24.2
More than once a day	57	46.0
Once a week	13	10.5
More than once a week	24	19.4
Takes Precaution		
Yes	106	85.5
No	18	14.5
Precaution Taken*		
Using protective pads	28	26.4
Going to the toilet frequently	56	52.8
Intaking less fluids	52	49.1
Sitting near the toilet	30	28.3

*Multiple choices were allowed.

Relationship between Comfort and Self-Care Agency

Table 2 shows the total mean scores of the Urinary Incontinence and Urinary Frequency Comfort Scale and the Self-Care Agency Scale. The mean total scores of the women with UI from these scales were 3.35±0.59 and 88.09±14.59, respectively (**Table 3**).

Table 3. Distribution of Mean Scores in the Urinary Incontinence and Urinary Frequency Comfort Scale and the Self-Care Agency Scale

Scales	Med	Min-Max	X±SD
Urinary Incontinence and Urinary Frequency Comfort Scale	3	1-6	3.35±0.59
Self-Care Agency Scale	89	54-116	88.09±14.59

The Spearman's rank correlation value between the mean scores of the Urinary Incontinence and Urinary Frequency Comfort Scale and the Self-Care Agency Scale was found as r=0.479 (p=0.001), which indicated a moderate, positive and significant relationship between the two scales (**Table 4**).

Table 4. Relationship between the Urinary Incontinence and Urinary Frequency Comfort Scale and the Self-Care Agency Scale

Scales	Urinary Incontinence and Urinary Frequency Comfort Scale		
	n	r	P
Self-Care Agency Scale	124	0.479*	0.001**

DISCUSSION

UI is one of the significant gynecological disorders that disrupt the health status of women and affect their quality of life. It was determined that, among the women who participated in the study, 36.3% experienced stress urinary incontinence (SUI), 33.1% experienced mixed urinary incontinence (MUI), and 30.6% experienced urge incontinence (UI). It was found that SUI was seen more frequently in the participants. Öztürk et al. (2012) found urge incontinence to be the most frequent type of incontinence, Terzi et al. (2013) observed MUI most frequently, followed by SUI in women, and in the study by Dinç and Özer (2019), the most frequently seen incontinence type was SUI (54.2%).[28-30] While the most frequently observed type of incontinence was MUI in some studies, it was SUI in some others. It is thought that this difference was caused by that these studies were conducted on different age groups.

In the study, 85.5% of the participants stated that they took precautions about UI. These precautions were determined as going to the toilet frequently, using protective pads, intaking less fluids and sitting near the toilet. According to the study by Demir and Kızılkaya (2015), the precautions of women related to UI included looking for a toilet that could be reached immediately at unknown places by 69.5%, frequent underwear change by 60.6%, using pads, fabrics, cotton, etc. by 57.2%, keeping the feet warm by 46.2%, going to the toilet frequently by 36%, not lifting heavy weights by 24%, taking frequent baths by 24%, and visiting only places that have toilets by 23.3%.[13] Esparza et al. (2018) determined that women and men with UI performed self-care activities like taking a bath, wearing comfortable clothes, finding the location of toilets outside the home, controlling fluid intake and using incontinence pads. The findings of this study were similar to those in the literature.[23] In this study, the mean total score of the women in the Urinary Incontinence and Urinary Frequency Comfort Scale was found as 3.35±0.59. This scale has a minimum score of 1 and a maximum score of 6.

Low scores indicate poor comfort, while high scores indicate good comfort. In this study, the comfort levels of the women who had UI were found to be moderate. Likewise, Rassin et al. also found the comfort levels of women with UI as moderate (2.95±0.04).[31] Studies have reported that UI affects the comfort, and therefore the quality of life, of women negatively.[2,15-17] Comfort is an important component of quality of life, and when the lives of individuals are more comfortable, their quality of life increases. It is considered that the physical, psychological and social effects of UI influence the comfort of the woman negatively.

In this study, the mean total score of the participants in the Self-Care Agency Scale was determined as 88.09±14.59. The lowest and highest possible scores in this scale are 35 and 140. High total scores in the scale indicate that the individual is independent and capable in performing their self-care. In this study, the self-care agency levels of the women with UI were found to be moderate. An individual with sufficient self-care agency can meet their self-care needs, take the responsibility of their own health and perform life activities without dependence on others. Although urinary incontinence is not a life-threatening problem, it negatively affects quality of life due to constantly being wet and having irritation and leads to economic, social and emotional problems.[32,33] Better self-care of women may help them seek treatment for urinary incontinence and cope more effectively with the problems they experience.

In this study, a moderate, positive and significant relationship was found between the mean scores of the Urinary Incontinence and Urinary Frequency Comfort Scale and the Self-Care Agency Scale. This result showed that, as the self-care agency of the women increased, their comfort levels also increased. Self-care involves personal fulfillment of one's own responsibilities to protect own life, health and wellbeing. Self-care agency is defined as the capacity of the individual to start and implement health activities to maintain their life, health and wellbeing. In UI, avoiding foods and drinks that irritate the bladder, regulating fluid intake, gaining toilet habits, having an ideal body weight, quitting smoking and preventing constipation are among self-care activities. If women who have UI can perform these self-care activities, their UI-related problems may decrease, and their comfort may increase. No studies investigating both the self-care and comfort of women with UI could be encountered in the literature. However, there are studies which determined that self-care training given to those with UI increased their quality of life.[34,35] Therefore, it is believed that it is needed to assess the self-care agency levels of women to be able to increase their comfort, and therefore, their quality of life.

CONCLUSION

In this study that was carried out to determine comfort levels and self-care agency in women with UI, it was determined that the participants had moderate levels of comfort and self-care agency, and as their self-care agency increased, their comfort levels also increased. In line with these results, nurses may be recommended to assess the comfort levels and self-care agency of women who have UI, provide training for women regarding information on and prevention of incontinence and offer counselling towards increasing women's comfort levels and self-care agency.

ETHICAL STATEMENTS

Ethics Board Approval: Before starting the study, the protocol was submitted to the Non-Interventional Clinical Studies Ethics Board of the School of Medicine at Çukurova University, and approval was obtained (06-11-2015/45).

Informed Consent: Written consent was obtained from the patients who participated in this study.

Reviewer Assessment Process: External double-blind reviewer assessment.

Conflict of Interest Status: The authors state that they do not have any conflict of interest regarding this study.

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Author Contribution: All authors participated in the design, implementation and analysis of the study and approve the final version of the manuscript.

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Orjinal Araştırma / Original Article

Is There a Relationship Between Ethmoid Roof Height and Anterior Ethmoidal Artery Trace in Children and Adolescents?

Çocuk ve Ergenlerde Etmoid Çatı Yüksekliği ile Ön Etmoidal Arter Trasesi Arasında Bir İlişki Var mı?

Merter Keceli

University of Health Sciences, Konya Educational and Research Hospital, Pediatric Radiology Department, Konya, Turkey

Abstract

Aim: The anterior ethmoidal artery course and the depth of olfactory fossa should be determined in paranasal sinus surgery to avoid complications. In this study, the relationship between anterior skull base height and anterior ethmoidal artery (AEA) anatomy was tried to be determined in children and adolescents.

Material and Method: The cranial magnetic resonance imaging of participants between 24 months and 18 years of age, who had no cranial pathology between 2014 and 2018, were re-examined. Of the participants, 101 (50.5%) were male. The participants were divided into age groups. All measurements were made in the section on the T2-weighted coronal plane images. The AEA's entry points into the nasal cavity were determined. The depth of olfactory fossa was determined according to the line drawn on the medial rectus muscle from the roof.

Results: The depth of olfactory fossa was type II in 97 (48.5%) of all cases. The AEA entry was on the skull base in 131 cases (65.5%) on the right and 154 cases (77%) on the left. In the 25 cases (12.5%), the AEA entry point was asymmetrical. No significant correlation was found between the depth of olfactory fossa and AEA entry (p=0.553 and 0.504).

Conclusion: No relation was found between the depth of olfactory fossa and sex or age. In adults, however, it was found to differ by sex. In MRI examination, the depth of olfactory fossa and the ethmoid roof are not a guide for AEA placement in children, which should be considered to avoid complications during operations.

Keyword: Etmoid roof, anterior etmoidal artery, surgical complications, children, imaging

Öz

Amaç: Komplikasyonları önlemek için paranazal sinüs cerrahisinde ön etmoidal arterin seyri ve etmoid çatı yüksekliği belirlenmelidir. Ön kafa tabanı yüksekliği ile ön etmoidal arter (AEA) anatomisi arasındaki ilişki çocuklarda ve ergenlerde belirlenmeye çalışıldı.

Gereç ve Yöntem: 2014-2018 yılları arasında kraniyal patolojisi olmayan 24 ay ile 18 yaş arasındaki katılımcıların kraniyal manyetik rezonans görüntülemeleri yeniden incelendi. Katılımcıların 101'i (% 50,5) erkekti. Katılımcılar yaş gruplarına ayrıldı. T2 ağırlıklı koronal düzlem görüntüleri üzerinde tüm ölçümler kesitte yapıldı. AEA'nın burun boşluğuna giriş noktaları belirlendi. Çatıdan medial rektus kasına çizilen çizgiye göre etmoid çatı yüksekliği belirlendi.

Bulgular: Tüm vakaların 97'sinde (% 48.5) Olfaktor fossa derinliği tip II idi. AEA girişi sağda 131 olguda (% 65.5) ve solda 154 olguda (% 77) kafa tabanında idi. 25 vakada (% 12.5), AEA giriş noktası asimetrikti. Ofkator fossa derinliği ve etmoid çatı ile AEA girişi arasında anlamlı bir ilişki bulunmadı (p=0.553 ve 0.504).

Sonuç: Etmoid çatı yüksekliği ile cinsiyet veya yaş arasında bir ilişki bulunamadı. Yetişkinlerde ise cinsiyete göre farklılık gösterdiği görülmüştür. MRI incelemesinde olfaktor fossa derinliği çocuklarda AEA yerleşimi için bir kılavuz değildir ve operasyonlar sırasında komplikasyonları önlemek için dikkate alınması gerekir.

Anahtar Kelimeler: Etmoid çatı, anterior etmoidal arter, çocuk, görüntüleme

Corresponding *(İletişim)*: Merter Keceli, University of Health Sciences, Konya Educational and Research Hospital, Pediatric Radiology Department. Ayanbey, Yeni Meram Cd. No:97, 42090 Meram, Konya, Turkey
E-mail *(E-posta)*: merterkeceli@gmail.com
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INTRODUCTION

Endoscopic sinus surgery (ESS) is a current and reliable approach in the treatment of sinonasal pathology. Due to their close proximity, the relationship between sinonasal structures and eye and cerebral tissue should be known, as well as the possible variations of these structures.[1,2] Thus, patient mortality and morbidity rates can be reduced. It is important to know the anatomy of the anterior skull base and anterior ethmoidal artery (AEA) in order to avoid complications related to ESS. There is a bone boundary between the ethmoid roof and the frontal cranial fossa. During interventions in ESS, the cranial cavity is associated with the nasal cavity if this roof is damaged. Skull base injury can then result in cerebrospinal fluid leakage, pneumocephalus, meningitis, or direct cerebral injury. The classification used in practice and adapted by Keros is aimed at reducing the risk of iatrogenic injury due to ethmoidectomy by determining the anterior skull base height.[3] Yenigun et al.[2] demonstrated that with the increase of the superior–inferior depth and anterior–posterior length and the presence of supraorbital pneumatization, the AEA is significantly more likely to be running freely inside the ethmoidal sinus, thus being more prone to being injured during surgery. With a new anatomical approach, they showed that the length of the cribriform plate is as clinically relevant as the depth, and three-dimensional evaluation is also mandatory. They also reported that knowing the course of the AEA and its relationship with other anatomical structures will reduce the risk of complications. The AEA is an important structure within the ethmoid cavity and its injury can result in significant blood loss and/or orbital hematoma with resultant loss of vision.[4]

Although several studies have been reported on the anatomical relationships between the AEA and olfactory fossa depth and ethmoid roof, the results of these studies were mostly obtained from adult patient groups. We concluded that there are not enough studies investigating the existence of a similar relationship in children. The aim of this study was therefore to determine the relationship between the height of the skull base and the location of the AEA in children and to test its usability in order to avoid surgical complications.

MATERIAL AND METHOD

A retrospective radiologic study was performed by re-evaluating the cross-sectional images of pediatric participants without otorhinolaryngologic problems between 2014 and 2018. Images of the participants were taken from the Picture Archiving and Communication System of the hospital. Institutional review board approval from the was obtained prior to data collection of Manisa Celal Bayar University School of Medicine Medical Sciences Ethics Committee (decision dated 02/02/2018 and numbered 20.478.486). All patients sign a document that allows their medical records to be used for scientific studies, provided that their personal information is stored at the time of admission to the hospital. Therefore, the personal consent of the participants was not required.

In the study of Anderhuber et al.[5] It was found that the children under 24 months had low ethmoid roof. In accordance with this conclusion, our study was performed on imaging of children over 24 months of age. Those with primary sinonasal and skull base pathology, history of malignancy, trauma/surgery, or facial anomalies were excluded. Since there was not a sufficient number of paranasal sinus computed tomography (CT) and magnetic resonance imaging (MRI) results between 2014 and 2018, the bilateral brain MRI scans with detectable AEAs of 200 cases were used.

The participants were divided into age categories of 24–72 months, 73–120 months, 121–168 months, and 169–216 months. The sex distribution was equalized in each determined age group.

The images of the participants had been obtained using a 1.5-T MRI system (Siemens Magnetom Era 1.5 T, Siemens Medical Solutions, USA). The parameters of coronal T2-weighted TSE were repetition time (TR) of 3.7 s, echo time (TE) of 80 ms, field of view (FOV) of 200 mm, slice thickness of 3–5 mm, and gap of 1 mm. MRI images of 25–40 coronal sections were obtained according to the slice thickness per case. All scans were examined in T2-weighted coronal plane images by a single pediatric radiologist to assess skull base height and AEA position. Measurements were made at the level of the olfactory sulcus (**Figure 1**). There is no widely used classification system to determine the olfactory fossa depth or the height of the ethmoid roof in growing children. Therefore, the Keros classification system was modified to determine the the depth of olfactory fossa in children. If level of ethmoid roof did not go down to the upper 1/3 of the medial rectus muscle, it was considered as type I (**Figure 2a**); if it went down to the upper third of the muscle, as type II (**Figure 2b**); and if it extended to half of the muscle, as type III (**Figure 2c**).

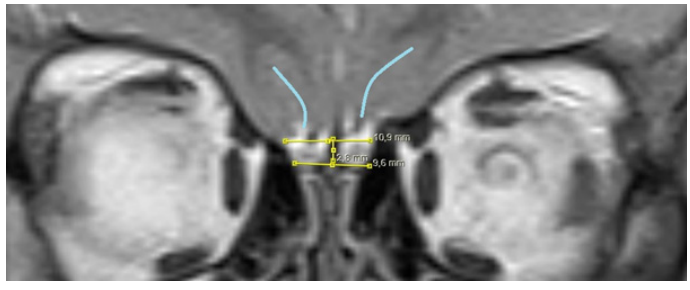

Figure 1. Coronal T2-weighted MR images show ethmoid roof height measurement was made from sections where the olfactory sulcus (blue lines) can be selected.

The AEA's entry point into the nasal cavity was divided into two categories according to locations below and within the front head base (ethmoid roof) (**Figure 3a and 3b**). The asymmetry of the arterial entry points on the right and the left was remarkable. The arterial entry point was recorded accordingly.

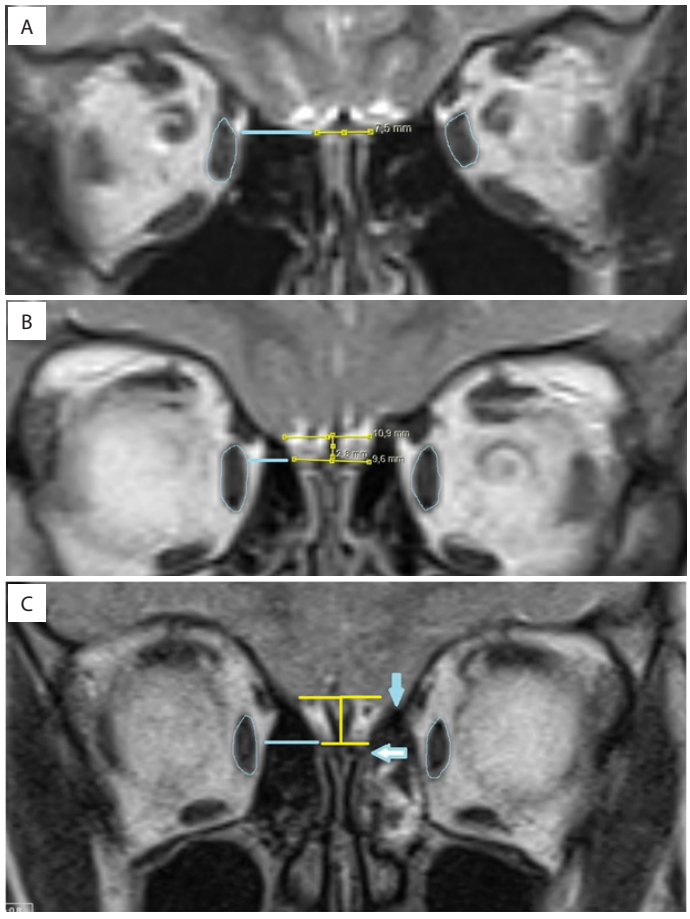

Figure 2. Coronal T2-weighted MR images show that: Type I Ethmoid roof **(a):** the line drawn from the upper contour of the ethmoid roof (yellow line) does not exceed the upper 1/3 section of the medial rectus muscle blue circles). Type II Ethmoid roof **(b):** the line drawn from the upper contour of the ethmoid roof (yellow line at the bottom) is at the border of the upper 1/3 of the medial rectus muscle (blue circles). The upper yellow line runs perpendicular to the upper contour of the cribriform plate. Type III Ethmoid roof **(c):** the line drawn from the ethmoid roof (blue line, open arrow) passes through 1/2 of the medial rectus muscle (blue circles). The closed arrow on the left shows the entry point of the anterior ethmoid artery to the nasal cavity.

The relationships between the depth of olfactory fossa, height of the ethmoid roof and the entry point of the AEA into the nasal cavity and sex and age groups were examined.

All radiographic measurements were performed using the institution's PACS system (Extreme PACS, Ankara, Turkey).

Descriptive statistics of the categorical data in the study were shown by using frequency and percentage values, and numerical data were shown using mean and standard deviation. Kruskal–Wallis non-parametric analysis of variance was used for the comparison of more than two groups and the chi-square test was used for categorical data comparisons. All statistical analyses performed in the study were performed in a two-way, 5% significance limit and 95% confidence interval. SPSS 24 for Windows (IBM Corp, USA) was used for data analysis.

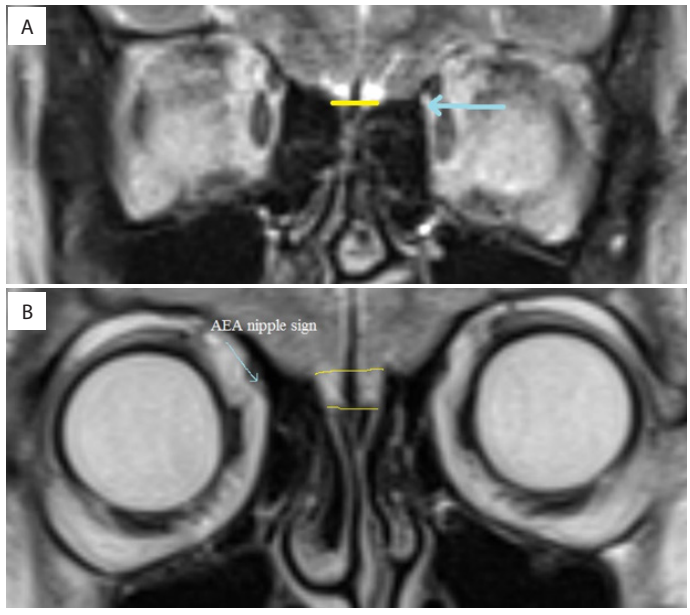

Figure 3. Coronal T2-weighted MR images show that: **(a)** The entry point of the anterior ethmoidal artery to the nasal cavity (blue line) is at the level of the ethmoid roof (yellow line). **(b)** The nipple sign showing the entrance point of the anterior ethmoidal artery to the nasal cavity is seen. The entry point is at the top of the ethmoid roof into the nasal cavity.

RESULTS

Two hundred cranial MRIs were included in the study. One hundred and one (50.5%) of the participants were male and 99 (49.5) were female. There were 64 participants aged 24–72 months, 51 participants aged 73–120 months, 38 participants aged 121–168 months, and 47 participants older than 169 months. Gender distribution in age groups is shown in **Table 1.** The mean age was 73 ± 22 months irrespective of sex. Regardless of gender, a type I ethmoid fossa depth was found in 92 participants (46%), type II in 97 participants (48.8%), and type III in 11 participants (5.5%) (**Table 2** and **Figure 4**). The distribution of the ethmoid roof height according to the age of the participants is shown in **Table 2** and **Figure 5.** There was no statistically significant correlation between age group and the ethmoid roof height (p=0.894). No statistically significant correlation was found between the ethmoid roof and gender (p=0.616). Gender distribution for the ethmoid roof types is shown in **Table 3** and **Figure 6.** In 131 cases (65.5%), the right AEA nasal cavity entry was above the skull base; in 69 cases (34.5%), it was at the skull base level. In 154 cases (77%), the left AEA nasal cavity entry was above the skull base; in 46 cases (23%) it was at the skull base level (**Table. 4**). There was no statistically significant relationship between the AEA entry points into the nasal cavity and the ethmoid roof height types on both sides (p-value for both sides 0.504–0.553). The relationship between the course of the AEA and the ethmoid roof height shown in **Table 5** and **Figure 7.**

Table 1. Gender distribution in age groups.

			Gender		Total
			Female	Male	
Age (months)	24-72 months	N	25	39	64
		%	39,1%	60,9%	100,0%
	73-120 months	N	23	28	51
		%	45,1%	54,9%	100,0%
	121-168 months	N	20	18	38
		%	52,6%	47,4%	100,0%
	169-216 months	N	33	14	47
		%	70,2%	29,8%	100,0%
Total		N	101	99	200
		%	50,5%	49,5%	100,0%
					Chi-Square =11,320 *p=,010

* Significance level according to the chi-square test result.

Table 2. Distribution of ethmoid roof types by age groups regardless of gender.

			Type			Total
			I	II	III	
Age (months)	24-72 months	N	28	34	2	64
		%	43,8%	53,1%	3,1%	100,0%
	73-120 months	N	24	24	3	51
		%	47,1%	47,1%	5,9%	100,0%
	121-168 months	N	16	19	3	38
		%	42,1%	50,0%	7,9%	100,0%
	169-216 months	N	24	20	3	47
		%	51,1%	42,6%	6,4%	100,0%
Total		N	92	97	11	200
		%	46,0%	48,5%	5,5%	100,0%
						Chi-Square =2,267 *p=,894

* Significance level according to the chi-square test result.

Table 3. The distribution of ethmoidal roof height types by gender.

			Type			Total
			I	II	III	
Gender	Female	N	43	52	6	101
		%	42,6%	51,5%	5,9%	100,0%
	Male	N	49	45	5	99
		%	49,5%	45,5%	5,1%	100,0%
Total		N	92	97	11	200
		%	46,0%	48,5%	5,5%	100,0%
						Chi-Square =,967 *p=,616

* Significance level according to the chi-square test result.

Table 4. The distribution of the ethmoid roof height and anterior ethmoidal artery (AEA) entry points grouping among participants. (1: The AEA enters the nasal cavity above the skull level, 2: The AEA enters the nasal cavity at the level of the skull base, Asym: The AEA entry to the nasal cavity on the right and left is asymmetrical).

			AEA			Total
			1	2	Asym	
Type	I	N	62	20	10	92
		%	67,4%	21,7%	10,9%	100,0%
	II	N	60	24	13	97
		%	61,9%	24,7%	13,4%	100,0%
	III	N	8	1	2	11
		%	72,7%	9,1%	18,2%	100,0%
Total		N	130	45	25	200
		%	65,0%	22,5%	12,5%	100,0%
						Chi-Square =1,992 *p=,737

* Significance level according to the chi-square test result.

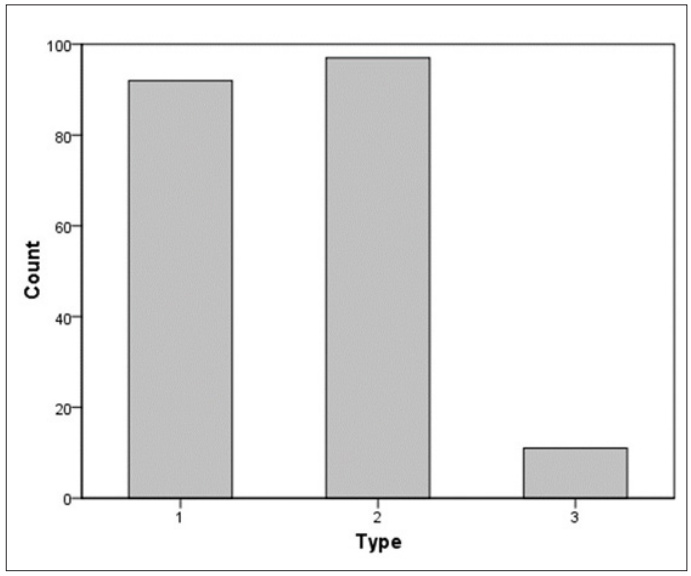

Figure 4. When gender was ignored, the most common type II ethmoid roof was found

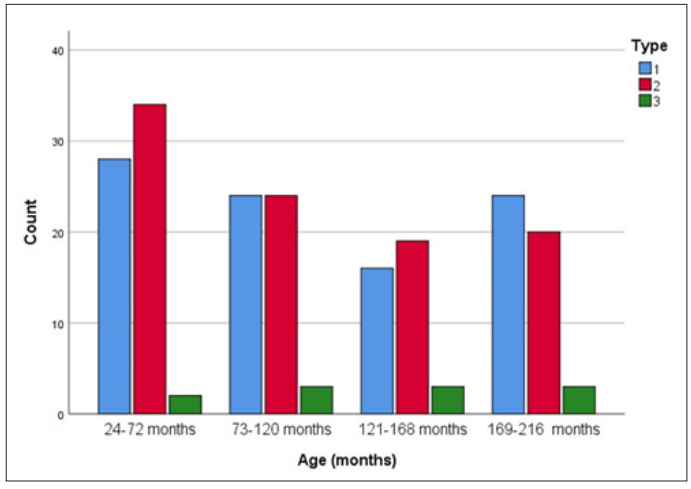

Figure 5. The distribution of ethmoid roof types in age groups

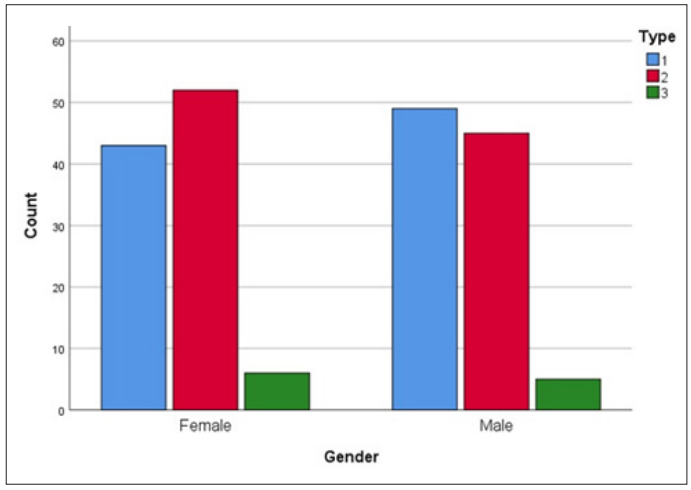

Figure 6. A graphic showing the gender distribution is seen in the ethmoid roof height types

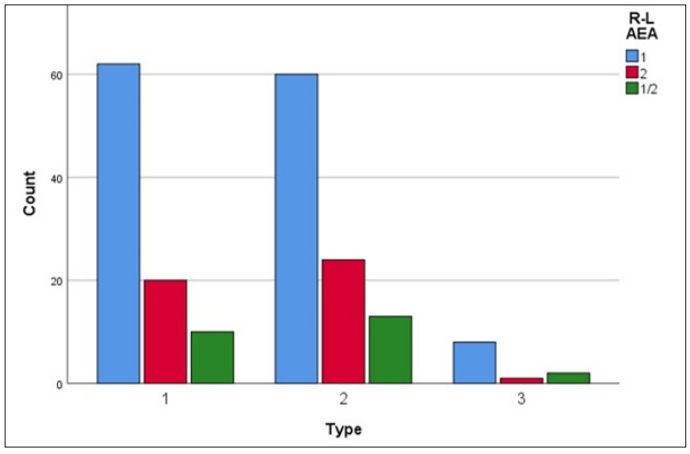

Figure 7. In the graph showing the relationship between the ethmoidal roof classification (Type) and AEA nasal cavity entry points:
It is seen that in all ethmoid roof types, AEA is located on the base of the skull. This is followed by the nasal cavity entry of the AEA from the base of the skull and its asymmetric entrance, respectively.
(Type: Ethmoidal roof height clasification, AEA: Anterior Ethmoidal Artery,
blue: The AEA enters the nasal cavity above the skull level.
red: The AEA enters the nasal cavity at the level of the skull base
green: The entry of the AEA to the nasal cavity on the right or left is asymmetrical)

Asymmetry was observed in the course of the AEA in 25 (12.5%) of 200 cases (**Table. 5**). Fifteen of these subjects were boys and 12 were girls. The age range was 28–192 months (average: 123 months). When sex was ignored, the ethmoid roof height in these cases was type I in 10 cases, type II in 13 cases, and type III in 2 cases. In cases of asymmetry, 18 right AEAs and 7 left AEAs entered the nasal cavity at the skull base level. There was no statistically significant relationship between asymmetrical AEA entry point into the nasal cavity and the ethmoid roof height (p=0.737) (**Figure 8**).

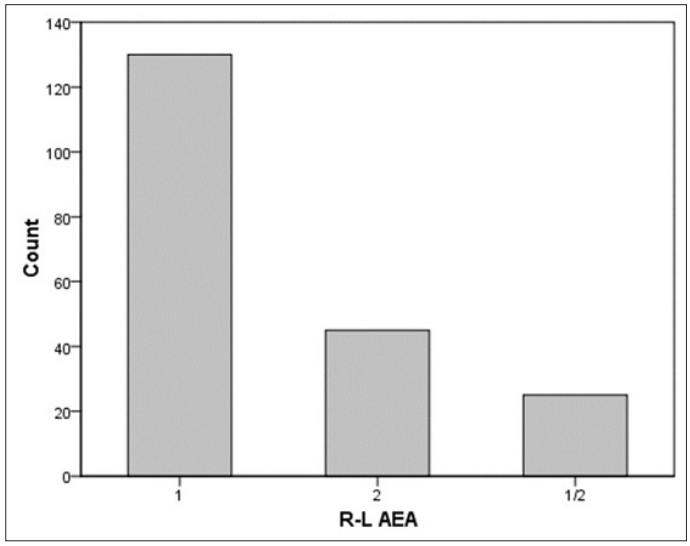

Figure 8. As seen in the graph, the point of entry of the anterior ethmoidal artery (AEA) into the nasal cavity is most often above the level of the skull base

Table 5. There was no statistically significant relationship between the ethmoidal roof types and the anterior ethmoidal artery (AEA) entry points. (1: The AEA enters the nasal cavity above the skull level, 2: The AEA enters the nasal cavity at the level of the skull base, Asym: The AEA entry to the nasal cavity on the right and left is asymmetrical).

		N	%
Type	I	92	46,0%
	II	97	48,5%
	III	11	5,5%
R AEA	1	131	65,5%
	2	69	34,5%
L AEA	1	154	77,0%
	2	46	23,0%
AEA	1	130	65,0%
	2	45	22,5%
	Asymm	25	12,5%

DISCUSSION

The Keros Classification, which classifies the depth of olfactory fossa, is used in adult populations.[3] This classification system has become widely adopted and is universally used by surgeons to identify patients with skull base configurations at risk of injury during sinonasal surgery. This system is not suitable for children under 24 months because the ethmoid roof is located more lowly.[5] Many cadaveric and CT imaging studies have shown various landmarks in both adults and children.[6-8] In addition, there are studies investigating the importance of AEA localization as a guide for preventing complications in sinonasal surgery and its relationship with the Keros classification.[9,10] These studies were performed on images of participants from adult groups or without age grouping. In this study, we aimed to investigate the relationship between the,ethmoid roof height and the AEA in the pediatric age group by evaluating participants between the ages of 2 years and 15 years.

According to the modified classification that we applied, the ethmoid roof height was most commonly type II regardless of age. Type III ethmoid roof heightis the least common. This finding is similar to results of applying the Keros classification in adult studies.[9-11] When the age group was not taken into consideration, it was observed that the ethmoid roof height was type I in males and type II in females in both children and adolescents. However, this difference was not statistically significant.

While there are known age-related variations in skull base height and structure, little has been reported on sex differences in skull base anatomy.[12] In Poteet et al.[13]'s study, men had Keros type II or III significantly more often than women. This confirms the results found in another CT-based study that males more commonly had Keros type II, whereas females more commonly had Keros type I. There are also studies showing that the depth of olfactory fossa varies according to sex in adults.[11,14] According to our data, there was no correlation between type of the ethmoid roof height and sex in children and adolescents.

In our study, it was observed that the entrance of the AEA into the nasal cavity was not associated with the he ethmoid roof height in children, regardless of age and sex. Başak et al.[10] reported that the course of the AEA is more variant in children than in adults. It has been stated that the reason for this may be the ethmoid cells pushing on the AEA during growth. On the other hand, Poteet et al. showed that patients with variant AEA tracings below the skull base were predominantly males and had type III depth of olfactory fossa according to the Keros classification. They reported that the depth of olfactory fossa, the ethmoid roof may be decisive to show variation in the AEA's path.[9] In our study, it was observed that there was no connection between the course of the AEA and the points of entry into the nasal cavity and the ethmoid roof height among the participants. In addition, in all three types of the ethmoid roof, both AEA nasal cavity entry points were predominantly at the level of the skull base. Unlike studies in adults, there was no guiding link between these landmark points in children and adolescents.

There are two major limitations of our study. First, there was no asymmetric the depth of olfactory fossa and the ethmoid roofs among the participants. However, Anderhuber et al.[5] reported 15% asymmetry in their participants with similar age and sex distributions. This difference may be due to the fact that in our retrospective study, asymmetric cases were not selected unconsciously when looking for patients with optimal MRI sections for accurate measurements.

In a cadaver study, it was found that the AEA is always adjacent to the basal lamella, but it was not indicated if variations in the basal lamella structure correlated with AEA location. The finding that pneumatization of supraorbital ethmoid cells (SOECs) is consistently a reliable indicator of AEA location is of special interest as SOECs are usually the closest adjacent structures to the AEA in its common course within the skull base.[15] These findings suggest that pneumatization patterns during embryological development influence the AEA's position. In our study, however, we did not include SOEC pneumatization among the examined parameters. The association between SOEC pneumatization and ethmoid roof height could be investigated. In a study in which Yenigun et al. determined a new ethmoid roof classification, the free course of the AEA in ethmoid cells was reported to be surgically dangerous. This rate was 25% in adults. Therefore, it is stated that the course of the AEA is important in preoperative imaging.[2] A similar rate was found in Başak et al.'s study of children.[10] In our series, free AEA could not be differentiated between ethmoid cells. This may be due to an inability to select the AEA in the vicinity of the vented ethmoid cells on MRI. This second limitation, which is thought to have been caused by the selected imaging method, can be overcome by extensive CT scans.

CONCLUSION

During MRI examination of the anterior skull base in children and adolescents, the depth of olfactory fossa and the ethmoid roof are not a guide for the placement of the AEA, which should be considered to avoid complications during the operation. There was no correlation between the height of the ethmoid roof and the entrance point of the AEA into the nasal cavity in growing children. These findings do not match the results obtained in adults. Therefore, we conclude that these findings cannot be used as a surgical guide to prevent complications in children.

ETHICAL DECLARATIONS

Ethics Committee Approval: Institutional review board approval from the was obtained prior to data collection of Manisa Celal Bayar University School of Medicine Medical Sciences Ethics Committee (decision dated 02/02/2018 and numbered 20.478.486).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: Concept, design, data collection and processing, analysis and interpretation, literature review, article writing, critical review, and statistical study were done by Merter Keçeli.

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Orjinal Araştırma / Original Article

The Evaluation of Nosocomial Infections Developing in Intensive Care Units of a Tertiary University Hospital

Üçüncü Basamak Bir Hastanade Yoğun Bakım Ünitelerinde Gelişen Hastane Enfeksiyonlarının Değerlendirilmesi

Arzu Tarakçı[1], Esma Eroğlu[1]

[1]Konya Eğitim ve Araştırma hastanesi, Konya, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji, Konya, Türkiye

Abstract

Objective: Nosocomial infections (NIs) in intensive care units (ICUs) are serious problems because of high mortality and morbidity. Here, it was aimed to evaluate diagnoses, distribution and pathogens of NIs in two tertiary general ICUs (GICU) of a hospital and develop new infection control strategies based on the data.

Material and Method: NIsfollowed in the infectious diseases department and recorded by active prospective surveillance between January 218-December 2019 in GICUs were retrospectively analyzed.

Results: Ninety-five NI episodes were identified in 90 patients during 8468 hospitalization days of 1189 patients in a two-year period. While NI rate in GICUswas 7.98, incidence of NI density was determined as 11.21. Considering the distribution of NIs, lower respiratory tract infections (LRTI) (36.8%) were detected as highest and followed as specific laboratory findingsby pneumonia (33.6%), ventilator-associated pneumonia (VAP) (10.5%), central venous catheter-related bloodstream infections (CVCR-BSI) (9.4%), laboratory-proven BSI (6.3%) and catheter-associated urinary tract infections (CR-URI) (3.1%). Given the distribution of the factors concerning system infections, agents leading to LRTI other than pneumonia were as follows: *Acinetobacter spp.* (48.7%), *Klebsiella pneumoniae* (25.6%), *Pseudomonas aeruginosa* (12.8%), *Serratia marcescens* (5.1%), *Escherichia coli* (2.5%), *Enterobacter cloacae* (2.5%) and *Candida albicans* (2.5%), and11.4% were polymicrobial.

Conclusion: NIs are inevitable entities in hospitals, especially in ICUs, andone of the vital goals of hospitals is to control and manage such a situation. Timely and appropriate therapeutici nterventions should be designed to reduce NI rates. If needed, catheters should be inserted with correct indication, andcatheter application should be reduced. It is importan tthat hospitals develop comprehensive antibiotherapy programs based on their own surveillance data.

Keywords: Intensive care unit, nosocomial infections, surveillance

Öz

Amaç: Yoğun bakım ünitelerinde (YBÜ) gelişen hastane enfeksiyonları (HE) yüksek mortalite ve morbidite sebebi olduğundan ciddi bir sorundur. Bu çalışmada üçüncü basamak genel yoğun bakım ünitesinde gelişen hastane kökenli enfeksiyonların tanıları, sistemlere göre dağılımları ve etken patojenleri değerlendirildi ve bu verilere dayalı olarak yeni enfeksiyon kontrol stratejileri geliştirilmesi amaçlandı.

Gereç ve Yöntem: Enfeksiyon Hastalıkları Kliniğince izlenen genel YBÜ'lerinde 01.01.2018-31.12.2019 tarihleri arasında aktif prospektif sürveyans ile kayıt altına alınan hastane kökenli enfeksiyonlar retrospektif olarak incelendi.

Bulgular: Genel YBÜ'lerde iki yıllık süreçte 1189 hastanın 8468 yatış günü takibinde 90 hastada 95 HE epizodu tanımlandı. Genel YBÜ'de Hastane enfeksiyon hızı 7,98; hastane enfeksiyon insidans dansitesi 11,21 olarak tespit edildi. HE dağılımına bakıldığında, hastalarda en sık pnömoni dışı gelişen alt solunum yolu enfeksiyonu (%36,8) tespit edilirken bunu sırası ile spesifik laboratuar bulguları olan pnömoni (%33,6), ventilatör ilişkili pnömoni (VİP) (%10,5), santral venöz kateter ilişkili kan dolaşımı enfeksiyonu (SVKİ-KDE) (%9,4), laboratuar tarafından kanıtlanmış KDE (LTD-KDE) (%6,3) ve kateter ilişkili üriner sistem enfeksiyonu (Kİ-ÜSE) (%3,1) izlemekteydi. Etkenlerin sistem enfeksiyonlarına göre dağılımına bakıldığında sırasıyla pnömoni dışı gelişen alt solunum yolu enfeksiyonun'da *Acinetobacter spp.* (%48,7), *Klebsiella pneumoniae* (%25,6), *Psödomonas aeruginosa* (%12,8), *Serratia marcescens* (%5,1), *Escherichia coli* (%2,5), *Enterobacter cloacae* (%2,5), *Candida albicans* (%2,5) yer almaktaydı, %11,4'ü polimikrobiyaldi.

Sonuç: Hastanelerde özellikle YBÜ'lerde hastane enfeksiyonlarının görülmesi kaçınılmazdır ve hastanelerin hayati önem taşıyan sağlık hedeflerinden biri de bu durumu kontrol etmek ve yönetmektir. Hastane enfeksiyonu oranlarını azaltmak için zamanında ve uygun terapötik girişimlerde bulunulmalıdır. İhtiyaç halinde doğru endikasyonla kateterler takılmalı ve kateter uygulaması azaltılmalıdır. Hastanelerin kendi sürveyans verilerine dayalı akılcı antibiyoterapi uygulama programları geliştirmeleri önemli bir noktadır.

Anahtar Kelimeler: Yoğun bakım ünitesi, hastane enfeksiyonu, sürveyans

Corresponding *(İletişim)*: Arzu Tarakçı, Konya Eğitim ve Araştırma hastanesi, Konya, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji, Konya, Türkiye
E-mail *(E-posta)*: aaaribas1972@hotmail.com
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INTRODUCTION

Although leading to preventable morbidity and mortality in intensive care units (ICUs), nosocomial infections (NIs) are the main reason for the long hospitalization periods. Therefore, despite all strategies developed to control infections, the patients in ICUs are more likely to acquire a NI thant he general hospital population. Timely recognition and management of such infections is a requirement of optimal care in ICUs (1).

The control programs of NIs carried out in order to prevent the formation of these infections and performed to provide the diagnosis and treatment in a short time when NIs develop are among the important health services (2). The factors leading to the development of NIs in ICUs mayvary, or exhibit different characteristics from a hospitalto another, even between the different ICUs of the same hospital. Therefore, it is required to carry out regular surveillance in each department (3). The algorithms to determine the type of ICUs, rates of invasive vehicle-related, invasive device-patient-day-related infections and rates of device uses are the best methods for comparing in-hospital and inter-hospita linfection rates (4). The scope of surveillance has been expanded with the acceptance of NIs as novel quality indicators in hospital settings. All of the undesirable situations that develop and are likely to prevent during the healthcare process are included into the surveillance studies (5). In the present study, the diagnoses, distribution rates and causative pathogens of NIs developed in thegeneral ICUs (GICUs) of a tertiary health facility were evaluated, and in light of these data, it was aimed to develop novel infection control strategies.

MATERIAL AND METHOD

Followed by the infectious diseases department in two GICUs of our tertiary hospital, one with seven and the other with eight beds, 1189 patients were hospitalized and followed-up with the active prospective surveillance method on a total of 8468 hospitalization days between January 2018 and December 2019. The study was approved by the University of Medical Sciences Konya Training and Research Hospital of Specialty in Medical Training (TUEK), dated on 5th March 2020 and with the registration number of 36-31.

The patients over 18 years of age were included into the study, and such samples as throat, blood, catheter, urine, tracheal aspirate and bronchoalveolar lavage cultures appropriate for the physical examination findings were accumulated from the cases. The blood and sterile samples obtained were incubated in the fully-automated blood culture device of BACTEC 9240 (Becton Dickinson, Diagnostic Instrument System, Spark, USA). The specimens likely to reproduce were inoculated from the tubes onto the media of eosinmethylene-blue (EMB) agar and 5% sheep blood agar. All petriplates were incubated at 35±2°C for 24 hours in aerospace environment. The colonies of isolated bacteria not fermenting lactose and having negative oxidase test results were identified using the VITEK 2 Compact® (BioMérieux, France) device, and the antibiotic susceptibilitiesof these bacteria were investigated under the criteria of The Informational Supplements to the Clinical and Laboratory Standards Institute (CLSI). Antimicrobial Susceptibility Guidelines (CLSI-2010 and CLSI-June 2010 -update) (6). NIs were defined according to the diagnostic criteria of Centers for Disease Control and Prevention (CDC) (7). A total of 95 NIs were diagnosed over a two-year period. While the ventilator-associated pneumonia (VAP) rate was defined as the number of VAPs per 1.000 ventilator days, the rates of central venous catheter-related bloodstream infections (CVCR-BSI), catheter-related upper respiratory infection (CR-URI) and the rate of usingi nvasivedevice were calculated with the following formulae:

Rate of CVCR-BSI =Number of CVCR-BSIs /number of centralvenouscatheterdays in ICU x 1000

Ratetae of CR-URI =Number of CR-URI / number of urinary catheter days x 1000

Rate of invasivedevice utilization=Number of device utilization days/number of disease days

Statistical analysis

In the statistical analyses of the data,the study findin gs were descriptively evaluated with the Statistical Package for the Social Sciences for Windows, software version 20.0, (SPSS Inc., Chicago, IL,USA).

RESULTS

In GICUs, 95 NI episodes were identified in 90 patients during 8468 hospitalization days of 1189 patient sover a 2-year period. Of 90 patients included into the study, 57 were male (63.3%), and 33 were female (36.6%). The age range of the patients was 18-99years, and the mean age found as 64±23. The mean age of female patients was 68±27, while that of male patients was calculated as 62±23. However, the rates and incidence density of NIs were determined as 7.98 and 11.21, respectively. The diagnoses of the patients with NIs on admission and accompanying comorbid diseases are presented in **Table 1**.

Among other diagnostic criteria, the patients were also diagnosed with burn injuries, mesenteric ischemia, acute cholecystitis, acute pancreatitis, pulmonary edema and gastrointestinal (GIS) hemorrhages. When the comorbid diseases accompanying the patients' clinical picture were examined except for acute diagnoses, while 19 (21.1%) patients had more than two comorbidities, one and two comorbidities were seen to accompany the acute picture in 29 (32.6%) and 27 (30%) patients, respectively. No comorbid diseases were encountered in 15 (16.6%) of the patients. Accompanying diseases, under the heading of others, included Parkinson, human immunodeficiency virus (HIV) infection, amyotrophic lateral sclerosis, multiple sclerosis and interstitial lung disease.

The number of the days fo rinvasive device utilization and infection rates followed-up in ICUs fort wo years are shown in **Table 2**.

Table 1. Diagnoses of patients with nosocomial infections on admission and accompanying diseases

Diagnoses (n=95)	n (%)
Community-acquired pneumonia	19 (21.1%)
CVD	12 (13.3%)
Sepsis	9 (10.0%)
Acute renal failure	8 (8.8%)
Poor prostration due to malignancy	7 (7.7%)
COAH	7 (7.7%)
Subarachnoid hemorrhage	5 (5.5%)
Respiratory failure	4 (4.4%)
Acute coronary syndrome	4 (4.4%)
Heart failure	4 (4.4%)
Trauma	3 (3.3%)
Pulmonary embolism	2 (2.2%)
Others	11 (11.5%)
Accompanying diseases (n=165)	
Hypertension	32 (33.6%)
CVD	28 (29.4%)
COAH	25 (26.3%)
DM	22 (23.1%)
Malignancies	16 (16.8%)
Heart failure	9 (10.0%)
CAD	8 (8.8%)
CRF	7 (7.7%)
Alzheimer's	6 (6.6%)
Atrial fibrillation	4 (4.4%)
Others	8 (8.8%)

CAD: Coronary artery disease, COAH: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, CVD: Cerebrovascular disease, DM: Diabetes mellitus

Table 2. Number of days and rates of invasive device utilization

	Number of days	Rate of device utilization		Number of infections	Rate of infections
CVC	4407	0.52	CVCR-BSI	9	2.04
UC	8057	0.95	CR-URI	3	0.37
MV	4304	0.5	VAP	10	2.32

CR-URI: Catheter-related upper respiratory infection, CVC: Central venous catheter, CVCR-BSI: Central venous catheter-related bloodstream infections, MV: Mechanical ventilator, UC: Urinary catheter, *VAP*: Ventilator-associated pneumonia

The rate of NI development in GICUs was calculated as 7.98%. When the distribution of NIs was investigated, the rate of lower respiratory tract infections other than pneumonia (LRTIOP) was detected as 36.8%, and this rate was followed by pneumonia having specific laboratory findings (33.6%), ventilator-associated pneumonia (VAP) (10.5%), central venous catheter-related bloodstream infections (CVCR-BSI) (9.4%), laboratory-proven BSI (6.3%) and catheter-related upper respiratory tract infections (CR-URI) (3.1%), respectively. Considering the distribution of all NI pathogens, Gram-negative, Gram-positive pathogens and yeast were seen at the rates of 93.1%, 4.9% and 1.9%, respectively. When Gram-negative pathogens were examined, *Acinetobacter spp.* Was detected to rank first as 57.8%. However, *Acinetobacter spp.* was respectively followed by *Klebsiella pneumoniae* (23.1%), *Pseudomons aeruginosa* (8.4%), *Escherichia coli* (3.1%), *Serratia marcescens* (2.1%), *Enterobacter cloacae* (2.1%), *Stenotrophomonas maltophila* (1.0%), *Morganella morganii* (1.0%) and *Sphingomonas paucimobilis* (1.0 %), respectively. When Gram-positive pathogens were examined, coagulase negative Staphylococcus (CNS) was observed to rank first (60%) and followed by *Staphylococcus aureus* (20%) and *Enterococcus faecium* (20%), respectively (**Table 3**).

Table 3. Agents and distributions of nosocomial infections

Diagnoses of NIs	AgentsleadingtoNIs	n (%)
LRTIOP	*Acinetobacter spp.*	19 (48.7%)
	K. pneumoniae	10 (25.6%)
	P. aeruginosa	5 (12.8%)
	S. marcescens	2 (5.1%)
	E. coli	1 (2.5%)
	E. cloacae	1 (2.5%)
	C. albicans	1 (2.5%)
Pneumonia with specific laboratory findings	*Acinetobacter spp.*	24 (72.7%)
	K. pneumoniae	4 (12.1%)
	E. coli	2 (6.0%)
	P. aeruginosa	2 (6.0%)
	S. aureus	1 (3.1%)
	polymicrobial	1 (3.1%)
VAP	*Acinetobacter spp.*	9 (75.0%)
	K. pneumoniae	2 (16.6%)
	P. aeruginosa	1 (8.8%)
CVCR-BSI	*K. pneumoniae*	5 (55.5%)
	Acinetobacter spp.	1 (11.1%)
	CNS	1 (11.1%)
	Stenotrophomonas maltophilia	1 (11.1%)
	C. glabrata	1 (11.1%)
Laboratory-proven BSI	CNS	2 (33.3%)
	Acinetobacter lwoffii	2 (33.3%)
	Enterobacter cloacae	1 (16.6%)
	Sphingomona spaucimobilis	1 (16.6%)
CR-URI	*K. pneumoniae*	1 (33.3%)
	Morganella morganii	1 (33.3%)
	Enterococcus faecalis	1 (33.3%)

BSI: Blood streaminfection, CNS: Coagulase negative staphylococcus, CR-URI: Catheter-related upper respiratory tract infection, CVCR-BSI: Central venous catheter-related bloodstream infections, LRTIOP: Lower respiratory tract infections other than pneumonia, *VAP*: Ventilator-associated pneumonia

DISCUSSION

Nowadays, the advances achieved in medical technologies in ICUs have enabled many patientst a live longer thanks to advanced equipments, also causing prolongation in hospital stays. Comorbid diseases, metabolic problems of the patients followed-up in ICUs, coming antibiotics into massuse, invasive interventions for diagnosis and treatment are the factors increasing the risks of NI developmentcaused by resistant pathogens in ICUs (8). In our study, the rate and the infection incidence density of NIs were determined as 7.98% and 11.21%, respectively. In two studies where NIs wereevaluated in other countries, the rates of NI development were found to be 13% and 4.5% (9,10). However, in the studies evaluating NIs in ICUs in our country, while the rate and the infection incidence density of NIs werefoundto be 11.1% and 23.6% respectively in a study (11), another study detected the rate

of NIs as 15% (12). Weconsider that different factors may have caused these different findings to be reported in various studies. These factors may have arisen from differences in the periods these studies were conducted, and the deficiencies in the surveillance practices of nosocomial care. In addition, the fact that NIs were examined in different units may also be a reason leading to these factors.

In a study where invasive device-associated nosocomia linfections (IDANIs) were examined, while the rates of mechanical ventilator utilization and VAP were found to be 0.46 and 1.34 respectively, ther ates of CVC use, CVCR-BSI, use of urinary catheter and CR-URI were detected as 0.72, 8.6, 0.99 and 3.45, respectively (13). In our study, however, while the rates of mechanical ventilator utilization and VAP were found as 0.5 and 2.32, the rates of CVC use, CVCR-BSI, use of urinary catheter and CR-URI were detected as 0.52, 2.04, 0.95 and 0.37, respectively. In hospitals, ICUs are the settings where especially critical patients are followed-up, andi nvasive interventions are used quite highly; therefore, the rates of infections in ICUs also increase (13). According to the National Nosocomial Infections Surveillance Network (UHESA) (NNISN) 2019 report, in the anesthesia and reanimation units in hospitals depending on the Ministry of Health around Turkey, the rates of mechanical ventilator utilization and VAP were found as 0.6 and 5.3 respectively, and VAP were reported to rank first as an IDANI(14). In our study, however, while the mechanical ventilator utilization rate was similar to that stated in the NNISN 2019 report, the VAP rate was lower. Because the levels of ICUs in all hospitals may be different around Turkey, the patients' profile and bedcapacity may also be different. When compared with the average rate of Turkey, the reason why our VAP rate was lower may have arisen from the different conditions in ICUs or hospitals. According to the NNISN) 2019 report, in the anesthesia andreanimation units in hospitalsdepending on theMinistry of Health aroundTurkey, the rate of CVC utilization was 0.54; the rate of CVCR-BSI was 4 and ranked the second frequently encountered IDANI. On the other hand, the rate of urinary catheter utilization was 0.97, and the rate of CR-URI was 1.5 and ranked as the third most frequent IDANI (14). When we compared our findings with those stated in the NNISN report 2019, IDANIs ranking second and third were seen to be CVCR-BSI and CR-URI, and our findings are consistent with those other studies found in Turkey. In our study, while the rates of CVC and urinary cathete rutilization were similar,the rates of CVCR-BSI and CR-URI were lower. Inlight of these data, it can be asserted that the inspections are carried out properly in ICUs in our hospital, and the precautions to be taken, especially in inserting catheters, are performed meticulously.

In different studies, pneumonia has been identified as one of the most widespread NIs (15,16). The National Nosocomial Infections System (NNIS) in the USA defines nosocomial pneumonia as one of the most common infections encountered in ICUs. The widespread utilization of mechanical ventilation and tracheal intubation, especially in critically ill patients, causes the risk of hospital pneumonia to increase (9). In our study, pulmonary infections were determined as the most common NIs with the rate of 80.9% (LRTIOP 36.8%, pneumonia with specific laboratory findings 33.6% and VAP 10.5%, respectively). Pulmonary infections were followed by BSIs (15.7%) (CVCR-BSI 9.4% and laboratory-proven BSI 6.3%, respectively) and CR-URI (3.1%). Gram-negative bacteria are among the leading causes of NIs (17-19). When the factors of all NIs were evaluated in our study, Gram-negative pathogens (93.1%) were seen to rank first. In the study conducted by Akin et al., Gram-negative bacteria were isolated as the mos tcommon infection agents in ICU. As consistent with our study findings, *A. baumannii* was the most frequently detected agent in the study by Akin et al. However, among Gram-positive bacteria, *S. aureus* was the most frequently isolated strain (20). In our study, CNS was detected to rank first. In a study examining NIs over a four-yea rperiod, *Acinetobacter spp.* (42.4%), *K. pneumoniae* (22.2%) and *P. aeruginosa* (14.8%) were found as the most widespread agents in pneumonia (21). In another study conducted in China, *A. baumannii* was found to be the mos tcommon pathogen among the lower respiratory tract infections in ICU with the rate of 18.9% (22). In our study, however, *Acinetobacter spp.* Ranked first among the lower respiratory tract infections. When pulmonar yinfections were looked at in detail, *Acinetobacter spp.* (48.7%), *K. pneumoniae* (25.6%) and *P. aeruginosa* (12.8%) were detected as the most widespread pathogens among other lower respiratory tract infections, *Acinetobacter spp.* (72.7%), *K. pneumoniae* (12.1%) and *E. coli* (6%) were determined as the causative agents in pneumonia with specific laboratory findings, as well as *Acinetobacter spp.* (75%), *K. pneumoniae* (16.6%) and *P. aeruginosa* (8.8%) as the most widespread agents in VAP. According to the NNISN 2019 report over the distribution of agents and antibiotic resistance, *Klebsiella spp*. (19.9%) was foundto be the most common agent across Turkey. Our findings are consistent with those reported in other studies from Turkey. In the same report, *Klebsiella spp*. (30%) and *E. coli* (24%) were stated as the agents ranking first and second. In another study, however, *K. pneumoniae* (54.5%) was found to rank first in CR-Url, followed by *E. coli* (18.1%) and *E. faecalis* (18.1%) (23). As similar tothe data in the NNISN 2019 report, *K. pneumoniae* (33.3%), *M. morganii* (33.3%) and *E. faecalis* (33.3%) were determined as the causative agents in CR-URI in our study. NIs cause an increase in mortality and morbidity, and so the hospitalization periods of the patients are prolonged. Inourstudy, the mortality rate wasfound as 51.1% in the patients hospitalized in ICU and presentingwithNIs. In several studies performed in Turkey and other countries, the mortality rates have shown to increase among the in-patients presenting with NIs (10,22-28). The higher rates of NIs among the patients treated and followed-upin ICUs, It can be considered to stem from other factors such as the presence of underlying diseases, the advanced age of the patients in ICUs and the severity of the disease as a reason for hospitalization and contributing to the morbidity and mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the University of Medical Sciences Konya Training and Research Hospital of Specialty in Medical Training (TUEK), dated on 5th March 2020 and with the registration number of 36-31.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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CONCLUSION

Based on our study findings, it is inevitable to see NIs in hospitals, especially in ICUs, and one of the crucial health goals of the hospitals is to control and manage such a situation. Timely and appropriate therapeutic interventions should be carried out in order to reduce the rates of NIs. If needed, catheters should be inserted with the accurate indication, and/or the procedures performed via catheters should be reduced. Considering the importance of ICUs in the development of NIs, healthcare staff in ICUs should be given a full healthcare training. Additionally, due to highe rincidence of NIs, hospitals are also recommended to develop rational antibiotherapy programs, based on thei rown surveillance data.

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Orjinal Araştırma / Original Article

Predictors of In-Hospital Mortality in Patients Admitted to the Emergency Department with Cardiogenic Pulmonary Edema

Acil Servise Kardiyojenik Pulmoner Ödem ile Başvuran Hastalarda Hastane İçi Mortalitenin Belirleyicileri

Ekrem Taha Sert[1], Kamil Kokulu[1], Murat Gül[2], Hüseyin Mutlu[1]

[1]Department of Emergency Medicine, Aksaray University Medical School, Aksaray, Turkey
[2] Department of Cardiology, Aksaray University Medical School, Aksaray, Turkey

Abstract

Background: Despite significant advances in the treatment of heart failure, the prognosis of acute cardiogenic pulmonary edema (ACPE) continues to be a serious problem. The objective of this study is to determine the risk factors affecting in-hospital mortality in patients with ACPE.

Material and Method: We enrolled 305 patients who were hospitalized with cardiogenic pulmonary edema as a diagnosis. Clinical, biochemical and echocardiographic variables were collected and analysed. The patients were divided into two groups according to the presence of mortality. Both groups were evaluated in terms of clinical features during admission to the emergency department (ED) and factors affecting in-hospital mortality.

Results: Forty-two patients died and the mortality rate was 13.8%. To determine the factors affecting mortality, multiple logistic regression analysis was performed. In the regression analysis, it was seen that age at admission to the ED (OR:1.75, 95% CI 1.18-3.05, p:0.014), systolic blood pressure (OR:0.95, 95% CI 0.31-0.98, p:0.040), presence of acute myocardial infarction (OR:4.17, 95% CI 1.85-7.13, p:0.001), positive troponin (OR:5.47, 95% CI 1.07-7.46, p:0.011), atrial fibrillation rhythm (OR;3.16, 95% CI 1.81-8.02, p:0.010), inotropic drug usage (OR;5.61, 95% CI 1.87-9.24, p:0.013) increased in-hospital mortality.

Conclusion: Our findings could help clinicians in identifying patients with poor prognosis early in the presence of identified risk factors.

Keywords: Cardiogenic pulmonary edema, mortality, emergency department, clinical presentation

Öz

Amaç: Kalp yetmezliği tedavisindeki önemli ilerlemelere rağmen akut kardiyojenik pulmoner ödemin (AKPÖ) prognozu ciddi bir sorun olmaya devam etmektedir. Bu çalışmanın amacı, ACPE gelişen hastalarda hastane içi mortaliteyi etkileyen risk faktörlerini belirlemektir.

Gereç ve Yöntem: Çalışmamıza AKPÖ nedeniyle hastaneye yatırılan 305 hastayı dahil ettik. Klinik, biyokimyasal ve ekokardiyografik bulgular analiz edildi. Hastalar, mortalite varlığına göre iki gruba ayrıldı. Her iki grup acil servise (AS) başvurudaki klinik özellikler ve hastane içi mortaliteye etki eden faktörler açısından değerlendirildi.

Bulgular: Hastaların %13.8'i hayatını kaybetti. Mortaliteye etki eden faktörleri belirlemek için çoklu lojistik regresyon analizi yapıldı. Yapılan regresyon analizinde, AS'ye kabulündeki yaş (OR:1.75, %95 CI 1.18-3.05, p:0.014), sistolik kan basıncı (OR: 0.95, %95 CI 0.31-0.98, p:0.040), akut miyokard infarktüsü varlığı OR:4.17, %95 CI 1.85-7.13, p:0.001), pozitif troponin (OR:5.47, %95CI 1.07-7.46, p:0.011), atriyal fibrilasyon (OR;3.16, %95 CI 1.81-8.02, p: 0.010), inotropik ilaç kullanımının (OR;5.61, %95 CI 1.87-9.24, p: 0.013) hastane içi mortaliteyi arttırdığı görüldü.

Sonuç: Bulgularımız, tanımlanan risk faktörlerinin varlığında, klinisyenlerin kötü prognoza sahip olacak hastaları erken dönemde tanımlamasına yardımcı olabilir.

Anahtar Kelimeler: Kardiyojenik pulmoner ödem, mortalite, acil servis, klinik tablo

Corresponding *(İletişim)*: Ekrem Taha Sert, Aksaray Üniversitesi Tıp Fakültesi Dekanlığı Adana Yolu Üzeri E-90 Karayolu 7. Km Merkez, Aksaray, Türkiye
E-mail *(E-posta)*: tahaekrem@hotmail.com
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INTRODUCTION

Acute pulmonary edema (APE) is one of the important clinical problems in patients admitted to emergency department (ED). Most patients in the emergency setting with pulmonary edema have the acute cardiogenic variety, resulting mainly from elevated left ventricle (LV) end-diastolic pressure. Acute cardiogenic pulmonary edema (ACPE), which is a subset of APE, is a common symptom of acute heart failure and often results in acute decompensated heart failure (ADHF).[1] In the United States, approximately 1 million patients are hospitalized annually due to ADHF, and its mortality rate is 4% according to the data.[2] Samsky et al.[3] analyzed heart failure mortality and readmission rates between 2005 and 2015. They detected that in the United States, 3.8% of patients admitted with heart failure died during hospitalization, and the rate of readmission was 19.9%.

In general, ACPE emerges suddenly with a dramatic clinical picture and is associated with poor in-hospital outcomes. ACPE is one of the common causes of acute respiratory failure. The primary objective in patients with ACPE is to provide adequate tissue oxygenation to prevent the development of organ dysfunction and multiple organ failure. Although rapid recovery is achieved in many patients with standard medical therapy such as vasodilators, diuretics, inotropic agents and supplemental oxygen therapy, a group of patients do not respond to these and develop hypoxemic respiratory failure. These patients need intensive care due to accompanying hypercapnia and respiratory acidosis. The objective of this study is to determine the risk factors affecting in-hospital mortality in patients with ACPE.

MATERIALS AND METHODS

Patient selection

In this study, the data of the patients aged 18 years and older, who were diagnosed with ACPE in tertiary ED in our hospital and hospitalized between January 1, 2017 and December 31, 2019, were analyzed. The data of the study were obtained from the hospital electronic database. Local ethics committee approval was obtained for the study (Ethics committee number: 2019/12-20).

The patients, whose records could not be completely reached, who were transferred to another hospital, who had severe respiratory distress caused by conditions other than ACPE (for example, pneumonia, severe anemia, renal failure), who were exposed to chemicals (for example, ammonia), who were pregnant, who had inflammatory and neoplastic disease, who underwent cardiopulmonary resuscitation and who were under 18 years of age, were excluded from the study.

Data collection and processing

The patients' demographic characteristics, vital signs at the time of admission to ED, physical examination findings, complaints at the time of admission, chronic diseases, chest X-ray and/or computed tomography (CT) findings, electrocardiogram (ECG) findings, transthoracic echocardiographic (ECHO) findings, laboratory results, mechanical ventilation (MV) requirement, intensive care need, length of hospital stay and in-hospital mortality rates were recorded. ECG, ECHO, radiological imaging and laboratory tests were performed in all patients following their admissions to ED. ECHO was performed by a cardiologist.

As the initial treatment procedure in the ED, the patients were treated with oxygen therapy, intravenous (IV) morphine sulfate and IV furosemide were administered, and IV nitroglycerine infusion was performed. Hypotension was initially treated with dobutamine and/or noradrenaline. While noninvasive ventilation support was provided to the patients with persistent respiratory failure, intubation and MV were used in refractory hypoventilation cases. Angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists and beta blockers were added to the treatment in the subacute phase of the disease.

The patients were divided into two groups according to the presence of mortality. Both groups were evaluated in terms of clinical features during admission to ED and factors affecting in-hospital mortality.

Definition and Diagnosis

ACPE was defined as the presence of pulmonary alveolar/interstitial congestion on chest X-ray and/or CT with at least two of the followings: 1) severe respiratory distress or worsening respiratory distress or persistent severe dyspnea, orthopnea 2) rales in lungs 3) high jugular venous pressure.[4]

Diagnosis of acute myocardial infarction (AMI) was established according to the criteria set by the European Society of Cardiology guidelines.[5] Vascular lesions detected in the coronary angiography of the patients were recorded. The presence of a lesion causing 50% or more stenosis in any coronary artery was recorded as significant stenosis. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, or antihypertensive drug use.

ECHO procedure was performed from parasternal and apical windows with two-dimensional, M mode, color doppler, pulsed wave doppler and tissue doppler imaging techniques. ECHO measurements were performed based on the criteria recommended by the American Society of Echocardiography.[6]

Outcome measures

The primary outcome measure was mortality rate of the patients admitted to the hospital from ED. This was used to determine the in-hospital mortality rate of the hospitalized patients. The secondary outcome was the effectiveness of clinical features during admission to ED on in-hospital mortality. Thus, the risk factors affecting mortality rate in patients with ACPE were determined.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). While evaluating the study data, descriptive statistical methods (percentage calculations, median, mean and standard deviation) were calculated. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as percentage. Normal distribution of the data was evaluated with Kolmogorov-Smirnov test. Student's t-test was used for the comparison of normally distributed continuous variables, while Mann-Whitney U-test was used for the comparison of non-normally distributed variables. Pearson's Chi-square or Fisher's test was used to compare the categorical variables. Univariate and multivariate logistic regression analysis was performed to determine the relationship between in-hospital mortality rate and possible clinical variables. Multivariate logistic regression analysis was applied to the variables with p<0.1 in univariate logistic regression analysis. Odds ratios and 95% confidence intervals were used to predict the relationship between independent determinants of hospital mortality rate. A value of p<0.05 was considered significant in all comparisons.

RESULTS

305 patients were included in our study. The mean age of the patients was 67±5 years; 57.4% (n=175) were male, and 42.6% (n=130) were female. Demographic and clinical characteristics of the patients are given in **Table 1**. In terms of vital signs, while there was no statistical difference between the two groups in terms of heart rate, oxygen saturation and body temperature, there was a statistically significant difference in terms of systolic blood pressure (p<0.05). The most common accompanying comorbidities were determined as congestive heart failure and hypertension (76.4% and 64.9%, respectively). The patients, who died, had lower LV EF compared to the survivors (p: 0.001). ECG and ECHO findings of the patients, who died and survived, are shown in **Table 2**. Noninvasive MV was needed in 69.2% of the patients (n=211). Endotracheal intubation was needed in 98 (32.1%) patients. The mean follow-up period of the patients who survived was 5±4 days, while the mean follow-up period of those who died was 9±5 days.

Forty-two (13.8%) patients died. When the patients, who died and survived, were compared; age, systolic blood pressure, atrial fibrillation/flutter, high troponin level, EF, moderate-severe mitral insufficiency and inotropic drug usage were found to be statistically significant. To determine the factors affecting mortality, multiple logistic regression analysis was performed (**Table 3**). In the regression analysis, it was seen that age at admission to the ED (OR:1.75, 95% CI 1.18-3.05, p:0.014), systolic blood pressure (OR:0.95, 95% CI 0.31-0.98, p:0.040), presence of AMI (OR:4.17, 95% CI 1.85-7.13, p:0.001), elevated troponin levels (OR:5.47, 95% CI 1.07-7.46, p:0.011), atrial fibrillation rhythm (OR;3.16, 95% CI 1.81-8.02, p:0.010), inotropic drug usage (OR;5.61, 95% CI 1.87-9.24, p:0.013) increased in-hospital mortality.

Table 1. Demographic and clinical characteristics of patients with ACPE and survival status

	Survivors (n=263)	Nonsurvivors (n=42)	p value
Age, years	66.7±5.5	70.6±4.9	<0.001
Sex, Female	115 (43.7%)	15 (35.7%)	0.330
Admission vital signs			
Body temperature (°C)	36.8 (36.7-37.0)	36.9 (36.6-37.1)	0.658
Heart rate (beats/min)	117±31	109±26	0.069
Systolic blood pressure (mmHg)	150±34	132±39	0.006
Diastolic blood pressure (mmHg)	93±19	87±18	0.065
Oxygen saturation (%)	88±11	86±8	0.645
Cardiovascular co-morbidities			
Hypertension	167 (63.7%)	31 (73.8%)	0.193
Diabetes mellitus	84 (31.1%)	18 (42.9%)	0.164
Chronic atrial fibrillation/ flutter	59 (22.4%)	19 (45.2%)	0.002
Coronary artery disease	110 (41.8%)	23 (54.8%)	0.155
Congestive heart failure	203 (77.2%)	30 (71.4%)	0.415
Heart valve disease	92 (35.0%)	14 (33.3%)	0.835
Peripheral vascular disease	38 (14.4%)	5 (11.9%)	0.660
Dyslipidaemia	20 (7.6%)	4 (9.5%)	0.427
Previous acute pulmonary edema	37 (14.1%)	8 (19.0%)	0.398
Acute myocardial infarction	20 (7.6%)	9 (21.4%)	0.005
Initial laboratory values			
Glucose (mg/dL)	241±131	234±138	0.846
Hemoglobin (g/dL)	13.2±2.2	12.1±2.4	0.822
Sodium (mmol/L)	137.9±4.7	135.6±4.3	0.105
Potassium (mmol/L)	4.3±0.7	4.4±0.6	0.326
Creatinine (mg/dL)	1.8±1.3	2.0±1.4	0.112
Urea (mg/dL)	71±57	81±46	0.087
AST (U/L)	20±15	25±16	0.610
ALT (U/L)	14± 8	18±7	0.772
Albumin (g/dL)	3.2±0.6	3.0±0.5	0.784
C-reactive protein (mg/dL)	17 ± 12	12±8	0.536
Positive troponin	33 (12.5%)	14 (33.3%)	0.001
BNP elevated, (n=116)	101 (38.3%)	15 (35.7%)	0.765
Arterial blood pH	7.2± 0.20	7.2± 0.18	0.981
Arterial blood lactate (mmol/L)	5.6 ± 3.2	6.0 ± 2.9	0.493

Data are expressed as mean ± standard deviation (SD), as number (percentage), or as median (IQR), AST: aspartate aminotransferase, ALT: alanine aminotransferase, BNP: B-type natriuretic peptide

Table 3. Factors associated with all-cause in-hospital mortality

In-hospital mortality	OR	95% CI	p value
Age	1.75	1.18-3.05	0.014
Systolic blood pressure	0.95	0.31-0.98	0.040
Atrial fibrillation rhythm	3.16	1.81-8.02	0.010
Positive troponin	5.47	1.07-7.46	0.011
Ejection fraction	1.04	0.65-3.52	0.063
Acute myocardial infarction	4.17	1.85-7.13	0.001
Moderate-severe mitral insufficiency	3.32	1.79-6.14	0.272
Inotropic drug usage	5.61	1.87-9.24	0.013

Multivariate regression analyses were performed, OR: odds ratio, CI:confidence interval

Table 2. Electrocardiography and echocardiography findings and follow-up management and events in patients with ACPE

	Survivors (n=263)	Nonsurvivors (n=42)	p value
Electrocardiography findings			
Atrial fibrillation	66 (25.1%)	20 (47.6%)	0.003
Left bundle branch block	78 (29.7%)	12 (28.6%)	0.886
Right bundle branch block	52 (19.8%)	7 (16.7%)	0.636
ST-segment elevation	5 (1.9%)	2 (4.8%)	0.248
ST-segment depression	21 (8.0%)	6 (14.3%)	0.182
T-wave inversion	30 (11.4%)	8 (19.0%)	0.164
Echocardiography findings			
Ejection fraction	44±8	39±7	0.001
Moderate-severe aortic stenosis	9 (3.4%)	3 (7.1%)	0.249
Moderate-severe aortic insufficiency	6 (2.3%)	2 (4.8%)	0.304
Moderate-severe mitral stenosis	1 (0.4%)	0	0.689
Moderate-severe mitral insufficiency	21 (8.0%)	9 (21.4%)	0.007
Inotropic drug usage	23 (8.7%)	14 (33.3%)	<0.001
Non-invasive MV at ED	180 (68.4%)	31 (73.8%)	0.484
Endotracheal intubation at ED	80 (30.4%)	18 (42.9%)	0.109
Procedures			
Coronary angiography	21 (8.0%)	9 (21.4%)	0.012
Non-significant CAD	10 (3.8%)	3 (7.1%)	0.320
Single-vessel CAD	2 (0.8%)	0	0.743
Double-vessel CAD	3 (1.1%)	2 (4.8%)	0.093
Three-vessel CAD	6 (2.3%)	4 (9.3%)	0.087
Outcome			
Days of hospitalization	5±4	9±5	0.543
ICU admission	164 (62.3%)	36 (85.7%)	<0.001
ICU mortality		29 (69.1%)	
In-hospital mortality		13 (30.9%)	

Data are expressed as mean ± standard deviation (SD), as number (percentage), ICU: intensive care unit, MV: mechanical ventilation, ED: emergency department, CAD:coronary artery disease

DISCUSSION

Despite significant advances in the treatment of heart failure, the prognosis of ACPE continues to be a serious problem. Although acute treatment of ACPE is similar in different heart diseases, diagnosis and treatment strategies can differ significantly. Therefore, it is important to evaluate the risk factors that will affect the early and late prognosis of the patient in determining the best treatment strategy for the patients who recovered from the acute event. In our study, we found the in-hospital mortality rate as 13.8% following ACPE development. We determined that advanced age, systolic blood pressure at admission, elevated troponin levels, AMI, atrial fibrillation rhythm and inotropic drug need were associated with in-hospital mortality. These findings suggest that specific clinical picture pattern plays an important role in terms of predicting mortality.

Acute heart failure, which includes different clinical conditions such as acute decompensation of chronic heart failure, right ventricular failure, cardiogenic shock, and APE, is associated with increased mortality rates and hospitalization.[7,8] In acute heart failure, in-hospital mortality rate is 4-7%, 3-month mortality rate after discharge is 7-11%, and readmission rate in the first 3 months is around 25-30%.[9] Previous studies revealed that advanced age, severe LV dysfunction, acute coronary syndromes, blood pressure at admission, presence of renal failure, inotropic drug need and anemia were the main determinants of mortality.[10,12] In-hospital mortality in ADHF was found to be associated with advanced age, high heart rate, hyponatremia, hypotension, LV systolic dysfunction, increased blood urea nitrogen level, creatinine, troponin or natriuretic peptides.[13,14] Fonarow et al.[15] developed a risk score for in-hospital mortality in patients hospitalized due to acute heart failure. In this study, they found that age, systolic blood pressure, blood urea nitrogen level and heart rate were independent predictors of mortality. Similarly, our study revealed that age, admission systolic blood pressure, positive troponin and the need for inotropic agents were associated with in-hospital mortality. Moreover, we observed that atrial fibrillation rhythm was an additional strong predictor which had not been previously reported.

Most commonly, ACPE occurs with acute myocardial ischemia or infarction, cardiomyopathy, valvular heart disease or hypertensive emergencies. AMI is the most common cause of heart failure and pulmonary edema. Myocardial muscle damage results in low cardiac reserve and an increase in LV diastolic, venous and pulmonary capillary pressure. This results in fluid extravasation into the interstitial and alveolar space. ACPE constitutes 10-20% of acute heart failure syndromes, and mortality may be higher especially when associated with AMI.[16,17] While the majority of the patients admitted with ACPE had normal or high systolic blood pressure, only 5-8% of them were admitted with low systolic blood pressure (<90 mmHg). If hypoperfusion findings accompany, this group has a poor prognosis.[18] In our study, certain traditional cardiovascular risk factors in the general population such as coexisting dyslipidemia and hypertension were not associated with mortality. In contrast, atrial fibrillation was associated with mortality in multivariate analysis. We found AMI in 9.5% (29) of the patients admitted with ACPE. We found the mortality rate as 21.4% in the patients with AMI. The relationship between AMI and high mortality rates in the patients admitted with ACPE may be caused by severe LV systolic dysfunction. Early diagnosis and treatment by evaluating the previous or concomitant cardiovascular disease, ECG and ECHO findings in these patients may help reduce in-hospital mortality.

It was revealed that noninvasive MV application in the treatment of acute cardiogenic pulmonary edema reduced the need for endotracheal intubation and mortality.[19-22] In a meta-analysis where standard oxygen therapy and noninvasive MV applications in the patients with cardiogenic pulmonary edema were compared, hospital mortality and intubation rates were significantly lower in the noninvasive MV group compared to standard therapy group.[21,22] In our study, similar to other studies, there was no significant difference in mortality in the patients who received noninvasive MV in ED.

This study has some limitations. The first limitation of the study was the limited number of subjects fulfilling the inclusion criteria. Secondly, the study is retrospective. The retrospective

nature of the study restricted data to those routinely collected. Our retrospective study design may be related to selection biases, because this study only included patients admitted to the hospital. Third, the study is single-centered. The single-center study design carries inherent risks of bias.

CONCLUSION

ACPE is a common condition in the ED and one of the most common causes of hospitalization. We determined that age, systolic blood pressure at admission, elevated troponin levels, AMI diagnosis, atrial fibrillation rhythm and inotropic drug need were associated with in-hospital mortality in the patients admitted with ACPE. Our findings could help clinicians in identifying patients with poor prognosis early in the presence of identified risk factors.

ETHICAL DECLARATIONS

Ethics Comittee Approval: Aksaray University School of Medicine, Aksaray Education and Research Hospital Scientific Research Evaluation Committee approval was obtained for this study (approval number: 2019/12-20).

Conflict of Interest Statement: No conflict of interest was declared by the authors.

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Orjinal Araştırma / Original Article

The Evaluation of Genetic Profiles of *UGT1A4 and UGT1A6 in* the Turkish Population

Türk Popülasyonund*a UGT1A4 ve UGT1A6* Genetik Profillerinin Değerlendirilmesi

Zuhal Uçkun Şahinoğulları[1]

[1]Mersin University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Yenisehir, Mersin, Turkey

Abstract

Aim: Uridine diphosphate glucuronosyltransferases (UGTs) are a superfamily of conjugation phase II enzymes and is responsible for catalyzing the glucuronidation of many endobiotic or xenobiotic substrates. The present study aimed to determine allele and genotype frequencies of *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and *UGT1A6* c.19T>G polymorphisms in the healthy Turkish population and also to compare them with different population data.

Material and Method: *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G polymorphisms were determined in DNA samples of 114 healthy Turkish volunteers using polymerase chain reaction and restriction fragment length polymorphism methods.

Results: The frequencies of variant alleles were 12.7% for *UGT1A4* c.142T>G, 39.9% for *UGT1A6* c.541A>G and 44.7% for *UGT1A6* c.19T>G. The frequencies of the *UGT1A4* and *UGT1A6* variant alleles determined were observed to be similar to those of the majority of European populations. However, the *UGT1A6* frequencies in the Turkish population differed significantly from those reported specifically for the Thai and East Asian populations.

Conclusion: This study introduces the frequencies of *UGT1A4* and *UGT1A6* polymorphisms in the Turkish population. As a result of our literature reviews, this study is the first report that investigated the frequencies of *UGT1A6* c.541A>G and c.19T>G polymorphisms in the healthy Turkish population. A study of the *UGTA1A4*3* polymorphism was found in Turkish epilepsy patients in the literature search, but not in healthy individuals. Therefore, it can be stated that this study is also the first report investigating the *UGT1A4*3* polymorphism in the healthy Turkish individuals. This study could ensure clinically beneficial information about drug metabolism by *UGT1A4* and *UGT1A6* in the Turkish population.

Keywords: *UGT1A4*, *UGT1A6*, glucuronidation, polymorphism, Turkish population

Öz

Amaç: Üridin difosfat glukuronosiltransferazlar (UGT'ler), konjugasyon faz II enzimlerinin bir süper ailesidir ve birçok endobiyotik veya ksenobiyotik substratın glukuronidasyonunu katalize etmekten sorumludur. Bu çalışmada, sağlıklı Türk popülasyonunda *UGT1A4* c.142T>G, *UGT1A6* c.541A>G ve *UGT1A6* c.19T>G polimorfizmlerinin allel ve genotip frekanslarının belirlenmesi ve farklı popülasyon verileriyle karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: *UGT1A4* c.142T>G, *UGT1A6* c.541A>G ve c.19T>G polimorfizmleri, polimeraz zincir reaksiyonu ve restriksiyon fragman uzunluğu polimorfizmi yöntemleri kullanılarak 114 sağlıklı Türk gönüllülerinin DNA örneklerinde belirlendi.

Bulgular: Varyant allel frekansları *UGT1A4* c.142T>G için % 12.7, *UGT1A6* c.541A>G için % 39.9 ve *UGT1A6* c.19T>G için % 44.7 idi. Belirlenen *UGT1A4* ve *UGT1A6* varyant allel frekanslarının, Avrupa popülasyonlarının çoğunluğuna benzer olduğu gözlendi. Ancak, Türk popülasyonundaki *UGT1A6* frekanslarının, özellikle Tayland ve Doğu Asya popülasyonlarının frekanslarından önemli ölçüde farklıydı.

Sonuç: Bu çalışma, Türk popülasyonunda *UGT1A4* ve *UGT1A6* polimorfizmlerinin sıklığını sunmaktadır. Literatür incelemelerimizin sonucu olarak, bu çalışma sağlıklı Türk popülasyonunda *UGT1A6* c.541A>G ve c.19T>G polimorfizmlerinin sıklığını araştıran ilk rapordur. Literatür taramasında Türk epilepsi hastalarında *UGT1A4*3* polimorfizmi ile ilgili bir çalışma bulunmuştur, ancak sağlıklı bireyler ile ilgili veri bulunmamıştır. Dolayısıyla bu çalışmanın, sağlıklı Türk bireylerinde *UGT1A4*3* polimorfizmini araştıran ilk rapor olduğu ifade edilebilir. Bu çalışma, Türk popülasyonunda *UGT1A4* ve *UGT1A6* ile gerçekleşen ilaç metabolizması hakkında klinik olarak faydalı bilgiler sağlayabilir.

Anahtar Kelimeler: *UGT1A4*, *UGT1A6*, glukuronidasyon, polimorfizm, Türk popülasyonu

Corresponding *(İletişim)*: Zuhal Uçkun Şahinoğulları, Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Mersin University, Mersin, Turkey
E-mail *(E-posta)*: uckunzuhal@mersin.edu.tr
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INTRODUCTION

Glucuronidation is one of the most important phase II metabolic pathways in human. It is catalyzed by the family of UDP-glucuronosyl transferase (UGTs) enzymes which are a superfamily of membrane attached proteins in the endoplasmic reticulum.[1] UGTs (EC 2.4.1.17) catalyze the conjugation of endobiotic or xenobiotic compounds with glucuronic acid from the cofactor UDP-α-D-glucuronic acid (UDPGA).[2] Glucuronidation is responsible for about about 40 to 70% of xenobiotic elimination[3] and commonly makes compounds biologically inactive and increases excretion of compounds through urine or bile.[2] Some of the UGT substrates are bile acids, bilirubin, thyroid hormones, fatty acids, environmental toxins and pollutants, dietary components, tobacco smoke carcinogens, and various prescribed medications including acetaminophen, morphine, tamoxifen, mycophenolic acid, ciprofibrate, SN-38, aromatase inhibitors (letrozole, exemestane and anastrozole), vorinostat, steroid hormones, lamotrigine, some tricyclic antidepressants, and antipsychotics such as olanzapine and clozapine.[4-6] UGTs are expressed in various tissues and organs, primarily in the liver as well as in lungs, placenta, uterus, brain and intestinal mucosa.[6]

The superfamily of UGT consist of four families; which are UGT1, UGT2, UGT3 and UGT8.[7] The enzymes UGT1 and UGT2 have significant roles in toxicology and pharmacology, but the contribution of the UGT3 and UGT8 enzymes to drug metabolism has been determined to be relatively small.[7] The *UGT1A* gene is located on chromosome 2q37 and encodes nine functional proteins (*UGT1A4* and *UGT1A3-1A10*), which are produced by the splicing of a unique first exon to the common exons 2–5.[8]

Many variants have been identified in the superfamily of UGT.[9] Genetic polymorphisms in genes encoding UGT enzymes have toxicological, physiological and pharmacological significance.[10] In the *UGT1A4* gene, more than 100 single nucleotide polymorphisms (SNPs) have been identified, and one of the best studied allele among them was *UGT1A4**3 which encodes a Leu48Val amino acid change (L48V; c.142T>G; rs2011425) in the corresponding enzyme.[6] The *UGT1A4**3 was associated with twice as high much glucuronidation activity *in vitro*.[11] Furthermore, L48V was suggested to associated with lower mean plasma concentrations of olanzapine in patients with schizophrenia.[5,12] Alterations in glucuronidation activities due to *UGT1A4* alleles have been reported to be substrate-dependent.[9]

In the *UGT1A6* gene, the three most common nonsynonymous polymorphisms were Thr181Ala (541 A>G), Arg184Ser (552 A>C) and Ser7Ala (19 T>G).[13] Both Thr181Ala and Arg184Ser variants are mostly (>98%) in complete linkage disequilibrium.[14] These two variants result in a 30–50% decline in enzyme activity as opposed to the wild type allele.[14,15] It has been suggested that *UGT1A6* polymorphism affect the glucuronidation rate of its substrates in *in vitro* studies, and also that the A541G, A552C and T19G SNPs in the coding sequence of *UGT1A6* gene may affect the pharmacokinetics of valproic acid, by that means, changing the adverse effect profiles and efficacy of the drug.[16] Alterations in the enzyme function of UGTs may influence the clearance of and thus, systemic exposure to their substrates.[17]

The frequencies of the SNPs of *UGT1A4* and *UGT1A6* included in the study may vary among diverse populations. Differences in the frequencies of these SNPs can cause individual and ethnic differences in glucuronidation capacity, leading to differences in drug response, drug efficacy, toxicity of drugs and other xenobiotics, predisposition to various diseases.

A study of the *UGTA1A4**3 polymorphism in the Turkish population was found in the literature survey. Gulcebi et al.[10] investigated the relationship between *UGT1A4**2 and *UGT1A4**3 polymorphisms and lamotrigine serum concentration in epilepsy patients. On the other hand, in the Turkish population, no studies of the polymorphism mentioned in *UGT1A4* gene in healthy individuals and data on the polymorphisms commonly found in *UGT1A6* gene were found. Therefore, the aim of this study is to determine allele and genotype frequencies of *UGT1A4**3 and *UGT1A6* A541G and *UGT1A6* T19G polymorphisms in the healthy Turkish population and also to compare them with different population data.

MATERIAL AND METHOD

Samples

The DNA samples extracted in the previous study (22/10/2015, protocol no: 2015/317) were included in the present survey. Additionally, the ethical approval of the current study was also obtained from Mersin University Ethics Committee (08/07/2020, protocol no: 2020/490). The genomic DNA samples isolated from whole blood were stored at -80°C until analysis. This study was carried out using DNA samples of 114 healthy, unrelated Turkish volunteers aged 18-65 and was conducted according to the Good Clinical Practices and the Declaration of Helsinki.

Genotyping

UGT1A4 c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs were analyzed using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods. PCR-RFLP methods were carried out in a MiniAmp Plus Thermal Cycler (Thermo Fisher, USA).

UGT1A4 c.142T>G, p.L48V, rs2011425

UGT1A4 c.142T>G SNP was identified according to Hakooz et al.[9] with slight modifications. The forward (F): 5'-GCCCATAACGAAAGGCAGT-3' and reverse (R): 5'-CACACAACACCTATGAAGGG-3' primers were used to amplify 567 bp of the *UGT1A4* gene that contain the polymorphic region. PCR products were digested at 37°C for 15 minutes using Fast Digest StuI restriction enzyme (Thermo Fisher Scientific). The genotypes of the wild type (319, 248 bp), mutant (567 bp) and heterozygous (567, 319 and 248 bp) were determined using 2% agarose gel with ethidium bromide (**Figure 1A**).

UGT1A6 c.541A>G, p.T181A, rs2070959

Analysis of the *UGT1A6* c.541A>G SNP was performed using primers set; F: 5'-GGAAATACCTAGGAGCCCT GTGA-3' and R: 5'-AGGAGCCAAATGAGTGAGGGAG-3'.[13] The primers were used to amplify the 992 bp fragment of the gene. PCR products were digested at 37°C for 15 minutes using Fast Digest NsiI restriction enzyme (Thermo Fisher Scientific). The genotypes of the wild

type (992 bp), mutant (616 and 376 bp) and heterozygous (992, 616 and 376 bp) were identified using 2% agarose gel with ethidium bromide (**Figure 1B**).

UGT1A6 c.19T>G, p.Ser7Ala, rs6759892

The 19T>G polymorphism in the *UGT1A6* gene was analysed using primer set; F: 5'-GATTTGGAGAGTGAAAACTCTTT-3' and R: 5'-CAGGCACCACCACTACAATCTC-3'.[13] The primers were used to amplify the 237 bp fragment of the gene. PCR products were digested in 15 minutes at 37°C using Fast Digest HhaI restriction enzyme (Thermo Fisher Scientific). The genotypes of the wild type (237 bp), mutant (165 and 72 bp) and heterozygous (237, 165 and 72 bp) were detected using 2.5% agarose gel with ethidium bromide (**Figure 1C**).

For each SNP analysis, 10% of the samples were randomly reanalyzed for quality assurance, which ensured 100% concordance.

Statistical analysis

Genotype and allele frequencies were calculated by genotype counting method. The observed frequencies of *UGT1A4* and *UGT1A6* SNPs were compared with the expected frequencies using the chi-square (X^2) test based on Hardy–Weinberg equilibrium. The obtained data of the present study were compared with previously reported data of various populations. Differences in the frequencies between populations were tested by X^2 test. Statistical analyzes were conducted with IBM SPSS 25.0 computer software for Windows. $p<0.05$, <0.01 and <0.001 were accepted statistically significant.

RESULTS

UGT1A4 c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs were detected with DNA samples of 114 healthy Turkish individuals using the PCR-RFLP methods. Of the 114 individuals included in the study, 52 (46%) were male, 62 (54%) were female. The mean age with standard deviation of the study population was 28.55±9.33 years (26.15±8.50 years for female and 31.42±9.55 years for male).

As shown in **Table 1**, distributions of the genotypes frequencies obtained were consistent with Hardy-Weinberg equilibrium. The frequencies of TT, TG and GG genotypes of *UGT1A4* polymorphism were 75.4%, 23.7% and 0.9%, respectively, and thus, the frequencies of T and G alleles were identified as 87.3% and 12.7%, respectively. The frequencies of AA, AG and GG genotypes of *UGT1A6* A541G SNP were 33.3%, 53.5% and 13.2%, respectively, and the frequencies of A and G alleles were found as 60.1% and 39.9%. The frequencies of TT, TG and GG genotypes of *UGT1A6* T19G SNP were 27.2%, 56.1% and 16.7%, respectively, and therefore, the frequencies of T and G alleles were detected as 52.3% and 44.7%, respectively.

Figure 1 shows agarose gel images of RFLPs of *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs determined by electrophoresis.

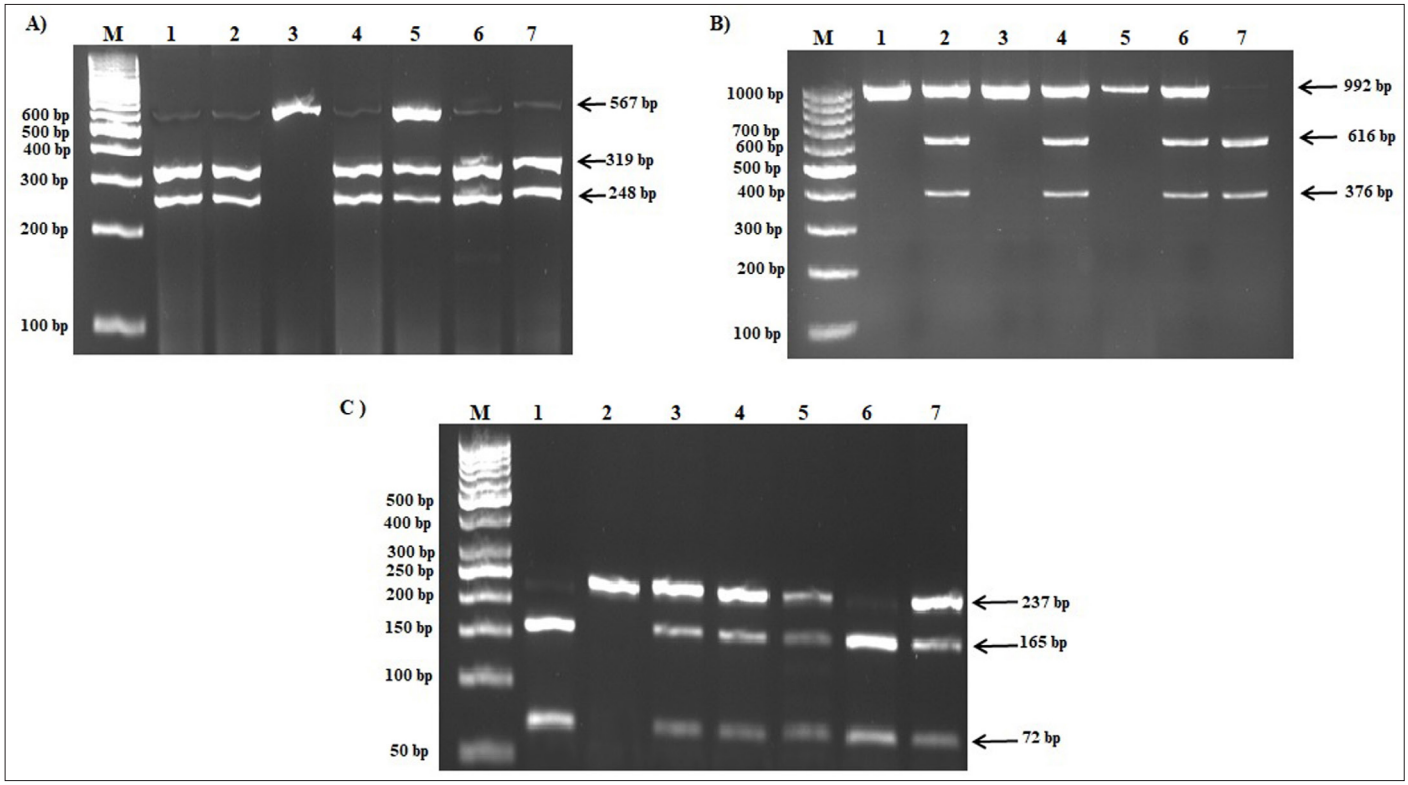

Figure 1. Agarose gel images of restriction fragment length polymorphisms of *UGT1A4* T142G, *UGT1A6* A541G and *UGT1A6* T19G single nucleotide polymorphisms (SNPs) determined by electrophoresis. For *UGT1A4* T142G SNP (**A part**); M: Marker (100 bp), Lane 1, 2, 4, 6 and 7: wild type genotype (319, 248 bp), Lane 3: mutant genotype (567 bp), Lane 5: heterozygous genotype (567, 319, 248 bp). For *UGT1A6* A541G SNP (**B part**); M: Marker (100 bp), Lane 1, 3 and 5: wild type genotype (992 bp), Lane 2, 4 and 6: heterozygous genotype (992, 616, 376 bp), Lane 7: mutant genotype (616, 376 bp). For *UGT1A6* T19G SNP (**C part**); M: Marker (50 bp), Lane 2: wild type genotype (237 bp), Lane 3-5 and 7: heterozygous genotype (237, 165, 72 bp), Lane 1 and 6: mutant genotype (165, 72 bp).

Table 1. Genotype and allele frequencies of *UGT1A4* and *UGT1A6* SNPs observed in this study (n=114)

Variants	Genotype	Observed genotype frequency, n (%)	Expected genotype frequency, n	HWE	Allele frequency, n (%)
*UGT1A4**3					
c.142T>G rs2011425	TT TG GG	86 (75.4) 27 (23.7) 1 (0.9)	86.8 25.3 1.8	X^2=0.507 p=0.476	T=199 (87.3) G=29 (12.7)
UGT1A6					
c.541A>G rs2070959	AA AG GG	38 (33.3) 61 (53.5) 15 (13.2)	41.2 54.7 18.2	X^2=1.523 p=0.217	A=137 (60.1) G=91 (39.9)
c.19T>G rs6759892	TT TG GG	31 (27.2) 64 (56.1) 19 (16.7)	34.8 56.4 22.8	X^2=2.089 p=0.148	T=126 (52.3) G=102 (44.7)

DISCUSSION

To our knowledge, this is the first report that investigated the allele and genotype frequencies of *UGT1A6* c.541A>G and c.19T>G in a healthy Turkish population. A study of the *UGTA1A4*3* polymorphism in the Turkish population was found in the literature survey. However, the study conducted by Gulcebi et al.[10] on the *UGTA1A4*3* polymorphism was conducted in epilepsy patients in the Turkish population, not healthy individuals. Therefore, it can be stated that this study is the first report investigating the *UGT1A4**3 polymorphism in the healthy Turkish individuals. The frequency found by Gulcebi et al.[10] was similar to the frequency of *UGT1A4**3 polymorphism observed in healthy individuals in the present study.

Table 2 shows a comparison of the frequencies *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs (%) observed in this study with those of other populations[10,12,17,19-28] and the 1000 Genomes Project.[18]

The variant frequencies of *UGT1A4* c.142T>G of the present study were similar to White ancestry, including Swedish, Utah Residents with Northern and Western European Ancestry (CEU), Finnish in Finland (FIN), British in England and Scotland (GBR), Iberian populations in Spain (IBS), Toscani in Italy (TSI), Colombian in Medellin, Colombia (CLM), Mexican Ancestry in Los Angeles, California (MXL), Peruvian in Lima, Peru (PEL), Puerto Rican in Puerto Rico (PUR). The frequencies of the variant allele in White ancestry were between 6.1% and 15.9%. Also, the frequency of *UGT1A4* c.142T>G was not different from frequencies previously found in East Asian populations, including Japanese, Korean, Chinese, Han Chinese, Japanese in Tokyo, Japan (JPT), Han Chinese in Bejing, China (CHB) but was found statistically significant lower than that in Kinh in Ho Chi Minh City, Vietnam (KHV). Among South Asian populations, no significant difference was observed between the frequency in Turkish and those in Gujarati Indian in Houston, Texas (GIH) and Punjabi in Lahore, Pakistan (PJL) populations; however, statistically significant difference was found between the study's findings and those in Sri Lankan Tamil in the UK (STU) and Indian Telugu in the UK (ITU) populations. There was no significant distinction between Turkish and Black ancestry, including Esan in Nigeria (ESN), Luhya in Webuye, Kenya (LWK), African Caribbeans in Barbados (ACB) and African ancestry in SW USA (ASW) in terms of *UGT1A4* T142G SNP. The frequencies of the variant allele in Black ancestry were between 8.1 and 10.1%.

The *UGT1A6* c.541A>G allele frequency differences between Turkish and White ancestry that include GBR, IBS, CLM, MXL, PEL, PUR were considered to be statistically significant; however, it was not statistically significant when compared to CEU, FIN, TSI populations. The A541G allele frequency in the Turkish population showed significantly difference when compared to South East Asian (Thai) and East Asian populations (Japanese, Korean, Han Chinese, Chinese, JPT, CHB, KHV), but no significant difference was observed in comparison to the South Asian populations (Indian, GIH, PJL, STU, ITU). The A541G variant allele frequencies ranged from 31.9 to 45.1% for South Asian populations. Statistically significant differences were observed between Turkish populations and African populations that include ESN, LWK and ACB except for ASW.

The *UGT1A6* c.19T>G allele frequencies in the Turkish population were similar to those in White ancestry that include CEU, FIN, GBR, TSI, CLM and PUR populations, but was found statistically significant higher than those IBS, MXL and PEL populations. The T19G allele frequency in the Turkish population showed significantly difference when compared to some Asian populations that include Thai, Japanese, Korean, Han Chinese, JPT, CHB, KHV and Indian; but was not significantly distinction when compared to the other Asian populations that include GIH, PJL, STU, ITU. In addition, there was no significantly distinction between Turkish and African populations that include ESN, LWK, ACB and ASW. The T19G variant allele frequencies ranged from 34.3 to 42.2% for African populations.

As seen in **Table 2**, the frequencies of the *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs vary among diverse populations. Differences in the distribution of the frequencies of these alleles may lead to intra- and inter-population differences in glucuronidation capacity, and this may give rise to inter-ethnic and inter-individual differences in response to drug therapy, therapeutic efficacy, toxicity of drugs and other xenobiotics, susceptibility to diverse diseases.

Table 2. Comparisons of the frequencies of *UGT1A4* c.142T>G and *UGT1A6* c.541A>G, c.19T>G polymorphisms in various population

Ethnicity	Population	n	*UGT1A4* c.142T>G *G* allele, %	*UGT1A6* c.541A>G *G* allele, %	*UGT1A6* c.19T>G *G* allele, %	References
WHITE						
	Saudi population	182	NA	31.6	NA	Alkharfy et al.[17]
European	Turkish	114	12.7	39.9	44.7	Present study
	Turkish	129	12.8	NA	NA	Gulcebi et al.[10]
	Swedish	112	12.9	NA	NA	Ghotbi et al.[12]
	Utah Residents with Northern and Western European Ancestry (CEU)	99	8.6	32.3	39.9	1000 Genomes project[18]
	Finnish in Finland (FIN)	99	6.1	38.4	46.0	1000 Genomes project[18]
	British in England and Scotland (GBR)	91	7.1	28.0*	34.6	1000 Genomes project[18]
	Iberian populations in Spain (IBS)	107	8.9	26.6**	33.6*	1000 Genomes project[18]
	Toscani in Italy (TSI)	107	15.9	29.9	37.4	1000 Genomes project[18]
American	Colombian in Medellin, Colombia (CLM)	94	8.0	27.1**	42.0	1000 Genomes project[18]
	Mexican Ancestry in Los Angeles, California (MXL)	64	12.5	24.2**	32.0*	1000 Genomes project[18]
	Peruvian in Lima, Peru (PEL)	85	13.5	7.6***	25.3***	1000 Genomes project[18]
	Puerto Rican in Puerto Rico (PUR)	104	7.7	28.8*	36.5	1000 Genomes project[18]
ASIANS						
South East Asian	Thai	84	NA	23.2***	19.0***	Aphichartphunkawee et al.[19]
East Asian	Japanese	301	13.0	21.4***	22.6***	Saeki et al.[20]
	Korean	40/50[a]	15.0	16.0***	20.0***	Yea et al.[21]
	Korean	132	15.2	NA	NA	Suh et al.[22]
	Chinese	214	18.0	NA	NA	Liu et al.[23]
	Han Chinese	106	12.3	NA	NA	Chang et al.[24]
	Han Chinese	534/531[b]	NA	22.0***	23.8***	Xing et al.[25]
	Chinese	242	NA	18.8***	NA	Chu et al.[26]
	Chinese	97	NA	24.2**	NA	Shen et al.[27]
	Japanese in Tokyo, Japan (JPT)	104	13.5	21.2***	22.1***	1000 Genomes project[18]
	Han Chinese in Bejing, China (CHB)	103	15.5	27.2**	28.6***	1000 Genomes project[18]
	Kinh in Ho Chi Minh City, Vietnam (KHV)	99	24.7**	12.1***	15.2***	1000 Genomes project[18]
South Asian	Indian	80	NA	31.9	35.6*	Jain et al.[28]
	Gujarati Indian in Houston, Texas (GIH)	103	20.4	45.1	48.5	1000 Genomes project[18]
	Punjabi in Lahore, Pakistan (PJL)	96	20.8	39.1	48.4	1000 Genomes project[18]
	Sri Lankan Tamil in the UK (STU)	102	23.0*	44.1	49.5	1000 Genomes project[18]
	Indian Telugu in the UK (ITU)	102	23.5*	42.2	47.5	1000 Genomes project[18]
BLACK						
African	Esan in Nigeria (ESN)	99	10.1	23.2***	34.3	1000 Genomes project[18]
	Luhya in Webuye, Kenya (LWK)	99	8.1	21.7***	40.4	1000 Genomes project[18]
	African Caribbeans in Barbados (ACB)	96	9.4	28.6*	42.2	1000 Genomes project[18]
	African ancestry in SW USA (ASW)	61	8.2	28.7	35.2	1000 Genomes project[18]

[a] The studied sample sizes were 40 for c.142T>G and 50 for c.541A>G and c.19T>G polymorphisms.
[b] The studied sample sizes were 534 for c.541A>G and 531 for c.19T>G polymorphisms.
Differences in the frequencies were examined using X^2 test.
n: total number of subjects. NA: not available.
Significant at *p<0.05, **p<0.01 and *** p<0.001 when compared to the current study.

Lamotrigine, which is widely used as an antiepileptic agent in the treatment of epilepsy, is metabolized by UGT enzymes[10], and its main metabolizing enzyme is *UGT1A4*.[24] Gulcebi et al.[10] reported that L48V polymorphism decreased the serum concentration of lamotrigine in epilepsy patients in the Turkish population who received monotherapy or polytherapy, and that the levels of lamotrigine were importantly lower for smoking or non smoking polymorphic alleles than for normal. In a study by Chang et al.[24] in Han Chinese patients with epilepsy, it was reported that patients with the *UGT1A4* 142TT polymorphism were observed to have a higher blood lamotrigine concentration and better therapeutic efficacy than those with the 142TG or 142GG genotypes. Du et al.[29] reported that in Chinese children with epilepsy, the TT genotype of T142G SNP was related to high serum content of lamotrigine and that T142G SNP showed effects on efficacy of lamotrigine. In a study by Ghotbi et al.[12] on Swedish patients with schizophrenia, it was reported that the *UGT1A4**3 was related with lower average plasma concentrations of olanzapine.

In a study by Dadheech et al.[13], it was conducted to evaluate the association of *UGT1A6* A541G, T19G and A552C SNPs with drug response and adverse drug reactions (ADRs) in β-thalassemia major patients receiving deferiprone therapy. While a significant difference in the genotypic distribution of the *UGT1A6* Thr181Ala polymorphism has been observed in responders and non-responders, no difference was observed in the genotypic distribution between patients with and without ADR. For genotypic distribution of the *UGT1A6* T19G polymorphism, there was an important distinction between non-responders with and without ADRs and between responders with and without ADRs. Aphichartphunkawee et al.[19] declared that *UGT1A6* 541A>G and 552A>C variants were associated with lower valproic acid dose in Thai epileptic patients. Oussallah et al.[30] reported that *UGT1A6* A541G, T19G and A552C SNPs were significantly associated with gallstone-related cholecystectomy risk and that the *UGT1A6* A541G SNP was related with the highest risk of gallstone–related cholecystectomy (odds ratio=4.58; 95% confidence interval=1.58–13.28; p=0.00321). Kua et al.[31] reported that in Chinese individuals, *UGT1A6* A541G, T19G and A552C SNPs indicated important relationship with increased lung cancer risk and that *UGT1A6* polymorphisms may modify lung cancer risk.

Genetic polymorphisms changing enzyme functions have clinical significance in predicting disease susceptibility and the capability of an individual to respond to particular medications.[32] Genetic polymorphisms could aid individualized drug dosage and improved therapeutics.[33]

CONCLUSION

This study introduces the genetic profiles of *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs in the healthy Turkish population and the comparison of the frequencies obtained with those of various populations. The detection of polymorphisms in the genes encoding the enzymes aforementioned may ensure benefit for dose adjustment of some medications and protection from xenobiotics for precaution and decreasion in adverse drug reactions. This study may help to improve toxicogenetic studies and contribute to epidemiological studies..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Mersin University Ethics Committee (08/07/2020, protocol no: 2020/490).

Informed Consent: The DNA samples used were obtained during the previous study, which was approved by Mersin University Ethics Committee (22/10/2015, protocol no: 2015/317). Informed consent form had been obtained while blood samples were taken from volunteers.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Orjinal Araştırma / Original Article

It's Not Always Appendicitis: Relatively Uncommon Conditions of Acute Abdomen in Children

Her Zaman Apandisit Değildir: Çocuklarda Daha Nadir Görülen Akut Karın Nedenleri

Berat Dilek Demirel[1], Beytullah Yağız[1]

[1]Ondokuz Mayıs University, School of Medicine, Department of Pediatric Surgery, Samsun, Turkey

Abstract

Aim: To evaluate the acute surgical conditions beyond acute appendicitis in children.

Material and Method: The children who underwent urgent abdominal surgery between January 2017-December 2020 are retrospectively evaluated. The newborns and patients with acute appendicitis are excluded.

Results: A total of 595 patients underwent urgent abdominal surgery. Acute appendicitis was the final diagnosis in 468 of them (78.7%). The median age of the rest of the 127 patients (21.3%) was 8 years (0.96-17.75 years). Fourteen patients admitted with trauma (11%) (12 boys and 2 girls, median age; 12.66 years), and the most common cause was firearm injuries with the most common injured system was the gastrointestinal system. Among the patients without trauma, 62 were boys (54.6%) and 51 were girls (45.1%) (median age; 6.41 years). Intussusception was most common in the Infant and Young Child Group. Adhesive small bowel obstruction was most common in adolescent boys and the Child Group while adnexal torsion was most common in adolescent girls. Intussusception, adhesive small bowel obstruction and gastrointestinal perforation were encountered in all age groups

Conclusion: Although acute appendicitis is the most common cause of acute abdomen in children, other causes are not uncommon and some need special attention as differential diagnosis and intervention are "more urgent" than others. Awareness of these "more urgent" conditions with respect to age groups may prevent complications, morbidity, and even mortality.

Keywords: Abdomen, acute, intussusception, adnexal torsion, intestinal obstruction

Öz

Amaç: Çocuklarda akut apandisit dışı akut cerrahi nedenlerin değerlendirilmesi.

Gereç ve Yöntem: Ocak 2017- Aralık 2020 tarihleri arasında acil karın cerrahisi yapılan çocuk hastalar retrospektif olarak değerlendirildi. Yenidoğan dönemindeki hastalar ve apandisit nedeniyle ameliyat edilen hastalar çalışma dışı bırakıldı.

Bulgular: 595 hastaya acil abdominal cerrahi yapıldı. 468'inde (%78,7) kesin tanı apandisitti. Apandisit dışı nedenle ameliyat edilen 127 hastanın (%21,3) ortanca yaşı 8 (0,96- 17,75) yıldı. Travma ile başvuran 14 (%11) hasta vardı (12 erkek, 2 kız, ortanca yaş; 12,66 yıl). En sık travma nedeni ateşli silah yaralanması ve en sık yaralanma gastrointestinal sistemde yaralanmasıydı. Nontravmatik Grupta 62 (%54,6) hasta erkek ve 51 (%45,1) hasta kızdı (ortanca yaş; 6,41 yıl). İnfantlarda ve küçük çocuklarda en sık invajinasyon görüldü. Ergen erkeklerde ve Çocuk Grubunda en sık adhesiv barsak tıkanıklığı görülürken, ergen kızlarda en sık adneksiyal torsiyon görüldü. İnvajinasyon, adhesiv barsak tıkanıklığı ve gastrointestinal perforasyon tüm yaş gruplarında görüldü.

Sonuç: Çocuklarda en sık akut karın nedeni akut apandisit olsa da, diğer nedenler de nadir değildir ve ayırıcı tanı ve müdahalenin "daha acil" olması nedeniyle dikkat edilmelidir. Yaş gruplarına göre bu "daha acil" durumların farkında olunması komplikasyonları, morbiditeyi ve hatta mortaliteyi önleyebilir.

Anahtar Kelimeler: Karın, akut, intususepsiyon, adneksiyal torsiyon, barsak tıkanıklığı

Corresponding *(İletişim)*: Berat Dilek Demirel, Ondokuz Mayıs University, School of Medicine, Department of Pediatric Surgery, Samsun, Turkey
E-mail *(E-posta)*: bdayhan@hotmail.com
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INTRODUCTION

The management of acute abdominal pain in children is challenging as the differential diagnosis of acute abdomen involves many medical and surgical conditions depending on the age groups.[1] As the most common surgical condition in children, acute appendicitis is commonly used as a synonym of acute abdomen.[2] However, other causes of the acute abdomen are not infrequent in children and differential diagnosis and intervention is more urgent than acute appendicitis as they may cause significant morbidity and mortality if recognition or intervention are delayed.[3] Acute abdomen is a relatively vague term which is used for a range of conditions, and a definitive diagnosis may not even be achieved by radiological and laboratory evaluations in some. In such a patient presenting with abdominal pain, vomiting and fever triad, surgical exploration may be needed to rule out or confirm a surgical condition.[4] The decision for the timing and urgency of the surgical intervention is critical when evaluating a child presenting with findings of the acute abdomen to prevent unnecessary interventions and to reduce morbidity and mortality.[3] The first clue for the differential diagnosis of children with acute abdomen may be the patients' age and even gender. In this study, our aim is to evaluate the surgical emergencies other than acute appendicitis in different age groups in children.

MATERIAL AND METHOD

The children (≤18 years) who underwent urgent abdominal surgery between January 2017-December 2020 in a tertiary referral center are enrolled in the study. Newborns (0-30 days old) and patients with acute appendicitis are excluded from the final analyses. Patients' age, gender, indication of the surgery, morbidity, and mortality are retrospectively evaluated. Patients were divided into subgroups according to age, as Infant (1 month-2 years), Young Child (2-6 years), Child (6-12 years), and Adolescent (>12 years) proposed by World Health Organization.

For descriptive statistical analysis, median, minimum and maximum values, frequency and percentage values were calculated. Kolmogorov-Smirnov test was used to evaluate for normal distribution of the variables and Kruskal Wallis test (Mann-Whitney U test for pairwise comparison) was used for the comparison of the quantitative data. Qualitative variables were analyzed by the Chi-Square test. SPSS® 22.0 program (IBM Corp., Armonk, NY, USA) was used for statistical analyses. A p-value < 0.05 was considered statistically significant.

RESULTS

During the study period, 595 patients had undergone urgent abdominal surgery excluding the newborns. Acute appendicitis was the most common indication (78.7%; n=468) encountered in 305 boys (65.2%) and 163 girls (34.8%) with a median age of 11.08 years (0.67-17.91 years). When acute appendicitis was excluded, the study group comprised of 74 boys (58.3%) and 53 girls (41.7%) with a median age of 8 years (0.96-17.75 years). Gender distribution was similar between the 2 groups but the median age was significantly lower in the non-appendicitis patients (p=0.000).

Fourteen patients (11%) with a median age of 12.66 years (5.25-17.58 years) were operated for abdominal trauma; 12 were boys and 2 were girls. In total, 62 boys (54.6%) and 51 girls (45.1%) were operated for indications other than trauma and acute appendicitis with a median age of 6.41 years (0.96-17.75 years). Male gender and median age were significantly higher in the patients operated for trauma(p=0.027 and p=0.04, respectively).

The most common cause of abdominal trauma was firearm injuries. Trauma patients were young children (n=1), children (n=6) or adolescents (n=7), and the most common injury was gastrointestinal perforation (**Table 1**). Two patients with trauma were deceased (14.3%); an 8 years old girl involved in a motor vehicle accident with multi-organ injuries and an 11.5 years old boy with intracranial bleeding who fell from a high place. Right nephrectomy was performed in another 13,5 years old boy. No other mortality or major organ loss was observed in any other trauma patient.

Table 1. Demographics and evaluation of the patients with trauma

Patient	Age years	Gender	Trauma	Involved organ
1	17.50	boy	Firearm injury	liver-diaphragma
2	14.75	boy	Penetrating stab injury	liver-diaphragma
3	8.00	girl	Motor vehicle accident	stomach-duodenum-jejunum-ovaries-ureter
4	11.25	boy	Firearm injury	liver-pancreas
5	17.58	boy	Motor vehicle accident	duodenum-jejunum
6	11.58	boy	Fall from a high level	jejunum
7	5.25	boy	Firearm injury	liver-duodenum
8	15.91	boy	Motor vehicle accident	diaphragma
9	10.50	boy	Bicycle accident	ileum
10	13.75	boy	Firearm injury	liver-kidney-duodenum-jejunum-colon-choledochus
11	9.08	girl	Firearm injury	ileum
12	14.66	boy	Firearm injury	colon-ileum
13	15.58	boy	Firearm injury	none
14	11.50	boy	Fall from a high level	none

Intussusception was the most common indication for urgent abdominal surgery after acute appendicitis and trauma. All patients with intussusception underwent surgery after at least one failed attempt of hydrostatic reduction. Intussusception was the most common indication of surgery in infants and young children. Adhesive small bowel obstruction was the most common cause in children and adolescent boys while adnexal torsion was most common in adolescent girls (**Table 2**). No definitive diagnosis could be achieved in 6 patients (5.3%) even after surgical exploration. Although distribution was heterogenous, intussusception, adhesive small bowel obstruction and gastrointestinal perforation were encountered in all of the age groups (**Figure 1**).

Table 2. Age distribution of the children who underwent urgent surgery for reasons other than trauma and acute appendicitis.

	Infant	Young children	Children	Adolescent	Total
Intussusception	15	9	6	2	32
Adnexal torsion	0	1	5	12	18
Incarcerated diaphragmatic hernia	3	1	0	0	4
Strangulated inguinal hernia	3	0	0	0	3
Meckel's diverticulum	0	2	0	2	4
Adhesive small bowel obstruction	2	5	7	7	21
Gastrointestinal perforation	4	1	2	7	14
Volvulus	4	1	0	0	5
Gallbladder perforation	0	0	0	1	1
Internal herniation	0	0	0	1	1
Colonic stricture	2	0	0	0	2
Colon tumor	0	0	0	1	1
Duplication cyst	0	0	1	0	1
Negative exploration	2	0	1	3	6
Boys/Girls	28/7	10/10	8/14	16/20	62/51
Total	35 (31%)	20 (17.7%)	22 (19.5%)	36 (31.9%)	113

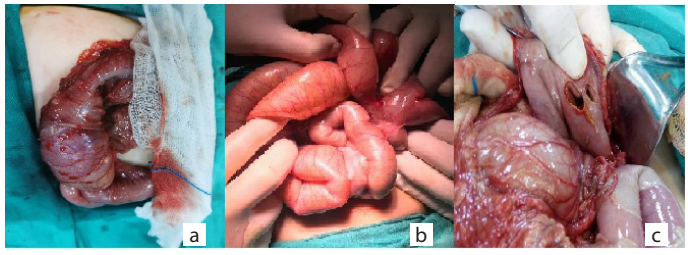

Figure 1. a: Ileo-colic intussusception. **b:** Adhesive small bowel obstruction due to previous abdominal surgery. **c:** Stomach perforation secondary to peptic ulcer.

Strangulated inguinal hernia and colonic stricture secondary to necrotizing enterocolitis (NEC) were seen only in infants while volvulus and incarcerated diaphragmatic hernia were only in infants and young children. Adnexal torsion was encountered in young children, children and adolescents while internal herniation (due to congenital band), gallbladder perforation and colonic obstruction (due to tumor) were encountered only in adolescents (**Figure 2**). With respect to underlying neoplastic conditions, a child had Burkitt's Lymphoma (intussusception) and another had rhabdomyosarcoma (jejunal perforation due to tumor invasion) while an adolescent had colonic adenocarcinoma (colonic obstruction) and another had an ovarian dermoid tumor (ovarian torsion).

When patients with trauma were excluded, 4 patients were deceased in the perioperative period; an infant with intestinal perforation secondary to NEC, a young child with adhesive small bowel obstruction who had previous multiple abdominal operations, a child with gastric perforation (with co-existing chronic kidney failure) and an adolescent with multiple intestinal perforations of unknown etiology. Two patients (rhabdomyosarcoma and colonic adenocarcinoma, respectively) were deceased due to malignancy during follow-up after the operation. The mortality rate was 14% (2/14) in patients with trauma and 5% (6/113) in the rest of the patients.

DISCUSSION

Abdominal pain is one of the most common complaints for hospital admittance in childhood and is a benign process in most instances.[5] However, among this crowded population, some patients require special attention as they need to be identified and managed appropriately and urgently due to the emergency of their disease process. The identification of these patients is challenging and even a diagnostic surgical exploration may be necessary for some as laboratory, clinical and radiological evaluations remain inconclusive.[6] Although acute appendicitis is the most common urgent surgical condition in children, there are more urgent conditions in children that can not wait to see the sunrise.[3] Differential diagnosis of these conditions is challenging and delay in diagnosis may cause significant morbidity and even mortality.[7]

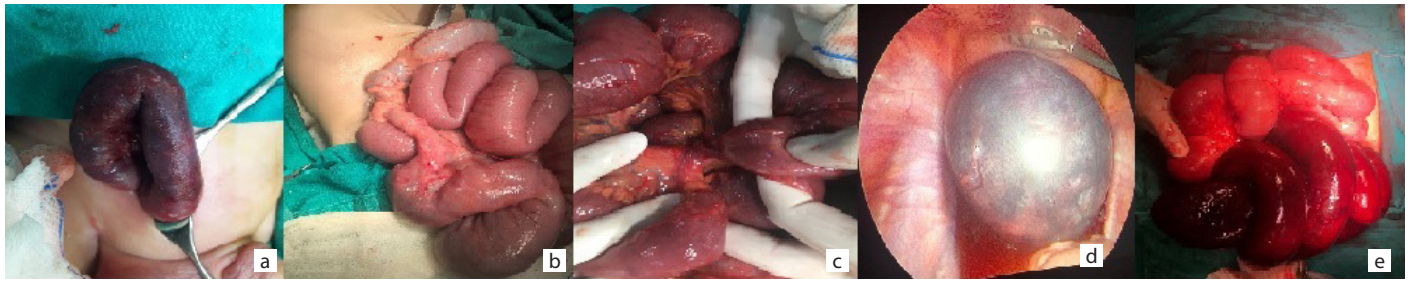

Figure 2. a: Strangulated inguinal hernia. **b:** Colonic stricture due to previous NEC and secondary ileal dilation. **c:** Internal herniation due to congenital band **d.** Ovarian torsion **e.** Intestinal ischemia and necrosis due to volvulus.

Although rare, abdominal trauma is a significant cause of morbidity and mortality in children. Although the majority are spleen or liver injuries due to blunt trauma that can be managed conservatively in most cases, penetrating firearm and/or stab injuries are not so uncommon and are more likely to require surgical intervention.[8,9] In our series, 8 of the 14 trauma patients had penetrating injuries. Although blunt trauma can be seen in all age groups, penetrating trauma is much more prevalent in adolescents.[10] In our series, all of the urgent interventions for trauma were in the Child and Adolescent Groups, and the median age was 2 fold higher than the patients operated for other reasons.

The most common reason for urgent surgery in children is acute appendicitis[11] and constituted 78.7% of the patients who received urgent abdominal surgery in our series. Although surgical emergencies beyond trauma and acute appendicitis are relatively rare in children, related morbidity and mortality are relatively high.[12] Diagnosis of medical conditions is challenging in children as poor verbal cooperation limits the valuable information obtained by history, which is more prominent in younger ages. Especially in infants, patients may admit with vague symptoms like persistent crying, refusal of feeding or restlessness.[13] Differential diagnosis is essential to determine the urgency of the surgical intervention as some conditions like acute appendicitis may wait for the sunrise while others better not. The indications of urgent surgery in infants include intussusception, strangulated inguinal hernia, volvulus, complicated Meckel's diverticulum and adhesive small bowel obstruction due to previous surgeries.[14] Acute abdominal surgery is least common in young children[12,15] and our results also indicate the same finding. Although young children may express their complaints and be more cooperative while story taking, they usually cooperate poorly during physical examination.[16]

In our study, intussusception was the most prevalent condition in infants and young children. Currently, non-surgical management is the first-line option for intussusception and commonly hydrostatic reduction under ultrasonography or fluoroscopy is commonly performed with success rates around 90%.[17,18] Intussusception was the surgical indication in 24 of the 55 infants and young children in our series, and all underwent operation after at least one failed attempt of hydrostatic reduction. Although most cases can be managed without surgery, some require surgical correction and delay in diagnosis and treatment may cause loss of a significant amount of intestine and even result in mortality.[19]

Volvulus is also a rare but serious condition in which prompt diagnosis and correction are essential in order to prevent significant morbidity and mortality. Although most present during the newborn period, about 30% may present later in life.[20] In our study, 1 of the 5 patients with volvulus was a young child and the rest were infants.

An incarcerated inguinal hernia is a common condition in children, and usually can be reduced manually by experienced hands obviating an urgent surgical intervention.[21] Urgent surgery is indicated when hernia can not be reduced and intestinal resection may be necessary in a minority of cases due to compromised blood flow of the incarcerated segment.[22] In our series, only 3 infants required urgent surgery for an incarcerated hernia.

Complicated Meckel's Diverticulum, adhesive small bowel obstruction, adnexal torsion are the common urgent surgical conditions in the Child age group after acute appendicitis.[23] In our study, adhesive small bowel obstruction was the most common condition in this age group and intussusception remained a significant cause of surgical intervention.

Adnexal torsion can be seen in the Child and Adolescent age groups and although rare, can cause organ loss and even compromise fertility if diagnosis and intervention are delayed.[24] As the uterine adnexa resides in the pelvis, these patients may present with non-specific symptoms and clinical findings may be vague; therefore, children and adolescent girls presented with acute abdomen should be carefully evaluated for adnexal torsion.[25,26] In our study, five of the 14 girls in the Child Group and 12 of the 20 girls in the Adolescent Group underwent surgery for adnexal torsion.

Adhesive small bowel disease can be seen in 1-9% of the patients with a previous history of abdominal surgery and more than 50% can be managed by conservative approach. A small portion of patients may require surgery due to failed conservative management.[27] Beyond trauma and acute appendicitis, adhesive small bowel disease was the second most common cause of urgent surgery after intussusception in our study. Although prevalent in all age groups, it was the most common surgical condition in the Child Group and adolescent boys.

The incidence of peptic and gallbladder diseases appear to increase in recent years, possibly due to changing trends in eating habits.[28] Peptic diseases are reported to be the most common cause of non-traumatic stomach perforations in children and gastric perforation was most common in adolescent patients.[29] Similarly, gastrointestinal perforation incidence was higher in adolescents in our series and we have encountered a very rare case of gallbladder perforation in an adolescent.

Despite amazing developments in medical knowledge and diagnostic technology, the final diagnosis can be achieved after surgical exploration in a significant amount of patients.[6] Even so, some of these explorations do not reveal a surgical cause but may help to exclude a surgical cause to re-direct the diagnostic process. In our study, we also could not be able to reach a final diagnosis even after surgical exploration in 2 patients with trauma and 6 patients with non-traumatic acute abdomen.

CONCLUSION

Although acute appendicitis is the most common cause of acute abdomen in children, a significant rate of patients suffer from other conditions. The incidence of these other conditions vary among age groups and appropriate and timely diagnosis requires knowledge and familiarity by the clinician and the radiologist. Although delay in differential diagnosis may cause morbidity and even mortality, rushing to the operation room may also increase the rate of unnecessary interventions or complications.

ETHICAL DECLARATIONS

Ethics Committee approval: This study was approved by Ethic Committee of Ondokuz Mayis University (IRB approval number:2020/711).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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Orjinal Araştırma / Original Article

Investigation of MMP-9 and E-Selectine Levels in Gunshot Injuries

Ateşli Silah Yaralanmalarında MMP-9 ve E-Selektin Düzeylerinin Araştırılması

Elif Demir[1], Ramazan Giden[2]

[1]Harran University Medical School Department of Medical Biochemistry, Şanliurfa, Turkey
[2]Sanliurfa Research and Training Hospital Emergency Department, Şanliurfa, Turkey

Abstract

Aim: Our aim in this study is to determine how matrix metalloproteinase-9 (MMP-9) and E-selectin levels are affected in the damage caused by gunshot injuries. At the same time, it is to investigate the value of these parameters in terms of biochemical parameters in these cases and to propose new opinions on the subject.

Material and Method: 40 control groups and 48 patients who were brought to the hospital emergency department as a result of gunshot wounds were included in the study. Venous blood samples of the patient and control groups were taken. Serum MMP-9 and E-selectin levels were measured quantitatively by using ELISA method. The obtained results were evaluated in the SPSS 25 program.

Results: MMP-9 levels measured in our patient group were significantly higher than in the control group ($p < 0.001$). Although the patient group was higher than the control group in terms of e-selectin levels, no statistical significance was found.

Conclusion: Various tissue damage occurred in the patient group. The release of MMP-9 by inflammatory cells indicates that serum MMP-9 levels are high in patients with intense inflammation and high inflammatory cell load. The increase in E-selectin level indicates endothelial cell damage.

Keywords: Gunshot, injury, MMP-9, E-selectin

Öz

Amaç: Bu çalışmadaki amacımız, ateşli silah yaralanmalarında meydana gelen hasarda matriks metaloproteaz-9 (MMP-9) ve E-selektin düzeylerinin nasıl etkilendiğini tespit etmek. Aynı zamanda bu parametrelerin bu vakalardaki biyokimyasal parametre açısından değerini araştırmak, konuyla ilgili yeni görüşler ileri sürebilmektir.

Gereç ve Yöntem: Ateşli silah yaralanmasına sonucu hastane acil servisine getirilen 48 olgu ile 40 kontrol grubu çalışmaya alındı. Hasta ve kontrol grubun venöz kan örnekleri alındı. Serum MMP-9 ve E-selektin düzeyleri ELISA yöntemi uygulanarak kantitatif olarak çalışıldı. Elde elden sonuçlar SPSS 25 programında değerlendirildi.

Bulgular: Hasta grubumuzda ölçülen MMP-9 düzeyleri kontrol grubuna göre anlamlı derecede yüksek iken ($p<0,001$), E-selektin düzeyleri açısından hasta grubu, kontrol grubundan yüksek olmasın rağmen istatistiksel olarak herhangi bir anlamlılık tespit edilmedi.

Sonuç: Hasta grubunda çeşitli doku hasarları meydana gelmiştir. MMP-9'un inflamatuvar hücrelerce salınması, inflamasyonun yoğun olduğu ve inflamatuvar hücre yükünün fazla olduğu hastalarda serum MMP-9 düzeylerinin yüksek olduğunu görülmüştür. E-selektin düzeyindeki bir miktar artış ise endotel hücre hasarını göstermektedir.

Anahtar Kelimeler: Ateşli silah, yaralanma, MMP-9, E-selektin

Corresponding *(İletişim)*: Elif Demir, Harran University Medical School Department of Medical Biochemistry, Şanlıurfa, Turkey
E-mail *(E-posta)*: e.deniz63@hotmail.com
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INTRODUCTION

In recent years, with the increasing rate of wars, terrorist incidents and individual armament, the frequency of injuries caused by gunshot has been increasing. Gunshot injuries are a group of trauma with difficulties in their treatment and high morbidity and mortality rates. The most important reason for that bullets and explosive weapon parts carrying high kinetic energy that cause such injuries can damage the surrounding tissues due to the blast effect (temporary cavity) while moving through the body.[1,2] In addition to the permanent and temporary cavity effects of high kinetic energy weapons, the damage they inflict increases with the effects of both the deflected bullet fragments and the bone tissues that they shred as they move through the body. For this reason, it is extremely difficult to predict the size of the actual injury and the complications that may develop in patients.[3] The modern wound ballistics bullet or projectile on which Kocher is based; examines penetration (puncture], permanent cavity (wound path), temporary cavity (blast effect), fragmentation and shock waves effects.[4] Penetration is the first and main effect of the bullet. The kinetic energy of a bullet determines the penetrating power.[5] Bone, cartilage, tendon and other hard tissues to which kinetic energy is transferred can also act like bullets and cause damage. Physical penetration of the bullet through the tissues causes a permanent tissue loss or tissue destruction.[6,7] When the bullet enters the body, it first encounters the skin tissue. Since the skin tissue is rich in elastic connective tissue, it shows a high resistance to penetration. Among the body tissues, the most resistant tissue against penetration is bone tissue. The organs that can cause death at first glance in the human body are protected with bones.[8] Muscle tissue is moderately resistant to bullet penetration, however, it is the overlying fascia layer that increases the resistance of the muscle tissue.[9] Hollow organs such as stomach and intestines show moderate resistance to bullets due to their wall structures. The factor determining the severity of the injury in hollow organs is the blast effect created by the bullet in the organ. Parenchymal organs such as the liver are extremely sensitive to penetration, and the bullet usually pierces these organs completely.[8] One of the factors that change the severity, depth and size of the injury in penetrating traumas due to gunshot is the rupture of the bullet. Pistol bullets often deform when colliding with a hard obstacle, but rifle bullets can easily break up when colliding with a hard object. Bone tissue is the biggest factor causing bullet disintegration in body tissues.[10]

The extracellular matrix (EM) is a dynamic structure that creates a special environment in the intercellular spaces. It helps hold cells in tissues together and acts as a reservoir for many hormones that control cell growth and differentiation. Matrix metalloproteases (MMPs) are a multigenic family of endopeptidases that break down EM and are active at neutral Ph.[11] Although MMP-9 breaks down EM, it proteolytically breaks down decorin, elastin, fibrilin, laminin, gelatin, and type IV, V, XI, and XVI collagen. MMP-9 plays a major role in normal tissue structuring such as axon development, embryonic development, angiogenesis, ovulation, mammary gland formation and wound healing.[12] MMP-9 is frequently encountered in invasive and highly tumorigenic cancers such as colorectal tumors, gastric carcinoma, pancreatic carcinoma, breast and mouth cancer, melanoma, malignant glioma, chondrosarcoma, and gastrointestinal adenocarcinoma.[13] Activation of MMP-9 has also been observed in diseases such as arthritis, autosomal recessive osteolysis disorder, coronary artery disease, emphysema and diabetic retinopathy.[14]

Selectins are multifunctional adhesion molecules that regulate the initial interactions between circulating leukocytes and endothelial cells. Adhesion molecules; they are involved in cell protection, wound healing, and tissue integrity.[15] Leukocytes attach to the vascular wall in response to tissue damage or infection via 3 types of adhesion receptors called selectin. Selectins are expressed on the surface of endothelial cells, leukocytes, and platelets.[16] Its expression increases against inflammatory stimuli.[17] Selectins (P, E and L) and their ligands are required for leukocyte rolling and binding in the vascular wall.[18] Circulating E-selectin (soluble) is accepted as a marker of endothelial cell damage or activation.[19]

MATERIAL AND METHOD

This study was approved by the Harran University Ethics Committee (no:2016/03-35). In this study, the necessary ethics committee approval was obtained and all participants included in the study were informed about what to do with the "Informed Consent Form" and their consent was obtained for their volunteerism.

Patient Group: Among the cases brought to the hospital emergency department as a result of Gunshot injuries, no additional pathology was found except for gunshot-related injuries and no systemic disease was detected in clinical and laboratory examinations, and those who did not use alcohol, cigarettes and drugs were included in our study. The age distribution of the cases, their characteristics such as the injured area and organs were determined and discussed. All 48 cases included in our study were male and the age range was between 18-51. The injuries were predominantly in the lower and upper extremities, but also in the chest, abdomen, thorax head and neck regions. All of our cases recovered and were discharged after the treatment they received.

Control Group: As the control group, 40 healthy adults with no history of complaints, no pathology detected in physical examination, no local or systemic disease detected in clinical and laboratory examinations, and no alcohol, smoking or drug use were included in the study. All of our control group was male and was in the age range suitable for the patient group.

Venous blood samples of the patients were collected. Centrifugation was done at 1000 rpm for 10 minutes. It was stored at -80 degrees until biochemical analysis. Serum MMP-9 and E-selectin levels were measured quantitatively by using ELISA method.

Statistical Analysis

While evaluating the study data, besides descriptive statistical methods (mean, standard deviation), the Independent simple T test was used for the comparison of the parameters between the groups for the comparison of quantitative data. One-Way ANOVA test was used in group comparisons consisting of more than 2 groups. Pearson and Spearman's correlation analysis was used to evaluate the relationships between parameters within the group of parameters with normal distribution. Significance was evaluated at the $p<0.05$ level.

RESULTS

In gunshot injuries included in our study, the patient group and our control group were all male, and the average ages of the participants were consistent (**Table 1**).

Table 1. Average age and standard deviation (SD) of the patient and control groups in gunshot injuries

	Mean ± SD
Patient (48)	27,79 ± 10,54
Control (40)	28,98 ± 11,10

MMP-9, E-selectin levels and P values measured in the patient group in our study and the control group are shown in **Table 2**. MMP-9 levels measured in our patient group were significantly higher than in the control group ($p<0.001$). Although the patient group was higher than the control group in terms of e-selectin levels, no statistical significance was found. No significant positive or negative correlation was found between these parameters in the gunshot injured patient group.

Table 2. Statistical comparison of MMP-9 and E-Selectin values in patient and control groups in gunshot injuries

	Group	Mean ± SD	P
MMP-9	Patient	1543.35 ±758.86	<**0,001**
	Control	903.27 ± 323.65	
E-Selectin	Patient	27.75 ± 11.43	0.489
	Control	25.95 ± 12.84	

MMP-9: Matrix Meteloproteinase-9, SD: Standard Deviation
* P value 0.05 was considered statistically significant.

DISCUSSION

Gunshot wounds are a group of trauma that has difficulties in treatment and has a high morbidity-mortality rate.[20,21] While the bullets traverse high-density tissues such as muscle, liver and spleen, a global destruction occurs in the tissues in front of them with the effect of a shock wave. With the effect of these shock waves, tissue damage may occur at a distant point other than where the bullet passes.[22,23] There is no study in the literature showing the comparison of MMP-9 and E-selectin levels in gunshot injuries.

MMPs have been found to play a role in many diseases in studies conducted to date. MMPs were found to be associated with stroke, multiple sclerosis, Alzheimer's disease, cancer, atherosclerosis, arthritis, nephritis, gastrointestinal ulcer, periodontal disease, corneal ulcer, skin ulcer, liver fibrosis and pulmonary diseases such as asthma, emphysema, and chronic obstructive pulmonary disease.[24]

In the group of gelatinases are MMP 2 (gelatinase A) and MMP 9 (gelatinase B). This group easily digests denatured collagen and gelatin.[25] Type IV collagen is the main component of basement membranes and constitutes 40-65% of the basement membrane total protein.[26] MMP-9, whose primary task is to break down EM, also plays a major role in normal tissue reconstruction such as axon development, embryonic development, angiogenesis, ovulation, mammary gland formation and wound healing.[12]

Many studies have determined different serum MMP-9 levels. Cojocarui et al.[27] found that MMP-9 level in the acute period in ischemic stroke. Eckart et al.[28] found MMP-9 levels to be low in acute myocardial infarction and it was stated that this low MMP-9 level could be an indicator of myocardial damage. Susskind et al. In his study, lung damage caused by ionizing radiation was examined by looking at the plasma levels of MMP-9, TIMP-1 and MMP-3, which are biological markers of tissue damage, and their relationship with pulmonary epithelial permeability, clinical signs, symptoms, and structural changes in the lung. MMP-9, TIMP-1 and MMP-3 levels were measured before treatment, during treatment and approximately 100th day after treatment in eight patients with breast and lung cancer who received radiotherapy to the chest region. In all of these patients, MMP-9 and TIMP-1 levels, which were very high before radiotherapy, were observed to have a sudden decrease only in MMP-9 after the first two weeks of radiotherapy.[29]

Inflammation is a protective response developed for the continuity of the organism to prevent microorganisms or toxins from damaging cells or to remove necrotic and dead tissues caused by damage.[30] Under normal conditions, strict control of the response prevents further damage and while the damaged tissues are cleaned, pathological inflammation that occurs in disease states causes EM destruction and organ dysfunction.[31] MMPs are secreted in response to a variety of inflammatory mediators and inhibited by tissue inhibitors of matrix metalloproteinases (TIMPs).

When the MMP-9 levels measured in the patient group and the control group were compared in gunshot injuries included in our study; The patient group was significantly higher than the control group ($p<0.001$). Various tissue damage occurred in the patient group. The release of MMP-9 by inflammatory cells explains the high serum MMP-9 levels in patients with intense inflammation and high inflammatory cell load.

Adhesion molecules are involved in cell protection, wound healing, and tissue integrity.[32] As is known, there are four types of adhesion molecule families. These are integrins, selectins,

immunoglobins and cadherins. Selectins are expressed on the surface of endothelial cells, leukocytes, and platelets.[16] E-selectin mainly plays a role in leukocyte adhesion. The role of the e-select in this phenomenon is to ensure that the rolling returns to slow rolling and tight adhesion. It has been shown that antibodies that act directly against E-selectin prevent inflammation and thus, E-selectin is an adhesion molecule that plays a role in inflammation.[33]

In recent studies, it has been shown that inflammation has a share in many diseases and health problems and is associated with different clinical forms of these diseases.[34-38] Adhesion molecules show endothelial activation or damage. Adhesion molecules stimulated by circulating cytokines direct the movement of cells instead of inflammation.[34] Excessive proteolytic enzyme release due to inflammation disrupts the connection of these epithelial cells with each other and with EM.[38] It is known that endothelial cells have many functions that regulate immune and inflammatory events. Cell adhesion molecules play a role in the leukocyte-endothelial relationship.[34] The first step in the development of the inflammatory response is the adhesion of leukocytes to the vascular endothelium. E-selectin, one of the various adhesion molecules whose expression is known to be the result of cytokine activation, is the earliest released adhesion molecule. Studies show that the expression of E-selectin increases in the first two hours when the inflammatory response begins to ocur.[35]

When the E-selectin levels measured in the patient group and the control group were compared in the gunshot injuries included in our study, although the patient group was higher than the control group, no statistically significant significance was found (p=0.489). However, the increase in the level of E-selectin in the patient group compared to the control group indicates that there is endothelial cell damage.

CONCLUSION

Our aim in this study was to determine how MMP-9 and E-selectin levels are affected in gunshot injuries. These parameters are not routine laboratory parameters. Although patients with lower and upper extremity gunshot injuries are prominent, a small number of patients with injuries to other body parts were also included in our study. Although the number of patients with extra-extremity injuries in our study was low, MMP-9 levels increased statistically significantly in our patient group. All our patients were discharged after treatment without any complications. With this study, we think that mmp-9 levels may be an important parameter in showing the level of tissue damage in this patient group. The significant increase in MMP-9 within hours in sudden situations such as gunshot injury suggests that it may be a routine parameter that can be used to monitor the increase or decrease of tissue damage in patient follow-up. Our study should be supported by comprehensive studies in order to get better and to reach more precise results results in terms of these parameters.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Harran University Ethics Committee (no: 2016 / 03-35, date: 01.04.2016).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The Effect of Internet Addiction in Students on Quality of School Life

Öğrencilerde İnternet Bağımlılığının Okul Yaşam Kalitesine Etkisi

Erhan Aksoy[1], Ülkühan Öztoprak[1]

[1]University of Health Sciences, Ankara Dr. Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital, Department of Pediatric Neurology, Ankara, Turkey

Abstract

Aim: Internet addiction in children is a mental disorder that negatively affects the quality of life. In this day and age, internet usage, and school life, which takes a significant amount of time for students, are specified as engaged concepts that affect each other. Therefore, this study has been addressed to investigate the effects of internet addiction on primary, middle, and high school students on school life quality.

Material and Method: This research was conducted as a questionnaire study by Dr. Sami Ulus Training and Research Hospital Pediatric Neurology in the 2018-2019 academic year for Primary School, Middle, and High School students. The questionnaire consisted of sociodemographic information, Internet Addiction Scale (IAS), and Quality of School Life Scale (QSLS).

Results: Seven hundred eighty-eight students were included in the study. Mean age was 12.94±2.79 years (range 8 - 17). Internet addiction scores were 57.67±20.63, and 106 (13.80%) children had internet addiction. The Quality of School Life Scale total scores were found as 112.65±18.42. It was observed that school success and school life quality decreased as the internet addiction score increased. It was observed that the students' education and puzzle games compared to other websites caused lower IAS scores. The most significant differences were observed among high school students. While it was observed that IAS scores, internet addiction, family negative relationships, and exposure to violence rates were highest in high school students, QSLS scores, and course success were found below.

Conclusion: There is a need to develop programs that would minimize the excessive and useless internet use of students and improve the environmental factors that regulate their relationships in the family, school, and other settings.

Keywords: Internet addiction, quality of school life, children, student, ınternet tendency problems

Öz

Amaç: Çocuklarda internet bağımlılığı yaşam kalitesini olumsuz etkileyen mental bir bozukluktur. Yaşam kalitesinin niteliğini en az mental ve fiziksel sağlık kadar okul performans ve akademik başarılar da etkilemektedir. Bu nedenle ilkokul, ortaokul ve lise öğrencilerin internet bağımlığının okul yaşam kalitesine etkilerinin araştırılması amacıyla bu çalışma ele alınmıştır.

Gereç ve Yöntem: Dr. Sami Ulus Eğitim ve Araştırma Hastanesi Çocuk Nörolojisi tarafından 2018-2019 eğitim-öğretim yılında İlkokul, Ortaokul ve Lise öğrencilerine yönelik anket çalışması yapıldı. Çalışma gereçleri olarak sosyodemografik bilgiler formu, İnternet Bağımlılık Ölçeği (İBÖ) ve Okul Yaşam Kalitesi Ölçeği (OYKÖ) kullanıldı.

Bulgular: Çalışmaya 788 öğrenci dahil edildi. Yaş ortalaması 12,94±2,79 (8 -17) idi. İnternet bağımlılık skoru 57,67±20,63 idi. Öğrencilerin %13,8(106)'inde internet bağımlılığı saptandı. Okul yaşam kalitesi ölçeği toplam puanları 112,65±18,42 idi. İnternet bağımlılık skoru artıkça okul başarısının ve okul yaşam kalitesinin düştüğü görüldü. Eğitim amaçlı ve puzzle şeklinde oyun sitelerini ziyaret eden öğrenciler daha düşük internet bağımlılık skoruna sahip idi. En belirgin farklılıkların lise öğrencileri arasında olduğu saptandı. Lise öğrencilerinde internet bağımlılığı, ailevi olumsuz ilişkiler ve şiddete maruz kalma oranlarının en yüksek olduğu görülürken, okul yaşam kalitesi puanları ve ders başarısının düşük olduğu görülmüştür.

Sonuç: Öğrencilerin aşırı ve faydasız internet kullanımını en aza indirecek, aile, okul ve diğer ortamlarda ilişkilerini düzenleyen çevresel faktörleri iyileştirecek programların geliştirilmesine ihtiyaç vardır.

Anahtar kelimeler: İnternet bağımlılığı, okul yaşam kalitesi, çocuk, öğrenci, internet eğilim sorunları

Corresponding *(İletişim)*: Erhan Aksoy, MD; University of Health Sciences, Ankara Dr. Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital, Department of Pediatric Neurology, 06022, Ankara, Turkey.
E-mail *(E-posta)*: aksoyerhan24@gmail.com
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INTRODUCTION

Unhealthy internet use has become increasingly common in recent years due to technological advances and accessibily.[1,2] As per the Internet World Stats (IWS, 2020) data, 63.2% of the world is reported to use the internet. North America and Europe have the highest usage rates (90.3%, 87.2%, respectively), and Africa (47.1%) the lowest usage rates in terms of internet usage. [3] Excessive use of the internet, lack of self-control, or family difficulties in this regard increase the risk of internet addiction in children. Internet addiction causes negative symptoms such as fatigue, sleep problems, posture disorders, memory problems, learning difficulties, difficulty in expressing oneself, school failure, and decreased productivity. In conclusion, many psychiatric problems, such as anxiety, depression, and social isolation, appear.[2,4,5]

Quality of life is explained by the quality of the positive and negative emotions that the individual has in family, school, friends, and work environment. The World Health Organization (WHO) emphasized that children and adolescents' school performance and success are as important as their mental and physical health. Therefore, it would be an appropriate approach to look at the school environment from a broad perspective as a standard solution point to improve the quality of life. This situation will create a significant opportunity to increase the quality of the school and to pass down the achievements to be gained.[6,7] Many factors play a role in determining the quality of school life, such as the structure of families, their perspective on education, income levels, attitudes and behaviors, school administrators, teachers, students' self-confidence, feelings towards the school and their friends. Identifying these factors and focusing on their solutions is essential for improving the school environment.[8]

Both internet use and school take up a significant portion of students' time today. Therefore, these two parameters should be considered as engaged concepts. However, there is not enough evidence to show the relationship between internet use disorder (IUD) and factors such as school-related academic achievement, learning, absenteeism, and social functionality to date.[9] Therefore, this study aimed to investigate the effects of internet addiction of primary, middle, and high school students on the quality of school life.

MATERIAL AND METHOD

Student selection

This questionnaire study was conducted by Dr. Sami Ulus Gynecology, Child Health, and Diseases Training and Research Hospital Pediatric Neurology Clinic in the 2018-2019 academic year. A questionnaire was conducted in the Telsizler Primary School (from the 2nd grade), Muhammer Şahin Middle School and Yıldırım Beyazıt Anatolian High School in Altındağ district where low and middle-income families live in Ankara, the capital city of Turkey. With the help of school principals and teachers, two pediatric neurologists (EA, ÜÖ) performed a questionnaire for each class in 20 classes for students between the ages of 8-17 and without systemic disease. Observations of teachers were also taken into account in terms of objectivity. The questionnaire consisted of sociodemographic information, Internet Addiction Scale (IAS), and Quality of School Life Scale (QSLS). Two hundred twenty-one students were excluded due to missing or inconsistent answers. The data obtained from the remaining 788 students were transferred to SPSS for statistical study.

Study Procedure

Before applying the questionnaire to the students, the study protocol was reviewed and approved by the institutional review boards (Ankara and Altındağ National Education Directorate and relevant school directorates). The study was approved by the clinical research ethics committee of Health Sciences University Ankara Child Health and Diseases Hematology and Oncology Health Research and Application Center (Approval number 2018-190). Permission was obtained from the researchers (Fatih Canan, Mediha Sarı), who conducted the Turkish validity and reliability study of the questionnaire scales used in this study. Informed consent was obtained from the families voluntarily.

Data collection tools

The first section of the form: Sociodemographic Characteristics Form

In this form developed by the researchers, age, gender, school class, parental education level, number of siblings, family structure (nuclear family or extended family), academic success level, relationships with parents, exposure to violence, and characteristics of internet use (usage preferences, daily Internet usage time) were included.

The second section of the form: Internet Addiction Scale (IAS)

IAS Turkish version, developed by Nichols and Nicky in 2004 and adapted by performing Turkish validity and reliability study (Cronbach α = .95), was used.[1,10] This scale is a five-point Likert type assessment consisting of 27 items. The items were scored between 1-5 as "never" (1 point), "rarely" (2 points), "sometimes" (3 points), "often" (4 points), and "always" (5 points). The total IAS score was obtained by arithmetically summing the scores of each item. The total IAS score obtained per this scoring ranges from a minimum of 27 to a maximum of 135 points. The resulting score of 81 (3x 27 items) and above was considered as internet addiction.[1]

The third section of the form: Quality of School Life Scale (QSLS)

Quality of school life criteria varies from country to country due to cultural and socio-economic differences.[6,11,12] For this reason, the QSLS developed for Turkey was preferred in this study.[13] This scale includes a total of 35 items consisting of 20 positive and 15 negative questions. It includes five sub-dimensions as nine items of "teachers" that determine the quality of their communication with students and their professional development level, nine items of "students" that determine the

quality of communication between students at school, eight items of "feelings towards school" that determine positive or negative emotions, six items of "principal" that determines the level of sensitivity towards the problems of the students at school, the quality of their communication with the students, the importance they attach to participation in the school, and three items of "status" that determines to what extent students feel important and valuable as individuals at school. Turkish validity and reliability Cronbach's alpha reliability coefficients for these 5 dimensions are .83, .80, .82, .77, .69, respectively. The fit indicators examined in the confirmatory factor analysis performed with the LISREL 8.30 package program also gave satisfactory results in terms of the model's good fit with the data [χ^2= 2003.03 (sd=547, p<0.001), (χ^2/sdi=3.66, RMSEA=0.068, NNFI=0.94, CFI=0.95 ve GFI=0.83]. Each item contains five options. These options are scored between 1-5 as "Strongly Disagree" (1 point), "Disagree" (2 points), "Slightly Agree" (3 points), "Agree" (4 points), and "Strongly Agree" (5 points). QSLS scores for the five sub-dimensions and consisting of the sum of these sums were calculated separately. As per this calculation method, the sum of reversed option points in negative items and option points in positive items was obtained.

Statistical Analysis

All analyses were performed on the SPSS v21 program (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used for the normality check. Normally distributed variables were analyzed with the independent samples t-test or one-way analysis of variances (ANOVA) depending on the count of groups. Pairwise comparisons of these variables were performed with the Tamhane test. Non-normally distributed variables were analyzed with the Mann-Whitney U test or Kruskal Wallis test depending count of groups. Pairwise comparisons of these variables were performed with the Bonferroni correction method. Categorical variables were analyzed with the Chi-square tests. P<0.05 values were accepted as statistically significant results.

RESULTS

Seven hundred eighty-eight children (438 girls and 350 boys) were included in our study, and the mean age was 12.94±2.79 years (range 8 - 17). Two hundred and sixty-one (33.12%) children were in primary school, 249 (31.60%) children were in middle school, and 278 (35.28%) children were in high school. The most common education status was high school both for mothers (32.08%) and fathers (37.34%). Most of the children were living with a nuclear family (77.93%, mother-father-single child). Two hundred and ninety-eight (38.90%) children were very good at school lessons while 219 (28.59%) children were good, 189 (24.67%) children were average and 60 (7.83%) children were unsuccessful. Most of the children described relationships with parents as "good" (72.48%). One hundred and seventy-nine (23.16%) children were exposed to violence. Characteristic features of the students are presented in **Tables 1** and **2.**

Table 1. General features of students

	n (%)/mean±sd	p
Student number	788	
Gender (F/M) (F %)	438/350 (55.5 %)	
Mean age	12.94±2.79 (8-17)	
Primary school	261 (33.12%)	
Middle school	249 (31.60%)	
High school	278 (35.28%)	
School success(very good/others**) (good %)	298/468 (37.8 %)	
Relationships with parents (good/ others**) (good %)	561/213 (71,1 %)	
Exposed to violence (yes/no) (yes %)	179/609 (22.7 %)	
Internet characteristic		
Internet use	741 (94.04%)	
IASs	57.67±20.63	
Internet Addiction	106 (13.80%)	
IASs (gender)		**0.042**
F	56.74±21.71	
M	58.83±19.14	
IAS s (school success)		**<0.001**
Very good [a]	49.68±17.65	
Good [b]	57.07±18.56	
Average [c]	65.87±20.18	
Unsuccessful [c]	74.45±23.34	
IASs(Daily duration of internet use)		**<0.001**
1 hour [a]	49.26±17.62	
2 hours [b]	57.32±17.90	
Equal or more than 3 hours [c]	67.49±21.13	
IASs(Negative family relationships)		**<0.001**
No	54.91±19.99	
Yes	67.84±19.90	
IASs(Exposed to violence)		**<0.001**
No	54.89±20.56	
Yes	66.51±17.97	
IASs (most commonly visited website)		**<0.001**
Education [b]	47.04±16.79	
Social media [a]	64.58±21.73	
Movies, TV [a]	58.98±19.42	
Game [a]	59.57±19.53	
IASs (type of games)		**<0.001**
Puzzle [b]	51.38±19.70	
Racing [a]	58.13±15.71	
Sport [a]	59.45±19.46	
Action [a]	59.70±20.92	
QSLS characteristic		
Teachers	29.65±6.58	
Students	29.12±6.78	
Feelings toward school	26.93±6.61	
Principal	17.31±5.26	
Status	9.65±3.17	
Total	112.65± 18,42	

sd: Standart deviation, F: female, M: male, IAS s: Internet addiction scale score, QSLS: Quality of School life scale Others**: good, average, unsuccessful for school success, moderate, bad for relationships with parents.
a,b,c ; statistical difference between a,b and c, a,b ; statistical difference between a and b.

Most of the children had used the internet actively 741 (94.04%). IAS scores were found as 57.67±20.63 (range 27 - 135) and 106 (13.80%) children had internet addiction. Also, we found that boys had significantly higher IAS scores than girls (p=0.042). It was observed that the IAS score gradually increased with daily use of the internet for ≥ 2 hours. Also, it was observed that the course success decreased as IAS score increased (p<0.001) (**Table 1**). One hundred and sixty-seven (21.92%) children had family negative relationships because of internet use and 359 (46.99%) children had family restrictions for internet use. It was observed that the IAS score increased in students with family negative relationships and who were exposed to violence (p<0.001) (**Table 1**). Family negative relationships and exposure to violence for internet use percentage were significantly higher in high school than the primary and middle school (p<0.001). Keep under control by the family was observed to be the least common in high school students (**Table 2**).

Among the visited websites, it was observed that education and playing puzzle IAS scores were found to be significantly lower than the others, while these two were preferred at least by high school students and mostly by primary school students. Internet addiction, on the contrary, was found at least in primary school students and most in high school students (**Table 1,2**).

QSLS total scores were found as 112.65± 18.42 (**Table 1**). Except for students, the scores of other sub-dimensions (teacher, feelings toward school, principal, status, and total) were the lowest for high school and the highest for middle school. Students had the highest score among primary school students (p<0.001, **Table 3**).

The most significant differences between parameters were observed in high school students (**Tables 2, 3**). Accordingly, it was observed that IAS scores, internet addiction, family negative relationships, and exposure to violence rates were highest in high school students, keep under control by family, QSLS scores, and course success were found to below.

There were no significant differences between groups about mother and father education status, number of siblings.

Table 2. Internet tendency problems and features of students in schools

n (%)/median (min-max)	P. School	M. School	H. School	p
Family negative relationships	50 (19.84%)	33 (13.87%)	84 (30.88%)	<0.001
Exposed to violence	40 (15.87%)	30 (12.24%)	109 (39.49%)	<0.001
Keep undercontrol by family	139 (54.94%)	139 (58.16%)	81 (29.78%)	<0.001
Internet use	243 (93,10 %)	231 (92,77 %)	267 (96,04 %)	0.211
IAS s	48 (27- 95) [a]	50 (27- 112)[a]	71 (27-135)[b]	<0.001
I.addiction	9 (3.52%)	17 (7.11%)	80 (29.30%)	<0.001
Most commonly visited website				**<0.001**
Education	82 (32.67%)	56 (23.63%)	24 (9.02%)	
Social media	15 (5.98%)	63 (26.58%)	116 (43.61%)	
Movies, TV	21 (8.37%)	14 (5.91%)	25 (9.40%)	
Game	119 (47.41%)	91 (38.40%)	85 (31.95%)	
Type of games				**<0.001**
Puzzle	78 (30.95%)	60 (25.10%)	39 (14.34%)	
Racing	50 (19.84%)	22 (9.21%)	35 (12.87%)	
Sport	33 (13.10%)	44 (18.41%)	46 (16.91%)	
Action	72 (28.57%)	76 (31.80%)	74 (27.21%)	

P: primary, M: middle, H: high, I. addiction: Internet addiction, IAS s: Internet addiction scale score. a,b; statistical difference between a and b.

Table 3. QLSS features in schools

mean±sd /median (min-max)	P. School	M. School	H. School	p
Teachers	31.44±6.43 [a]	31.64±6.40 [a]	26.25±5.43 [b]	<0.001
Students	30.61±7.30 [a]	26.67±7.12 [b]	29.93±5.25 [a]	<0.001
Feelings toward school	28.41±6.37 [a]	30.12±6.28 [b]	22.75±4.70 [c]	<0.001
Principal	17.20±4.96[a]	20.01±5.05 [b]	15.02±4.58 [c]	<0.001
Status	10 (3 -15) [a]	11 (3-15) [b]	9 (3- 15) [c]	<0.001
Total	117.16±18.67[a]	119.06±19.20 [a]	102.86±12.48 [b]	<0.001

QSLS: Quality of school Life scale scores, P: primary, M: middle, H: high, sd: Standart deviation
[a,b,c]; statistical difference between a,b and c, [a,b]; statistical difference between a and b.

DISCUSSION

Internet use disorder (IUD), which is a widespread problem of today, is defined as a mental disorder that negatively affects the quality of life of children and adolescents, just like adults.[14,15] Internet addiction is closely related to the amount of time spent on the internet. Especially, internet use over 2 hours a day is a risk factor for addiction.[16] Gaming disorder in younger age groups, communication, and social media use in older people are other risk factors for IUD.[9,14,16,17] Internet addiction prevalence ranges from 5.9% to 18.3% among university students.[18] This prevalence was found to be 11.6% in a study on high school students.[1] Contradictory arguments are seen in studies in terms of gender. In a study conducted with university students aged 18-27, internet addiction was observed in 12.6% of boys and 5.5% of girls.[19] In another study conducted with high school students, these rates were shown as 15.3% for boys and 13.1% for girls.[20] In another study, it was concluded that girls had higher IAS scores than boys and all those who were internet-addicted were girls.[16] While internet addiction was observed at a rate of 13.80 % in our study, it was observed that approximately one third (29.30%) of this rate was high school students and boys had higher IAS scores than girls.

On the other hand, parallel to the amount of time spent on the internet, it was noted in our study that there was a statistically significant increase in the IAS score, especially when using the internet more than 2 hours per day. The daily duration of internet use was significantly higher in high school than in the others. Also, while the internet was used mainly for the puzzle, playing online games and educational information searching in primary school, it was seen that the internet was mostly used for social media purposes in high school ($p<0.001$). On the other hand, it was statistically significant that internet addiction and IAS scores were the highest for high schools and the lowest for primary school students. We think that the reason for this distinct difference is related to the duration of internet use, and the use of social media for communication purposes to solace the loneliness of high school students and reach a high level of life satisfaction is related to internet usage (e.g., puzzle and education) preferences of primary school students. In a related study, it was observed that while children's internet activities such as education and homework do not bother families, the use of social media for communication purposes worries them.[21]

Internet use disorder has various negative effects on school life. Besides, an important issue that parents worry about is the academic performance of their children. In general, girls exhibit a superior skill in school and other life activities than boys.[6,22] However, studies have stated the opposite or that there is no gender difference.[23,24] Parents' attitudes, family communication, family cohesion, and exposure to domestic violence (e.g. parent-to-child violence) trigger addiction to the internet.[25] On the other hand, internet addiction leads to the risk of stress and impulsive self-behavior in individuals and weakens intra-family relationships.[20,21] All these factors lead to psychosocial problems, poor cognitive performance, and low academic achievement in children and adolescents, as well as school burnout.[9,26-29] Apart from the IUD, low socio-economic status and exposure to violence in various environments (such as at home, school, or peer communities) increase students' risk of school failure. Individual efforts of teachers are often insufficient to prevent this failure. This situation becomes more apparent in schools with limited resources.[30] Supporting these views, it was found in our study that high IAS scores and internet addiction caused a low QSLS score. Family negative relationships, reduced family control, and increased exposure to violence increased IAS scores and internet addiction. It was also observed that these high scores were closely related to failure on courses of students, especially in high school students.

The fact that socio-economic differences cannot be reflected on the internet and quality of school life due to the similar cultural structure, education, and income levels of students' families constituted the limitation of this study. However, the large participation in the questionnaire, the wide range of students' age, the primary school, middle school, and high school groups have created the opportunity to compare them with each other in terms of internet and quality of school life characteristics. We think that this is a strong aspect of this study in that it contributes to revealing the unclear points that are not sufficiently known between the internet and the quality of school life.

As a result, the distribution of the quality of school life reflecting self-confidence, school motivation, learning behavior, and academic achievement in primary, middle, and high school and where the IUD is in this distribution has not been studied sufficiently until today. To close this gap, we believe that the results of our study analysis will shed light on future studies by identifying the student's concerns in the school environment, the introduction of school-based support programs, and the contribution to the increase of motivation and feeling good. According to our results, male gender, high school group, spending more than 2 hours a day on the internet, social media, family negative relationships, reduced family control, and increased exposure to violence was determined as risk factors that increase the tendency to high IAS scores and thus internet addiction. It was observed that high school students had these risk factors the most. At the same time, QSLS scores which reflect academic achievement were found as the lowest for high school students, and as the highest for middle school students. However, both QSLS scores and IAS scores, and internet addiction results were close to each other in middle school students compared to primary school. QSLS scores decreased as IAS scores and internet addiction increased significantly with the high school period. When we consider from this point of view, it brought to our mind that high IAS scores that determine internet addiction and risk factors that lead to this may be among the reasons that reduce the quality of school life.

On the other hand, it was noteworthy that playing puzzles and educational information searching, which are most common in primary schools, are associated with low IAS scores and internet addiction. Considering these reasons, we recognize the concerns of families with children in high school. To eliminate these concerns, we believe that it is necessary to develop programs where families will play an essential role in preventing internet addiction, minimizing excessive and unhelpful internet use of high-risk adolescents, and improving environmental factors that regulate the relationship of students in families, schools and other environments. These programs in question should focus on students' efforts to establish positive social relationships and beneficial internet use. Considering children's Internet usage preferences and durations, directing internet usage to useful websites such as education and puzzle as much as possible will undoubtedly have a positive reflection on the quality of school life. Consequently, improving the quality of school life will have a positive reflection on the academic performance of the student, will enable the elimination of bad habits, and will be determinant in the development of a healthy society. However, further studies are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the clinical research ethics committee of Health Sciences University Ankara Child Health and Diseases Hematology and Oncology Health Research and Application Center (Approval number 2018-190).

Informed Consent: Written consent was obtained from all patients who participated in the study and their relatives.

Referee Evaluation Process: Externally peer-reviewed.

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Orjinal Araştırma / Original Article

Evaluation of Tp-e/QTc Ratio in Determining the Risk of Arrhythmia in Electric Shocks in Children

Çocuk Acile Başvuran Elektrik Çarpmalarinda Aritmi Riskini Belirlemede Tp-e/QTc Süresi

Sinem Sarı Gökay[1], Şener Çınıçev[1]

[1]Adana City Training and Research Hospital, Department of Pediatric Emergency, Adana, Turkey

Abstract

Introduction: Patients who have electrical accidents can apply to hospital with clinical signs ranging from simple skin burns to serious organ injuries. Our aim in this study is to evaluate whether QT, QTc interval and QT/QTc, Tp-e/QT, Tp-e/QTc ratios can be a marker for determine the risk of arrhythmias in children in cases of electric shock injuries that can be fatal.

Material and Method: In our study, 36 patients who were admitted to pediatric emergency with an electric shock between July 2018 and September 2019 and followed up in our clinic were included. As a control group, 25 healthy patients were included in the study. The files of the patients were examined retrospectively ECG (electrocardiogram) findings in leads DII and V5 were recorded.

Results: Thirty-six (41%) patients who were admitted to our study due to electrical shock and followed up in our pediatric emergency were included. Sinus tachycardia was observed in two patients and no arrhythmias were detected in others. There was no statistically significant difference between the two groups between QT, QTc interval and QT/QTc, Tp-e/QT and Tp-e/QTc ratios measured in DII and V5 leads on ECG (p> 0.05). Also there was no statistically significant difference between ECG findings of genders(p> 0.05).

Conclusion: Electric shock can cause life-threatening situations by causing fatal arrhythmia. Although ECG findings are used to determine cardiac arrhythmia, it should be shown whether QT, QTc interval and Tp-e/QT, Tp-e/QTc ratios are significant arrhythmogenic markers by prospective studies in more specific age groups.

Keywords: Tp-e/QTc, electrical injury, children

Öz

Amaç: Elektrik kazaları basit cilt yanıklarından ciddi organ yaralanmalarına kadar değişen klinik bulgu ile gelebilmektedir. Bu çalışmadaki amacımız aritmiye neden olarak ölümcül olabilecek elektrik çarpmasına bağlı yaralanmalarda QT, QTc sürelerinin ve QT/QTc, Tp-e/QT, Tp-e/QTc oranlarının çocuklarda aritmi riskini belirleyebilecek bir belirteç olup olmadığını değerlendirmektir.

Gereç ve Yöntem: Çalışmamızda Temmuz 2018 ve Eylül 2019 tarihleri arasında elektrik çarpması şikayeti ile başvuran ve çocuk acilimizde takip edilen 36 hasta alındı. Kontrol grubu olarak da sağlıklı 25 hasta çalışmaya alındı. Hastaların dosyaları retrospektif olarak incelenerek DII ve V5 derivasyonlarında EKG (elektrokardiyogram) bulguları kaydedilmiştir.

Bulgular: Çalışmamıza elektrik çapması nedeni ile başvuran ve çocuk acilimizde takip edilen 36(%41) hasta alındı. İki hastada sinus taşikardisi görüldü diğerlerinde aritmi saptanmadı. EKG' de DII ve V5 derivasyonlarında ölçülen QT, QTc süreleri ve QT/QTc, Tp-e/QT ve Tp-e/QTc oranları arasında her iki grup arasında istatistiksel olarak anlamlı farklılık yoktu (p>0.05).Erkek kız gruplarına bakıldığında da cinsiyet ve EKG'deki QT, QTc süreleri ve QT/QTc, Tp-e/QT ve Tp-e/QTc oranları arasında istatistiksel olarak anlamlı bir farklılık saptanmadı(p>0.05)

Sonuç: Elektrik çarpması malign aritmiye sebep olarak hayatı tehdit eden durumlara sebep olabilir. Kardiyak aritmiyi belirlemede EKG bulguları kullanılmakla birlikte daha çok sayıda belirli yaş gruplarında prospektif yapılacak çalışmalarla QT, QTc sürelerinin ve Tp-e/QT, Tp-e/QTc oranlarının anlamlı aritmojenik bir belirteç olup olmadığı gösterilmelidir.

Anahtar Kelimeler: Tp-e/QTc, elektrik yaralanması, çocuk

Corresponding *(İletişim)*: Sinem Sarı Gökay, Adana City Training and Research Hospital Department of Pediatric Emergency, Adana, Turkey
E-mail *(E-posta)*: sinemsr@yahoo.com
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INTRODUCTION

Injuries due to electric shock continue to be a problem for all countries in the world because of the widespread use of electricity. Although electric shock injuries occur in every group of age, they often develop as a result of home accidents in the childhood age group. Electrical accidents can come with clinical signs ranging from simple skin burns to serious organ injuries. Home accidents cause simple injuries, while high-voltage injury can result in multiple organ damage and death.[1,2]

Cardiac rhythm disturbances can occur after electric shocks, often the first few hours of admission to the hospital. Among high voltage accidents, asystole is more common in lightning shock of ventricular fibrillation. In addition, patients may have ST-T changes, supraventricular tachycardia, atrioventricular extrasystoles, right bundle branch block or complete heart block.[3-5]

Although the first serious effects on the heart occur immediately after exposure, the necessity and/or ideal follow-up time for post-injury monitored follow-up, especially of patients presenting with low-voltage electric shock, is controversial.[2,3,6,7]

The first thing to do to evaluate arrhythmias after electric shock is to perform ECG monitoring. In recent studies in adults, it has been shown that the Tp-e interval can be used to determine the total (transmural, apicobal and global) repolarization distribution in ECG. It is also stated that increased Tp-e interval may be a useful predictor in ventricular tachyarrhythmias and cardiovascular mortality. There are studies describing Tp-e and Tp-e/QTc rates as predictors and mortality in ventricular arrhythmias, long QT syndrome, sudden cardiac death, hypertrophic cardiomyopathy, myocardial infarction. It is also thought that the Tp-e/QT ratio may be a more accurate measurement than other heart rate-independent measurements (QT, QTc and Tp-e interval).[8-10]

In the literature, there are very few studies on the rate of Tp-e/QTc in children, but there is no study on electric shock in children. Our aim in this study is to evaluate whether QT, QTc interval and QT/QTc, Tp-e/QT, Tp-e/QTc ratios can determine the risk of arrhythmias in children in cases of electric shock injuries that can be fatal.

MATERIAL AND METHOD

In our study, 36 patients who were admitted to Adana City Training and Research Hospital Pediatric Emergency Department between July 2018- September 2019. As a control group, 25 healthy patients were included in the study. Approval was obtained from the Adana City Training and Research Hospital Ethics Committee for the study (11-09-2019/39-551). The files of the patients were examined retrospectively and age, gender, clinical findings and physical examination findings, vital signs, treatment and results, ECG (electrocardiogram) findings, QT, QTc interval and Tp-e, Tp-e/QT and Tp-e/QTc ratios in leads DII and V5 were recorded. Patients with underlying disease and inaccurate results were excluded from the study.

The Tp-e/QT and Tp-e/QTc ratios were calculated by measuring the interval from the peak of the T wave to the end of the Tp-e interval from the ECGs of the patients, measuring the QT interval from the beginning of the QRS complex to the end of the T wave, and adjusting it according to the corrected QTc Bazett formula [QTc = QTd$\sqrt{}$ (R-R interval)].

Statistical analysis

IBM SPSS Statistics Version 20.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, while numerical measurements were summarized as mean and standard deviation, summarized as mean and standard deviation and as median and minimum-maximum where appropriate. Whether numerical measurements provide the normal distribution assumption was tested with the Kolmogorov Smirnov test. A t test was used to compare normally distributed data, and the Mann-Whitney U test was used to compare data without a normal distribution. Statistical significance level was taken as 0.05 in all tests. SPSS reference: IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

RESULTS

Thirty-six (41%) patients who were admitted to our study due to electrical shock and followed up in our pediatric emergency department were included. The control group was 25 healthy children(59%). The mean age of the patients was 99.17±62.03 and the control group was 98.76±71.8 months. The number of female patients was 11 (30.6%) and the control group was 12 (48%) . There was no statistically significant difference between the patient and the control group in terms of age and gender (p>0.05). All of the patients were followed up in the pediatric emergency observation and discharged with recovery (**Table 1**). All patients were monitored in the pediatric emergency service and followed up for 24 hours with hydration and symptomatic treatment, and were discharged with recovery. Two patients had sinus tachycardia and other patients had no arrhythmia.

Table 1. Epidemiological features of patients

	Patients (n:36) (%)	Control (n:25) (%)
Gender		
Girl	11 (30.6)	12 (48)
Boy	25 (69.4)	13 (52)
Age (Months)	99.17±62.03	98.76±71.83
Clinic		
No symptoms	13 (36.1)	
Burned limbs	19 (52.8)	
Burn + Central nervous system symptoms	4 (11.1)	
Cardiovascular system symptoms	2 (5.5)	
Treatment		
Hydration	36 (100)	
Observation	36 (100)	
Other	19 (52.7%)	
Hospitalization		
Pediatric Emergency Service	36 (100)	
Result		
Recovery	36 (100)	
Exitus	0 (0)	

The laboratory values in the patient group were CK 209 (76-3971), CK-MB 4.35 (1.1-107) ng/mL and troponin values were 2 (0-6) ng/mL. Other laboratory values of the patients are summarized in **Table 2**.

Table 2. Laboratory results of patients presenting with electric shock

	Patient (n:36) median (min-max)
WBC(10^3 µL)	9.4 (4.1-16.5)
Hemoglobin (g/dL)	12.6 (9-16.3)
Hematocrit (%)	36.4 (29.3-46.4)
Platelets (10^3 µL)	306 (207-584)
Glucose (mg/dL)	100 (11-168)
BUN (mg/dL)	23 (11-38)
Creatinine (mg/dL)	0.36 (0.2-1)
SGOT(U/L)	33.3 (19-94)
SGPT(U/L)	15.15 (5-32)
Sodium (mmol/L)	138 (134-141)
Potassium (mmol/L)	4 (3.2-4.8)
Calcium (mg/dL)	9.8 (8.3-10.7)
CK	209 (76-3971)
CK-MB (ng/mL)	4.35 (1.1-107)
Troponin-I (ng/mL)	2 (0-6)

In ECG of patients in DII derivation; QT interval 0.31±0.03 s, QTc interval 0.40±0.02 s, QT/QTc interval 0.78±0.08, Tp-e/QT interval 0.22±0,04 and Tp-e/QTc ratio was 0.18±0.03. In ECG of control group in DII derivation; QT interval 0.30±0.04 s, QTc interval 0.40±0.03 s, QT/QTc ratio 0.76±0.09 , Tp-e/QT ratio 0.22±0.04 and Tp-e/QTc ratio was 0.16±0.03. In the ECG of patients, in the V5 derivation the QT interval was 0.31±0.03 s, QTc interval 0.40±0.03 s, QT/QTc ratio 0.79±0.08 , Tp-e/QT ratio 0.23±0.04 and Tp-e/QTc ratio 0.18±0.03. In ECG of control group in V5 derivation QT interval was 0.30±0.03 s, QTc interval 0.39±0.02 s, QT/QTc ratio 0.76±0.09 , Tp-e/QT ratio 0.24±0.04 and Tp-e/QTc ratio 0.17±0.02. There was no statistically significant difference between the two groups in the time measured in leads DII and V5 on the ECG (p> 0.05) (**Table 3**). There was no statistically significant difference between QT, QTc interval, QT/QTc, Tp-e/QT and Tp-e/QTc ratio and gender (p> 0.05) (**Table 4**).

Table 3. Comparison of electrocardiographic results

ECG	Patient (mean±SD)	Control	p
QT DII (s)	0.31±0.03	0.30±0.04	0.396
QTc DII (s)	0.40±0.02	0.40±0.03	0.956
QT/QTc (s)	0,78±0.08	0.76±0.09	0.323
Tp-e/QT DII	0.22±0.04	0.22±0.04	0.540
Tp-e/QTc DII	0.18±0.03	0.16±0.03	0.130
QT V5 (s)	0.31±0.03	0.30±0.03	0.186
QTc V5 (s)	0.40±0.03	0.39±0.02	0.794
QT/QTcV5 (s)	0,79±0.08	0,76±0.09	0.157
Tp-e/QT V5	0.23±0.04	0.24±0.04	0.457
Tp-e/QTc V5	0.18±0.03	0.17±0.02	0.380

Table 4. Comparison of electrocardiography results by gender groups

ECG	Female (mean±SD)	Male	p
QT DII (s)	0.31±0.04	0.31±0.03	0.728
QTc DII (s)	0.40±0.02	0.40±0.02	0.990
QT/QTc (s)	0.77±0.09	0.77±0.08	0.899
Tp-e/QT DII	0.22±0.04	0.22±0.04	0.298
Tp-e/QTc DII	0.17±0.03	0.17±0.03	0.260
QT V5 (s)	0.31±0.03	0.31±0.03	0.923
QTc V5 (s)	0.39±0.02	0.40±0.03	0.184
QT/QTcV5 (s)	0.78±0.09	0.78±0.09	0.775
Tp-e/QT V5	0.23±0.04	0.23±0.04	0.749
Tp-e/QTc V5	0.18±0.03	0.18±0.03	0.803

DISCUSSION

Electric shock is rare but important because of its very serious vital effects.[11] Mortality rate due to electric shock, especially cardiac arrest and arrhythmias, is 3-15%.[12-14] Although electric shock is a high risk for arrhythmia, arrhythmic complications due to the low number of cases in studies; guidelines on evaluation and treatment contain limited information.[2] Ventricular fibrillation, which is fatal at the time of electric shock, may develop, and the most common arrhythmias at the time of admission to the hospital after electric shock are sinus tachycardia, bradycardia, and atrial-ventricular arrhythmias.[1,15]

The effect of electrical injury on myocardial cells and its electrocardiographic effects are unclear. Although the pathogenesis of cardiac effects is not fully understood, it is thought to be multifactorial. In electrical injury, primarily the electrical pathway in the heart and ion channels are affected. Therefore, complications of arrhythmia can be detected before myocardial damage occurs. It is stated in the literature that ECG changes occur at lower currents.[16-18]

Gokdemir et al. detected the sinus tachycardia as the most common arrhythmia in their studies on 36 patients with low voltage electric shocks and reported that they did not develop secondary arrhythmia in their patients.[19] In their study, Kramer et al.[15] detected arrhythmia in 7% of 84 patients aged 0-17. Celik et al.[20] followed 24-hour cardiac monitoring during their study with 38 patients and Bailey et al.[21] in their study with 141 patients, they showed that secondary arrhythmia did not develop. In the study in which Claudet et al. evaluated 48 pediatric patients with low voltage, 8 patients had sinus tachycardia, right bundle branch block and t wave changes in ECG.[6] ECG findings improved in all patients and no late arrhythmia was detected. Pawlik et al. did not encounter malignant arrhythmia in their study and their mortality was 0%.[22] Searle et al. In their study, they did not detect 0% mortality and life-threatening arrhythmia in their studies.[1] Similar to the literature in our study, sinus tachycardia was observed in 2 of our patients, malignant arrhythmia was not observed in other patients during the observation and all our patients were discharged with recovery.

Electrocardiography is an important diagnostic tool for detecting arrhythmias. While it is necessary to evaluate with ECG in patients with electric shock, the effects of electric shock on ECG parameters have not been investigated in the literature.[16]

There are studies in the literature showing that QTc, Tp-e interval and Tp-e/QT and Tp-e/QTc ratios are arrhythmogenic markers associated with cardiovascular mortality and morbidity.[23] Although studies in the literature in children are limited, there are no studies on Tp-e and Tp-e/QT interval in ECG related to electric shock in children. Karataş et al. in their study of electric shock in adults, QTc, QTD, Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio were significantly longer compared to patients' admission and control ECGs.[16]

Türe et al.[23] In their study with children who had dilated cardiomyopathy and exitus, they found a statistically significant difference in QT, QTc and Tp-e interval. In studies on mitral valve prolapse and ECG findings in children, the interval of QT, QTc, Tp-e and the ratios of Tp-e/QT and Tp-e/QTc were significantly increased.[23] Turker et al.[25] did not detect a significant difference in QT and QTc interval in mitral valve prolapsus patients with ventricular arrhythmia.

In our study, we used the ECG findings in leads DII and V5, as the left precordial leads were shown to reflect the best values in demonstrating transmural repolarization.[26] In our study, there were no statistically significant differences between ECG and QT, QTc interval, QT/QTc, Tp-e/QT and Tp-e/QTc ratios measured in DII and V5 leads ($p>0.05$). There was no statistically significant difference between QT, QTc interval, QT/QTc, Tp-e/QT and Tp-e/QTc ratios by gender ($p>0.05$). We think that we did not find a significant difference in terms of time, since the number of patients was low, the control ECG of the patient group was not included in the study, and the patient age distribution was in a wide range such as 0-18 years.

Electric shock is generally more common in children and boys in the form of home accidents.[6,19] In our study, the average age of our patients was 99.17±62.03 months, and similar to the literature, electric shock was more common in male.

Recent studies of electrical burns in children have shown that creatine kinase and CK-MB are a weak marker in demonstrating myocardial damage, and therefore these studies have suggested that they should not be used to show cardiac damage caused by electric shock. The effectiveness of the height of the troponin level in showing myocardial damage due to electric shock is uncertain.[20,22,27] Pilecky et al. in their study, they observed that troponin and CK-MB were not useful in risk assessment after electrical shock. Similarly, in our study, no significant high values were found in CK, CK-MB and troponin values.[2]

CONCLUSION

As a result, electric shock can cause life-threatening situations by causing arrhythmia. There are limited reports of arrhythmias due to electric shock in children in the literature. Although ECG findings are used in determining cardiac arrhythmia, it should be shown whether QT, QTc, Tp-e interval and Tp-e/QT, Tp-e/QTc ratios are significant arrhythmogenic markers with more prospective studies in certain age groups.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from the Adana City Training and Research Hospital Ethics Committee for the study (11-09-2019/39-551).

Informed Consent: Written consent was obtained from all patients who participated in the study and their relatives.

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Case Report / Olgu sunumu

Klippel-Feil Syndrome: A Case Report

Klippel-Feil Sendromu: Olgu Sunumu

Zeliha Fazlıoğulları[1], Abdussamet Batur[2], Ekrem Solmaz[1], Ayşe Gamze Özcan[1], Mehmet Cengiz Tatar[1]

[1]Selcuk University School of Medicine Department of Anatomy, Konya, Turkey
[2]Selcuk University School of Medicine Department of Radiology, Konya, Turkey

Abstract

Klippel-Feil syndrome is a syndrome that may involve other skeletal and extra-skeletal anomalies as well as fusion of the spine due to the absence of normal segmentation in cervical structures. In our case, we aimed to describe this rare syndrome, to show the findings obtained by imaging methods, and to emphasize the importance of directing it to early diagnosis and necessary treatment modalities. A 41-year-old female patient presented to our hospital with neck pain. Using cervical magnetic resonance imaging, we observed a decreased anteroposterior diameter; fusion between the corpora of the 2nd - 4th cervical spine; and an appearance consistent with fusion between the arches of the same vertebrae in sagittal slices. Cadaver studies and radiology tests were performed to identify the variations and anomalies of the cervical spine. Although computed tomography scanning is more frequently performed for the purpose of evaluating spine, magnetic resonance imaging may be performed to evaluate the adjacent soft tissue structures and the symptoms associated with vertebral pathologies. These imaging modalities are necessary and beneficial for anatomists, radiologists, neurosurgeons, and orthopedists so that they may evaluate the findings, coexisting anomalies, and risk factors of Klippel-Feil syndrome in order to reach appropriate diagnosis, follow-up, and treatment.

Keywords: Klippel - Feil syndrome; spine; magnetic resonance imaging

Öz

Klippel-Feil sendromu, servikal yapılarda normal segmentasyonun oluşmaması sonucu vertebraların füzyonu yanı sıra diğer iskelet ve iskelet dışı anomallileri de içerebilen bir sendromdur. Vakamızda nadir görülen bu sendromu tanımlamayı, görüntüleme yöntemleri ile elde edilen bulguları göstermeyi ve erken teşhis ve gerekli tedavi modalitelerine yönlendirmenin önemini belirtmeyi amaçladık. Boyun ağrısı şikâyeti ile hastanemize başvuran 41 yaşındaki kadın hastanın çekilen servikal manyetik rezonans görüntülemesinde sagital kesitlerde 2. – 4. servikal vertebra korpusları arasında füzyon ve anteroposterior çapta azalma ile aynı vertebraların arkusları arasında füzyon ile uyumlu görünüm tespit edildi. Servikal vertebraların varyasyonlarını ve anomalilerini tanımlamak için kadavra çalışmalarından ve radyolojik tetkiklerden faydalanılır. Bilgisayarlı tomografi, vertebraların değerlendirmesinde daha sık kullanılsa da komşu yumuşak doku yapılarının ve vertebrae patolojilerine bağlı semptomların değerlendirilmesinde manyetik rezonans görüntüleme kullanılmaktadır. Klippel-feil sendromuna ait bulguların, eşlik eden anomalilerin ve risk faktörlerinin değerlendirilmesi için kullanılan bu görüntüleme yöntemleri uygun tanı, takip ve tedavi için anatomist, radyolog, nöroşirurjist ve ortopedistler açısından gerekli ve faydalıdır.

Anahtar kelimeler: Klippel-Feil sendromu, vertebra, manyetik rezonans görüntüleme

INTRODUCTION

Klippel-Feil syndrome (KFS) was first described by Maurice Klippel and Andre Feil in 1912 as an anomaly that is characterized by fusion of at least two cervical spine vertebraes.[1] KFS is a rare congenital anomaly and is slightly more prevalent in women than in men, with an incidence of 1 in 42,000.[2]

This syndrome is except phenotypic features such as short neck, generally asymptomatic in pediatric patients, but the symptoms become more distinct in adulthood. KFS may coexist with various skeletal, renal, and cardiovascular anomalies.[3] Although diagnosis of this syndrome is generally based on radiology tests performed on patients who present with short neck, low hairline at the back of the head, neck pain, and limited range of motion in the neck, it may also be diagnosed incidentally via radiological imaging tests performed for other purposes.[4]

Although KFS is mainly sporadic, some KFS types are autosomal dominant or recessive due to an anomaly in the GDF6, MEOX1, GDF3, and MYO18B genes on chromosomes 8, 17, 12, and 22, respectively.[5]

Corresponding *(İletişim)*: Zeliha Fazlıoğulları, Selcuk University School of Medicine Department of Anatomy, Konya, Turkey
E-mail *(E-posta)*: z_topal@yahoo.com
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Physical therapy and surgery may contribute to quality of life in eligible patients. In this case report, we aimed to describe this rare syndrome, show its findings using imaging tests, and demonstrate its clinical importance.

CASE REPORT

A 41-year-old female patient presented to our hospital with a stiff neck and neck pain. Informed constent of the patient was obtained. Upon cervical magnetic resonance imaging (MRI), we noted a decreased anteroposterior diameter; fusion between the corpora of the 2nd, 3rd, and 4th cervical vertebrae; and an appearance consistent with fusion between the arches of the same vertebrae as well as a minimal diffuse protrusion in the 5th and 6th intervertebral discs in sagittal slices. Structures of the craniovertebral junction and cervical spinal cord were normal. Furthermore, direct radiographs and sagittal slices previously obtained via computed tomography (CT) revealed mild scoliosis, with a curve facing to the right and with fusion between the corpora of the 2nd, 3rd, and 4th cervical vertebrae (**Figure 1**). These findings were consistent with type 1 (diffuse vertebral fusion in the cervical region) KFS according to Feil's classification. There is no genetic diagnosis or any other accompanying pathology in the patient.

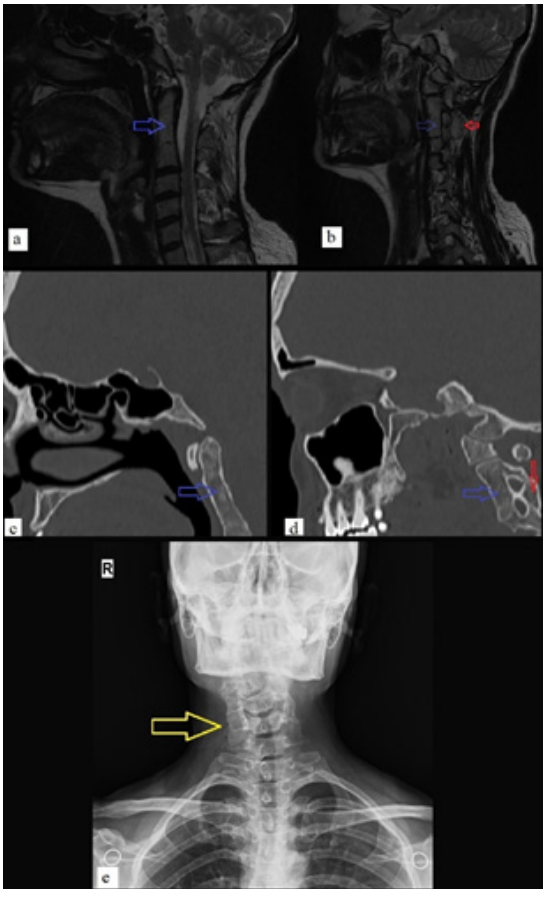

Figure 1. Sagittal slices of the cervical region in T2-weighted MR images (Blue arrow, fusion in the vertebral corpus (a, b); red arrow, fusion in the vertebral arch (b)). Sagittal slices in CT images (Blue arrow, fusion in the vertebral corpus (c, d); red arrow, fusion in the vertebral arch (d)). Direct anteroposterior radiographs (Yellow arrow, scoliosis (e)).

DISCUSSION

KFS is a congenital malformation that develops as a result of a defect in the segmentation of cervical somites between gestational weeks three and eight, and genetic factors are involved in its etiology. KFS may originate from mutations or changes in genes involved in the formation of segmentation.[3,5,6] The most common clinical symptoms of the typical triad of a short neck, a low posterior hairline, and a limited range of neck motion owing to the fusion of cervical vertebrae include a stiff neck and neck pain; these symptoms are similar to those presented by the patient described in this report. As of today, the aforementioned triad is not observed in half of all patients with KFS.[1] Although KFS is frequently diagnosed in childhood, it is diagnosed in adulthood in some patients, as it was in our patient.[7]

Feil's classification divides KFS into three main types based on radiologic appearance. Type 1 exhibits diffuse vertebral fusion in the cervical region (consistent with our case), type 2 exhibits one or two fusions, and type 3 exhibits additional vertebral fusion in the lumbar region.[8]

According to Samartzis classification, KFS is classified as type 1 in the presence of vertebral fusion in one segment of the cervical region, classified as type 2 in the presence of non-contiguous vertebral fusions in multiple segments, and classified as type 3 in the presence of contiguous vertebral fusions in multiple segments based on radiologic evaluation.[9] Our patient had type 3 KFS according to Samartzis classification.

Although the highest extent of fusion has been observed at the 2nd and 3rd cervical vertebrae in some studies, the 4th cervical vertebra was also fused in our patient.[10] The appearance of the corpora of these vertebrae was consistent with that of block vertebrae.

KFS is most frequently accompanied by skeletal anomalies, including kyphosis or scoliosis (60%), Sprengel deformity (20%), torticollis (20%), and facial asymmetry (20%). Genitourinary system anomalies (35–65%), hearing loss (30%), and congenital heart diseases (5–15%) are among the most commonly encountered systemic anomalies that coexist with KFS. Renal agenesis is the most commonly observed genitourinary anomaly, and VSD is the most commonly observed cardiac anomaly.[3,9] In patients with KFS, the prevalence of scoliosis is 70% and that of cervical scoliosis is 53%.[1,9] Our patient also had mild scoliosis with a curve facing to the right.

The first choices of imaging modalities for patients suspected of having KFS should include anteroposterior, lateral, and oblique cervical vertebra radiographs. However, because bone deformities make it difficult to position such patients, overlapping of the mandible, the occipital bone, and the foramen magnum on images may be misleading and may therefore complicate the evaluation of cervical vertebrae. Lateral and odontoid radiography and CT may be necessary when trauma, trauma-related fractures, or subluxation

are suspected.[11] If a patient has neurologic deficits, MRI is recommended to evaluate the patient's spinal cord. Differential diagnoses of infection, juvenile idiopathic arthritis, and rheumatoid spondylitis with radiologic findings similar to those of KFS should also be considered when vertebral fusion is present.[6]

KFS should also be considered in the preliminary diagnosis of adult patients with shoulder and neck pain as well as limited neck movement. Additionally, patients should also be examined and evaluated for coexisting anomalies. KFS can be diagnosed with suitable imaging modalities by considering risk factors, and patients can be provided with appropriate follow-up and treatment.

ETHICAL CONSIDERATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Status of Peer-review: Externally peer-reviewed.

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Case Report / Olgu sunumu

Occlusion of Common Iliac Artery as an Unexpected Complication Following Angioplasty via Retrograde Popliteal Access: A Case Report

Anjioplasti Sonrası Ana İliak Arterde Meydana Gelen Beklenmedik Okluzyonun Retrograd Popliteal Yaklaşımla Tedavisi: Vaka Sunumu

Ömer Faruk Çiçek[1], Kerim Esenboğa[2]

[1]Department of Cardiovascular Surgery, Selçuk University Medical Faculty, Konya, Turkey
[2]Department of Cardiology, Ankara University Medical Faculty, Ankara, Turkey

Abstract

Treatment of the lesions located in the popliteal artery and superficial femoral artery are potentially clinical challenge because of the long length of lesions, high- calcium content in the vessel wall and inside the plaques, and individual dynamic forces found within these vessels. Intraluminal or subintimal recanalization of the vessel lumen is achieved mostly by ipsilateral antegrade or contralateral retrograde femoral approach in the treatment of total occlusion of the superficial femoral artery. In the event of failure, retrograde access into the popliteal artery is considered as an essentially different method. In our case report, we aimed to present rescue retrograde popliteal intervention following an unsuccessful antegrade approach which resulted in an unexpected atherothrombotic complication that occurred in the common iliac artery of the contralateral side.

Keywords: Atherothrombosis, peripheral arterial disease, retrograde popliteal intervention

Öz

Yüzeyel femoral ve popliteal arterlerdeki ciddi lezyonların tedavisinde lezyonların uzunluğu, lokalizasyonu ve plak yapısındaki ya da damar duvarındaki yüksek kalsiyum içeriği nedeniyle uygulanacak strateji her vakada bireysel farklılık göstermektedir. Yüzeyel femoral arter okluzyonlarının tedavisinde ipsilateral antegrad ya da kontralateral retrograd yaklaşım sık kullanılmakla birlikte özellikle bu tedavi seçeneklerinin başarılı olmadığı durumlarda retrograd popliteal girişim de alternatif olarak kullanılabilmektedir. Bu vaka sunumunda, antegrad yaklaşımın başarısız olması üzerine popliteal arter yoluyla retrograd yaklaşımın başarılı bir şekilde uygulandığı ancak işlem sonrası karşı taraf ana iliak arterde gerçekleşen beklenmedik aterotrombotik komplikasyon ve başarılı çözümü takdim edilmiştir.

Anahtar Kelimeler: Aterotromboz, periferik arter hastalığı, retrograd popliteal girişim

INTRODUCTION

The worldwide prevalence of peripheral artery disease (PAD), an important cause of cardiovascular morbidity and mortality, is between 3 to 10%.[1] The aim of the management of patients with PAD is relieving symptoms and lowering the risk of cardiovascular disease progression and complications. For patients with disabling symptoms resistant to lifestyle modification and pharmacologic therapy, intervention (percutaneous, surgical) is reasonable. One of the most common vessels involved in symptomatic lower limb atherosclerosis is superficial femoral artery (SFA). Treatment of the lesions located in the popliteal artery (PA) and SFA are potentially clinical challenge because of the long length of lesions and high calcium content in the vessel wall and inside the plaques.

Corresponding *(İletişim)*: Ömer Faruk Çiçek, Selcuk Universitesi Tıp Fakultesi Kalp ve Damar Cerrahisi Anabilim Dali, Selcuklu, Konya, Turkiye
E-mail *(E-posta)*: farux@hotmail.com
Received *(Geliş Tarihi)*: 22.09.2020 **Accepted *(Kabul Tarihi)*:** 07.12.2020

Intraluminal or subintimal recanalization of the vessel lumen is achieved mostly by the ipsilateral antegrade or contralateral retrograde femoral approach in the treatment of total occlusion of the superficial femoral artery. In the event of failure, retrograde popliteal access (RPA) is considered as an essential alternative method. Initially, the RPA was used as a backup option since there were some limitation factors.[2] However, refinements to this method have made this option an attractive alternative technique.[3]

In this case report, we aimed to present a successful retrograde approach through the PA following an antegrade approach that failed due to the inability to enter the distal true lumen. We also drew attention to the unexpected atherothrombotic complication that occurred in the common iliac artery of the contralateral side after the retrograde approach in our case.

CASE REPORT

A 51-year-old man presented to our outpatient clinic for left leg pain with a maximal walking distance of 150 meters. Patient's Society for Vascular Surgery Lower Extremity Threatened Limb (SVS WIfI) classification for right lower extremity was wound 0, ischemia 1, foot infection 0, which corresponded to stage 1 and for left lower extremity was wound 0, ischemia 2, foot infection 0, which corresponded to stage 2.[4] The patient was under appropriate medical treatment involving acetylsalicylic acid, perindopril, metoprolol, cilostazol, and atorvastatin. We have learned from the past medical history of the patient that he has been followed for the last six months due to peripheral arterial disease and that his complaints have increased in the last 3 months despite medical treatment and exercise therapy. Color Doppler ultrasound examination revealed that the peripheral arterial pathology by demonstrating the monophasic flow pattern with increased acceleration time indicating proximally severe stenosis in all arterial structures in left lower limb and preserved biphasic circulation in right lower extremity. The ankle-brachial index was 0.38 on the left side with non-palpable pedal pulses and 0.63 on the right side with palpable dorsalis pedis and posterior tibial artery pulses. He had coronary artery bypass surgery 5 years ago and his comorbidities included uncontrolled diabetes mellitus, current smoking, hypertension, and a recent non-ST segment elevation myocardial infarction in which coronary angiography revealed distal vessel disease with open bypass grafts. The patient's body mass index was 22.6 kg/m^2 without a distinct pulmonary disease. Additionally, the patient had chronic kidney disease due to resistant hypertension with a creatinine level of 1.5 mg/dl. His left ventricular function was normal (ejection fraction=60%) without any regional wall motion abnormality and clinically important valve pathology.

Peripheral angiography performed through the right common femoral access demonstrated a total occlusion in approximately 15 cm segment in left SFA with the reconstitution of the PA and the distal SFA, and bilateral severe stenosis in common iliac arteries (**Figure 1A–1C**). Percutaneous intervention was decided to be performed due to disabling symptoms resistant to lifestyle modification and medical treatment. A 7 Fr peripheral guiding sheath (Destination®; Terumo, Tokyo) was inserted into the left common iliac artery (LCIA), and an angled 0.035-inch hydrophilic guidewire (Radifocus; Terumo Corporation, Tokyo, Japan) with a microcatheter support was used to pass the totally occluded segment in left SFA. After placement of the long sheath 7000 units of unfractionated heparin was administered intravenously. Unfortunately, the total occlusion in SFA was blunt-ended and adjacent to a large side branch that prevented the guidewire to enter the occluded segment. Since the distal SFA and PA were normal in caliber and do not have severe stenotic lesions, a retrograde approach via the left PA was thought as an alternative option. We obtained the roadmap of the arteries by injecting the contrast from LCIA in an antegrade direction to perform a retrograde approach via the PA. The PA was then punctured at approximately 4-5 cm above the knee joint with a Terumo radial sheath seldinger needle by the guidance of roadmap fluoroscopy in the prone position. A 0.035-inch guidewire was advanced to the distal part of SFA after a successful puncture, and an angiogram was performed after 6 Fr radial sheath insertion to confirm that the PA access was accomplished

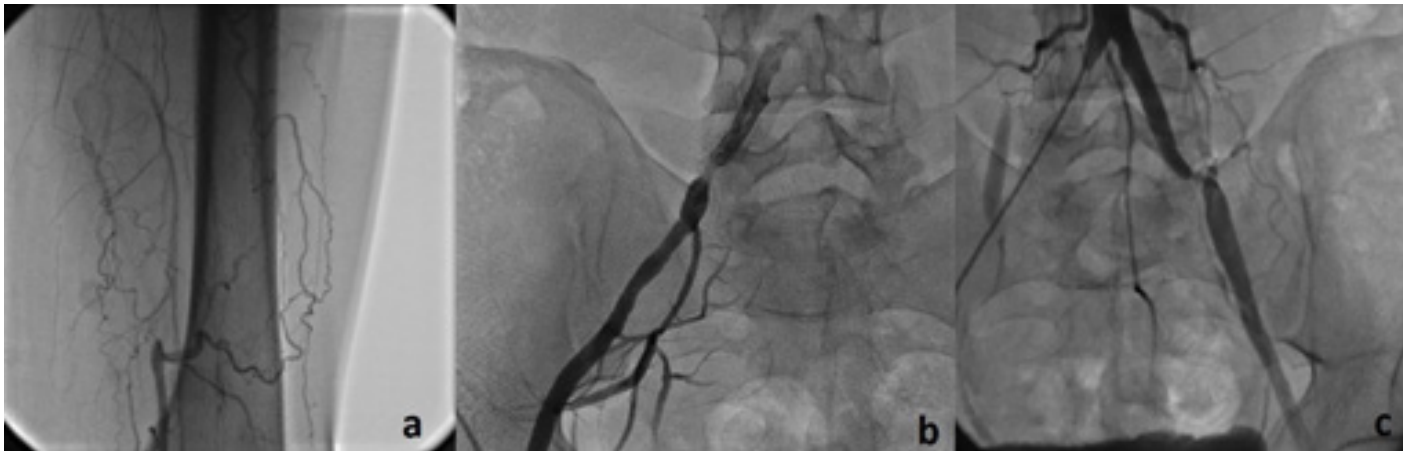

Figure 1. Angiographic image of total occlusion in left SFA (A), severe stenosis in right (B) and left (C) common iliac arteries.

properly. After passing the retrograde wire into the true lumen of the left common femoral artery (CFA) successfully, a 6.0×120 mm drug-coated balloon was used for dilatation of the total occluded segment (**Figure 2**). The guidewire could be successfully passed through the severe lesion located in the LCIA, and a balloon-expandable cobalt-chromium stent (RESTORER 8×58 mm; iVascular, Barcelona, Spain) were placed here. No hemostatic tool other than a sponge and manual compression was used for complete hemostasis after removal of the sheath from the PA, and complications related to access site were not observed. The total duration of our procedure was approximately 3 hours. During the procedure, the activated clotting time (ACT) value was checked with an interval of half an hour. Additional heparin was administered if the ACT value was found to be lower than 300 seconds. A total volume of 350 cc contrast media was used.

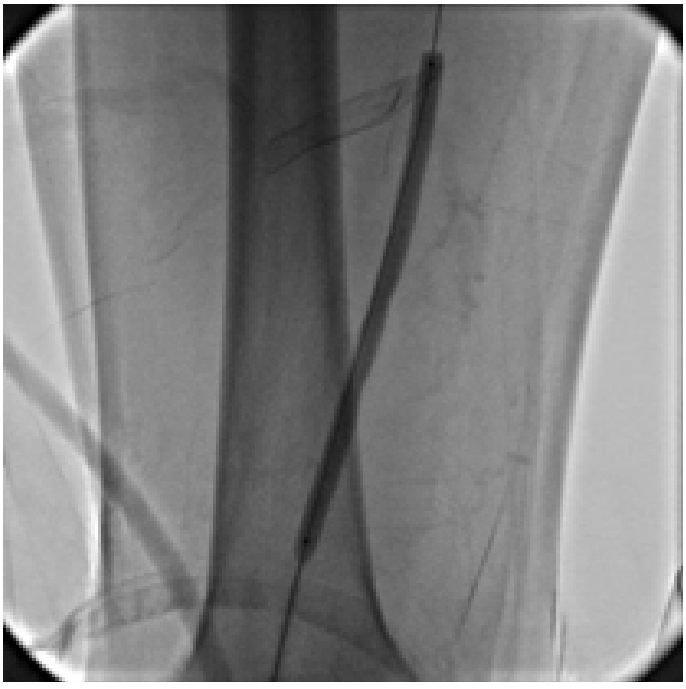

Figure 2. Angiographic image of percutaneous transluminal angioplasty with drug coated balloon for the total occlusion in the left SFA.

Following the procedure, it was decided to postpone the intervention to right common iliac artery (RCIA) not only to avoid contrast nephropathy but also the time of procedure was too long. Two days after the procedure the patient was taken to the catheter laboratory again for planned intervention to RCIA. After performing the angiography, a total occlusion in a severely diseased segment in the RCIA was observed unexpectedly (**Figure 3**). Interestingly, the patient did not have any complaints during this time. A 0.035-inch guidewire was advanced to the abdominal aorta by passing the totally occluded segment in RCIA and following the dilation with 5.0x60 mm balloon, a balloon-expandable cobalt-chromium stent (RESTORER 7.0×58 mm; iVascular, Barcelona, Spain) were placed here which yielded a satisfactory final result (**Figure 4A, 4B**). The period after interventions was uneventful and the patient was discharged home 3 days after the second procedure. Written informed consent was obtained from the patient who participated in this study.

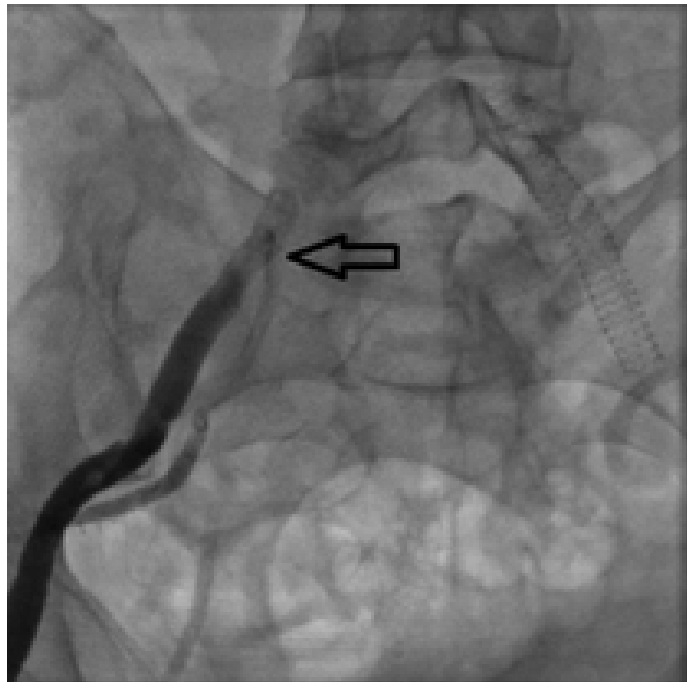

Figure 3. Newly formed total occlusion (arrow) in severely diseased segment in the RCIA.

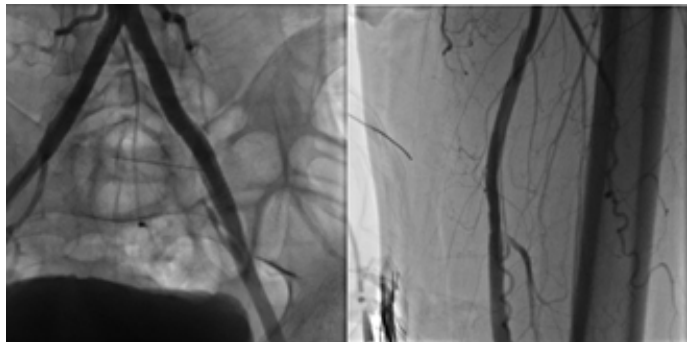

Figure 4. Final result of successful revascularization of bilateral common iliac arteries (A) and left SFA (B).

DISCUSSION

The development of endovascular treatments and the innovations in various endovascular instruments and methods have overcome many of the previous anatomic obstacles that restricted their safe and frequent use. Alternatives of arterial access for SFA lesions, inter alia, currently make easier this complicated percutaneous transluminal angioplasty if considered as inaccessible. The unique features of the SFA complicate the revascularization procedure either requiring the retrograde contralateral or the antegrade ipsilateral CFA approach.[2,5] The contralateral approach can be so difficult

in patients whose angle of aortic bifurcation is so narrow and is not possible in patients formerly had treatment for an aneurysm of the abdominal aorta. Additionally, long introducers and instruments are needed, and pushability of these devices is not enough. Although the ipsilateral femoral approach provides better advance ability due to the use of short devices, this technique is not easy to use in obese patients. In addition, it is not possible to use if there are severe stenotic lesions affecting the CFA, and furthermore, it may be very complicated when there is a diseased segment in the proximal SFA. Transradial or trans-axillary approaches are also alternative methods. Blunt lesions in SFA and the emergence of a large side branch or collateral from the side of the total occlusion hinder these approaches, as well as one of the most important limiting factor, is the fact that the devices used must be quite long. The contralateral (crossover) and antegrade femoral approaches have been well established, however, the retrograde PA approach is still considered as a conceivably efficacious option for the endovascular intervention of infra-inguinal severe arterial stenotic lesions in patients that antegrade procedures are unavailable.[6]

Tandem SFA/CFA lesions and antegrade approach failure are the major indications for RPA.[2,3] It has been claimed that passing through the lesion may be more advantageous, given the less severely calcified or fibrotic plaque formation by approaching from the distal end.[2,3,5] Possible complications of the RPA method involve iliac–femoral dissection, arteriovenous fistula, distal embolization, PA occlusion at the access site, and hematomas. But recent studies demonstrated that frequencies of major complications are low.[7] In our case, we had no vascular complications. After antegrade approach failure, usually, it is not easy for a patient to turn to prone position from supine position. This causes an increase in the patient's distress and this position is uncomfortable, especially for those who were overweight and had poor respiratory function. In our case, our patient's body mass index was normal in range and respiratory status was good, so proceeding with the procedure in the prone position did not constitute a problem for the patient and the operator.

The risk of puncture of both vessels by the needle is so high, because the PA is located just anterior to the vein, so the most probable vascular complication in RPA is an arteriovenous fistula. On the other hand, performing puncture by ultrasound guidance to refrain from fistula formation can essentially ensure real-time imaging of the vessels and the needle. As the operator visually checks the needle, the vein, and the PA, the risk of perforation of the vein is low, and consequently, the possibility of fistula formation is limited as well. In a series of 234 cases by Yilmaz et al.[7] no arteriovenous fistula was observed. Albeit ultrasound guidance is safer compared to roadmap in terms of having the advantage of visualizing the vein to avoid an accidental puncture, safe PA puncture can also be accomplished using the roadmap technique. In our case since we did not have an ultrasound, so the roadmap method was used.

In this case report, the retrograde approach was used successfully for revascularization of severely diseased LCIA and totally occluded SFA, but unexpectedly a total occlusion was observed in the contralateral side possibly due to plaque rupture or erosion with a silent clinic. It should be kept in mind that in such similar cases with long procedural time, some unexpected atherothrombotic events in different regions, except for lesion zones can occur by different pathophysiological mechanisms. Although plaque structure does not appear to be ulcerative or thrombotic in the baseline, it is suggested that we should pay more attention to follow-up of atherothrombotic complications after such a prolonged procedure.

ETHICAL CONSIDERATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report / Olgu sunumu

Paroxysmal Headache as First Finding of Pheochromocytoma: A Case Report

Feokromasitomanın İlk Bulgusu Olarak Paroksismal Baş Ağrısı: Olgu Sunumu

Betül Pehlivan Zorlu[1], Uğur Seyhan[2], Özlem Dur[1], Büşra Koç Galip[1], Aslı Kantar Özşahin[1], Mehmet Coşkun[3], Fatma Devrim[1], Nida Temizkan Dinçel[1]

[1]University of Health Sciences, Dr. Behcet Uz Children Hospital, Department of Pediatric Nephrology, Izmir, Turkey
[2]Sancaktepe Şehit Prof .Dr. İlhan Varank Training and Research Hospital, Istanbul, Turkey
[3]University of Health Sciences, Dr. Behcet Uz Children Hospital, Department of Radiology, Izmir, Turkey

Abstract

Pheochromocytoma is a rare tumor that develops from the chromaffin cells of the sympathetic nervous system. Although hypertension is the most common manifestation of pheochromocytoma, it is less common in children than in adults. This condition may be overlooked like in our patient who had an undiagnosed headache for several years. Our patient was admitted to our emergency department due to the increase in headache, which lasted for about 6 years, and a neurological evaluation was performed. Due to the high blood pressure in her follow-up, she was examined further. Abdominal USG revealed a 36x26x27 mm solid lesion in the right adrenal gland with a mild hyperechogenic appearance with a cystic component. With supporting findings in magnetic resonance imaging and high catecholamine levels in blood, she was diagnosed with pheochromocytoma. Our aim in sharing this case is to emphasize the importance of measuring blood pressure in patients accurately and at each examination, evaluating them with percentile charts, and monitoring them closely.

Keywords: Pheochromocytoma, children, headache, hypertension

Öz

Feokromasitoma sempatik sinir sisteminin kromaffin hücrelerinden gelişen nadir görülen bir tümördür. Hipertansiyon feokromasitomanın en sık bulgusu olmasına rağmen, bu durum çocuklarda erişkinlere göre daha az sıklıkta görülmektedir. Uzun zamandır tanı konulamayan baş ağrısı şikayeti ile başvuran hastamızda gözden kaçırılabilecek bu kliniği değerlendirdik. Hastamız yaklaşık 6 yıldır süren baş ağrısı şikayetinin artması nedeni ile acil servisimize başvurmuş, takibinde nörolojik değerlendirme yapılmıştır. İzleminde kan basıncı yüksekliği saptanması üzerine ileri tetkik edilmiş ve abdominal ultrasonografide sağ sürrenal bezde 36x26x27 mm boyutlarında içerisinde kistik bileşeni bulunan hafif hiperekojen görünümde solid lezyon saptanması, kitlenin manyetik rezonans görüntüleme ve katekolamin yüksekliği ile desteklenmesi ile feokromasitoma tanısı konulmuştur. Olguyu paylaşmamızdaki amacımız hastalarda kan basıncı ölçümünün doğru şekilde ve her muayenede yapılması, persentil çizelgeleri ile değerlendirilmesi ve yakın takibinin önemini vurgulamaktır.

Anahtar Kelimeler: Feokromasitoma, çocuk, baş ağrısı, hipertansiyon

INTRODUCTION

Pheochromocytoma is a tumor that develops from chromaffin cells of the sympathetic nervous system.[1] Pheochromocytomas originate from the adrenal medulla, paragangliomas originate from extra-adrenal cells. It is mostly located in the head and neck but it can be found in the thorax, abdomen, pelvis and bladder.[2] Although hypertension is the most common manifestation of pheochromocytoma, it is less common in children than in adults.[3,4] Palpitations, headache, excessive sweating, and pallor are the main symptoms that may cue pheochromocytoma, but the classic symptoms in children are less common and are characteristically more persistent than paroxysmal as in adults. Sweating, nausea, vomiting, weight loss, polyuria, anxiety, and visual disturbances have been reported more frequently in children than in adults.[5,6] Although the percentage of hereditary cases is not clearly known, there is a high and heterogeneous genetic predisposition. However, pheochromocytomas may

Corresponding *(İletişim)*: Betül Pehlivan Zorlu, University of Health Sciences, Dr. Behcet Uz Children Hospital, Department of Pediatric Nephrology, Izmir, Turkey
E-mail *(E-posta)*: betulpehlivantr@gmail.com
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be associated with Von Hippel-Lindau (VHL) disease, familial paraganglioma, and multiple endocrine neoplasia type 2A.[4]

Hereditary, bilateral, extra-adrenal, and multifocal pheochromocytomas are more common in children than adults.[5] This condition is rare and may be overlooked. In this paper, we present a case who was admitted with a headache that could not be diagnosed for several years.

CASE

A previously healthy 16 years old girl was admitted to our emergency department due to her headache which has occured often for 6 years, lasts 6-7 hours and does not respond to painkillers, worsened in the last 2 weeks. Our patient did not describe photophobia- phonophobia or nause and vomiting. Palpitations and flushing were also not accompanied. There was a 1st degree cousin marriage between mother and father, an abortion history of the mother in her family history. There was no history of migraine in the family.

On physical examination; height: 164 cm (SD: 0.26), weight 61 kg (SD: 0.79), heart rate: 152/min, blood pressure: 140/110 mmHg, respiration rate: 24, body temperature: 36.6 °C. Other physical examination findings were normal. In laboratory examination; hemoglobin:12.1 g/dL (RR: 11.7-15.3), white blood cells:10280/microL (RR: 4.1-11.0), platelets: 582000/microL (RR: 150000-450000), kidney, liver and thyroid function tests, urine analysis were normal; there was no ion imbalance. CRP was negative, no acidosis, lactate was normal. The patient consulted to pediatric neurology. Neurological examination was normal, vitamin B12 level was 240 pg/nl (RR: 200-900), there were moderate atrophic changes in contrast-enhanced cranial MR. Due to high blood pressure levels during the follow-up, the patient consulted to pediatric nephrology.

There was no previous urinary tract infection, use of herbal medicine used for energy or weight loss in the patient's history. There were no risk factors such as obesity or sleep apnea. It was learned that her father, uncle and aunt had kidney stones and also her aunt had a history of nephrectomy. There was no known high blood pressure value in previous admissions. The patient was hospitalized and evaluated. Complete blood count, renal function tests and urine analysis were found to be normal. Upon the persistence of high blood pressure, the etiology of hypertension was examined, amlodipine and enalapril treatments used for treatment. Abdominal ultrasonography revealed a 36x26x27 mm solid lesion in the right adrenal gland with a mild hyperechogenic appearance with 2 cystic components, approximately 7 mm in diameter. In contrast-enhanced abdominal magnetic resonance imaging (MRI); liver long axis was measured 166 mm, hepatomegaly was present, both kidneys were normal in size, parenchyma and echogenicity. In the right adrenal gland, a solid lesion, 30x27 mm in size, with circumscribed and round appearance was observed. It had low signal in T1 weighed imaging (WI), high signal in T2WI, and no contrast enhancement. Post-contrast imaging was standard T1WI fast spin echo. Since there was no dynamic- fast imaging, it was thought that the lesion had washed out from contrast in standard T1WI. Due to the high T2 signal, the pre-diagnosis was pheochromocytoma (**Figure 1**). The patient examined for end organ damage due to hypertension, there was no microalbuminuria, fundus was normal, cardiological examination was normal. Metanephrine and normetanephrine levels were found to be high in urine, and blood levels of vanillylmandelic acid acid were found to be high, and 5-hydroxyindoleacetic acid and homovanillic acid were within normal limits (**Table 1**).

Table 1. Biochemical values

	Pre-op	Post-op 6th month	Reference Range
Metanephrine (µg/24h)	93	122.9	(52-341)
Normetanephrine (µg/24h)	101224	152,9	(88-444)
Urine 24-hour volume		2100	
Vanillylmandelic acid (mg/24h)	12		(1,6-7,3)
Homovanillic acid (Urine 24-hour) (mg/24h)	3		(1,82-6,92)
5-Hydroxyindoleacetic acid (Urine 24-hour) (mg/24h)	5		(2-8)

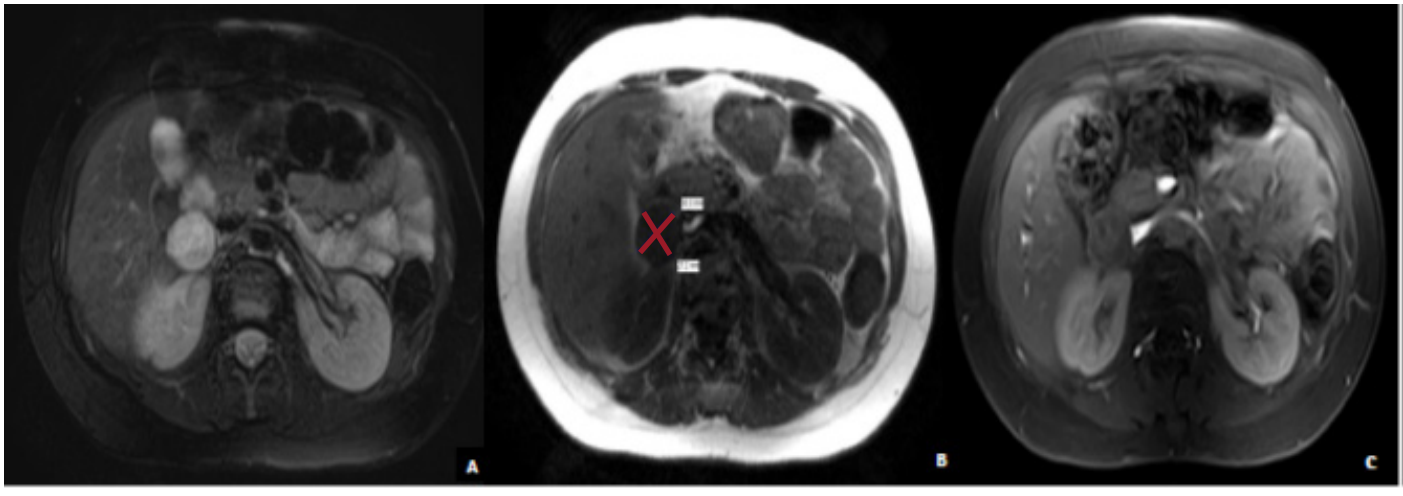

Figure 1. A: T2 weighed imaging **B**: T1 weighed imaging **C**: Contrast in T1 weighed imaging

The antihypertensives that the patient was taking were stopped and doxazosin treatment was started. In order to exclude multiple endocrine neoplastic syndromes, blood tests were performed; IGF-1: 162 ng/ml (RR: 153-611), IGFBP-3: 5.03 µg/ml (RR: 3.4-9.5) ve calcitonin: <2 pg/ml (RR:≤5.0). Pituitary MRI and thyroid ultrasonography were normal. VHL gene analysis has been done. NSE:14,98 µg/L (RR:≤15.0) , AFP:<2,72 µg/L (RR:<8.4) CA15-3: 5,05 U/mL (RR: <30) were found to be normal. Positron emission tomography performed for surgical evaluation, revealed a mass lesion with increased somatostatin receptor expression in the right side of the vena cava inferior, posterior to the duodenum, anterior adjacent to the kidney, caudal to the right surrenal gland, between the adrenal gland corpus and the lateral crus. There was no zone with increased Ga-68 DOTATATE uptake that might indicate a metastasis.

During the surgical preparation process, her blood pressure progressed to stage 2 hypertension and an alpha-beta blocker was started. It regressed to pre-hypertensive values in the follow-up. Adrenal-sparing surgery was performed. In the postoperative follow up; a hypertensive value was found only once, her headache did not persist, she had no additional problems, therefore she was discharged. Metanephrine and normetanephrine values were found to be normal in the urine examined 6 months later. (**Table 1**) Pathological examination revealed a well-circumscribed tumor with a diameter of 3.5 cm in pheochromocytoma morphology with a prominent Zell Ballen pattern in the right adrenalectomy material. There were no findings suggesting malignancy.

DISCUSSION

Pheochromocytoma in children is rare, accounting for 5% of all diagnoses. Approximately 80% of the cases originate from the adrenal medulla.[5] Most cases are sporadic, but around 40-60% can be part of hereditary syndromes. Hypertensive crisis in pheochromocytoma is an endocrine emergency associated with severe mortality. This is a catecholamine-induced acute severe hemodynamic disorder that causes end organ damage or dysfunction.[7] The most common complaints are headache and hypertension. Although our patient has had a headache for about 6 years, no high blood pressure was detected in her admissions. According to the study of Babic et al., the percentage of admission with headache was 2% and with hypertension was 17%. Our patient had a complaint of constant headache. Persistent hypertension is present in 60-90% of children. However, there is no requirement of hypertension for a diagnosis, and there is no clear relationship between catecholamine levels and the symptoms. While the mean age at diagnosis was 13.9 years in the study of Babic et al.,and 11 years in the study of Havakes et al., the age at diagnosis of our case was 16.[5,8]

Family history is encountered at a percentage of 10%, and family history is not present in our case.[4,9] Among the hereditary syndromes, multiple endocrine neoplasia type 2, von Hippel Lindau syndrome, neurofibromatosis type 1 and familial paraganglioma syndromes are most frequently observed in relation with pheochromocytoma. Genetic defect in intracellular oxygen balance in Von Hippel Lindau Syndrome can lead to intense excessive cell proliferation in blood vessels. It mostly occurs as angioma in retina of the eye, hemangioblastoma in brain or spinal cord, endolymphatic sac tumor in inner ear, kidney cell carcinoma, pheochromocytoma in adrenal gland, serous cystadenoma in pancreas, or papillary cystadenoma in epididymis or uterine ligament. The occurrence of the disease can vary significantly and patients may show symptoms at any time from early childhood to adulthood. Phenotypically the disease is divided into 4 types; VHL type 1 is predominantly without pheochromocytoma, and VHL type 2 is predominantly with pheochromocytoma. Type 2 is subdivided to type 2A (with renal cancer) and type 2B is (without renal cancer). In type 2C, there are solely pheochromocytomas. Therefore, the VHL gene mutation we examined in our patient resulted as negative. It should be noted that, together with the increased knowledge and expanding genetic test analysis, patients with negative genetic screening may have germline mutation in the future. Genetic screening is very important because it indicates an increased risk of recurrence and malignancy.[10]

It is known that malignant pheochromocytoma cases are less common in children. 10-15% of pheochromocytomas and 20-50% of paragangliomas may be malignant.[10] In our patient, no malignancy was detected as a result of the pathological examination. Biochemical markers are very important in diagnosis, they include examination of catecholamine levels and urinary vanillylmandelic acid in 24-hour urine and plasma. Metanephrine and normetanephrine levels in blood are 100% sensitive and 94% specific in children, and the level of normetanephrine was found to be significantly higher in our patient at diagnosis. Although magnetic resonance imaging is 90-100% sensitive in diagnosis, it may be insufficient to distinguish pheochromocytoma from other abdominal lesions. Therefore, as in our patient, 123 metaiodobenzylguanidine (MIBG) scintigraphy should be added to the examinations to confirm the diagnosis, to catch clues about malignancy, and to detect other foci, if any.[5]

In our case, the patient was diagnosed with pheochromocytoma with detection of a solitary lesion in abdominal ultrasonography after normal results of urinary ultrasonography performed for hypertension, abdominal MRI and high levels of metanephrine and normetanephrine in the urine. The gold standard in diagnosis is the elevation of catecholamine and its metabolites in urine, which was also present in our patient. In pheochromocytoma crisis, treatment management includes the use of alpha-blockers and surgical intervention should be delayed until medical stabilization is established.[7,8] Alpha-blocker was used in our patient during the surgical preparation process. In the study of Havekes et al., it was stated that calcium channel blockers alone are not sufficient to control blood pressure or may be useful when side effects are seen.[5] Our patient, who did not have metastatic lesions on scintigraphy, was hospitalized approximately 2 weeks before the planned operation date and was operated after blood pressure regulation was achieved.

CONCLUSION

Finally, as pheochromocytoma can be accompanied with many findings and symptoms, it should also be considered with the differential diagnosis of headache. Hypertension may be absent, or it can be seen paroxysmally as in adults. It is very important to measure blood pressure in patients accurately and at each examination, evaluate them with percentile charts, and monitor them closely. It is necessary to be suspicious in certain situations and the pheochromocytoma should be brought to mind. In this disease, in which family history is significant, family screening or follow-up is also important in terms of cases that are missed or have not yet shown any symptoms.

ETHICAL CONSIDERATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Status of Peer-review: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review / Derleme

SARS-CoV-2 in Cellular Level: Do We Dominate the Whole Picture and How Can We Intervene?

Hücresel Düzeyde SARS-CoV-2: Resmin Tamamına Hakim Miyiz ve Nasıl Müdahale Edebiliriz?

Muhammed Emin Düz[1], Aydın Balcı[2], Elif Menekşe[1]

[1]Amasya University Sabuncuoğlu Şerefeddin Training and Research Hospital, Division of Clinical Chemistry, Amasya, Turkey
[2]Afyon University School of Medicine Department of Pulmonology, Afyon, Turkey

Abstract

Coronaviruses are a family of viruses present in various animals, and alpha and beta types can infect humans. Human coronavirus varieties settle in different regions of the respiratory tract epithelium, causing disease with varying severity. We conducted a comprehensive academic search to aggregate data and added our own ideas to create a good research article. As a result of many studies carried out in a short time, detailed information was obtained about the entry of the virus into the cell and its cellular cycle. Although vaccination studies are about to come to an end, we do not yet have an agent that provides a definitive treatment that will facilitate millions of people's lives. At this point, humanity needs detailed genetic research, especially on cellular interactions. Because although we think that we are in control of the subject, science is a field that changes daily, and new data are added to it. It is evident that we need marginal ideas for a virus that has affected the whole world, can easily be transmitted by respiratory and droplets, and has destroyed everyday life. This research aims to examine the data we have so far in detail on all of the topics we have mentioned and try to make some suggestions within our knowledge.

Keywords: SARS-CoV-2, Covid-19, Coronavirus

Öz

Koronavirüsler, çeşitli hayvanlarda bulunan bir virüs ailesidir ve alfa ve beta türleri insanları enfekte edebilir. İnsan koronavirüs çeşitleri, solunum yolu epitelinin farklı bölgelerine yerleşerek değişen şiddette hastalığa neden olur. Verileri toplamak için kapsamlı bir akademik araştırma yaptık ve iyi bir araştırma makalesi oluşturmak için kendi fikirlerimizi ekledik. Kısa sürede yapılan birçok çalışma sonucunda virüsün hücreye girişi ve hücresel döngüsü hakkında detaylı bilgiler elde edildi. Aşılama çalışmaları bitmek üzere olsa da henüz milyonlarca insanın hayatını kolaylaştıracak kesin tedavi sağlayacak bir ajana sahip değiliz. Bu noktada insanlığın özellikle hücresel etkileşimler konusunda detaylı genetik araştırmalara ihtiyacı var. Çünkü konunun kontrolünde olduğumuzu düşünsek de bilim her geçen gün değişen bir alan ve ona yeni veriler ekleniyor. Tüm dünyayı etkilemiş, solunum ve damlacıklarla kolaylıkla bulaşabilen ve günlük yaşamı mahvetmiş bir virüs için marjinal fikirlere ihtiyacımız olduğu aşikardır. Bu araştırma, bahsettiğimiz tüm konularda bugüne kadar sahip olduğumuz verileri detaylı bir şekilde incelemeyi ve bilgimiz dahilinde bazı önerilerde bulunmayı amaçlamaktadır.

Anahtar Kelimeler: SARS-CoV-2, Covid-19, Koronavirüs

Corresponding *(İletişim)*: Muhammed Emin DÜZ, Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital, Clinical Biochemistry, Amasya, Turkey
E-mail *(E-posta)*: cerrahemin@gmail.com
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INTRODUCTION

The SARS-CoV-2 virus, which emerged in Wuhan, China, in late 2019, was identified as the cause of the Covid-19 disease that swept the world and caused the death of millions. Coronaviruses are a family of viruses present in various animals, and alpha and beta types can infect humans. [1] Human coronavirus varieties settle in different regions of the respiratory tract epithelium, causing disease with varying severity. Although alpha and beta coronaviruses are common in humans, they usually cause mild-severe flu-like upper respiratory tract complaints. However, beta coronaviruses such as MERS-CoV (Middle East respiratory syndrome coronavirus), SARS-CoV (severe acute respiratory syndrome-coronavirus), and SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) are less common in humans, but more deadly.[2] The three viruses mentioned are believed to be transmitted to humans by bats and other intermediate mammals.[3] Like other coronaviruses, SARS-CoV-2 is a genome close to 30 kb long; this was similar to 80% with SARS-CoV, 50% with MERS-CoV, and more bat-associated coronaviruses (88% bat-SL-CoVZC45 and bat-SL-CoVZXC21, 93% with RaTGT13) (**Figure 1**). The first 2/3 of the genome encodes the replicase-transcriptase complex, and the last third one translates into four structural proteins. Within all viral proteins, the replicase-transcriptase complex is the only protein directly translated from the genome. ORF1a and ORF1b encode two polyproteins (pp1a and pp1b) that are spontaneously processed to grant 16 non-structural proteins (**Figure 2**). Structural proteins are expressed from spike (S), envelope (E), membrane (M), nucleocapsid (N), and other auxiliaries subgenomic mRNAs.[4]

Cellular Adhesion

SARS-CoV-2, an enveloped positive-sense single-stranded RNA virus, uses glycoprotein spikes for receptor recognition and membrane fusion to initiate infection.[5] In mature viruses, the spike protein exists as a trimer with the S1 head attached to the three receptors that sit atop the S2 stalk. The S1 subunit of the coronavirus spike glycoprotein contains the receptor-binding domain (RBD) that binds to the peptidase domain (PD) of host cell angiotensin-converting enzyme 2 (ACE-2). The RBD frequently alters between a standing-up position for receptor binding and a lying-down position for immune evasion. Simultaneously, the S2

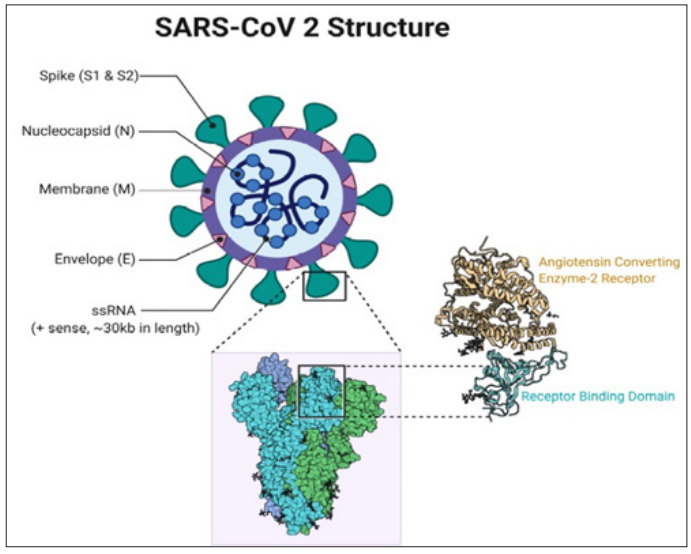

Figure 1. Structure of SARS-CoV 2. From Marco Cascella et al. Features, Evaluation and Treatment Coronavirus (COVID-19).
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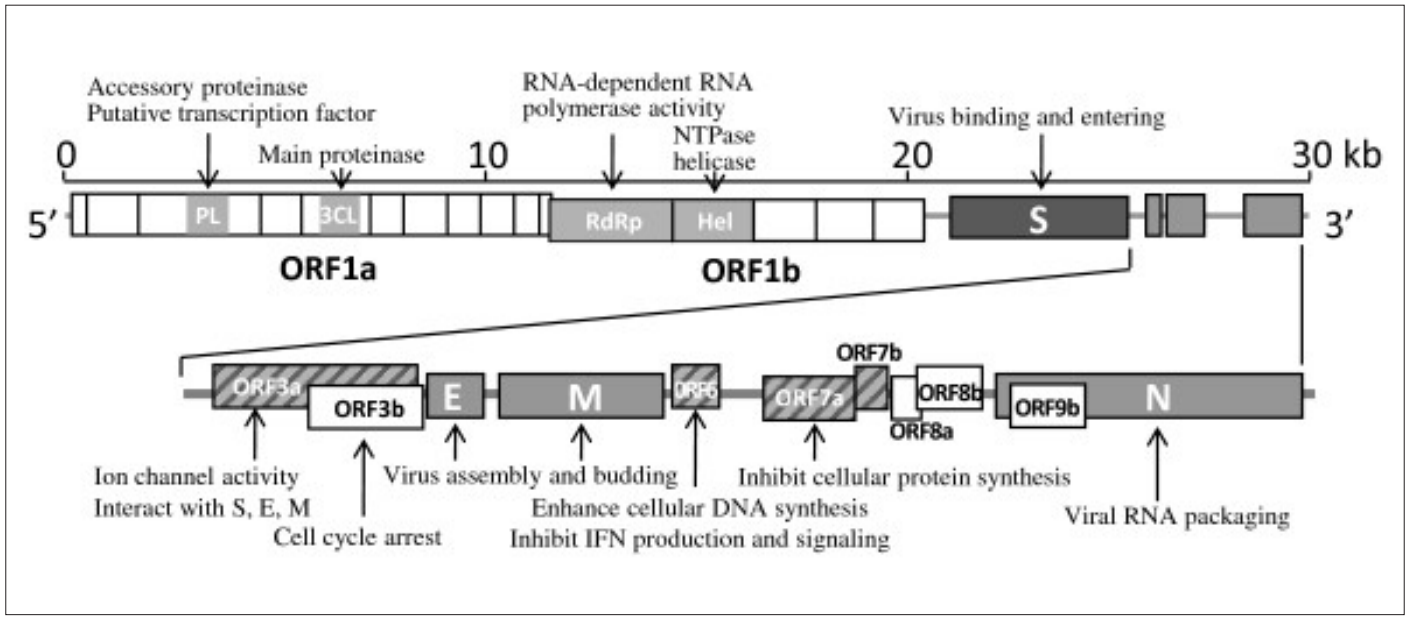

Figure 2. SARS-CoV genome organization. Attribution: Xianchun Tang, Gang Li, Nikos Vasilakis, Yuan Zhang, Zhengli Shi, Yang Zhong, Lin-Fa Wang, and Shuyi Zhang, CC BY 2.0, via Wikimedia Commons.
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subunit of the spike glycoprotein provides membrane fusion with the host cell. Human ACE-2 is a type 1 membrane glycoprotein that produces angiotensin, which balances blood pressure by vasoconstriction. In coronavirus infections, ACE-2 is seized by some coronaviruses such as SARS-CoV and SARS-CoV-2 for cell entry purposes.[6] Relative to SARS-CoV, SARS-CoV-2 is believed to bind human ACE-2 more accurately, thereby boosting its chance of human to human transmission. In contrast, SARS-CoV-2, like SARS-CoV, uses host cell transmembrane protease serine 2 (TMPRSS2) to cleave the spike glycoprotein.[7] Moreover, to fuse membranes, the SARS-CoV-2 spike needs to be proteolytically activated at the S1/S2 borderline. Thus, S1 decomposes, and S2 calls upon a theatrical structural change. Proteases that activate this SARS-CoV-2 entry include the cell surface protease TMPRSS2 and cathepsins among lysosomal proteases. The entry also requires the regulation of the S protein by cellular proteases. This process involves S protein cleavage at the S1/S2 level to allow viral and cellular membrane fusion, a process carried out by the S2 subunit.[8] A highly conserved epitope has been identified to explain cross-neutralization with antibodies specific for SARS-CoV-2 S. However, neutralizing antibodies are directed against this S protein.

Viral adhesion theories in the light of new studies

To date, the whole world knows about SARS-CoV-2 adhesion and cellular entry mechanism but, specifically, restricting the production of phosphatidylinositol 4,5-bisphosphate (PIP2) fetters the fusion of the SARS-CoV-2 envelope with the endolysosomes and viral entry.[9] Additionally, viral entry-related membrane fusion needs a priming step intervened by multiple host proteases, including the lysosome-localized Cathepsin B/L and serine proteases of the TMPRSS family.[10] Although some TMPRSS proteases can act at the cell surface, increasing lysosomal pH in TMPRSS2-positive Caco-2 or TMPRSS2-negative HEK293 cells both inhibit SARS-CoV-2 cell entry, suggesting that endolysosomes are the leading entry site for SARS, at least in specific cell types.[11] A study on the intercellular transmission of misfolded α-Synuclein (α-Syn) fibrils, a cellular process reminiscent of viral infection, demonstrated a mechanism of endocytosis in which cell surface heparan sulfate (HS)-bearing protein assemblages facilitate receptor-mediated uptake. HS is a negative charge-enriched linear polysaccharide molecule that binds to the various membrane and extracellular proteins collectively referred to as heparan sulfate proteoglycans (HSPG). Cell surface HS can act as an anchor to facilitate the endocytosis of many burdens involving SARS-CoV-2 related coronaviruses.[12] Other evidence supporting HS's role in introducing HS mimetic glycan heparin and coronaviruses associated with SARS-CoV-2 Spike and SARS-CoV-2 could guide scientists in terms of the possibility of targeting HS as a Covid-19 therapeutic strategy.[13]

The core polymerase assembly proteins structure SARS-CoV-2 nsp12-nsp7-nsp8 (catalytic subunit and two cofactors, respectively) could be elucidated very similar to SARS-CoV. This may give an idea about a successful infection than SARS-CoV, perhaps explaining the increased ribonucleic acid (RNA) production.[14]

Scientists have discovered that high-density lipoprotein (HDL) scavenger receptor B type 1 (SR-B1) facilitates cellular SARS-CoV-2 entry linked to ACE-2 in a recent study. The study demonstrated that the S1 subunit of SARS-2-S binds to cholesterol and possibly HDL components to increase viral uptake in vitro. They stated that SR-B1 expression facilitated the entry of SARS-CoV-2 into cells expressing ACE-2 by enhancing the connecting of the virus to the cell surface. They noted that blocking the cholesterol-binding site on SARS-2-S1 or closing it with pharmacological SR-B1 antagonists could prevent HDL-enhanced SARS-CoV-2 infection. They also noted in their study findings that SR-B1 is co-expressed with ACE-2 in human pulmonary tissue and various extrapulmonary tissues.[16]

Cellular Entry and Membrane Fusion

The virus enters target cells by infecting via different entry patterns by droplet or contact. First, it passes through ACE-2, thanks to the S protein RBD, on the most accepted pathway.[16] This entry also requires the S protein cleavage by the transmembrane protease serine 2 (TMPRSS2). Thus, the fusion peptide located in the S2 domain can be released and dramatically increases the SARS-CoV-2 entry.[17] Also, separation by cathepsin L can be performed during endocytosis. Differently, like the classical cleavage site known in the SARS-CoV S protein, SARS-CoV-2 S presents a furin-like cleavage site often observed in highly virulent influenza viruses. This can provide cleavage provided that formal integrity is maintained in the Golgi apparatus during biosynthesis and prolonged tropism and transmissibility due to the nearly ubiquitous furin-like protease.[18] Although the accepted binding is ACE-2/RBD in the literature, a new entry route has been recently demonstrated via CD147 (Basigin), but we need more evidence.[19]

In Vivo Interactions

After the virus completes cell fusion and entry, viral proteins are released. Genomic RNA is then released, producing enzymes essential for the necessary viral protein synthesis, which is a process that requires ribosomal frameshift.[20] The encoded polyprotein is processed to give 16 nsp, which combines to form the replicase-transcriptase complex. As a result, host viral membrane fusion and the RNA genome release into the host cell cytoplasm occurs. First, the host translation mechanism is captured for the translation of vital proteins and essential viral proteases. The polyproteins (pp1a and pp1ab) are cleaved by 3CLpro and PLpro into 16 effector proteins, allowing the replication complex to be synthesized with RNA-dependent RNA polymerase that synthesizes a full-length negative RNA chain template. In this way, both viral RNA to be copied and mRNAs that will synthesize proteins are created. The newly synthesized and viral structural and helper proteins are then sent from the ER to the Golgi apparatus, reminiscent of normal cellular glycoprotein synthesis. The new virions are assembled in budding Golgi vesicles. Finally, mature SARS-CoV-2 virions are released from the host cell into the surrounding environment to repeat the exocytosis infection cycle (**Figure 3**).[21,22]

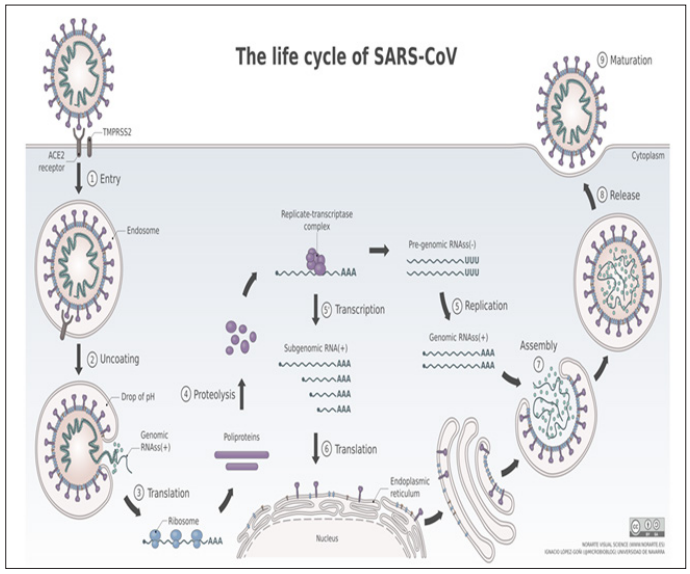

Figure 3. The SARS-CoV life cycle, which is very similar to SARS-CoV 2, can give us detailed information regarding COVID-19 disease. From SARS and MERS: recent insights into emerging coronaviruses. De Wit E, van Doremalen N, Falzarano D, Munster VJ. Nat Rev Microbiol. 2016 Aug;14(8):523-34.

https://upload.wikimedia.org/wikipedia/commons/2/23/SARS-CoV-2_cycle.png

New interactions discovered at ACE-2 level

Recent data provide evidence that ACE-2 effectively scatters through membranes. This process is fine-tuned at different levels involving two cell membrane proteases: protein 17 (ADAM17) and transmembrane protease serine 2 (TMPRSS2), which contains the lytic and metalloproteinase domain.[23] ADAM17 acts directly on ACE-2, causing it to be thrown into the intercellular space, while TMPRSS2 cleaves ACE-2 and the S protein of SARS-CoV-2, thus leading to membrane fusion and the entrance of the virus into the cell. As a result, while ADAM17 and TMPRSS2 both act on ACE-2, they can adversely affect net ACE-2 shedding. When the known proteolytic activities of ADAM17 and TMPRSS2 cause more ACE-2 shedding than internalization, it follows that this can create a natural barrier to infection. This may be due to the interaction between soluble ACE-2 and the virus, located away from sensitive tissues.[24]

Treatment trials and vaccine studies

To date, treatment products are (25);

- Antibodies have been taken from the blood of people who have survived Covid-19 infection or neutralizing antibodies produced in the laboratory, antibodies to turn down the known catastrophic immune response of Covid-19 "cytokine storm".
- Antivirals to stop viruses from reproducing by blocking one or more steps in the process.
- Cell-based therapies such as transferring into patients' live cells to treat a specific disease. Different cell types taken from different tissues can be used for this purpose.
- Devices, such as blood purification devices, filter patients' blood to remove cytokines that cause a "cytokine storm" that can lead to respiratory or organ failure.
- RNA-based therapies stop viral replication by disrupting viral proteins' structure and blocking the virus's synthesis that invades our cells.
- Scanning compounds to repurpose (previously known and well-informed materials) can play a role in treatment.
- Other drugs include steroids, malarial drugs, cancer drugs, anti-immune-system drugs, etc.

To date (**Figure 4**), there are 237 vaccines are in development, 38 are now in clinical testing, and ten leading candidates are in the clinical phase three.[26] ;

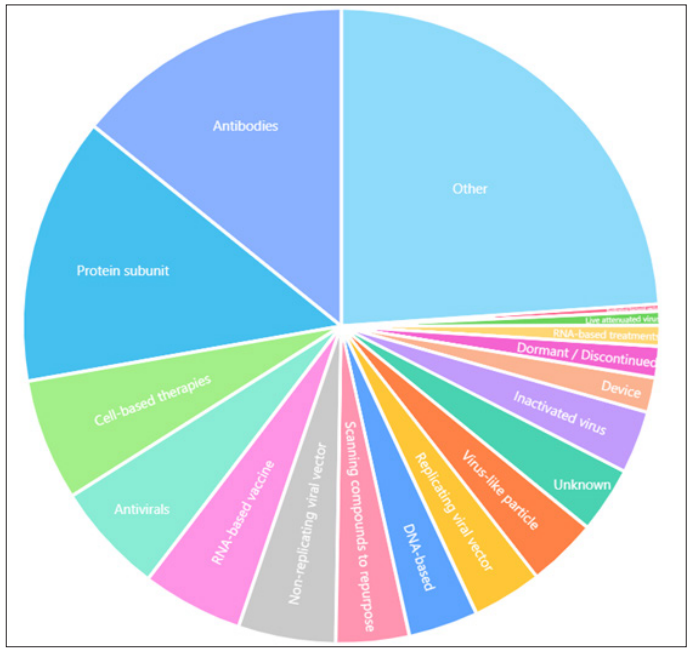

Figure 4. All COVID-19 treatment methods and vaccine candidates so far in Research Pipeline. Via 2020 Milken Institute. Achieved with Airtable membership.
https://airtable.com/shrSAi6t5WFwqo3GM/tblEzPQS5fnc0FHYR/viwDBH7b6FjmIBX5x?blocks=bipZFzhJ7wHPv7x9z

- Live attenuated virus that must be able to reproduce (self-replicate) and generate a robust immune response, but it must not make people sick.
- The deactivated virus is the killed version of the virus and is expected to generate an adequate immune response. They are preferred, especially in patients with immunodeficiency syndrome where attenuated vaccine cannot be used due to its side effects.
- Subunit vaccines (protein subunit or virus-like particles) use the virus's fragments, rather than the whole virus, to trigger an immune response inside the body.
- Nucleic Acid Vaccines or gene-based vaccines reflect a "state of the art" approach to vaccination. Compared to vaccines containing all or part of the virus, this ingenious method uses genetic engineering to deliver nucleic acids

(DNA or RNA) that carry genetic instructions for viral protein synthesis to the target cell. After the nucleic acid pieces enter the cell, it synthesizes viral proteins that will trigger an immune response. Because these vaccines consist only of nucleic acids (DNA or RNA) and do not contain other viral parts, they are both easy to manufacture and safe.

- Viral Vector Vaccines are similar to nucleic acid vaccines in that they provide instructions for viral protein production. However, instead of using plasmids or lipids to introduce them into the cell, these vaccines use attenuated viruses (vector virus) other than the virus that caused the disease to carry the viral genes' blueprint.

Extreme ideas for tough times

As the world approaches after Covid-19 vaccine studies, we still do not have a cure, and it is not yet luminous to what extent and in what variety vaccines will be offered to the service of all humanity. Since we are faced with a virus that affects the whole world and is transmitted by air-droplets, it has been necessary to limit this pathogen's effects to return to everyday life almost everywhere in the world. Mosquitoes modified with gene drive systems control infectious diseases by reducing the targeted number of disease carriers (population suppression) or reducing their ability to transmit the pathogen to humans (population change/modification). Gene driver systems provide preferential (super-mendelian) inheritance of genetic traits included in hybridizing mosquito populations. These systems can be self-limiting when limiting impacts are desired or provide continuity when the features are intended to spread across the local population. The impact is planned to be permanent.[27] It may not be an acceptable idea, but it can be released into the environment by producing a genetically modified SARS-CoV-2 virus with inactivated selected genes, with higher binding affinity with ACE-2 and TMPRSS2, and will not cause disease. At this point, if genetically modified SARS-CoV-2 is to be used, genetic engineering should work so fine-tuned that the genetically driven virus should perform the intracellular stages detailed so far as a one-to-one active pathogen and enter a kind of competitive inhibition with the real SARS-CoV-2. Differently, a different agent with the same protein-binding sites containing similar tissue tropism can also be used. This approach's main idea is that the non-pathogenic agent provides social immunity, rather than the attenuated virus, through the transmission like Oral Polio Virus (OPV) vaccine. If the produced genetically modified non-pathogenic virus is successful, it can be applied primarily in communal living areas to breathe at critical points of life. This idea is only a theory, but it should not be forgotten that no one even predicted the point reached in the pandemic.

CONCLUSION

Being able to illuminate the nature of the virus is essential to develop treatments that can remedy humanity. Besides, it is vital to understand the microscopic structuring in order to obtain effective efficiency from vaccines and to act by predicting possible mutations. Although the light was seen at the end of the tunnel, the massive blow to the world and humanity due to Covid-19 is obvious. Just as the virus attacks us with all its might, we have to attack everything we have. Vaccines, medicines, supportive care, masks, social distance, etc. We hope that humanity will take care of this scourge by turning to science entirely and transparently.

ETHICAL DECLARATIONS

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Review / Derleme

The effect of Telomere Lengthening on Genetic Diseases

Telomer Uzatmanın Genetik Hastalıklara Etkisi

Marko Bojkovic, Sathees B. Chandra

Biomedical Sciences Program, College of Nursing and Health Sciences, Barry University, Miami Shores, USA

Abstract

Telomeres are a characteristic of chromosomes that have increasingly large significance in research. They are studied in various diseases to discover potential treatment strategies. Their most vital characteristic is their length because the length can be used to describe different characteristics about the cell, such as its age. The length of telomeres can also be used as a potential way to treat disease. This review article's purpose is to explore how telomeres can be potentially used as a method to treat genetic diseases such as trisomy 21 and cancer.

Keywords: Telomere, telomere shortening, telomere homeostasis, down syndrome, carcinoma, hepatocellular

Öz

Telomerler, araştırmalarda gittikçe artan önemi ile kromozomların bir özelliğidir. Potansiyel tedavi stratejilerini keşfetmek için çeşitli hastalıklarda incelenirler. En hayati özellikleri uzunluklarıdır çünkü uzunluk, hücre hakkında yaşı gibi farklı özellikleri tanımlamak için kullanılabilir. Telomerlerin uzunluğu, hastalığı tedavi etmenin potansiyel bir yolu olarak da kullanılabilir. Bu inceleme makalesinin amacı, telomerlerin trizomi 21 ve kanser gibi genetik hastalıkları tedavi etmek için potansiyel olarak nasıl kullanılabileceğini keşfetmektir.

Anahtar Kelimeler: Telomer, telomer kısalması, telomer homeostazı, down sendromu, karsinom, hepatoselüler

INTRODUCTION

Telomeres are the terminal ends of chromosomes that contain repetitive nucleotide sequences. They prevent chromosomal deterioration and the fusion of the chromosomes with adjacent chromosomes. Telomeres also restrict how frequently cells divide, thereby preventing malignant transformations that are caused by a buildup of mutations. Their repeated sequence of nucleotides is AGGGTT, with the complementary strand being TCCCAA, and has a TTAGGG overhang. When a cell replicates DNA, the chromosomes are shortened by approximately 25-200 bases per replication. However, telomeres are lost because of their role in protecting the chromosomes' ends, but DNA remains undamaged.

Telomere length has been studied extensively due to its potential impact on illness. One theory claims that telomeres are vital in trisomy families. Trisomy 21 is the chief abnormality of chromosomes that causes Down Syndrome. Nondisjunction errors that involve Chromosome 21 happen mostly in the oocyte, and this statistic depends primarily on the age of the mother when the sample is studied.[1] Additional studies show that Telomere loss could form classical breakage-fusion bridge cycles and dicentric chromosomes, which are then proceeded by aneuploidy and genome arrangements. Faster dementia and impairments are also caused by this, as studied in Down syndrome other many disorders that are associated with age.[2] Despite this, it is still unknown if the severity of a pre-existing cognitive impairment can predict DS cognitive deterioration rate, or if any other factors led to telomere loss and increased aging in DS patients.[3] Scientists also do not understand how advanced maternal age can be associated with the risk for DS because the exact mechanisms and triggers that are caused by telomere shortening on DS remain unknown.[4] Other factors that are considered are the metabolic profile of the mother, environmental factors, or initial telomere length at birth.[5,6]

Corresponding *(İletişim)*: Sathees B. Chandra, Biomedical Sciences Program (BMS) College of Nursing and Health Sciences Barry University, Miami, Shores, FL 33161
E-mail *(E-posta)*: schandra@barry.edu
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This review article will explore the possibility of using telomeres as a method to treat genetic diseases. Different characteristics of telomeres will be observed as to how they can be used to treat diseases. The diseases that will be discussed in this article are Trisomy 21 and different forms of cancer. This review article will summarize available research regarding telomeres and their use in treatment of diseases.

Telomere Length as a Description of Age

A telomere's length is considered to be a heritable biomarker of genomic aging.[7] When a cell divides, telomeres shorten because DNA polymerase cannot replicate the DNA strand's 3' end in its entirety.[8] Protein complexes such as the Shelterin complexes and DNA helices bind telomeres to regulate their length and structure.[9] In some cells, the enzyme telomerase, a ribonucleoprotein that has a reverse transcriptase, accessory proteins, and the RNA template TERC, maintains the telomere's length.[10] The loss of a telomere's components and telomerase has been studied extensively to observe a link between them and diseases. Premature aging is linked to shorter telomere length, as evidenced by several age-related diseases. However, it is unclear if telomere length truly played a role in these diseases or if the studied associations were caused by reverse causation. Additionally, no two individuals have the same telomere length, and telomere length is very heritable.[11,12]

Li et al. analyzed leukocyte telomere length (LTL) by pooling imputed association and densely genotyped results across large-scale European-descent studies. They used a quantitative PCR technique that could express telomere length as a telomeric repeat number (T) to a single-copy gene (S) ratio.[13,14] Any detected variant was observed to find any association with the average LTL in each cohort by way of additive models that were adjusted for cohort specific covarities, gender, and age, and the variants were then combined by way of inversevariance-weighted meta-analysis. The results indicated that, 20 sentinel variants could be associated independently genome-wide with LTL, which included six loci that were not seen with LTL. They also identified significant variants from a Singaporean Chinese population, which included the 4 loci POT1, PARP1, MPHOSPH6, and ATM. They also confirmed seven European loci (DCAF4, RTEL1, STN1, NAF1, ZNF208, and TERT). The results show that overall, genetic variation may be specific to a region, and can contribute to LTL.[7]

Li et al. also showcased shorter telomere length as more likely to cause higher age-related illnesses, they demonstrated shorter TL to other illnesses such as thyroid cancer and lymphoma. Shorter TL protected the cells from those diseases, possibly by way of limiting cell proliferation, which makes potential oncogenic mutations less common, and may stabilize DNA replication. Their findings linked nucleotide metabolism to TL regulation to gain information on the link between TL disorders that are related to age and cancer, which hints that cells that have a longer telomere length have higher dNTP levels that cause less DNA replication commitment, leading to higher proliferation and more mutations.[7]

Maternal Telomere Length on the Offspring Telomere Length

Trisomy 21 is heavily studied as a chromosome nondisjunction model. Most of the errors that nondisjunction causes happen in the oocyte, and the amount of errors on the age of the mother.[15] The errors are classified as happening during meiosis I (MI) or meiosis II (MII), which feature different mechanisms.[16] Recombinant patterns that involve telomeres increase MI risk factors, but recombinant patterns at the chromosomes' centromeres increase MII risk factors.[17-20] If maternal age truly increases errors from nondisjunction, telomeres are expected to be shorter if mothers had nondisjunction.[1]

According to Albizua et al.[21], mothers who featured a nondisjunctional error that birthed offspring with down syndrome have shorter telomere lengths than mothers who birthed offspring without Down syndrome. This suggested that the mothers of children who had DS appeared "biologically older" than the euploid children's mothers. The cases were the mothers that birthed infants who contained a nondisjunctional maternal error, which included a sample of 404 cases; the controls included the mothers that birthed an infant that had Down syndrome because of a post-zygotic mitotic error or a paternal error, which included a sample of 24 controls; mothers who had an infant without Down syndrome were also randomly drawn from the general population, in a sample of 18 mothers.[1] Over 1500 polymorphisms that were specific to chromosome 21 and spanned 21q in the probing with DS were genotyped, and Albizua et al. determined the meiotic error's parental origin by determining which parental alleles probed with trisomy 21, also enabling them to decipher whether the error occurred in meiosis I or meiosis II.[20] Parental heterozygosity in the proband at a pericentromeic marker indicated an error at meiosis I, and parental homozygosity indicated an error at meiosis II.[19-20] Linear regression models determined the maternal age T/S ratios, and other models were used to observe a correlation between meiotic outcome group and maternal age in the regression.

Albizua et al.[21] confirmed a T/S ratio that was statistically significant by using maternal age and quantitative PCR in all maternal-derived cases of nondisjunction and in controls. To do this, they analyzed their result using the cases that informed the origin stage, which included a sample of 241 cases. The cases displayed the maternal age and T/S ratio's exact and significant association, suggesting that the selected cases on the analyses that were further conducted represented the maternal errors' overall group. They then analyzed how maternal age range affects maternal telomere length, and discovered a major decrease in maternal aged T/S ratio controls and errors from meiosis I but not meiosis II. Ultimately, the results confirmed the original hypothesis, which stated younger mothers who featured a nondisjunctional error which birthed infants with Down syndrome being "biologically older" than mothers in the same age group that birthed euploid offspring.[20]

Telomeric Alternative Lengthening

Telomeric alternative lengthening and activation of telomerase are the two main mechanisms involved with the stabilization of telomere length.[22] Soft tissue sarcoma is a disease that appears to involve telomeric alternative lengthening. In cancerous cells, telomerase is activated to maintain the telomere's length. It goes about this by activating the TERT gene's promoter region, leading to the creation of the telomerase riboprotein complex's catalytic subunit.[23,24] The mutations lead to enhanced protein expression and transcription, thereby also enabling the E-twenty-six family of transcription factors to have new binding motifs.[25]

Telomeric alternative lengthening is an elongation that telomerase works on by recombination. The lengths of the telomeres can be maintained by using this technique in some cancers. For example, tumors that feature telomeric alternative lengthening display marked heterogeneity in telomere length that Southern blotting detects, and the alternative lengthening of promyelocytic leukemia bodies that are associated with telomeres.[25] The results of a study indicated that 61% of pancreatic neuroendocrine tumors exhibited telomeric alternative lengthening, causing a phenotype that perfectly correlated with the inactivation of two proteins: the death domain-associated protein 6 (DAXX) protein or the a-thalassemia/mental retardation syndrome X-linked protein (ATRX).[26,27] A dimer is then created by these proteins, displaying their importance for the telomeres' stability and incorporation of histone 3.3 into them.[28-30]

Lee et. al investigated the phenotype of telomeric alternative lengthening in liposarcoma's various subtypes and the relationship between the expression of ATRX or DAXX in liposarcoma and telomeric alternative lengthening was examined. 111 liposarcoma samples overall came from 8 patients, and the liposarcoma categories were as follows: 52 dedifferentiated liposarcomas, 28 well-differentiated liposarcomas, 11 pleomorphic sarcomas, and 20 myxoid/ round cell liposarcomas. The results revealed that the telomeric alternative lengthening was highly correlated with high grade cancer, presence of necrosis, high stage cancer, high mitotic count, and advanced age. However, these clinicopathological parameters appeared to be linked to the well-differentiated liposarcomas, the liposarcomas that were usually mitotically inactive, low grade, devoid of humor necrosis, and low stage, so they omitted the liposarcomas that were well-differentiated from the analysis, which led them to discover that telomeric alternative lengthening still had a strong association with the aforementioned factors, but found no association with the' modified FNCLCC 'grade 1 dedifferentiated liposarcoma and negative results of alternative lengthening of telomeres.[25]

Dosage of Genetic Regions' Effect on Relomere Lengthening

Scientists have generated models that can contain additional copies of regions which are synonymous to chromosome 21 to decipher how genetic segments contribute to Down syndrome phenotypes. One model in particular is the transchromosomic Tc1 mouse model that carries an extra freely-segregating copy of human chromosome 21. Since this model's inception, further analyses have combined different models to distinguish the subregions' contributions to specific DS phenotypes.[31] Its copy of Hsa21, which is nearly complete, resides in Tc1 cells and only differs in six duplications, one deletion, and 25 structural rearrangements de novo that were potentially from the model's exposure to gamma radiation during its creation.[32] The Tc1 mouse line displays phenotypes that affect the hippocampal function,[33] locomotor activities, and short term memory impairment, all of which are characteristics in a damaged Hsa21.[34,35]

Marechal et al. studied the 13 mouse genes that are between Abcg1 and U2af1, both of which are in the telomeric part of Hsa21. Mouse chromosome 17 houses The Abcg1-U2af1 region and contains 14 conserved genes: Tmprss3, *Tff1, Tff2, Tff3, Abcg1, Rsph1, Ubash3a, Pde9a, Ndufv3, Pknox1, Slc37a1, Wdr4, Cbs,* and *U2af*. In a preliminary study, the subjects that featured the Abcg1-U2af1 trisomy displayed recognition of novel objects, conserved gene overexpression, and working memory, with the exceptions of Abcg1 due to it being inactive during the genetic engineering, and U21af1, which is outside the cell.[36] In a Tc1 mouse model, all of the Abcg1-U2af1's genes are trisomic, with the Ndufv3 gene being rearranged.[37] Ms2Yah, which is the monosomy that corresponds to the Abcg1-U2af1 region, lacks the 12 genes but carries the last exons of Abcg1, and showed social recognition defects and fear conditioning.[38] In their main study, the Ms2Yah was paired with the Tc1 model to observe how different behavioral phenotypes are affected.[31]

The results indicated that the Tc1/Ms2Yah mice and the controls learned the platform location equally quickly, but the Tc1 learned it more slowly. Learning memory was unaffected, so Marechal et al. suspect that the Tc1 mice's worse performance was due to an absence of cognitive flexibility. This decreased flexibility reinforced the result that Abcg1-U2af1's increase will affect cognitive thinking, which is also observed in Down syndrome patients.[39] Tc1 mice also exhibited major deficits in motor skills, which was tested when the mice learned to stay on a rotarod. In the learning phase, Tc1/Ms2Yah mice and Tc1 mice's performances were unimproved. This demonstrated the alteration of locomotor function's learning mechanisms, which could not be resolved by the Abcg1-U2af1's decreasing number of copies.[31]

DNA Repair's Effects On Telomeres

DNA damage is caused by exogenous factors or endogenous sources. Any damaged DNA can lead to genomic instability if left untreated, and may eventually grow tumors. Telomeres prevent these genomic instabilities from happening. Base excision repair, nucleotide excision repair, and mismatch repair are the three mechanisms of DNA repair.

1. Base Excision Repair's Effects On Telomeres

Base excision repair fixes lesions of small DNA bases that are caused by deamination, alkylation and oxidation. The lack of BER leads to a higher mutation rate, and can lead to many forms of cancer. DNA glycosylases remove the damaged bases to start BER. After the damaged bases are removed, Apyrimidinic/apurinic endonuclease 1 (APE1) slices the backbone of the DNA at apurinic or apyrimidinic sites to leave behind a single nucleotide gap, followed by a long-patch repair or a short-patch repair.[40]

In base excision repair, telomeres are susceptible to oxidative lesion formation because of their long TTAGGG repeats. Oxidative damages can reinforce shortening of the telomere, which is shown by telomere attrition rate significantly decreasing when cells mature in hypoxic conditions or with an antioxidant near them.[41,42] Telomeres feature oxidized guanine derivatives and uracil.[43–45] There is increasingly large evidence that both in vitro and in vivo studies actively promote telomeric BER.[40]

Telomeric oxidative guanine lesions are caused by a deficiency in OGG1, thereby disrupting telomere length homeostasis. In an experiment conducted by Wang et al., primary MEFs and OGG1−/− mouse hematopoietic cells had shortened telomeres with normal oxygen concentration (20%) or when an oxidant was present. Other telomeric abnormalities which were featured in OGG1−/− mouse cells included lost preferential telomere G-strands, altered telomere sister chromatid exchanges, and a higher presence of telomere singleand doublestrand breaks. These results confirm the the BER pathway's cruciality in maintaining telomeric integrity in mammals.[46] Telomeric 8-oxo-G residues removal by way of BER remains unknown along with the role BER has with shelterin. 8-oxo-G incorporation abolishes or majorly reduces TRF1 and TRF2's ability to bind to a certain telomeric substrate,[47] but TRF1 and TRF2 have no effect on OGG1 incision activity. These data imply that certain telomere configurations and the sequence context of telomere repeats cause oxidative damage to the telomere, thereby weakening it.[48]

2. Nucleotide Excision Repair's Effects On Telomeres

Nucleotide excision repair repairs DNA by removing lesions such certain forms of oxidative damage, bulky chemical adducts, and UV-induced pyrimidine dimers.[49]

NER proteins excise a fragment that is 24-32 nt that contains the damaged residue. DNA polymerases fill the gap by synthesizing a new complementary strand from the undamaged strand, and DNA ligase I or III ligates the two strands together to complete this process.[50-52] NER undertakes two distinct pathways which depend on the recognition of initial damage: global genome nucleotide excision repair (GG-NER), which erases and detects lesions from the silent chromatin and any gene that is not transcribed throughout the whole genome; and transcription coupled nucleotide excision repair (TC-NER), which repairs the sense strand's lesions more quickly.[50,53] These pathways proceed in an identical manner after initial damage recognition.[40]

Telomeric DNA sequences are hypothesized to create pyrimidine dimers following Ultraviolet irradiation, and these dimers can be detected at the telomere.[54,55] Scientists are expecting NER to be enhanced at telomeres because of the importance of telomeres in maintaining the chromosome's stability. NER studies regarding telomeres are currently uncommon,[54] and led to the reports of inconsistent results on the dimers being potentially fixed.[50] One study shows that non-mutated somatic cells that are in different states of disease and donor ages can effectively repair telomeres that were damaged by UV light, and as the donor's age increases, the extent and rate of telomeric repair decreases.[54] According to a finding, NER repairs Ultraviolet-induced cyclobutane pyrimidine dimers (CPDs) that are located on telomeres faster than CPDs that are on the human skin fibroblasts' bulk region that express exogenous telomerase, which supports that NER can function well at telomeres.[56] Rochette et al.,[55] in contrast, dismiss CPD repair of NER,[54] but confirmed CPD formation is 7 times higher at telomeres than at the regions without telomeres.[55] More studies must be done to determine how NER works at telomeres.

Unrepaired lesion tolerance potentially requires mechanisms that can bypass CPDs to completely replicate the telomeric DNA and avoid breaking apart DNA and accumulating singlestranded DNA. One of these mechanisms involves specialized DNA polymerases such as Polη, the polymerase that the XPV gene (which does not function in a variant type of xeroderma pigmentosum) codes for and can bypass CPDs by incorporating adenine to a thymine or cytosine in a CPD.[57] Consistently, exposure to hexavalent chromium (Cr(VI)) or ultraviolet light that creates sturdy DNA lesions will enable Polη to accumulate at telomeres, which suppresses the formation of telomeric DNA damage foci. Polη deficiency heightens telomeric aberrations that are associated with replication, which suggests Polη's necessity to properly replicate the telomeres if they contain bulky DNA adducts.[58] Scientists currently cannot conclude if telomeres can promote NER, but numerous NER factors are confirmed to have vital jobs in the maintenance of telomere, which implies the potential connection between NER and telomere regulation.[40]

3. Mismatch Repair's Effects On Telomeres

Mismatch repair recognizes and corrects nucleotides in erroneous positions, which include mismatched nucleotides that are a side-effect of DNA replication, heteroduplexes that are formed during recombination, and chemically or physically-induced DNA lesions.[59-61] MMR proteins also act during mitotic and meiotic recombination, triplet-repeat expansion, DNA damage signaling, class-switching recombination, and somatic hypermutation.[60,61] In eukaryotes, functional heterodimeric complexes are formed by multiple MuSt and MutL homologs, which make up MMR systems.[62] MutSαα (hMSH2-MSH6) recognizes base-base mismatches and small insertion/deletion loops, whereas MutSβ (hMSH2-hMSH3) recognizes large insertion/deletion loops. RPA stabilizes the

single-stranded DNA, and Polδ fills the stranded gap and stabilizes, which is then ligated by Ligase I.[61] MMR deficiency commonly causes micro-satellite instability, Lynch syndrome development, and an increased rate of mutation. Lynch syndrome most commonly mutates the hMSH2 and hMLH1 genes.[63,64]

MMR deficiency is hypothesized to be linked to shortening of telomeres. An analysis that studied families that had members that featured Lynch syndrome displays that telomere lengths that contained MMR gene mutations were significantly shorter in cancer patients' leukocytes than healthy controls and mutation carriers who did not exhibit symptoms. Additionally, as age increased, attrition of telomeres increased in MMR gene-mutated patients.[65] Despite these results, the scientists could not conclude whether the cancer patients' shorter telomere length truly reflects MMR deficiency's effect or only represents one of the cancer's consequences. According to a study that involves colon carcinomas, defective MMR may have an effect on telomere length, as demonstrated by the results, which state that tumors that have a high microsatellite instability (which can deduce MMR deficiency) have shorter telomere lengths in comparison to the tumors that feature stable microsatellites.[66] An additional finding of telomere shortening is that telomeres shorten as hMSH2 in normal lung fibroblasts are down regualted. MMR deficiency may lead to accumulating mutations in telomeres, which then cause accelerated telomere shortening and telomeric repeat instability.[67] Interestingly, animal model studies show significantly different results from human cell studies, showing how MMR deficiency may affect telomere length differently depending on the species. This is confirmed by primary MEFs or tissues deriving from MSH2−/− mice having normal telomerase activity and lengths of telomeres.[68]

It is currently unknown if MMR actually functions on telomeres. For example, it is unknown if telomeres can incorporate or are resistant to DNA mismatches. While the abundance of cytosines in the telomere repeats theoretically makes telomeres vulnerable to mismatches with uracil to guanine, telomeres create special chromatin structures whose shelterin proteins can inhibit mismatch incorporation. If scientists are to fully comprehend the mechanism of telomere maintenance, they must be able to conclude if mismatches can actually occur at telomeres and if so, how the mismatches are created and interpreted.[40] How mismatch incorporation affects the efficiency of the telomere's shelterin proteins on the DNA mismatch is also unknown. New research suggests that assembly factors of nucleosomes, modifications of histones, and chromatin organization regulate the activities of MMR.[69] However, MMR deficiencies are confirmed to frequently display instability of microsatellites.[70,71]

Effect of Cancer on Telomeres

Cancer is often defined as rapid cell division. While the overall mechanism of cancer's effect on telomeres remains unknown, scientists are studying possible effects.

1. Childhood cancer survivors' Telomere Attrition

Song et. al measured the length of telomeres in the leukocytes of participants who lacked cancer and explored how LTL is associated with different treatments of cancer, variation in individual health behavior, and diagnosis of comorbid health conditions.[72] Their results showed that the childhood cancer survivors exhibited significantly shorter LTL within all cancer subgroupings (which included tumors of the central nervous system, Hodgkin lymphoma, sarcomas, neuroblastoma, non-Hodgkin lymphoma, acute lymphoblastic leukemia, and Wilm's tumor) following adjustments for sex, polymorphisms that were associated with LTL, ancestry, and age when DNA sampling took place. The average LTL value was 36.8 years of age for survivors and for controls, it was 48.2 years of age. These data suggest a telomere attrition that was accelerated by approximately eleven years among survivors of cancer from childhood. In survivors, as age increased, LTL decreased at a similar rate to the controls, which indicated that many telomere reserves were lost after treatment, but their loss was not accelerated.[72-73]

Song et al. also studied LTL for potentially being associated with overall mortality and various chronic health conditions. Shorter LTL had a correlation with more common diagnosis of 14 chronic conditions, which included: cardiomyopathy, chronic hepatitis C, cholecystitis, hypercholesterolemia, hypertriglyceridemia, gastritis/duodenitis, fibrosis/cirrhosis, gastrointestinal ulcer, hypertension, headaches, obesity, obstructive and restrictive pulmonary deficits, and lymphatic infections. Higher overall mortality and shorter LTL were revealed to have a potential association, but it was statistically insignificant (P=0.08).[72] Longer LTL showed a tremendously greater chance of causing secondary thyroid cancers, and the finding supports that longer LTL can cause numerous cancers, including cancers that occur in childhood. [74] Some of the health conditions that were analyzed were potentially diagnosed before or after DNA sampling took place. These separate analyses revealed that restrictive pulmonary deficit risk and shorter LTL were related, along with hypertriglyceridemia and obstructive pulmonary deficit also being potentially related. This implies that LTL can affect childhood cancer survivors prognostically.[72-73]

One vital finding in this study was that factors in behavior or lifestyle can modify childhood cancer survivors' telomere attrition rates. Diet, physical activity, alcohol overconsumption, tobacco use, and resistance training enabled Song et al. to create a composite score which revealed that among survivors aged 18-35 years old, significantly longer age-adjusted LTL was caused by favorable health behaviors. On the contrary, the score also revealed that ageadjusted LTL among survivors that were older than 35 years of age was similar regardless of health behaviors. The result potentially hints about a critical discovery that follows childhood cancer treatment, which is that any healthy lifestyle modification can heavily impact telomere

attrition rates. The result also reinforces the substantial loss of telomere reserves that seemed to happen after treatment, which led to similar attrition rates among survivors and controls that lack cancer.[72-73]

2. Using HKR3 to Inhibit hTERT in Hepatocellular Carcinoma Cells to Regulate the Cell Cycle

Hepatocellular carcinoma is a very common form of cancer.[75] Its progression is characterized by genetic and epigenetic abnormalities that eventually enable the cancerous cells to proliferate and escape apoptosis.[76] Scientists are studying how HCC cells regulate apoptosis and the cell cycle, which can lead to better clinical management.[77] The enzyme telomerase confers immortality to cancer cells by synthesizing telomeric repeat at the chromosomes' ends and replacing the lost end sequences with new sequences during each cell division, granting the cell a longer life cycle and enabling it to divide indefinitely. A kind of telomerase called human telomere transferase (hTERT), which is expressed as a fetus develops and is eventually deactivated in adult tissues, activates HCC. hTERT's mechanism in the regulation of changes of expression during HCC is currently unknown, leading to the importance of deciphering how to regulate apoptosis and the cell cycle.[78]

In cancer cells, hTERT is over-expressed to create telomeres as a mechanism to prevent apoptosis.[11,79] However, it is still unknown if hTERT inhibits other factors to reinforce the cell cycle. Choi et al. hypothesized that if hTERT is somehow regulated, an anti-tumor strategy could be developed in HCC management by using human kruppel-related 3 and factors that are involved in the cell cycle of HCC cell lines. According to their results, hTERT was approximately 15 times more expressed in HCC tissues expression than in normal tissues when HKR3 is uninvolved. When they inhibited hTERT, they observed changes in genes relating to apoptosis, cell cycles, and senescence, which enabled them to confirm that HKR3 and hTERT had a correlation.[78]

Additional findings stated that HKR3 was hardly expressed within HCC patients' cancer tissues, but was more expressed around the liver tissue's bad prognosis, and hTERT was more prevalent in the HCC cell strains. When they found that hTERT expression and HKR3 expression were inversely related, they also confirmed that CDKNN2A expression was increased, which reduced the cyclin A1, B1, and D1 expressions. Choi et al. confirmed that hTERT inhibition causes apoptosis, so they investigated how the cell cycle was controlled in HCC cells. This was reinforced by the finding that the majority of the genetic changes were in apoptosis genes. Overall, the results of their experiment concluded that using HKR3 to inhibit hTERT can prevent the progress of HCC.[78]

Future Directions/Conclusion

The experiments that were observed in this review article are highly beneficial to our understanding of using telomeres to treat diseases. Our current understanding is that while these studies are limited, adjusting the lengths of telomeres are useful in treating diseases such as trisomy 21. However, these experiments were not without their limitations. For example, while it is confirmed that the increase maternal age leads to a greater risk of birthing a DSinfected child, the exact mechanism, triggers, and association remain unknown.[4] If a mechanism is discovered, scientists can test treatments for it, which is a solid step for successful treatment of Down Syndrome.

Consequently, it can be difficult to draw conclusions of studies with very limited data and research on telomeres' effects on diseases currently available. To achieve more precise results, the mechanisms of telomeres' effect on diseases must be studied more thoroughly. One example of this is MMR's true function on telomeres being unknown. The effect of DNA mismatch incorporation on telomeres is currently unknown, but scientists hypothesize that telomeres that can form shelterin proteins and special chromatin structures potentially inhibiting mismatch incorporation. If scientists can eventually apprehend the possibility of mismatches appearing at telomeres and how the mismatches can be recognized and generated, this will lead to a greater understanding on MMR's function on telomeres, which can lead to further research to study how telomeres can be used to treat diseases.

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