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Baskent Universitesi, Dişhekimliği Fakültesi, Periodontoloji AD.Ankara/Türkiye

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Alanya Alaaddin Keykubat Üniversitesi, Tıp Fakültesi, İç Hastalıkları AD. Alanya/Türkiye.

Bayram Ünver, Prof.Dr. unverbay@gmail.com
Dokuz Eylül Üniversitesi, Fizik Tedavi ve Rehabilitasyon Yüksek Okulu, Fizyoterapi Bölümü, İzmir/Türkiye

Davran Çicek, Prof.Dr. davrancicek@gmail.com
Alanya Alaaddin Keykubat Üniversitesi, Tıp Fakültesi, Kardiyoloi AD, Alanya/Türkiye

Doğa Türkkahraman, Doç.Dr. drdoga@hotmail.com
Sağlık Bilimleri Üniversitesi, Antalya Eğitim ve Araştırma Hastanesi, Çocuk Endokrinoloji Kliniği, Antalya/Türkiye

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Sağlık Bilimleri Üniversitesi, Kartal Eğitim ve Araştırma Hastanesi, Hematoloji Kliniği, İstanbul/Türkiye

Hakan Gür, Prof.Dr. hakangur2001@gmail.com
Uludağ Üniversitesi, Tıp Fakültesi, Spor Hekimliği AD, Bursa/Türkiye

Hacer Erdem Tilki, Prof. Dr. hacererdem@gmail.com
Ondokuz Mayıs Üniversitesi, Tıp Fakültesi, Klinik Nörofizyoloji BD. Samsun/ Türkiye

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ALKÜ, Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları/ Çocuk Gastroenteroloji BD. Alanya/Türkiye

İnci Meltem Atay, Doç.Dr. incimeltem@gmail.com
Süeyman Demirel Üniversitesi, Tıp Fakültesi, Psikiatri AD, Isparta /Türkiye

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Mustafa Öztürk, Prof.Dr. muozturk32@gmail.com
Karabük Üniversitesi, Tıp fakültesi, Halk Sağlığı AD, Karabük/Türkiye

Mustafa Adlı, Prof.Dr. madli@hotmail.com
Marmara Üniversitesi, Tıp Fakültesi, Radyasyon Onkolojisi AD. İstanbul/ Türkiye

Mustafa Sait Gönen, Prof.Dr. gonen.sait@gmail.com
İ.Ü. Cerrahpaşa Tıp Fakültesi ,İç Hastalıkları AD, Endokrinoloji ve Metabolizma BD, İstanbul/Türkiye

Neşe Demirtürk, Doç.Dr. nesed60@hotmail.com
Afyon Sağlık Bilimleri Üniversitesi, Tıp Fakültesi, Enfeksiyon Hastalıkları AD, Afyonkarahisar /Türkiye

Nilay Şahin, Doç.Dr. dincernilay@yahoo.com
Balıkesir Üniversitesi, Tıp Fakültesi, Fizik tedavi ve Rehabiliatasyon AD, Balıkesir /Türkiye

Tayfun Kara, Dr. Öğr. Üyesi, tayfun.kara@alanya.edu.tr
ALKÜ, Tıp Fakültesi, Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları AD. Alanya/Türkiye

Süleyman Kutluhan, Prof.Dr. skutluhan@hotmail.com
Süeyman Demirel Üniversitesi, Tıp Fakültesi, Nöroloji AD, Isparta /Türkiye

Hatice Lakadamyalı, Prof.Dr. hatice.lakadamyali@alanya.edu.tr
Alanya Alaaddin Keykubat Üniversitesi, Tıp Fakültesi, Radyoloji AD. Alanya/Türkiye

CERRAHİ TIP BİLİMLERİ (Alfabetik sırayla, Güncelleme: 27.03.2022)

Adalet Demir, Prof.Dr. dradalet@hotmail.com
Özel Medical Park Bahçeşehir Hastanesi, Göğüs Cerrahisi Kliniği, İstanbul/Türkiye

Altuğ Tuncel, Prof.Dr. tuncelaltug@yahoo.com
Sağlık Bilimleri Üniversitesi, Ankara Numune Eğitim ve Araştırma Hastanesi, Üroloji Kliniği, Ankara/Türkiye

Atilla Sezgin, Prof.Dr. asezgin@baskent.edu.tr
Başkent Üniversitesi, Tıp Fakültesi, Kalp-Damar Cerrahisi AD, Çocuk Kalp Damar Cerrahisi BD. Ankara/Türkiye

Cemil Ertürk, Doç.Dr. erturkc@yahoo.com
SBU, İstanbul Kanuni Sultan Süleyman SUAM, Ortopedi ve Travmatoloji Kliniği , İstanbul, Türkiye

Fevzi Yılmaz, Doç.Dr. fevzi_yilmaz2002@yahoo.com
Sağlık Bilimleri Üniversitesi, Antalya Eğitim ve Araştırma Hastanesi, Acil Tıp Kliniği. Antalya/Türkiye

Hakan Kaya, Prof.Dr. drhakankaya2002@yahoo.com
Özel Isparta Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Isparta/Türkiye

Hasan Kamil Sucu, Doç.Dr. hksucu@gmail.com
İzmir Katip Çelebi Üniversitesi, Atatürk Eğitim ve Araştırma Hastanesi, Nöroşurji Kliniği, İzmir/Türkiye

Müberra Seğmen Yılmaz, Uzm.Dr. muberraseg@gmail.com
Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim ve Araştırma Hastanesi, Patoloji Kliniği, İstanbul /Türkiye

N. Cenk Sayın, Prof.Dr. ncsayin@trakya.edu.tr
Trakya Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum AD, Perinatoloji BD. Edirne/Türkiye

Ömer Faruk Recep, Doç.Dr. omerfarukrecep@yahoo.com
Özel Ortadoğu 19 Mayıs Hastanesi, Göz Hastalıkları Kliniği, Ankara/Türkiye

Ömer Karahan, Prof.Dr. omer.karahan@usak.edu.tr
Uşak Üniversitesi, Tıp Fakültesi, Genel Cerrahi AD, Uşak/Türkiye

Pakize Kırdemir, Prof.Dr. pkirdemir@gmail.com
Süeyman Demirel Üniversitesi, Tıp Fakültesi, Anestezi ve Reanimasyon AD, Isparta /Türkiye

Serdar Nazif Nasır, Doç.Dr. snasir72@gmail.com
Hacettepe Üniversitesi ,Tıp Fakültesi, Plastik Rekonstrüktif ve Estetik Cerrahi AD, Ankara/Türkiye

Yavuz Uyar, Prof.Dr. yavuzuyar@mail.com
Sağlık Bilimleri Üniversitesi, Okmeydanı Eğitim ve Araştırma Hastanesi, KBB Kliniği, İstanbul/Türkiye

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Abdelsalam Hegazy, Assist. Prof of Clinical Orthopedics at Qatar Weill Cornell Medical School,
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Bahare Fazeli, MD , PhD. Assist.Prof. of Immunology, Mashhad University of Medical Sciences,
Vascular Inflammation Research Center, Clinical Immunology, Iran. bahar.fazeli@gmail.com

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Heidelberg, Germany. caner.suesal@med.uni-heidelberg.de

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Zajceva 19, 10 000 Zagreb, Croatia. ivancvjetko@yahoo.com

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sonngan82@gmail.com

N.A.Uvais, MD, Iqraa International Hospital and Research Centre, Department of Psychiatry,
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EDITORIAL

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Osteoporosis and Fragilty Fractures: An Overview.

Osteoporoz ve Kırılganlık Kırıkları: Genel Bir Bakış.

Ahmet Aslan[1*]

1.Alanya Alaaddin Keykubat University, Department of Orthopedic surgery, School of Medicine, Antalya, Turkey

ABSTRACT

Osteoporosis (OP); It is a metabolic bone disease characterized by decreased bone mineral density (BMD) and bone strength, increased bone fragility and fracture risk, and deterioration in the microarchitecture of bone tissue. The most important cause of morbidity and mortality in OP are fragility fractures such as osteoporotic hip fractures. Prevention and treatment of osteoporosis can prevent hip fractures and comorbidities. In this paper, the available information about Osteoporosis and Osteoporotic fractures is briefly reviewed.

Key words: Osteoporosis, bone mineral density, osteoporotic fractures, bisphosphonates, treatment,

ÖZ

Osteoporoz (OP); kemik mineral yoğunluğu (KMY) ve kemik gücünde azalma, kemik kırılganlığı ve kırık riskinde artma, kemik dokusunun mikromimarisinde bozulmayla karakterize metabolik kemik hastalığıdır. OP'daki en önemli morbidite ve mortalite nedeni osteoporotik kalça kırıkları gibi kırılganlık kırıklarıdır Osteoporozun önlenmesi ve tedavisi, kalça kırıklarını ve eşlik eden hastalıkları önleyebilir. Bu yazıda, Osteoporoz ve Osteporotik kırıklarla ilgili mevcut bilgiler kısaca gözden geçirilmiştir.

Anahtar Kelimeler:Osteoporoz, kemik mineral yoğunluğu, osteoporotik kırık, bifosfonat, tedavi.

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* Corresponding Author: Ahmet ASLAN, MD, Medical School of Alaaddin Keykubat University, Department of Orthopedics and Traumatology, Alanya/Antalya, Turkey. +905056462411 ahmet.aslan@alanya.edu.tr

ORCID: 0000-0001-5797-1287

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Osteoporosis (OP); It is a metabolic bone disease characterized by decreased bone mineral density (BMD) and bone strength, increased bone fragility and fracture risk, and deterioration in the microarchitecture of bone tissue. Osteoporosis is an important public health problem that increases with age and causes morbidity and mortality. The most important cause of morbidity and mortality in OP are fragility fractures such as osteoporotic hip fractures [1-4]. The diagnosis of osteoporosis is defined by double X-ray absorptiometry (DXA)-derived BMD that is below ≤2.5 standard deviations (SD) which is the mean of a young, healthy reference population. Age-related reduction in BMD increases the risk of fractures seen in advanced age [3- 5]. BMD values are affected by regional factors such as ethnicity, genetics, gender, age, environment, and exposure to sunlight, and it has been reported that the BMD values of the Turkish population are lower than the reference values in various DXA devices and the prevalence of osteoporosis is higher [1,2]. At the same time, the risk of osteoporotic fractures in the Turkish population has also increased significantly [3].

A web-based logarithmic table, called FRAX®, which is used to calculate osteoporotic fracture

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risk, has been developed. The result that is obtained, shows the 10-year probability of having a hip fracture and a major osteoporotic fracture. It is stated that the history of major osteoporotic fracture, advanced age and low t-score are the most important risk factors. However, there are concerns that the Frax® Turkey model should be revised [3].

Prevention and treatment of osteoporosis can prevent hip fractures and comorbidities [6]. It is important to use pharmacological and non-pharmacological methods in the prevention and treatment of osteoporotic fractures. Interventions such as resistance training, optimal dietary protein, vitamin D and calcium intake have positive effects on bone and muscle, reducing falls, fractures and therefore disability [7]. Pharmacologically, there is a wide range of drug groups, including antiresorptive and anabolic agents. Antiresorptive drugs such as bisphosphonates and the RANKL inhibitor denosumab are currently the most widely used osteoporosis drugs [5]. The choice of medical treatment in osteoporosis is decided according to bone mineral density and personal risk factors. Bisphosphonates, which are antiresorptive, are drugs with proven efficacy in reducing the risk of OP hip fracture [6,8]. Bisphosphonates used in the treatment of OP are available in oral or parenteral forms. Various studies have reported varying efficacy and side-effect rates [4]. Oral and parenteral bisphosphonates are effective in the treatment of postmenopausal OP. Of the oral bisphosphonates, however, Aledronate appears to be most effective [4,9]. Recently, anabolic therapy with teriparatide has been shown to be superior to the bisphosphonate risedronate in preventing vertebral and clinical fractures in postmenopausal women. Treatment with the sclerostin antibody romosozumab increases BMD more deeply and rapidly than alendronate [5]. On the other hand, when patient compliance and regular use are taken into account, parenteral bisphosphonates may be more effective in terms of mean improvement in BMD values [4]. In addition, parenteral agents can be preferred in the treatment of osteoporosis in patients with co-morbidities, who use multiple drug therapy, or who have difficulty in using oral drug therapy. However, it should always be kept in mind that drug-related side effects may be seen more frequently with parenteral agents [8].

On the other hand, there are some concerns about the effect of BPs on the fracture healing process. However, it has been reported that the correct timing of ZolA administration in elderly patients with hip fractures has no effect on fracture healing and incidence of complications [6]. Research on the treatment of OP continues. It has been reported that Ramelteon, a peripheral melatonin agonist, can be used to prevent osteoporosis [10]. Unfortunately, fragility fractures still cannot be properly treated [7]. Despite the proven efficacy and safety of antiresorbtive drugs used in OP, few patients at high risk of fracture receive treatment [5,7]. The aging of the population in the world and in our country and the increase in health care costs make OP even more important. In the future, the focus should be on the prevention and treatment of OP, as well as the application of multidisciplinary care models to prevent osteoporotic fractures.

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1. Aslan A, Karakoyun O, Güler E, Aydin S, Gök MV, Akkurt S. Kastamonu'da yaşayan Türk kadınlarında kemik mineral yoğunluğu, osteoporoz yaygınlığı ve bölgesel risk faktörlerinin değerlendirilmesi: KASTÜRKOS çalışması. Eklem Hastalik Cerrahisi. 2012;23(2):62-7. Turkish. PMID: 22765482.
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RESEARCH ARTICLE

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Diagnostic accuracy of kidney shear wave elastography at the diagnosis of ureteral stones

Üreter taşlarının tanısında böbrek shear wave elastografinin tanısal doğruluğunun araştırması

Utku Mahir Yıldırım[1*], Erkan Sahin[1], Aynur Solak[1], Bumin Örs[2], Selim Serter[1]

1.Izmir University of Economics, Faculty of Medicine, Department of Radiology, Izmir, Turkey
2.Izmir University of Economics Faculty of Medicine, Department of Urology, Izmir, Turkey

ABSTRACT

Aim: To determine the efficacy of kidney shear wave elastography (SWE) in patients diagnosed with ureteral stones
Method: Both kidneys of 30 patients were evaluated prospectively with SWE. The ureteral stone size and the degree of hydronephrosis were determined by sonographic examination. The contralateral kidney was accepted as the control parameter. Stone size, grade of hydronephrosis and kidney shear wave speed changes were noted and their relations were examined for statistical significance.
Results: Affected kidney group had significantly increased SWE values than the control group. (3.87+-1.22 vs 2.06+-0.72 m/sec) (p=0.01). Neither the stone size nor the kidney SWE values showed a correlation with the gender. There was a positive correlation between the grade of hydronephrosis and the stone size (p=0.047, r=0,36). Kidneys with grade 2 hydronephrosis had significantly higher SWE values than those with grade 1 hydronephrosis.
Conclusion: SWE is a promising tool to observe the parenchymal elasticity changes in patients with hydronephrosis secondary to ureteral stones. Further studies are necessary to confirm the research results.

Key words: elasticity imaging techniques, ureterolithiasis

ÖZ

Amaç: Üreter taşı olan hastalarda böbrek shear wave elastografi (SWE) incelemenin tanısal etkinliğinin değerlendirilmesi.
Metot: 30 hastanın her iki böbreği prospektif olarak SWE ile incelendi. Üreter taşı boyutu ve hidronefroz derecesi ultrasonografi incelemesi ile değerlendirildi. Karşı taraf normal böbrek kontrol grubu olarak değerlendirildi. Üreter taşı boyutu, hidronefrozun derecesi ve böbrek shear wave hızındaki değişiklikler not edildi ve aralarındaki ilişkiler istatiksel anlamlılık açısından incelendi.
Bulgular: Üreter taşından etkilenen böbrek SWE değerlerinde normal böbrek ile karşılaştırıldığında anlamlı artış mevcuttur (3.87+-1.22 vs 2.06+-0.72 m/sec) (p=0.01). Cinsiyet ile üreter taşı boyutu arasında ve SWE değerleri arasında korelasyon yoktur. Hidronefroz derecesi ile ureter taşı boyutu arasında pozitif korelasyon saptandı (p=0.047, r=0,36). İkinci derece ve üstünde hidronefroz saptanan böbreklerde SWE değerleri grade 1 olanlara göre daha fazladır.
Sonuç: Üreter taşına bağlı hidronefrozu olan hastalarda böbrek parankim elastisitesindeki değişiklikleri değerlerndirmede SWE gelecek vadeden bir yöntemdir. Gelecek çalışmalar sonuçlarımızı netleştirecektir.

Anahtar kelimeler: Kesme, dalga, elastografi, ureter, taş

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*Corresponding Author: Utku Mahir YILDIRIM, Department of Radiology, Izmir University of Economics School of Medicine, Izmir,Turkey, +905326589477, utkumahir@yahoo.com

ORCID: 0000-0003-1863-2981

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Introduction

Ureteral stones, over 5 mm, usually cause hydronephrosis. They can be painless or may present with colic-like pain extending from the flank to the groin, which is more often in stones that cause obstruction [1]. Early management of ureteral stones allows immediate relief of the patient's symptoms and early return to normal life. Kidney functions are better preserved with an early diagnosis [2]. Ultrasonography is a safe and sensitive imaging method for detecting ureteral stones, especially in pregnant women and children. Ultrasound imaging has high specificity (81%) and sensitivity (100%) in detecting renal stones and hydronephrosis but it has low sensitivity (46%) in detecting ureteral stones and this is an important drawback. Non-contrast CT is the gold standard imaging examination in the diagnosis of ureteral stones [3]. A fast, efficient and safe non-invasive method to support ultrasonographic findings in the detection of ureteral stones would be beneficial.

Ultrasound elastography (UE) is a growing alternative method for assessing the elastic tissues in recent years, which has already been demonstrated in the liver [4]. Ultrasound elastography of the kidney has also shown satisfactory results. However, the kidney is a more complex organ than the liver. In contrast to the liver, the kidney consists of two separate compartments which cause inhomogeneity. High vascularity is another difficult characteristic of the kidney [5]. Two-dimensional (2D) shear wave elastography (SWE) is the most recent elastography technique that uses acoustic radiation force and the main advantages are real-time visualization of a color quantitative elastogram, superimposed on a gray scale image, and it reveals tissue stiffness in numeric information simultaneously with the provided anatomical information [6-7].

Ureteral stones may cause ureteral obstruction, leading to urinary pressure elevation, which may be responsible for elasticity changes. The aim of the present study was to analyze the role of point shear wave elastography in patients with ureteral stones and to identify the factors affecting the kidney shear wave speed.

Material and method

Patients

The study was launched on July 3, 2020 at Izmir University of Economics Radiology Department and the study was approved by the local ethics committee (Izmir University of Economics B.30.2.İEÜSB.0.05.05-20-095). It was conducted in accordance with the Helsinki Declaration of 1975. All patients signed an informed consent; we collected thirty patients' data after the ethical committee approval and the study concluded January 6, 2021.

Thirty patients with ureteral stones detected with initial ultrasound were included in our prospective case-control study. The patients suspected of having ureteral stones were first examined by the urology clinic and their laboratory tests were evaluated. The presence of stones was confirmed by second Ultrasound imaging. The stone size and the degree of dilatation of the collecting system detected in ultrasonography were noted. All thirty patients with demonstrated ureteral stones were shown with Ultrasonography to have unilateral ureteral stones; their contralateral kidney and collecting system were normal. Contralateral kidney had to be within normal limits, whereas exclusion criteria were bilateral ureteral stones, renal stones, vesicoureteral reflux disease and other causes of postrenal obstruction of contralateral normal kidney. Further exclusion criteria included that both kidneys should not have stones and no history of ureterolithiasis or parenchymal disease.

All ureteral stones were clearly visible with the ultrasound imaging. We did not use CT imaging as a complimentary test for any of patients. The initial ultrasound was not noted and was performed by different radiologist. The present study's corresponding author did the second ultrasound examination, UE and recorded for the study.

Ultrasound examination

Ultrasound examinations and ultrasound elastography were performed in each subject, on the same day. The presence and grade of hydronephrosis were evaluated with the radiological grading system as follows: Grade 0: no dilatation, calyceal walls are opposed to each other; Grade 1: only the renal pelvis is visible and

the renal pelvis anterior-posterior diameter: 5-7 mm; Grade 2: some calyces visible, AP diameter: 7-10 mm; Grade 3: marked dilation of calyces and AP diameter: >10 mm; Grade 4: narrowing parenchyma; Grade 5: extreme hydronephrosis with only a thin, membrane-like renal parenchyma) [8]. The location of the ureteral stone and its size, kidney length and parenchymal thickness was recorded.

Ultrasound Elastography examination

SWE was performed in all patients with the Aplio 500 series ultrasound system and Acoustic Structure QuantificationTM (ASQ) software by Toshiba. This system enables real-time visualization of a color quantitative elastogram superimposed on a grayscale image (Fig. 1). We used convex array probe (1–6 MHz) for all patients.

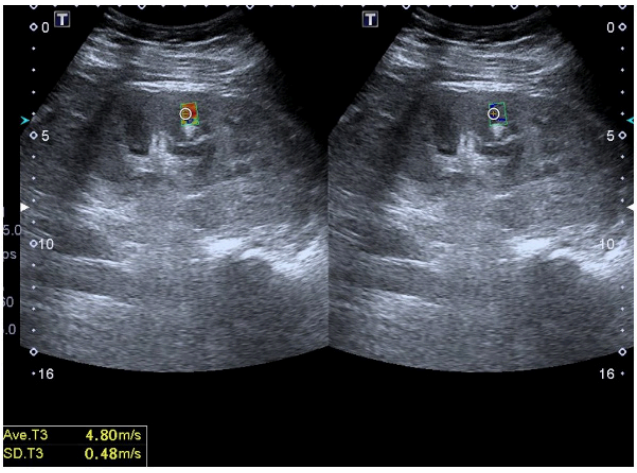

Figure 1. Two-dimensional (2D) shear wave elastography (SWE) images of a patient with long axis of normal kidney (contralateral side) real-time visualization of a color quantitative elastogram superimposed on a gray scale image and it reveals normal calyceal system without dilatation. Tissue stiffness in numeric information SWE values calculated from the region of interest (10 mm x 10 mm square) was placed on the superficial area in the mid-portion of the kidney cortex.

The lateral decubitus position and breath control (during the SWE imaging) were executed to reduce the motion artefacts. The region of interest (10 mm x 10 mm square) was placed on the superficial area in the mid-portion of the kidney cortex (renal medulla was not included as much as possible) and we used the long axis of kidney for ultrasound examination (Fig. 2). The UE was performed without pressure. In all patients, three different ASQ shear wave elastography sequences were aimed and eight measurements from different parts of the range of interest box were collected. The median elastography values (meters/second (m/sec)) were calculated for each kidney.

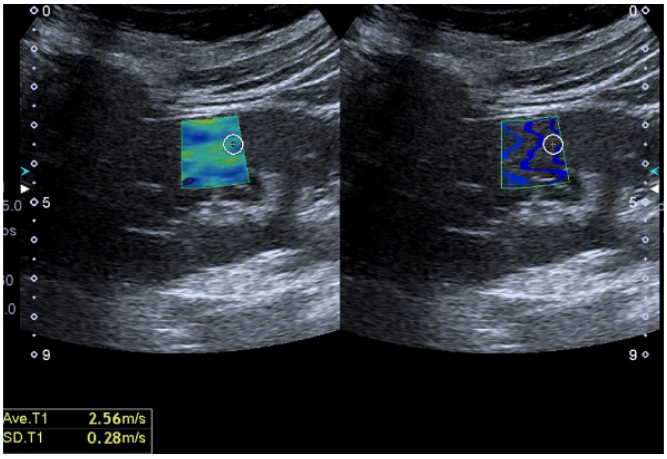

Figure 2. Two-dimensional (2D) shear wave elastography (SWE) images of a patient with long axis of kidney (ureteral stone side) real-time visualization of a color quantitative elastogram superimposed on a gray scale image and it reveals grade 1 hydronephrosis. Tissue stiffness in numeric information SWE values was calculated from the region of interest (10 mm x 10 mm square) placed on the superficial area in the mid-portion of the kidney cortex.

Statistical Analysis

The statistical package program (SPPS 25, IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) was used to evaluate the data. Mean and median values, standard deviation, maximum, minimum, number and percentiles were calculated (for the continuous and categorical variables). Homogeneity of the variances was checked with the Levene test. The normality assumption was examined with the "Shapiro-Wilk" test. "Student's T Test" was used when the parametric test met its prerequisites, and if it did not, we used "Mann Whitney-U test". Relationship between two continuous variables were interpreted with the Pearson Correlation Coefficient. The Spearman Correlation Coefficient was used if the parametric test did not meet the prerequisites. The relationships between the categorical variables were analyzed using the Chi-Square test and Fisher's Exact Test. A p level of <0.05 and <0.01 were accepted as statistically significant.

Results

Twelve female and eighteen male patients aged 24 to 57 (mean 40.8 +- 10,9 years) were included in the study. Twenty-one patients had grade 1

hydronephrosis and nine patients had grade 2 hydronephrosis. Seventeen patients had left sided renal pathology and thirteen had right sided pathology. There was no significant difference between the groups with regard to the gender and age (p=0.28).

The mean stone size was 6.2 mm ± 1.9 mm (3.2-11mm). The mean SWE value for the pathologic kidney was 3.8±1.2 (2.2-6.2) m/sec and the normal side was 2,06 (0,7-3,3) m/sec. Gender and side of the ureter stone did not significantly affect stone size and SWE (Table 1).

Table-1. Comparison of SWE values of Kidneys of Affected Side and Stone Size Variables

	Left n=17	Right n=13	Test Statistic	P value
Pathological Side of Kidney	3,85±1,20	3,82±1,32	0,079	0,938*
Stone size	6,30±2,41	6,11±1,34	-0,222	0,825**

* Two Independent Group T test (Student's t test), € Mann Whitney-U test

The mean SWE value was found to be 3.87 m/sec on the affected kidney, while the mean SWE value was 2.065 m/sec on the normal side. The kidney on the affected side had a statically significant increase in the SWE values than the normal side (3.87±1.22 vs 2.06±0.72 m/sec) (p=0.01).

There was a statistically significant difference between grade of hydronephrosis and SWE values (p<0.05). The mean SWE value of the patients with Grade 2 hydronephrosis was significantly higher than that of Grade 1.

There was a statistically significant difference between grade of hydronephrosis and stone size (p<0.05). The mean stone size detected in the patients with Grade 2 hydronephrosis was significantly higher than that of Grade 1 (Table 2).

Table-2. Comparison of Hydronephrosis Grade with SWE and stone size variables

	Female n=12	Male n=18	Test Statistic	P value
Gender	4,08±1,17	3,74±1,27	-0,868	0,385*
Stone size	6,52±2,14	5,96±1,90	0,756	0,456**

* Two Independent Group T test (Student's t test), € Mann Whitney-U test

There was a significant positive correlation of 45.4% between SWE and grade of hydronephrosis. There was a significant positive correlation of 36.6% between the stone size and the grade of hydronephrosis (Table 3).

Table-3. Relationships between SWE and all variables

		SWE	Stone size	Age	Normal kidney SWE	Gender	Hydro-nephrosis Grade
Stone size	r	0,088					
	p	0,646					
	N	30					
Age	r	0,167	0,358				
	p	0,376	0,052				
	N	30	30				
Normal kidney SWE	r	0,335	-0,008	0,254			
	p	0,076	0,967	0,184			
	N	30	30	30			
Gender	r	-0,137	-0,141	-0,099	0,264		
	p	0,469	0,456	0,605	0,167		
	N	30	30	30	29		
Hydronephrosis Grade	r	0,454	0,366	0,278	0,290	-0,208	
	p	0,012	0,047	0,137	0,128	0,270	
	N	30	30	30	29	30	
Pathological Side of Kidney	r	-0,015	-0,046	0,071	0,149	-0,147	0,108
	p	0,938	0,814	0,715	0,442	0,447	0,577
	N	30	30	30	30	30	30

Discussion

Ureteral stones cause hydronephrosis and increased pressure in the pyelocalyceal system. Urinary pressure changes have an impact on the SWE values. In our prospective case-control study, we investigated the changes in the kidney shear wave speed secondary to ureter stones.

We found that the affected side had a statically significant increase in the SWE values than the normal side (p=0.01). To the best of our knowledge, our study is the first to assess the SWE values changes during ureteral stone and hydronephrosis and report in the English literature.

In an in vivo study on pigs, the relationship between renal elasticity and urinary pressure has been investigated. In this study, the gradual increase

in pressure was simulated by injecting retrograde fluid from the ureter. As a result, a progressive increase in renal elasticity was observed with the elevation of urinary pressure, and the increase in elasticity was correlated to the increase in urinary pressure [9]. Similarly, in our study, a statistically significant increase in kidney elasticity was found in the kidneys with hydronephrosis. There was a positive correlation between increased hydronephrosis and increased SWE values. Patients with grade 2 hydronephrosis had higher parenchymal SWE values than patients with grade 1 hydronephrosis. We found a positive correlation between the stone size and hydronephrosis and have concluded that the larger the stone, the greater the increase in pressure, resulting in more hydronephrosis and an increase in renal elasticity (and SWE values). Increased elasticity due to increased urinary pressure should be considered when evaluating the transplanted kidney USG elastography. In many studies on transplanted kidneys, inconsistent results were more common than native kidney elastography studies [10]. In light of the results we have reached in our study, we think that the elasticity evaluations may be inconsistent in transplanted kidneys due to the short ureters and the higher reflection of the pressure of the full bladder, on kidney elasticity.

There are many studies investigating the relationship between reduced kidney elasticity and fibrosis. In one study, the SWE values were measured in patients with diabetes mellitus causing fibrosis, in order to predict chronic kidney disease. It was revealed that patients with diabetic kidney disease had a significantly lower kidney shear wave speed compared to patients without chronic kidney disease [11].

Similar to ours, the only study in which an increase in renal elasticity was found is the study examining the changes in SWE values after ESWL. In that study, the authors suggested that the increase was related to the acute inflammation due to the examination performed immediately after ESWL. The authors assumed that edema and inflammation after ESWL might be detected as an increase in SWE values [12]. We suggest that urinary retention may also occur immediately after ESWL and urinary pressure increases simultaneously with an increase in SWE values. We did not encounter any post ESWL procedure related hydronephrosis in our study.

This presented study which relates to renal shear wave elastography in patients with high ureteral pressure may be the first prospective study in the English literature as far as we could investigate.

Limitations: firstly, the study population was limited to thirty patients. A large cohort study would indicate better results for evaluation. Secondly, we did not have an adequate number of patients in the grade 3 and grade 4 hydronephrosis group. Evidently, the examination of patients with higher grade dilatation would be helpful to better understand the evaluation of renal parenchymal tissue damage. In addition, we aimed to diagnose patients in the adult age group: a research study group including the childhood age, such as vesicoureteral reflux, would be beneficial to the literature. Finally, we didn't include transplanted kidneys in our study group: evaluation of ureteral stenosis or ureteral stones with UE would be beneficial in this group, due to short length of the ureter.

Conclusion

SWE is a fast, accurate, accessible non-ionizing diagnostic tool to identify renal parenchymal tissue elasticity in the adult age group, and may be used for diagnosing ureteral stones.

Conflict of Interest: The authors declare no conflict of interest related to this article.

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ORCID and Author contribution: **UMY (0000-0003-1863-2981)**: Concept and design, data collection and processing, literature search, analysis, writing, critical review. **EŞ (0000-0002-1922-5280):** Data collection, analysis, literature search, writing. **AS (0000-0003-3000-3854):** Practices, processing, analysis, writing,

critical review. **BÖ (0000-0002-9471-7031):** İnterpretation, analysis, writing, critical review. **SS (0000-0001-5364-2398):** Practices, processing, literature search, writing.

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RESEARCH ARTICLE

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CT angiography and Doppler ultrasound evaluation of congenital portosystemic shunts

Konjenital portosistemik şantların BT anjiyografi ve doppler ultrason ile değerlendirilmesi

İsmail Akdulum[1*], Melih Akyüz[2], Enes Gürün[3], Mehmet Öztürk[4], Ahmet Sığırcı[5], Öznur Leman Boyunağa[1]

1.Department of Pediatric Radiology, Gazi University, 06560, Ankara, Turkey
2.Department of Radiology, Rush University Medical Center, 60612, Chicago, USA
3.Department of Radiology, İskilip Atıf Hoca State Hospital, 19400, Çorum, Turkey
4.Department of Pediatric Radiology, Selcuk University, 42130, Konya, Turkey
5.Department of Pediatric Radiology, Inonu University, 44280, Malatya, Turkey

ABSTRACT

Aim: The aim of the study was to describe the Doppler ultrasonography and computed tomography findings that should be considered in the diagnosis and treatment of congenital portosystemic shunts.
Methods: Archive retrospectively scanned. In consideration of shunts: communication type and aneurysm were defined. Additional imaging modalities were utilized.
Results: 11 patients were included in the study. The ages ranged from 0 to 158 months. There were two patients with shunt connecting segment-4 portal vein - middle hepatic vein, two patients with segment-3 portal vein - left hepatic vein, two patients with left portal vein – middle hepatic vein, two patients with portal vein - left renal vein, two patients with portal vein -inferior vena cava, and one patient with portal vein - perirectal venous plexus.
Conclusion: Some classifications used in congenital portosystemic shunts are insufficient in guiding treatment. Elaborate definition of the imaging findings including the involved vessels, type of communication, and presence of aneurysm or dilated vessels is of the prime importance for tailoring clinical management of the patients.

Keywords: Congenital portosystemic shunt; Computed tomography; Doppler ultrasonography,

ÖZ

Amaç: Konjenital portosistemik şantların tanısında ve tedavinin yönlendirilmesinde dikkat edilmesi gereken Doppler ultrasonografi ve Bilgisayarlı tomografi bulgularını tanımlamaktır.
Metod: Arşiv geriye dönük olarak taranmıştır. Şantlar göz önüne alındığında: bağlantı tipi ve anevrizma varlığı tanımlandı. Ek görüntüleme yöntemleri varsa not edildi.
Bulgular: Çalışmaya 11 hasta dahil edildi. Yaşlar 0 ile 158 ay arasında değişiyordu. Şant bağlantısı segment-4 portal ven - orta hepatik ven olan iki hasta, segment-3 portal ven - sol hepatik ven olan iki hasta, sol portal ven - orta hepatik ven olan iki hasta, portal ven - sol renal ven olan iki hasta, portal ven - inferior vena kava olan iki hasta ve portal ven - perirektal venöz pleksuslu bir hasta vardı.
Sonuç: Konjenital portosistemik şantlarda kullanılan bazı sınıflamalar tedavi yönlendirmesinde yetersiz kalmaktadır. İlgili damarlar, iletişim tipi ve anevrizma veya dilate damarların varlığı dahil olmak üzere görüntüleme bulgularının ayrıntılı tanımı, hastaların klinik yönetiminin özelleştirilmesi için birincil öneme sahiptir.

Anahtar Kelimeler: Konjenital Portosistemik Şant; Bilgisayarlı Tomografi; Doppler Ultrasonografi

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*Corresponding Author: İsmail AKDULUM. Department of Pediatric Radiology, Gazi University, Faculty of Medicine, Ankara, Turkey, +905055304795, iakdulum@gmail.com

ORCID: 0000-0001-6109-5240

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Introduction

Congenital portosystemic shunt (CPSS) is a rare disease seen in about one in thirty thousand children. CPSS is an abnormal connection between the portal and venous vessels. The exact etiology is still unknown. Previous studies suggest complex genetic origin, congenital malformative processes developing in response to portal hypertension, congenital liver hemangioma and others [1-4]. As a result of the diversion of portal blood to the systemic circulation, CPSS may result in serious complications, both in intrauterine life and after birth, such as intrauterine growth retardation (IUGR), galactosemia, hepatopulmonary syndrome, hepatic encephalopathy and liver tumors. However, complications such as ascites and portal hypertension are rarely seen as opposed to cirrhosis and portal vein thrombosis [5-7]

The Doppler ultrasound (d-US) is the imaging modality of choice in diagnosis, follow-up and post-treatment monitoring. Antenatal d-US screening may provide early diagnosis. Although the d-US is radiation-free, easy to access and inexpensive, it might not provide elaborate information related to shunt anatomy, intrahepatic portal vasculature and some of the complications [2-4]. With d-US imaging we can analyze vascular flow velocity and flow direction. Computed Tomography Angiography (CTA) is usually performed when the d-US is inadequate in diagnosis, during treatment planning for further analysis of shunt and proper anatomic definition, and probable complication evaluation. Magnetic Resonance Imaging (MRI) is utilized in the suspicion of liver tumor and evaluation of the brain, in the presence of neurological symptoms. Direct Subtraction Angiography (DSA) on the other hand is usually considered for treatment planning or evaluation of CPSS, when the portal system is not visualized via other imaging modalities [8-12].

Due to the aforementioned complications, all of the shunts are required to be closed as early as possible for proper intellectual and physiological growth, with the exceptions of small intrahepatic shunts that might close spontaneously within the first one to two years of life. Invasive treatment might be postponed for the children with galactosemia, which may be controlled with dietary modifications and neonatal cholestasis, and which may resolve spontaneously [1, 3, 5]. The aim of this study was to describe the sonographic and CTA findings of CPSS.

Material and Method

This study was approved by the local Ethics Committee and complies with the Helsinki Declaration (2019-292). We retrospectively reviewed clinical information, imaging findings, disease complications of pediatric age group patients diagnosed with CPSS, who were admitted between February 2016 and June 2020. We included all patients diagnosed with CPSS via CTA and d-US. The exclusion criteria for the study were non-diagnostic imaging due to patient incoordination and patients lost to follow-up. In consideration of shunts: shunt quantity, communication type (side-to-side, end-to-site), and presence or absence of aneurysm were defined. In this study, we sub-grouped CPSS according to flow dynamics. When all the portal blood flows to systemic vessels it is referred to as 'end-to-site shunt'; if only part of the blood is diverted from the portal system to the venous system it is referred to as 'side-to-side shunt. Additional imaging modalities were utilized, such as cranial MRI for evaluation encephalopathy, and thorax CTA for assessment of cardiovascular complications. Patients' age, gender, clinical findings and concurrent pathologies, were recorded.

CTA exams were performed using the Siemens Somatom force (Siemens Healthcare GmbH, Erlangen, Germany). CTA parameters were as follows: 2×192×0.6-mm slice collimation using z-axis flying focal spot technique; 0.25 second gantry rotation time. Automated tube voltage was used according to the patient's size. A dose of 1.5-2.0 mL/kg of iodinated contrast medium (Iohexol, iodine content 350 mg/mL; Omnipaque TM, GE Healthcare) was intravenously administered via the peripheral vein. Images were acquired at arterial, portal, and venous phases.

Statistical analyses were performed via the SPSS (Statistical Package for the Social Sciences) v.22 package program. Mean and standard deviation values were used for descriptive statistics.

Results

Eleven patients diagnosed with CPSS were included in the study. Five patients were female and the remaining six patients were male. Ages ranged from 0 to 158 months. The mean age was 68.7 ±57.78 months. Demographic findings, vascular communication types and additional pathologies are summarized in Table 1.

Table 1: Demographic findings, involved vessels, type of communication and additional pathologies

	Gender	Age (month)	Involved vessels	Type of communication	Additional pathologies and notes
1	M	87	PV-Left renal vein	End-to-side	-
2	F	145	Segment 4 PV-Middle HV	With aneurysm	-
3	M	101	PV-Perirectal venous plexus	End-to-side	Pulmonary hypertension
4	M	78	PV-IVC	Side-to-side	Pulmonary AVF Globus pallidus T1 hyperintensity
5	F	7	Segment 3 PV-Left HV	With aneurysm	
6	F	49	PV-Left renal vein	End-to-side	Pulmonary hypertension
7	M	128	PV-IVC	Side-to-side	Pulmonary hypertension
8	M	158	Segment 4 PV-Middle HV	With aneurysm	-
9	M	0	Segment 3 PV-Left HV	Subcapsular shunt	Shunt disappeared at 3-month-old follow-up
10	F	1	Left PV-Left HV	With aneurysm	-
11	F	2	Left PV-Left HV	Subcapsular shunt	-

(PV: portal vein; HV: hepatic vein; IVC: inferior vena cava; AVF: arteriovenous fistula)

In our study, six patients had intrahepatic and five had extrahepatic CPSS. None of the patients had mixed CPSS. Two patients had CPSS between segment-4 portal vein (PV) branch and middle hepatic vein (HV), two patients between the left PV and middle HV, two patients between segment 3 branches of the PV and left HV, two patients between the main PV and left renal vein, two patients between the PV and inferior vena cava, and one patient had a dilated vascular structure connecting perirectal venous plexus.

One patient had an intrahepatic CPSS. The diagnosis was made during antenatal ultrasound screening and postnatal d-US confirmed diagnosis of CPSS between segment 3 PV and left HV with an aneurysmatic vein, in the anterior subcapsular area. CTA was utilized for evaluation of probable complications and further treatment planning when he was 1-months-old. CTA depicted a decreased size of the CPSS diameter compared to the US. The patient was booked for follow up and d-US was scheduled for 3 months later. During the follow up the patient was asymptomatic and the shunt could not be visualized during d-US, suggestive of spontaneous resolution.

In all intrahepatic CPSS patients, d-US and CTA imaging depicted asymmetric dilatation of the hepatic vein to which portal flow diverted when compared to uninvolved hepatic veins (Figure 1).

Aneurysmatic dilatation of the shunt was observed in four patients (two had shunt between PV segment 4 branch and middle HV, one had between PV segment 3 branch and left HV, and one had between left PV and left HV) (Figure 1).

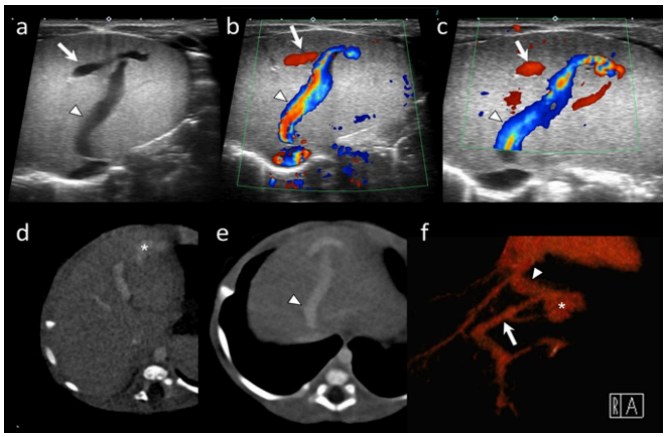

Figure 1. One-month-old female patient. B-mode US (a), Doppler US (b, c), axial CTA (d, e), and volume rendering technique (VRT) image (f) of aneurysmatic (*) CPSS between left portal vein (arrow) and middle hepatic vein (arrowhead). Note that the asymmetric dilatation of the middle hepatic vein (arrowhead) due to diverted blood flow from the portal system

Four patients had pulmonary vascular pathologies. Two patients with pulmonary hypertension had end-to-side type shunts one terminating at the left renal vein (Figure 2) and the other one at the perirectal venous plexus (Figure 3). Intrahepatic portal venous branches of these two patients could not be observed via d-US. The other two patients had side-to-side shunts between the portal vein and inferior vena cava (IVC) (Figure 4). One of the patients with pulmonary hypertension and the other with pulmonary arteriovenous fistula (AVF) diagnosis. These two patients had a hypoplastic intrahepatic portal venous system due to the diversion of portal blood flow to the systemic circulation.

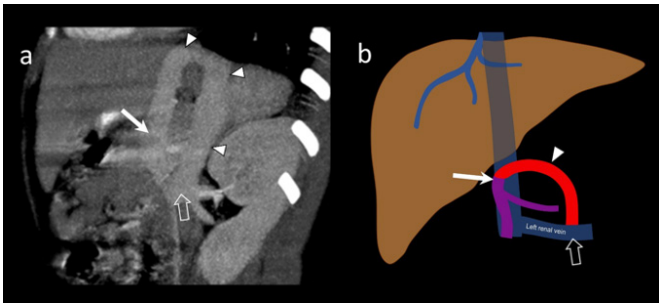

Figure 2. A 7-year-old male patient. Coronal oblique maximum intensity projection (MIP) CT images (a) and schematic drawing (b) of CPSS between the portal vein and left renal vein. CPSS (arrowhead) originating from portal confluence (arrow) ascending till the level of the diaphragm, then makes a 180-degree turn and coursing caudally towards the pelvis and drains into the left renal vein (blank arrow)

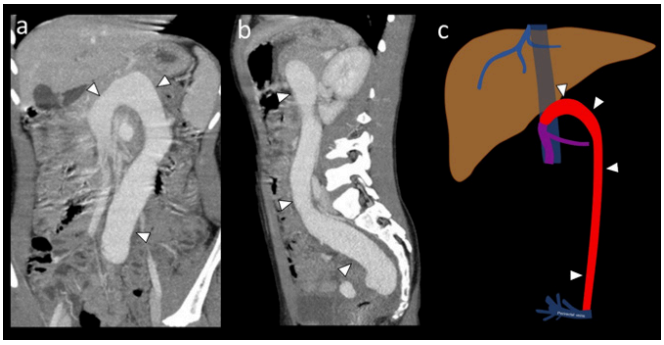

Figure 3: 8 years old male patient with CPSS between the portal vein and perirectal venous plexus. Coronal and sagittal MIP images (a, b) and the schematic drawing (c) of the dilated vessel (arrowhead). Shunt caliber reaches up to 2,5 cm diameter.

Six patients had cranial MRI due to abnormal neurological examination. Two patients had increased T1 intensity in globus pallidus, suggestive of hepatic encephalopathy (Figure 4). One of them had an end-to-sides type shunt between the portal vein and perirectal venous plexus and the other one had side-to-sides type shunt between the PV and IVC.

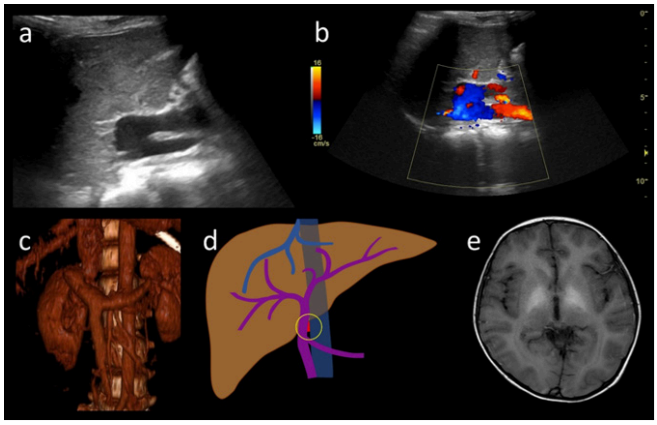

Figure 4: 6 years old male patient. Previously follow up for pulmonary arteriovenous fistula (AVF). Sagittal ultrasound image (a) depicts a side-to-side connection between the portal vein (PV) and inferior vena cava (IVC). Sagittal Doppler US (b) demonstrates the flow portal vein to IVC. Volume rendering technique (VRT) (c) image and schematic drawing (d) of the shunt. Cranial MRI (e) of the same patient, T1 weighted sequence image shows increased intensity in bilateral globus pallidus.

Discussion

In the literature, there are several classification systems for CPSS, which is essentially divided into two groups, namely intrahepatic and extrahepatic. Extrahepatic CPSS are further divided into two subgroups that are type 1 -congenital absence of an intrahepatic portal system, and type 2 -hypoplasia of the main trunk. Kobayashi et al. sub-grouped the extrahepatic shunts according to drainage vein. If the shunt is drained to IVC it is referred to as type A, to the renal vein as type B, and to the iliac vein as type C [13]. For intrahepatic shunts, the 'Park classification' is most commonly used, in which intrahepatic shunts are sub-grouped into 4 types: Type 1: A single vessel communication between the main branch of the portal vein and IVC; Type 2: Peripheral location in one segment; Type 3: Peripheral location in one segment through an aneurysm; Type 4: Multiple small communications distributed diffusely in both lobes [1,4,5,14,15] (Table 2).

Another concern is for the 'Abernethy Classification'. Type 1 CPSS is defined as the absence of an intrahepatic portal system and liver transplantation is considered solely as a treatment modality. However, advances in imaging revealed that the hypoplastic intrahepatic portal system might not be able to be visualized with routine imaging modalities due to small

caliber or diminished blood flow. In that sense, the term 'absence' might not be 'the grim truth'. Kanazawa et al. sub-grouped intrahepatic portal system in a series of eighteen patients using shunt occlusion test based on the severity of hypoplasia (mild, moderate, severe). In that study, liver transplantation was required only for two patients [10]. A balloon occlusion test is utilized during transcatheter angiography and is useful for the patients with severe hypoplastic portal veins in whom closure of the shunt may cause colon necrosis. Treatment modality for these patients is staged interventional or surgical closure. Liver transplantation is taken into consideration as the last option [3-5].

Table 2: Mostly used classifications for intra and extrahepatic CPSS of Kobayashi et al and Park et al (11, 12).

Most Commonly Used Classifications	Types	Shunt from	Drainage vein
Extrahepatic Shunt (Kobayashi et al)	Type A	PV	IVC
	Type B	PV	Renal vein
	Type C	PV	Iliac vein
Intrahepatic Shunts (Park et al)	Type 1	PV	IVC
	Type 2	Peripheral sides of PV	Peripheral sides of HV
	Type 3	Peripheral sides of PV with aneurysm	Peripheral sides of HV
	Type 4	Multiple peripheral sides of PV	Multiple peripheral sides of HV

PV: portal vein; IVC: inferior vena cava; HV: hepatic vein.

Bernard et al. found that previously used CPSS classification systems might not be sufficient for treatment planning. Probability of the presence of both intra and extrahepatic shunts, the presence of ductus venosus, and plasticity of intrahepatic portal system is also important for prognosis and clinical management, but not taken into consideration in any of aforementioned classification systems [1]. In our study, we did not use any of the classification systems in the literature. We believe that an elaborate definition of the shunt is of prime importance for clinical patient management. Detailed definition of the involved vessels, type of communication (side to side -partial diversion of blood flow-, end to side – a total diversion of blood flow), and the presence of aneurysm or dilated vessels, are essential for treatment planning.

Once the diagnosis is made, the patients should also be evaluated for probable concurrent congenital abnormalities. Cardiovascular system abnormalities (atrial septal defect, ventricular septal defect, etc.) are the most common, followed by spleen (polysplenia, asplenia) and other vascular anomalies (splenic artery aneurysm, primitive hypoglossal artery, etc.) among the congenital abnormalities [5]. Hence, vice versa, patients with the aforementioned abnormalities should be investigated for CPSS. In our study, two patients who had pulmonary hypertension and pulmonary AVF were incidentally diagnosed with CPSS.

Clinical management depends on the type of the CPSS and the age of the patient. Follow-ups might be sufficient, in particular for asymptomatic patients with small intrahepatic shunts which may spontaneously disappear within the first two years of life. In one patient the shunt that we detected in the neonatal period disappeared at a 3-month follow-up, suggestive of spontaneous resolution. In symptomatic patients or over two years of age, treatment of choice for the closure of the CPSS is interventional radiological procedures due to the lower invasiveness. Surgery is not taken into consideration unless interventional radiological procedures are failed [3-5,10]. Patients with portosystemic shunts might suffer from hepatic encephalopathy due to hyperammonemia. In our study, six patients had cranial MRI due to abnormal neurological examination and two patients had T1 hyperintensity in globus pallidus bilaterally, suggestive for hepatic encephalopathy [1, 4, 5, 10].

Limitations: The major limitation was the limited number of patients. This is mainly due to the rarity of the disease. Additionally, we excluded some cases lost to follow up, lack of CTA imaging and non-diagnostic CTA examinations.

Conclusion

Abnormalities in liver function tests, galactosemia, IUGR, and some congenital abnormalities might be related to CPSS. Dedicated detailed imaging of the portal system not limited to main branches, portal trunk, superior mesenteric vein, and splenic vein, but also including tiny intraparenchymal end branches, aids in the diagnosis of CPSS.

Radiologists should be aware of clues leading to the diagnosis, such as asymmetric enlargement of the involved hepatic veins which might be related to portosystemic shunt due to asymmetric drainage. Current classification systems of CPSS might not be adequate for clinical management. Detailed definition of involved vessels, type of the shunt and presence of aneurysm/dilatation, should be reported.

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Evaluation of Congenital Mediastinal Vascular Anomaly Types and Frequencies Among 2000 Cases.

2000 Hastada Konjenital Mediastinal Vasküler Anomali Tiplerinin ve Sıklığının Değerlendirilmesi

Yeliz Dadalı[1], Sercan Özkaçmaz[2*], Mustafa Demir[3], İlke Bursalı[4]

1. *Department of Radiology, Ahi Evran University Faculty Of Medicine, Kirsehir, Turkey*
2. *Department of Radiology, Yüzüncü Yıl University Faculty Of Medicine, Van, Turkey*
3. *Department of Radiology, Umraniye Training and Research Hospital, Istanbul, Turkey*
4. *Department of Radiology, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey*

ABSTRACT

Aim: In this study, it was aimed to examine the incidence of congenital thoracic vascular anomalies in our region.
Methods: The features of the patients with non-specific complaints who underwent a thorax Computed Tomography over a two years period were retrospectively reviewed on the hospital database, and demographical data (Gender and age) were recorded. All the Computed Tomography images were interpreted regarding thoracic vascular anomalies, including persistent left superior vena cava, azygos lobe, aberrant right subclavian artery, dilated left superior intercostal vein, right-sided aortic arch, situs inversus, and partial anomalous pulmonary venous return. The incidences of these thoracic vascular anomalies were calculated and compared with previous studies.
Results: Mediastinal vascular anomaly was detected in 62 (3.1%) patients. A mediastinal vascular anomaly was observed in 27 (3.5%) female patients and 35 (2.6%) male patients. The most common mediastinal vascular anomaly in this study was the right aberrant subclavian artery (n:17, 0.9%) and the rarest was partial anomalous pulmonary venous return (n:1, 0.1%). Persistent left superior vena cava incidence was 0.3% (n:6), azygos lobe 0.7% (n:14), right-sided aortic arch 0.3% (n:5), situs inversus totalis 0.2% (n:3), and dilated left superior intercostal vein 0.8% (n:16).
Conclusion: Mediastinal vascular anomalies are rare and usually asymptomatic. But the imaging findings of these conditions must be well-known to accurately planning the interventions and also to prevent iatrogenic injuries.

Key Words: Computed Tomography, Partial anomalous pulmonary venous return, Aberrant right subclavian artery, Situs inversus totalis, Dilated left superior intercostal vein

ÖZ

Amaç: Bu çalışmamızda bölgemizde konjenital mediastinal vasküler anomalilerin sıklığını araştırmayı planladık.
Yöntem: Yaklaşık 2 yıllık bir süreçte non-spesifik semptomlar ile kontrastlı toraks Bilgisayarlı Tomografi çekilen hastaların özellikleri hastane veri tabanından retrospektif olarak tarandı. Yaş ve cinsiyet gibi demografik özellikler kaydedildi. Tüm Bilgisayarlı Tomografi görüntüleri, persistan sol superior vena kava, azygos lobu, aberran sağ subklavien arter, dilate sol superior interkostal ven, sağ taraflı arkus aorta, situs inversus ve parsiyel anormal pulmoner venöz dönüş anomalileri açısından yorumlandı. Çalışmamızda bulunan insidans değerleri ile önceki çalışmaların sonuçları karşılaştırıldı.
Bulgular: Mediastinal vasküler anomali 62 (%3.1) hastada saptandı. Kadın hastaların 27 (%3.5)'inde ve erkek hastaların 35 (%2.6) 'inde bir mediastinal vasküler anomali gözlemlendi. Çalışmamızdaki en sık saptanan mediastinal vasküler anomali, sağ aberran subklavien arter (n:17, %0.9) ve en nadir görüleni ise parsiyel anormal pulmoner venöz dönüş anomalisi idi (n:1, %0.1). Persistan sol superior vena kava insidansı %0.3 (n:6), azygos lobu %0.7 (n:14), sağ taraflı arkus aorta %0.3 (n:5), situs inversus totalis %0.2 (n:3) ve genişlemiş sol superior interkostal ven ise %0.8 (n:16) olarak bulundu.
Sonuç: Mediastinal vasküler anomaliler nadir olup sıklıkla asemptomatiktir. Ancak bu durumların görüntüleme bulgularının iyi bilinmesi, girişimsel işlemleri doğru biçimde planlamada ve aynı zamanda iatrojenik yaralanmaları önlemede gereklidir.

Anahtar Kelimeler: Bilgisayarlı Tomografi, Parsiyel anormal pulmoner venöz dönüş anomalisi, Sağ aberran subklavien arter, Situs inversus totalis, Genişlemiş sol superior interkostal ven

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*Corresponding Author: Sercan ÖZKAÇMAZ, Ass Prof., Department of Radiology, Yüzüncü Yıl University, Faculty of Medicine, Van, Turkey, +905323276412, sercanozkacmaz@hotmail.com

ORCİD: 0000-0002-9245-0206

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INTRODUCTION

Various development conditions may affect the anatomy of intrathoracic arterial and venous structures including superior vena cava, pulmonary veins, aorta and their branches. The variations of these vascular structures may be isolated or associated with a syndrome. Most of these anomalies are asymptomatic and are detected incidentally on thorax imaging. But for especially accurate pre-operative/intervention evaluation of the thoracic vascular structures, the vascular anatomical variations of the thorax must be well-known. Computed Tomography (CT) is the most frequently performed imaging modality for detection of these anomalies while Magnetic Resonance Angiography and conventional catheter angiography can be also used. CT has excellent spatial resolution but a high-radiation dose is its' principal disadvantage. For diagnosis of thoracic vascular anomalies, conventional catheter angiography is accepted as the gold standard method, but it is an invasive procedure that involves ionizing radiation. Magnetic Resonance Imaging (MRI) is a non-invasive modality not involving ionizing radiation although it has a poor spatial resolution, when compared with CT and conventional catheter angiography [1].

In this study, we aimed to evaluate the incidence of congenital mediastinal vascular anomalies among patients with non-specific complaints in our region, and to compare these results with previous studies.

MATERIAL AND METHODS

Patients

The patients who underwent a CT of the thorax in a tertiary chest disease hospital with non-specific complaints including cough, dyspnea and chest pain, between the years 2011 and 2013, were included in this study. Demographical-medical data and the CT images of the patients were reviewed on the hospital database. The patients with a previous thoracic-vascular surgery, arterial and venous thrombosis or systemic, or thoracic chronic disease history were excluded from this study. Because we aimed to evaluate congenital Mediastinal vascular anomalies.

This retrospective study was approved by the institutional ethics committee (Ankara Atatürk Chest Diseases and Chest Surgery Training and Educational Hospital ethics committee) with a number of 005070 on 22.08.2013. No written informed consent could be obtained from the patients because of the retrospective nature of the study.

CT technique

A Somatom Emotion 6 scanner system (Siemens Medical Systems, Forchheim, Germany), with a pitch of 0.75, a 6x3 mm collimation and a reconstruction thickness of 10 mm were used to obtain CT images. In all patients, an intravenous iodine contrast agent (iohexol-300) was administrated with a dose of 1.2 ml/kg at speed of 3-4 mL/s. Images were obtained from common carotid artery bifurcation level to the level of renal artery origins and the image withdrawal was started 25th second after contrast agent administration. A cut-off diameter >4mm was considered as significant for the definition of a dilated left superior intercostal vein. Images were interpreted by two radiologists with 14 and 11 years of thoracic imaging experience in consensus regarding thoracic vascular anomalies mentioned above.

Statistical Analysis

The descriptive variables were presented as the mean ± standard deviation, minimum/maximum, and percent (%). For the statistical analysis, a software program (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp., USA) was used.

RESULTS

Nineteen patients with previous thoracic surgery, 43 with chronic diseases and 36 whose medical data was not available were excluded from the study. A total of 2 000 patients (mean age 56.13±14.62, 12-93 years) were included in this study. Among them 776 were female (38.8%) (mean age 56.93±15.19, 13-93) and 1 224 were male (61.2%) (mean age 55.63±14.23, 12-88 years). Female/male ratio was 0.63. A thoracic vascular anomaly was detected in 3.1% (n:62) of the patients while in 96.9% (n:1938) of them

no anomaly was observed. A thoracic vascular anomaly was observed in 3.5% (27/776) of the females and 2.6% (25/1224) of the males. The detailed features of the patients are summarized in Table 1.

Table 1: Prevalence of mediastinal vascular anomalies among males and females

Variation	Female		Male		Total	
	N	%	N	%	N	%
No anomaly	749	96.5	1189	97.1	1938	96.9
Aberrant right subclavian artery	10	1.3	7	0,6	17	0.9
Dilated left superior intercostal vein	7	0.9	9	0.7	16	0.8
Azygos lobe	3	0.4	11	0,9	14	0.7
Persistent left superior vena cava	2	0.3	4	0,3	6	0,3
Right-sided aortic arch	4	0.5	1	0.1	5	0.3
Situs inversus	1	0.1	2	0.2	3	0.2
PAPVR*	0	0.0	1	0.1	1	0.1
Total	776	38.8	1224	61.2	2000	100

*PAPVR: Partial anomalous pulmonary venous return

The most common vascular variation in this study was aberrant right subclavian artery which was detected in 17 (0.9%) patients. Dilated left superior intercostal vein (DLSIV) (Figure 1) was observed in 16 (0.8%), azygos lobe in 14 (0.7%), persistent left superior vena cava (PLSVC) (Figure 2) in 6 (0.3%), right-sided arcus aorta (Figure 3) in 5 (0.3%), and situs inversus in 3 (0.2%) patients. Partial anomalous pulmonary venous return (PAPVR) (Figure 4) was the rarest thoracic vascular variation, which was seen in one (0.1%) patient. Normal venous anatomy is illustrated in Figure 5.

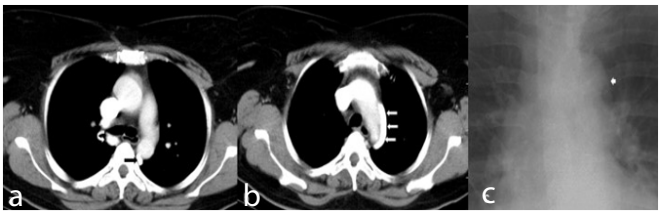

Figure 1a-c. (Dilated left superior intercostal vein) Dilatation of both azygos vein (curved arrow), accessory hemiazygos vein (black arrow) and left superior intercostal vein (white arrows) in a patient with congestive heart failure on axial CT images (a,b). The "aortic nipple" sign (little white arrow) is seen close to aortic knob on chest x-ray (c).

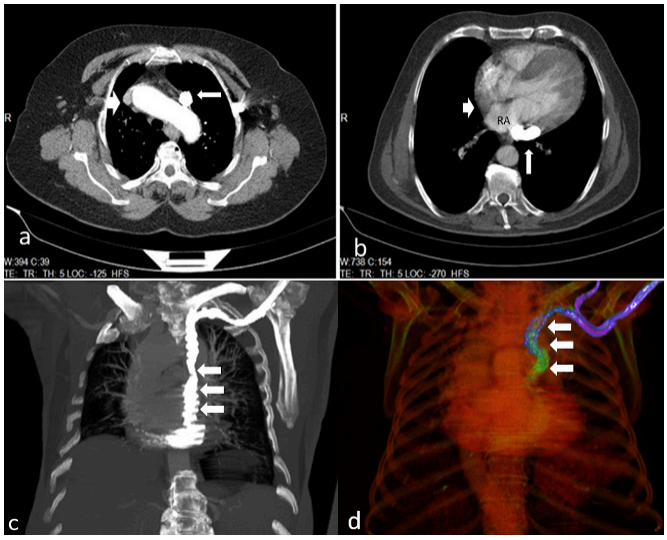

Figure 2a-d. (Persistent left superior vena cava) Right superior vena cava (short arrows) left superior vena cava (long arrows) that draining to right atrium (RA).

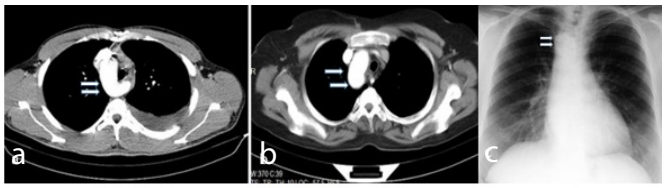

Figure 3a-c. (Right-sided aortic arch) Arcus aorta coursing to the right of the esophagus and trachea (white arrows) on axial CT images (a,b) and on chest x-ray (c).

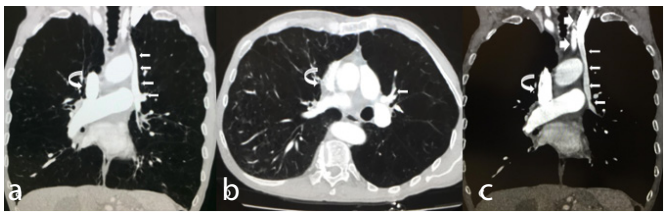

Figure 4a-c. (Partial anomalous pulmonary venous return) Left superior pulmonary vein (Long arrows) joins to left brachiocephalic vein (short arrows) and drained to superior vena cava (curved arrow) and then to right atrium.

DISCUSSION

Persistent left superior vena cava (PLSVC) is the most frequent congenital venous anomaly of the thorax that is reported in 0.5% of the general population and 4% of the patients with congenital cardiac diseases [2,3]. PLSVC occurs due to failure in regression of the left anterior cardinal vein and is frequently accompanied by right-sided superior vena cava. However, it may be rarely detected in isolation when the right anterior cardinal vein regressed. If a superior vena cava

duplication is present, left superior vena cava lies caudally lateral to mediastinum and anterior to the left hilus [4].

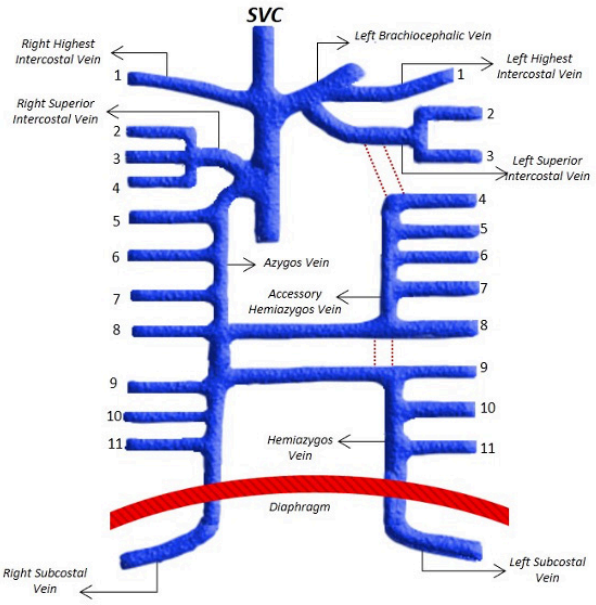

Figure 5. (Normal venous anatomy of mediastinum) The illustration of venous structures of the mediastinum.

PLSVC is a usually asymptomatic condition that is detected incidentally on thorax CT or x-ray imaging. Left or right cardiac enlargement in the patients with PLSVC must raise a suspicion of an atrial or ventricular septal defect. It has no clinical importance even in the patients with right-to-left shunt also when drained to left atrium. But when detected, it must be described for optimal planning of implantation of cardiac pacemakers or venous ports [5-7]. The incidence of the condition was suggested to be between 0.3-0.5% in recent studies [5,6]. We detected PLSVC in 0.3% (n:6) of our patients. Among these 6 patients, two (0.3%) were female and the remaining four (0.3%) were male. In all these cases right superior vena cava was also present. Our results of PLSVC were consistent with previous studies and the incidence of the condition in males and females is the same.

An anomalous course of the azygos vein in apex of the right lung results in azygos lobe that is detected in 0.42-1.2% of the general population [8]. In most cases, the diagnosis can be made by x-ray while in some patients CT may be required [9]. The incidence of the condition was reported as 0.4% on x-ray and 1.2% on CT images with a male predominance [10]. In this study, we observed azygos lobe in 0.7% (n:14) of the patients. Consistent with the literature, the incidence of the condition in males (0.9%, n:11) was markedly higher than in females (0.4%, n:3). Azygos lobe is almost always asymptomatic and does not require intervention. Azygos lobe may be misdiagnosed as an abscess or air cyst on chest x-ray. Also, consolidation in the azygos lobe may be misinterpreted as a malignant tumor [11].

The most frequent congenital anomaly of aortic arch is the aberrant right subclavian artery, which is seen in 0.5-2% of the general population [12]. The condition occurs from the regression of right fourth innominate artery, the persistence of the seventh intersegmental artery, and the abnormal arise of the right subclavian artery from the aortic arch as the last branch in embryonic period [13]. It crosses upwards and to the right in the mediastinum. The condition is usually asymptomatic unless it compresses by the esophagus or trachea [12]. Computed Tomography is more sensitive (100%) for the recognition of aberrant subclavian artery than x-ray (92%) and doppler ultrasound (20%) [14]. Previous studies suggested the incidence of aberrant right subclavian artery as 0.4%-0.5% [15,16]. In our study, we detected this condition in 0.9% (n:17) of the patients. When compared with previous studies we detected a higher incidence. Among 17 patients with aberrant right subclavian artery, ten were female and seven were male. In the literature, the condition was more commonly observed in females than males (58% versus 42%, respectively) [17]. In our study, consistent with the literature, we also found female dominance.

The right-sided aortic arch occurs by the total obliteration of the left fourth aortic arch and left dorsal aorta and the development of the right fourth aortic arch and right dorsal aorta. The major subtypes of the condition are: 1-with mirror image branching, 2-with aberrant left brachiocephalic artery 3-with aberrant left subclavian artery, 4-with isolated left subclavian artery. Aortic arch anomalies may be detected by x-ray but usually CT and MRI are required for the confirmation [18,19]. The right-sided aortic arch is detected in 0.1% of the adults [19]. In this study, the incidence of the condition was 0.3% (n:5). Among the five patients, four (0.5%) were female and the remaining one (0.1%) was male.

Partial anomalous pulmonary venous return (PAPVR) is another congenital vascular anomaly that is characterized by the drainage of one or more pulmonary veins to systemic circulation or right atrium [20,21]. Four variants of PAPVR have been reported: supra-cardiac, cardiac, infra-cardiac and mixed [22]. The most common venous return anomaly is the drainage of the right superior pulmonary vein to superior vena cava or right atrium. In some cases, the right pulmonary vein may drain to inferior vena cava (Scimitar syndrome). Very rarely, drainage to azygos-portal and hepatic veins is reported. Left pulmonary veins drain to left brachiocephalic vein or coronary sinus [23-24]. The only case of PAPVR in our study was a supracardiac type in which the left superior pulmonary vein joins the left brachiocephalic vein and then drains to the right atrium.

PAPVR is rare, as detected in an incidence of 0.4% in pediatric autopsy series [23]. Ho et al, reviewed thorax CT images of 45 538 individuals and detected PAPVR in 0.1% of them. In their series, 58% of the individuals were female and 42% were male [20]. In our study, the incidence of the condition was found to be 0.05%, as the only patient with PAPVR was male.

PAPVR is usually asymptomatic as does not require treatment unless accompanied by other severe cardiovascular pathologies. But awareness of this condition is important to prevent iatrogenic complications such as malposition, perforation, or thrombosis, during and after interventions [25].

Situs inversus totalis is characterized by the reversion of the major visceral organs from their normal locations. In this condition, not only the heart and bronchial tree but also the intestines and mesenteric structures are mirrored from their normal position. Jejunum, stomach, descending colon are seen on the right side while ileum, ascending colon and the Treitz ligament are located in left side. It is seen in approximately 1/8 000-25 000 and the diagnosis is usually made in childhood based on radiological examinations. Sometimes congenital heart defects and immune deficiency syndromes are associated with situs inversus. In isolated cases, the condition is usually detected in adulthood when being evaluated for non-specific complaints [26]. In our study, two males (0.2%) and one female (0.1%) with situs inversus were identified. Total situs inversus incidence in the study was 0.2%.

The earlier diagnosis of situs inversus is essential for the accurate interpretation of the visceral organ complaints which are not localized to their normal position, as well as to prevent iatrogenic injuries in the interventions.

Intercostal veins drain into the hemiazygos, whereas accessory hemiazygos veins drain into the left side and into the azygos vein in right. Right superior intercostal vein joins to azygos vein above right main bronchus and close to the proximal segment of aortic arch. Left superior intercostal vein forms by union of 2nd and 3rd (and sometimes 4th) intercostal veins. In 75% of the individuals, the left intercostal vein joins to accessory hemiazygos vein and then drains to the left brachiocephalic vein. It is seen close to the aortic knob on chest x-rays and is termed as ‘aortic nipple’. It is seen in the chest x-rays of 1.4-9.5% of healthy individuals [27]. When the diameter of this vessel is >4 mm, it is termed as Dilated Left Superior Intercostal Vein (DLSIV). The patients with DLSIV must be further examined regarding venous anomalies. Inferior-superior vena cava occlusions, congestive heart failure, Budd-Chiari syndrome, left brachiocephalic vein hypoplasia, accessory hemiazygos vein hypoplasia and azygos vein aplasia, may be associated with DLSIV [28]. In this study, DLSIV was detected in 0.8% (n:16) of the patients and among these, nine were male and seven were female. Of 16 patients with dilated left superior intercostal vein, three had hypoplasia of hemiazygos vein and two had congestive heart failure. No additional findings were observed in the remained eleven patients on imaging.

Limitations: The limitations of this study are that it is a retrospective and single-center study.

Conclusion

Mediastinal vascular anomalies are usually asymptomatic and detected incidentally on the imaging for various complaints. However, these anomalies must be well identified for an accurate diagnosis and optimal planning before intervention, in order to prevent iatrogenic

complications. To evaluate the prior imaging of the patients undergoing interventional procedures is essential to investigate mediastinal vascular anomalies. In addition, a preliminary MRI or CT angiography may be performed to detect possible associated vascular anomalies in the patients with congenital heart defects or suspicious clinical (such as collaterals) and radiological (such as mediastinal widening on chest X-rays) findings.

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Functional and radiological results of the surgical treatment of pediatric femoral neck fractures

Pediatrik femur boyun kırıklarının cerrahi tedavisinin fonksiyonel ve radyolojik sonuçları

Duran Topak[1*], Mustafa Abdullah Özdemir[1], Fatih Doğar[1], Ökkeş Bilal[1]

1.Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Orthopaedic and Traumatology, Kahramanmaras, Turkey

ABSTRACT

Objective: Our aim in this study was to evaluate the demographic data on femoral neck fractures, postoperative complications, and functional and radiological results following its surgical treatment in the pediatric age group. Pediatric femoral neck fractures often occur after high-energy trauma and seen rarely.

Material and Methods: Twenty-six patients who underwent surgery after the diagnosis of femoral neck fracture in our clinic between 2012 and 2019 were examined. Demographic data, trauma mechanism, accompanying injuries, and postoperative complications of the patients were recorded from our registry system. Functional radiological evaluation was performed using Ratliff criteria.

Results: The mean age of the participants in the study was 11.11 (3–16) year, and the mean follow-up time was 29.34 (12-60) months. According to Ratliff criteria, 18 patients (69.2%) achieved good, 6 patients achieved (23.1%) moderate, and 2 patients achieved (7.7%) poor results after surgery. Avascular necrosis was observed in 5 patients (19.2%) in total. Avascular necrosis did not occur in 10 patients who underwent surgery within first 6 hours. Avascular necrosis occurred in 5 (31.25%) out of 11 patients who underwent surgery after 6 hours. This result was statistically significant (p = 0.049). Of the 5 patients with avascular necrosis, 3 were female and 2 were male. The clinical and radiological results were evaluated according to the Ratliff criteria, and the results were found to be worse in females than in men. There was a statistically significant difference between the genders (p=0.029).

Conclusion: Although femoral neck fractures are rare injuries in the pediatric age group, they are important due to the high risk of complications. The most important complication is avascular necrosis. Results are better males than in females. The results of surgical treatments aimed at anatomical reduction in the shortest possible time are satisfactory.

Keywords: Femoral neck fracture, pediatric, avascular necrosis, Delbert classification.

ÖZ

Amaç: Bu çalışmamızda pediatrik yaş grubunda femur boyun kırığı nedeniyle opere edilen hastaların demografik verilerini, komplikasyonlarını ve tedavi sonuçlarını değerlendirmeyi amaçladık.

Materyal ve Metot: 2012-2019 yılları arasında kliniğimizde femur boyun kırığı tanısı ile opere edilen 26 hasta incelendi. Kayıt sistemimizden hastaların demografik bulguları, travma mekanizması, eşlik eden yaralanmaları ve ameliyat sonrası gelişen komplikasyonları kaydedildi. Hastalarda fonksiyonel radyolojik değerlendirme Ratliff kriterleri kullanılarak yapıldı.

Bulgular: Çalışmaya katılanların yaş ortalaması 11,11 (3-16) yıl, ortalama takip süresi 29,34 (12-60) aydı. Hastaların %65,4' ü erkek (n=17), %34,6 'sı (n=9) kadın hastaydı. Delbert sınıflama sistemine göre ameliyat öncesi 14 hasta tip 2, 12 hasta tip 3 kırıktı. Ameliyat sonrası Ratliff skorlama sistemine göre 18 hasta (%69,2) iyi, 6 hasta (%23,1) orta, 2 hasta (%7,7) kötü sonuç olarak değerlendirildi.

Toplamda 5 hasta da (%19,2) avasküler nekroz görüldü. Bu 5 hastanın 2' si delberte göre tip 2, 3 tanesi delbert tip 3 kırıktı. İlk 6 saat içinde ameliyat edilen 10 hastada avasküler nekroz görülmedi. 6. Saatten sonra opere edilen 11 hastadan 5'inde (%31,25) avasküler nekroz gözlendi. İki grup arasında istatiksel olarak anlamlı fark saptandı (p=0,049). Avasküler nekroz görülen 5 hastanın 3'ü kız, 2'si erkek idi. Ratlife göre kadın hastaların 7'sinde iyi-orta sonuç, 2'sinde kötü sonuç saptandı. Erkek hastaların tamamında iyi-orta sonuç görülürken kötü sonuç saptanmadı. Klinik ve radyolojik sonuçlar Ratliff kriterlerine göre değerlendirildi ve sonuçların kadınlarda erkeklere göre daha kötü olduğu görüldü. Cinsiyetler arasında istatistiksel olarak anlamlı bir fark vardı (p=0.029).

Sonuç: Pediatrik yaş grubunda femur boyun kırıkları nadir görülen yaralanmalar olsa da yüksek komplikasyon riski sebebiyle önem taşır. En önemli komplikasyon avasküler nekrozdur. Sonuçlar erkeklerde kadınlara göre daha iyidir. Mümkün olan en kısa sürede anatomik redüksiyonu amaçlayan cerrahi tedavinin sonuçları tatmin edicidir.

Anahtar kelimeler: Femur boyun kırığı, Çocuk, Avasküler nekroz, Delbert sınıflaması

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*Corresponding Author: Duran TOPAK, Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Orthopaedic and Tra-umatology, Kahramanmaras, Turkey. +903443003331, drdtopak@gmail.com

ORCİD: 0000-0002-1442-3392

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Introduction

In the pediatric age group, a femoral neck fracture is a rare injury that accounts for <1% of all pediatric fractures [1, 2]. This is due to the strong periosteum and bone structure in children [3]. The anatomy and supply of the proximal femur is different in the pediatric and adult age groups. The primary blood supply of the proximal femur is from the medial circumflex artery. Damage to the superior retinacular branch of the medial circumflex artery is often considered to be the cause of the development of avascular necrosis [4].

Pediatric femoral neck fractures often occur after high-energy trauma. It is categorized by Delbert classification, which both guides the treatment and helps determine the risk of developing avascular necrosis [5]. The Ratliff criteria are used in the classification of functional and radiological results after surgery and they are the most commonly used assessment system in the pediatric age group [6]. Femoral neck fractures have a high rate of complications despite proper diagnosis and treatment [5]. Complications at a rate of 20%–50% have been reported in long-term follow-ups [3, 7, 8]. The most important complication is the development of avascular necrosis and other significant ones include coxa vara, physeal arrest, limb-length inequality and nonunion. Damage to the trochanteric apophysis and abductor musculature during trauma disrupts the angulation and growth of the femoral neck, causing coxa valga, whereas excessive growth causes coxa vara [5]. The main factors affecting the treatment results include age, gender, fracture type and time until surgery.

The aim of this study was to evaluate the etiology of femoral neck fractures and functional and radiological results after surgical treatments, in the pediatric age group.

Materials and Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethical Committee of Kahramanmaras Sutcu Imam University (Approval Date: 2020-08-26, Decided Number: 08, Session: 2020/16). In this study, thirty-five patients aged between 3 to 16 years who underwent surgery after a diagnosis of femoral neck fracture in the clinic between 2012 and 2019, were retrospectively analyzed. Patients with open proximal epiphysis without additional injury were included in the study. Patients younger than age 3 and with metabolic diseases and pathological fractures, were excluded from the study. Nine additional patients who did not meet the criteria were excluded from the study. Demographic findings, trauma mechanism, accompanying injuries, and complications of the patients were recorded from our registry system.

Prior to surgery, fractures of the patients were classified according to the Delbert classification: type 1 fractures are transepiphyseal fractures, type 2 fractures are transcervical fractures, type 3 fractures are cervicotrochanteric fractures and type 4 fractures are intertrochanteric fractures. The Ratliff criteria were used for the classification of postoperative functional and radiological results. Based on this criteria, the patients were evaluated according to postoperative pain, joint range of motion, activity status and radiological features of the proximal femur. Avascular necrosis was diagnosed by magnetic resonance imaging [Figure 1].

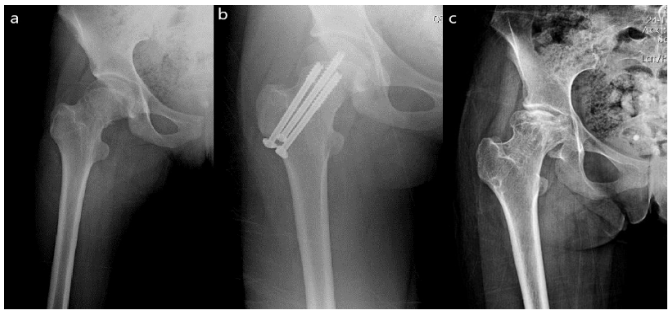

Figure 1. Preoperative (a), early postoperative (b) and postoperative first-year (c) radiography of the patient who developed avascular necrosis.

The patients underwent surgery as soon as possible after being evaluated in the emergency department. All patients were placed in the supine position under general anesthesia and closed reduction was achieved with the help of fluoroscopy. After reduction was achieved, percutaneous fixation was performed with two cannulated screws (2 cannulated screws 4 mm or 5 mm, depending on the patient's bone structure and age). The entry points of the screws were fixed proximal to the trochanter minor, parallel to each other in the coronal plane, with one screw

anterior and one screw posterior in the sagittal plane. All patients were operated by the same surgical team. Open reduction was performed in one patient in whom closed reduction could not be performed. Fixation was performed using the same brand of cannulated screws (4 mm or 5 mm) in all patients [Figure 2]. Antibiotic prophylaxis was given to all patients. Splint was not applied to any patient after the surgery. All patients were told not to bear any weight while walking for 6 weeks, and they were allowed to bear partial weight after 6 weeks as well as full weight after 12 weeks.

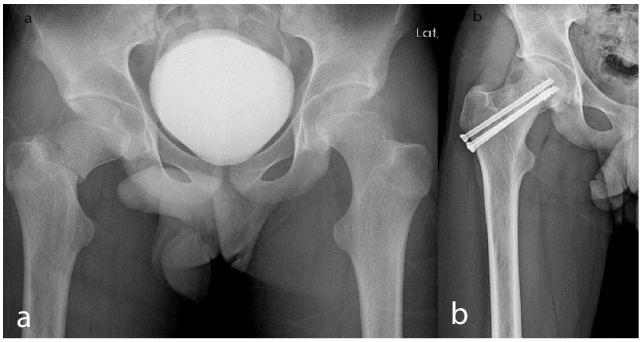

Figure 2: Preoperative (a) and postoperative second-year (b) radiography of a male patient with a femoral neck fracture

Results

The mean age of the participants in the study was 11.11±4.42 (3–16) year, and the mean follow-up time was 29.34±17.34 (12–60) months. The right side was operated in 15 patients (57.7%) and the left side in 11 patients (42.3%). Of the patients, 65.4% (17 patients) were male and 34.6% (9 patients) were female. Before surgery, 14 patients (53.8%) had type 2 and 12 patients (46.2%) had type 3 fractures according to the Delbert classification. The most common etiology was fractures due to motor vehicle accidents, with a rate of 38.5%. Moreover, 5 patients had fractures due to falling indoors, 3 patients due to falling from a height, 2 patients as a result of sports injuries, 2 patients due to falling from a bicycle, and 4 patients due to falling from stairs. Among the patients, 38.5% (10 patients) underwent surgery within first 6 hours, 42.3% (11 patients) between 6 and 24 hours and 19.2% (5 patients) after 24 hours (Table 1).

According to the Ratliff criteria, 18 patients (69.2%) achieved good results, 6 patients (23.1%) achieved moderate results and 2 patients (7.7%) achieved poor results after surgery. Additionally, there was no statistically significant difference between fracture types (p=0.241). Comparison of clinical and radiological results of cases according to constant variables is shown in Table 2. Avascular necrosis occurred in 5 patients (19.2%) in total and of these 5 patients, 2 had type 2 fractures and 3 had type 3 fractures, according to the Delbert classification (Table 1).

Table 1. Demographics of the patients and fractures

Age (year)		11,11±4,42 (3-16)
Follow-up (months)		29,34±17,34 (12-60)
Gender	Female	9 (34.6%)
	Male	17 (65.4%)
Fracture classification (Delbert)	Type 2	14 (53.8%)
	Type 3	12 (46.2%)
Side	Right	15 (%57.7)
	Left	11 (%42.3)
Operation time (hour)	0-6	10 (38.5%)
	6-24	11 (42.3%)
	>24	5 (19.2%)
Ratliff's Classification of Avascular Necrosis	Type 2	2 (7.7%)
	Type 3	3 (11.5%)
	Female	3 (11.5 %)
	Male	2 (7.7 %)

There was no statistically significant difference between fracture types in terms of development of avascular necrosis (p=0.150). Comparison of the incidence of AVN according to constant variables is shown in Table 3. Of the 5 patients with avascular necrosis, 3 were female and 2 were male [Figure 2]. There was no statistically significant difference between genders in terms of the development of avascular necrosis (p=0.184). Seven of the female patients achieved good to moderate results and 2 achieved poor results, again according to the Ratliff criteria. All male patients achieved good to moderate results and no bad results. According to the applied criteria, the results were worse in female and there was a statistically significant difference between the genders (p=0.029). Avascular necrosis did not occur in 10 patients who underwent surgery within first 6 hours, although it was observed in 5 (31.25%) out of 16 patients who underwent surgery after 6 hours [Table 2]. This result was statistically significant (p=0.049). Ten patients who underwent surgery in the first 6 hours achieved good to moderate results, whereas 14 patients achieved good to moderate results and

2 patients achieved poor results, according to the Ratliff criteria, among patients who underwent surgery after 6 hours. It was found that the time of surgery did not have any statistically significant effect on functional and radiological results [Table 2].

Table 2. Comparison of radiological and functional results of cases according to constant variables

		Good	Fair	Poor	P value
Gender	Female	7	0	2	0.029
	Male	11	6	0	
Fracture type (Delbert classification)	Type 2	9	3	2	0.241
	Type 3	9	3	0	
Operation time	<6 hour	9	1	0	0.177
		9	5	2	

Table 3. Comparison of AVN incidence of cases according to constant variables

		AVN -	AVN +	P value
Gender	Female	6	3	0.184
	Male	15	2	
Fracture type (Delbert classification)	Type 2	12	2	0.150
	Type 3	9	3	
Operation time	<6 hour	10	0	0.049
		11	5	

Discussion

Femoral neck fractures are relatively rare injuries in the pediatric age group compared to the adult age group [9]. Due to the growth pattern of the pediatric femur and the high risk of complications, treatment should be planned and provided as soon as possible. Femoral neck fracture occurs as a result of high-energy trauma in this age group due, resulting from the characteristics of the bone structure. Falling from a height and motor vehicle accidents have been reported as the most common etiological factors in the literature [6, 10]. Apart from this, femoral neck fracture can also occur due to slipped proximal femoral epiphysis, bone cysts and stress fractures [11, 12]. In the present study, motor vehicle accidents constituted the most common etiological factor, with a rate of 38.5%.

The Delbert classification is the most commonly used system for the classification of pediatric femoral neck fractures [6]. It is an anatomical classification that provides useful information about the development of avascular necrosis. In a meta-analysis study, it has been reported that fracture type and patient age at the time of injury, are the most important factors in the development of avascular necrosis [13]. The increase in the risk of avascular necrosis in elderly patients is due to a decrease in the revascularization ability of the femoral head with age [4]. In studies about femoral neck fractures in the literature, type 2 fractures have been reported most frequently, followed by type 3 fractures. Type 2 and type 4 fractures account for 65% to 85% of all pediatric femoral neck fractures [12, 14]. Some studies in the literature report that the development of avascular necrosis is most common in type 1 fractures and least common in type 4 fractures [15]. In the present study, 14 patient (53.8%) had type 2 fractures and 12 patients (46.2%) had type 3 fractures, which was consistent with the literature.

Some studies in the literature have reported that open reduction and internal fixation cause fewer complications than closed reduction and internal fixation [1, 14]. Additionally, there are studies reporting that open reduction and internal fixation reduces the incidence of avascular necrosis [16]. They attributed this to the reduction of intracapsular pressure by capsulotomy and the chance for better evaluation of fracture reduction in open reduction. Since we believed that open reduction would not be appropriate in the pediatric age group, we primarily preferred closed reduction and internal fixation in our patients. We performed open reduction and internal fixation in only one patient, on whom we could not perform closed reduction.

Implant selection depends on the child's weight, age, bone structure and the surgeon's preference. There are studies in the literature suggesting that the use of fewer implants reduces the rate of complications, since it causes less damage to the vascular structure [17]. In our patients, we performed fixation with two cannulated screws (4 mm or 5 mm), depending on the bone structure and age of the patient.

Complication rates of pediatric femoral neck fractures are high. There are studies in the literature reporting complications at rates of 10%

to 60% [3, 15, 18]. Avascular necrosis is the most common complication after femoral neck fracture in children [10]. In addition, other potential complications include infection, nonunion or delayed union, coxa vara and leg length inequality. Postoperative infection occurs in <1% of cases [19]. No postoperative infections occurred in our patients, although the risk of avascular necrosis depends on a number of factors such as age, time until surgery and fracture type. The most important risk factor is the degree of vascular damage that occurs during trauma [20-22]. In our study, the rate of avascular necrosis was 19.2%. Coxa vara, leg length inequality and nonunion, which have been reported in the literature, were not observed in the present study.

Another factor that increases the risk of avascular necrosis is the time between injury and surgery. In the literature, there are studies reporting that the risk of avascular necrosis increases as the time until surgery increases [23, 24]. Bombaci reported the rate of avascular necrosis to be 54.6% in patients who underwent surgery after 24 hours [25]. In another study in which patients underwent surgery within the first 12 hours, this rate was reported to be 25%. Moreover, there are studies reporting that the time until surgery does not increase the risk of avascular necrosis [26]. In our study, avascular necrosis did not occur in patients who underwent surgery within first 6 hours, whereas the incidence of avascular necrosis was 31.25% in patients who underwent surgery after 6 hours. This result was also statistically significant (p=0.049). According to the Ratliff criteria, the rate of good results was 90% in patients underwent surgery within first 6 hours, whereas the rate of good results was 56.25% in patients who underwent surgery after 6 hours. According to our study, avascular necrosis rates were lower in patients who underwent surgery early and the results were better according to the Ratliff criteria.

In our study, 18 patients (69.2%) achieved good results, 6 patients (23.1%) achieved moderate results and 2 patients (7.7%) achieved poor results, according to the Ratliff criteria. Our results were consistent with the data in the literature [6, 24, 27]. The avascular necrosis rate was 11.76% in males and 33.33% in females. Although this result was not statistically significant, the avascular necrosis rate in females was higher in our study. The clinical and radiological results were evaluated according to the Ratliff criteria, and the results were found to be worse in females than in males and there was therefore a statistically significant difference between the genders.

The limitations of the study are that it is a retrospective study and the low number of cases.

Conclusion

Although femoral neck fractures are rare injuries in the pediatric age group, they are significant due to the high risk of complications, the most important of which is avascular necrosis. The patient's age, gender, fracture pattern and time until surgery are the main factors that determine the results of the treatment. Results are better in males than in females. The results of surgical treatment aiming at anatomical reduction and internal fixation within the shortest possible time are promising.

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ORCID and Author's contributions: **DT (0000-0002-1442-3392):** Concept and design, materials and practices, data collection and processing, analysis and interpretation, literature search, writing, supervision and critical review. **MAÖ (0000-0002-8281-3528):** Concept and design, data collection, analysis, literature search, writing, critical review. **FD (0000-0003-3848-1017):** Concept, materials, processing, analysis, literature search, critical review. **ÖB (0000-0002-7949-5434):** Design, practices, interpretation,

critical review.

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The effect of self glucose monitoring on glycemic control of patients with diabetes mellitus fasting during Ramadan

Ramazan Orucu Tutan Diabetes Mellitus Hastalarında Kendi Kendine Glikoz Takibinin Glisemik Kontrole Etkisi

Nazire Aladağ[1], Seydahmet Akın[1]*, Yasemin Özgür[1], Banu Böyük[1], Özcan Keskin[1]

1.Internal Medicine Clinic, Kartal Dr Lutfi Kırdar City Hospital /Institution, İstanbul, Turkey

ABSTRACT

Background: It is known that a significant number of patients with diabetes insist on fasting in the month of Ramadan, despite the advice of their physicians and reliable authorities. In order to provide the best possible care and support to these patients, the International Diabetes Federation (IDF) and the Diabetes and Ramadan (DAR) International Alliance created practical guidelines. The aim of this study was to investigate the effect of consulting a physician and glucose self-monitoring on diabetes management during Ramadan in patients with fasting diabetes.

Methods: With this retrospective observational study, patients over 18 years of age who were diagnosed with diabetes, who came to the diabetes outpatient clinic for control after Ramadan and who made their follow-up from our outpatient clinic before Ramadan, were included. Participants intending to fast (previous or not) were asked about previous fasting experiences, questions about whether they consulted the doctor before Ramadan, and for those who fasted, how they spent this Ramadan. The biochemical data of fasting patients before and after Ramadan were analyzed.

Results: A total of 394 patients with diabetes participated in the questionnaire and 98 of them (24.9 %) who were fasted were included in the study. The mean age of the fasting patients with diabetes was 59.7 ± 12.3 years and39.2 %were female. It was detected that 86.7% of the fasting people were fasting for more than 15 days. Fasting rates were higher in males than females (32.4% to 20.8%). It was found that 25.9% of patients with type 2 DM and 10.3% of patients with type 1 DM were fasting. It was determined that 62.8% of the patients intending to fast were consulted to the physician about this subject, 55.3% of them were determined risk by physician and 70% of them followed up with self monitoring blood glucose (SMBG).It was determined that 23.4% (23/98) of fasting patients had a reduction in the number or dose of diabetes medications used; 5.1% (5/98) experienced a complication that would disrupt fasting; 16.3% gained weight (2.8 ± 2.4 kg) and 23.5% lost weight (2.7 ± 1.9 kg). A significant increase in HbA1c and a significant decrease in UACR were detected. It has been determined that A1c control of those who follow with SMBG is better protected than those who do not.

Conclusion: In our study, it was seen that a quarter of patients with diabetes fasted. The most valuable result of this study is that the diabetic patients have achieved a more successful diabetes control by providing auto control mechanisms with SMBG, regardless of whether or not they have received medical advice by physician consultation during the Ramadan period.

Keywords: Ramadan fasting, diabetes mellitus, glycemic control

ÖZ

Amaç: Diyabetli hastaların önemli bir bölümünün, doktorlarının ve güvenilir otoritelerin tavsiyelerine rağmen Ramazan ayında oruç tutmakta ısrar ettiği bilinmektedir. Bu hastalara mümkün olan en iyi bakım ve desteği sağlamak için, International Alliance tarafından Uluslararası Diyabet Federasyonu (IDF) ve Diyabet ve Ramazan (DAR) Uluslararası İttifakı pratik kılavuzları oluşturulmuştur. Bu çalışmanın amacı, Ramazan orucu tutan diyabetik hastalarda hekime danışma ve kendi kendine glukoz izleminin diyabet yönetimine etkisini araştırmaktı.

Metod: Bu retrospektif gözlemsel çalışmaya diyabet tanısı konan, diyabet polikliniğine Ramazandan sonra kontrole gelen ve Ramazan öncesi poliklinik takibini yapan 18 yaş üstü hastalar dahil edildi. Oruç tutmuş olan hastalara (öncesinde tutmuş olan ve olmayan) daha önceki oruç deneyimleri, Ramazandan önce doktora danışıp danışmadıkları, oruç tutanların bu Ramazanı nasıl geçirdikleri sorulup anket doldurulmuştur. Oruç tutan hastaların Ramazan öncesi ve sonrası biyokimyasal verileri analiz edildi.

Bulgular: Çalışmaya 98'i (%24.9) oruç tutan 394 diyabetli hasta katıldı. Oruç tutan diyabetli hastaların yaş ortalaması 59.7 ± 12.3 yıl olup, % 39.2'si kadındı. Oruç tutanların %86.7'sinin 15 günden fazla oruç tuttuğu tespit edildi. Erkeklerde açlık oranları kadınlara göre daha yüksekti (%32.4 - %20.8) Tip 2 DM'li hastaların %25.9'unun, tip 1 DM'li hastaların %10.3'ünün oruç tuttuğu saptandı. Oruç tutmak isteyen hastaların %62.8'inin bu konuda hekime başvurduğu, %55.3'ünün hekim tarafından risk tespit edildiği ve %70'inin kendi kendine kan glukoz izlemi(SMBG) ile takip edildiği belirlendi. Oruç tutan hastaların %23.4'ünün (23/98) kullanılan diyabet ilaçlarının sayısında veya dozunda azalma olduğu; %5.1 (5/98) orucu bozacak bir komplikasyon yaşandığı; %16,3'ünün kilo aldığı (2.8 ± 2.4 kg) ve %23.5'i kilo verdiği (2.7 ± 1.9 kg) gözlendi. HbA1c'de belirgin bir artış ve idrar albumin atılımında anlamlı bir düşüş saptandı. Kişisel kan şekerini takip edenlerin A1c kontrolünün takip etmeyenlere göre daha iyi korunduğu belirlendi.

Sonuç: Çalışmamızda diyabetli hastaların dörtte birinin oruç tuttuğu görüldü. Bu çalışmanın en değerli sonucu, diyabet hastalarının, Ramazan ayında doktor konsültasyonu alıp almadıklarına bakılmaksızın, SMBG ile kendi kendine oto kontrol mekanizması sağlayarak daha başarılı bir diyabet kontrolü elde etmiş olmasıdır.

Anahtar kelimeler: Ramazan orucu, diabetes mellitus, glisemik kontrol

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*Corresponding Author: Seydahmet AKIN, Asist Professor, Kartal Dr Lutfi Kırdar City Hospital İstanbul, Turkey, +905057136820, seydahmeta@hotmail.com

ORCİD: 0000-0002-2557-3812

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Introduction

Ramadan is the month in which fasting Muslims undergo a radical change in the type and frequency of their meals, their sleep and wake patterns, as well as their hunger and satiety period. It is a month that Muslims have avoided eating, drinking, smoking and using oral / subcutaneous medications from the time of dawn until sunset. It is important to mention that the Quran has made a clear exemption for the sick, elderly, travelers, children, expectant and breastfeeding mothers, not to fast during Ramadan [1]. However, a significant number of patients with diabetes insist on fasting in Ramadan despite the advice of their doctors and the permission of the trusted authorities. The Epidemiology of Diabetes and Ramadan (EPIDIAR) study from 2001, which included 13 countries, found that 42.8% and 78.7% of patients with Type 1 or Type 2 diabetes mellitus respectively, fasted for at least 15 days during Ramadan [2]. More recently, the CREED study reported that 94.2% of T2DM patients fasted for at least 15 days and 63.6% fasted every day [3]. Existing recommendations on the management of people with diabetes who fast during Ramadan are mostly based on expert opinion rather than evidence gained from clinical studies [4].

As a result of the complexity of diabetes management during Ramadan, understanding the fasting pathophysiology with diabetes is important for the treating physician. Fasting patients with diabetes have an increased risk of hypoglycemia, hyperglycemia, dehydration and ketoacidosis [5]. Therefore, training on physical activity, food consumption and drug adjustment is essential to protect against complications. The International Diabetes Federation (IDF) and the Diabetes and Ramadan (DAR) International Alliance joined resources to provide the best possible care and support to diabetes patients fasting in Ramadan, and created IDF-DAR practical guides for patients and healthcare professionals [4].

As it is timed in accordance with the lunar calendar of Ramadan and since the latter is 11 days shorter than the solar calendar, the onset of the fasting period falls back eleven days every year, corresponding to the same day approximately every 33 years. Thus, the Ramadan period covers all seasons of the year, including long and hot summer. The fasting period starts before dawn and ends with twilight, therefore Turkey is experiencing the longest period in June when the maximum period of daytime fasting period occurs. With this study, we aimed to investigate the effect of consulting a physician prior to Ramadan and glucose self-monitoring during Ramadan on diabetes management in fasting patients in 2019, which in that particular year fell from May to June.

Material and Method

Our study observed the tenets of the Helsinki Declaration and it was planned to be performed at the Kartal Dr Lutfi Kırdar Training and Research Hospital. It has been reported that Muslims who have fasted during Ramadan avoid consulting doctors and therefore, prospective studies are difficult to carry out [6]. As a result, our research was designed before Ramadan and was planned to be done retrospectively, in order to avoid any intervention in the natural course of the patient participation process. The patients over the age of 18, diagnosed with diabetes and consenting to participate in the survey study, who came to the diabetes out-patient clinic after Ramadan and were also followed before Ramadan, were included in the study.

Socio-demographic data of all participating patients such as age, height, weight, body mass index (BMI), diabetes type and disease duration, were recorded. In the second stage, a questionnaire was filled including questions about how the patients spent Ramadan: previous fasting experiences, whether a doctor was consulted before Ramadan, whether the risk scale was determined, whether the diabetic medication doses were reduced, whether the medical condition caused a breakdown in the fasting, whether personal glucose monitoring was performed and the reasons of those who did not, and finally, whether they experienced weight change during Ramadan. In the third stage, fasting plasma glucose (FPG), glycolyzed hemoglobin A1c(A1c), creatinine, cholesterol, triglycerides, HDL cholesterol, VLDL cholesterol, LDL cholesterol levels, estimated glomerular filtration rate (eGFR) by CKD-EPI and urinary albumin creatinine ratio (UACR), were recorded from the hospital information system in patients

who were fasting during Ramadan.

Descriptive statistics of socio-demographic characteristics were made according to fasting status. Data is presented as means (standard deviations) for continuous variables and number (percentages) for categorical variables. Comparison of two continuous independent variables with normal distribution used the Student t test, while comparison of two independent variables without normal distribution used the Mann Whitney U test. Patient characteristics among each group were compared by the Chi-squared test or the Fisher exact test for categorical variables. Whether biochemical changes were significant before and after Ramadan was analyzed with Paired Sample T test. Whether these changes were affected by consultation with the physician prior to Ramadan or control by personal blood glucose measurement was analyzed by One-Way Analysis of Covariance (ANCOVA). P <0.05 was considered significant. All statistical analyses were performed using SPSS version 22 software (SPSS Inc. Chicago, IL, USA).

Results

In the survey conducted after 2019 Ramadan, a total of 394 (64.7% women; mean age 60.5 ± 12.5 years) diabetes patients were included. 7.4% of the patients were type 1 DM (n: 29); 1 of them was MODY. The mean diabetes duration of all patients was 16.6 ± 7.3 years. It was observed that 24.9% (n: 98) of the patients had fasted. It was determined that 86.7% of the fasting people were fasting for more than 15 days. In patients with fasting diabetes, 77.6% of OAD was metformin, 54.1% Dipeptidyl peptidase-4 (DPP-4) inhibitors, 23.5% of sodium glucose cotransporter 2 (SGLT2) inhibitors, 12.2% of Sulfonylureas (SU), and 42.9% of basal insulin, 11.2% of short-acting, 8.2% were using mix insulin

The socio-demographic characteristics of the fasting and non-fasting patients are presented in Table 1. The means height of fasting people were determined longer. Fasting rate was higher in males than females (males were 32.4% to 20.8%). Excluding one fasting Mody patient, type 2 DM patients fasted more than patients with type 1 DM (25.9% and 10.3% respectively)

It was determined that 58.7% of patients (174/296) who did not fast this year, were fasting in previous years. It was found that 157 of these patients did not prefer to fast due to health reasons that particular year. It was determined that 62.8% of patients(142/226) who intended to fast consulted with a physician about this issue and 55.3% of them (125/226) were identified at risk by their physician.

Table 1: Socio-demographic characteristics of the study population by fasting status

		Non-fasting (n:296)		Fasting (n:98)		p sig
Age, years		61	(12.8)	59.9	(11.5)	0.142
Duration of DM, years		16.9	(7.0)	15.3	(8.1)	0.11
Height, cm		160.4	(8.3	162.6	(9.1)	0.035
Weight, kg		79.4	(15.5)	81.7	(13.4)	0.189
Body mass index (kg/m^2)		30.9	(6.1)	31	(5.0)	0.867
Gender, n (%)	male	94	(67.6%)	45	(32.4%)	0.011
	female	202	(79.2%)	53	(20.8%)	
DM	type 1	26	(89.7%)	3	(10.3%)	0.03
	type 2	269	(74.1%)	94	(25.9%)	

Data was given as mean (SD) and number (%)

That year, 23.4% of fasting patients (23/98) were found to have reduced the number or dose of their diabetes medications. It was determined that 5.1% of the patients who fasted that year (2 of them from hypoglycemia, 2 of them from hyperglycemia and 1 of them from hypertension) had a condition that would require disruption of fasting, and only 1 of them required hospitalization. 70% of fasting patients followed up with personal blood glucose measurement: the rest did not feel it was necessary. It was determined that they did not follow up blood glucose measurements by reasoning that it would disrupt the fasting. It was determined that 40% of fasting patients experienced weight change during the month of Ramadan. Some of them (n: 16) gained weight (2.8 ± 2.4 kg); while some of them (n: 23) lost weight (2.7 ± 1.9 kg).

Laboratory changes of fasting patients before and after Ramadan are shown in the Table 2. Accordingly, although there is a statistically insignificant decrease in fasting plasma glucose(FPG) levels, a significant increase in HbA1c is noteworthy. A significant decrease in Urine Albumin-to-Creatinine Ratio(UACR) was

also noted.

Table 2: Change of laboratory findings of patients before and after Ramadan

	Before Ramadan		After Ramadan		p sig
Fasting Plasma Glucose, mg/dl	152,9	(44.0)	144.6	(51.4)	0,072
Hb Alc (%)	7.8	(1.2)	7.9	(1.3)	0.031
Creatinine, mg/dl	0.84	(0.25)	0.85	(0.27)	0.246
eGFR (mL/min/1.73m^2)	87.3	(21.2)	87.5	(21.1)	0.904
Total cholesterol (mg/dl)	192.9	(39.2)	196.1	(37.7)	0.382
Triglycerides (mg/dl)	154.8	(86.7)	170.7	(99.6)	0.064
HDL cholesterol (mg/dl)	48.7	(11.5)	48.8	(11.2)	0.957
VLDL cholesterol (mg/dl)	31.4	(17.1)	34.3	(20.1)	0.082
LDL cholesterol (mg/dl)	111.1	(35.1)	110.9	(26.5)	0.375
Urinary albuminin creatinine ratio, µg/mg	47.1	(129.5)	37.9	(87.7)	0.032

Data was given as mean (SD)

Prior to the start of Ramadan, 52% of fasting patients consulted their physician and 48% of them did not. The differences in FPG, A1c and LDL cholesterol levels before and after Ramadan were determined similarly. The changes of all laboratory findings before and after Ramadan was statistically insignificant.

Regarding self-monitoring blood glucose (SMBG), it was determined that 70% of the fasting patients (58/83) followed their fingertip blood sugar during Ramadan and 30% of them (25/83) did not. As seen in Table 3, Figure 1, and Figure 2, it was found that A1c control of those who followed personal blood glucose levels better than non-followers (p: 0.023). While FPG averages of those who did not monitor blood sugar increased after Ramadan, those who did on the other hand were observed to decrease, although not in a statistically significant way (p: 0.105). Similarly, although the UACR averages were not statistically significant, it was found that patients who followed blood glucose decreased more than those who did not.

Discussion

Our study did not show any effect of consulting a doctor prior to Ramadan on glucose regulation, but the positive effects of SMBG have been proven. The most valuable determination offered by this study is that the individual's instant status determination by glucose monitoring plays a role in the control of diabetes, probably through the auto control mechanism, more so than the doctor's consultation.

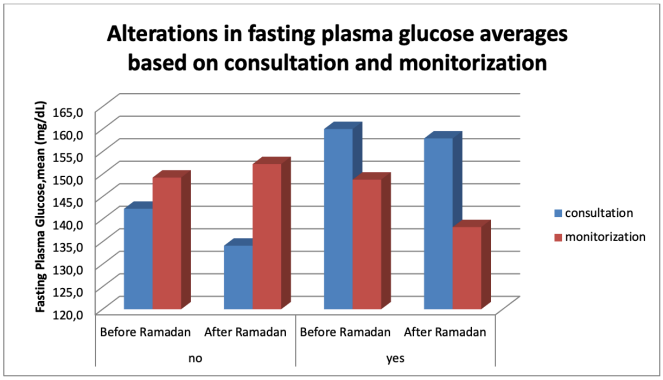

Figure 1. Alterations in fasting plasma glucose averages based on consultation and monitorization

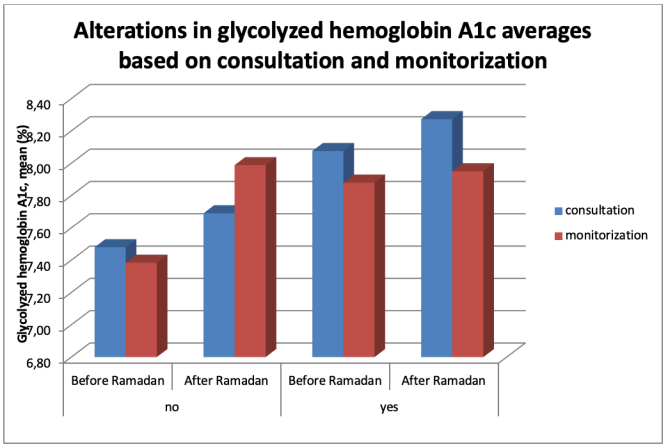

Figure 2. Alterations in glycolyzed hemoglobin A1c averages based on consultation and monitorization

In addition, our study showed that FPG in patients with fasting diabetes decreased after Ramadan compared to before Ramadan, but A1c levels increased significantly. This situation, explained by the high level of post prandial glucose levels, suggests that diabetic patients have also been influenced by the attractiveness of Turkish cuisine with a high content of carbohydrates reflected the iftar feast. This result was somewhat different from literature. There were studies so far showing that fasting in Ramadan has healing effects [7-12], has no negative effects [13-18], that the frequency of severe hypoglycemia was increasing [2], that glycemic control is impaired [19]. For example, in a study conducted by Bauguera et al. on a very limited number of diabetic patients (n: 38), it was found that those with impaired glycemic control before the Ramadan were further impaired during

Table 3: Changes in laboratory findings according to the status of blood glucose monitoring by the patient

	not-followed (n:25)				followed (n:58)				p sig
	Before Ramadan		After Ramadan		Before Ramadan		After Ramadan		
FPG (mg/dL)	149.2	(52.2)	152.2	(62.2)	148.8	(33.6)	138.2	(34.5)	0.105
HBA1C (%)	7.38	(1.2)	7.99	(1.8)	7.88	(1.1)	7.95	(1.1)	0.023
Creatinine (mg/dl)	0.83	(.3)	0.87	(.3)	0.80	(0.2)	0.80	(0.3)	0.310
eGFR (mL/min/1.73m^2)	87.1	(23.4)	84.6	(23.4)	94.2	(45.7)	87.8	(20.1)	0.765
Total cholesterol (mg/dl)	197.8	(32.0)	193.8	(35.4)	191.1	(36.9)	198.4	(38.5)	0.247
Triglycerides (mg/dl)	153.0	(99.1)	175.0	(81.7)	156.1	(87.0)	169.0	(112.9)	0.702
HDL cholesterol (mg/dl)	51.6	(12.9)	50.5	(12.2)	47.9	(10.2)	48.6	(10.2)	0.948
VLDL cholesterol (mg/dl)	32.0	(18.8)	35.0	(16.4)	31.2	(17.4)	34.1	(22.8)	0.874
LDL cholesterol (mg/dl)	113.3	(28.2)	105.0	(29.8)	109.7	(33.3)	111.9	(27.3)	0.51
UACR (µg/mg)	40.9	(64.0)	39.6	(81.0)	56.4	(162.3)	43.9	(101.0)	0.167

Data was given as mean (SD). 15 cases had missing values. FPG: Fasting Plasma Glucose, eGFR: Estimated glomerular filtration rate , UACR: Urinary albumin creatinine ratio,

Ramadan, but returned to their baseline levels afterwards. In the same study, it was found that patients who were good before their metabolic control were not adversely affected during Ramadan [20].

In addition, microalbuminuria levels were found to decrease after Ramadan (mean 47.1 mg/g before Ramadan and 37.9 mg/g after Ramadan). There are conflicting publications on this subject in the literature. For example, in a study by Şahin et al, similar to ours, microalbuminuria levels decreased significantly after the Ramadan compared to the levels before Ramadan [13], but in the study performed by Kamar et al., it was found that UACR increased after the Ramadan [21]. In a study by Esmaeilzadeh, it was shown that intermittent fasting improved endothelial and non-endothelial dependent vasodilations. In this study, microvascular endothelial functions of skin vessels were measured with laser doppler imager, and endothelial-dependent and independent dilatations were evaluated with acetylcholine and sodium nitroprusside iontophoresis [22]. Based on the fact that the endothelial tissue is a whole, it may be thought that the change in the skin vessels will parallel the change in the renal vessels and therefore the excretion of the microalbumin during the Ramadan, with the improvement of the endothelial functions.

In our study, it was observed that approximately 30% of diabetes patients fasted. Esen from Turkey reported that 41.6% of 190 diabetic patients fast and 65% of them did not consult during Ramadan in his study [23].These results were not compatible with the results of our study.

Since healthy individuals were not included in the study or there was no study to represent our society in the literature, it is impossible to make any evaluation about the rate of fasting in diabetics, compared to the non-diabetic population. In the EPIDIAR study, which included Algeria, Bangladesh, Egypt, India, Indonesia, Jordan, Lebanon, Malaysia, Morocco, Pakistan, Saudi Arabia, Tunisia and Turkey, it was determined that 42.8% of patients with type 1 diabetes and 78.7% of type 2 diabetes fasted, 78.7% of them fasted for at least 15 days [2]. In our study, fasting rates for at least 15 days were 10% in patients with type 1 DM and 25% in patients with type 2 DM.

Our study did not show any effect of consulting a doctor prior to Ramadan on glucose regulation, but the positive effects of personal blood sugar monitoring have been proven. Compared to before Ramadan, the mean of FPG of those who performed SMBG decreased afterwards, while those who did not increased. It was determined that means of hemoglobin A1c levels increased in both groups, but those who did not perform SMBG increased significantly more than those who did.

Microalbuminuria levels of the patients who consulted the physician before Ramadan decreased and the eGFR increased; in addition, it was observed that those who were not consulted had an increase in microalbuminuria and a decrease in eGFR. This may probably be attributed to the better preservation of renal hemodynamics with the arrangements made in oral antidiabetic

medicines with the advice of the physician. It was also shown in another study that education given to patients with diabetes before Ramadan minimizes the risk of hypoglycemic events, and potential weight gain can be prevented [24]. In our study, it is notable that five patients who had a negative experience throughout Ramadan were in the not-consulted group.

We observed that there was a minimal deterioration in lipid parameters after Ramadan compared to before Ramadan, but it was not statistically significant. Studies conducted so far show that there is some deterioration in lipid levels in Ramadan [9][10][22], included data on some improvement [11][19] or reported no change [20]. It was thought that the reason for the negative effect was the unhealthy diet and sedentary lifestyle, incompatible with the spirit of Ramadan.

Limitations

Our study had limitations. Instead of hemoglobin A1c, fructosamine, which shows glucose regulation in a shorter period of time, could be used as used in some of the studies related to Ramadan fasting. Since glycolyzed hemoglobin A1c was used in our routine practice, this could not be included. These results may not be compatible with the normal population. Patients followed in the diabetes center may be more attentive to their treatment.

Conclusion: As a result, we strongly recommend SMBG, which has been found to play very effective role in glucose control during Ramadan, to all fasting diabetic patients.

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Ethics Committee Approval: In this study, national and international ethical rules are observed.

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RESEARCH ARTICLE

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Effectiveness of Clinical Parameters and Laboratory Values in Predicting The Clinical Course of Sarcoidosis

Sarkoidoz'un Klinik Gidişatini Öngörmede Klinik Parametreler ve Laboratuvar Değerlerinin Değerlendirilmesi - Tek Merkez Deneyimi

Deniz Çelik[1*], Sertan Bulut[2]

1.Alanya Alaaddin Keykubat University, Medical Faculty, Department of Pulmonology, Alanya, Antalya, Turkey

2.University of Health Sciences Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Department of Pulmonology, Ankara, Turkey

ABSTRACT

Aim: The natural course of sarcoidosis is heterogeneous. There is no clear marker that can predict the course of this disease and its characteristics over months/ years. We aimed to analyze our patients' data to identify a prediction parameter at admission.

Methods: The patients with sarcoidosis and followed-up between 2015-01-01 and 2020-12-31 comprised the study group. The patients were staged by a Scadding staging system. Improvement or deterioration in at least two of the clinical-laboratory-radiological parameters indicates regression, stable disease, progression, or relapse of sarcoidosis.

Results: The study group comprised four cases (6.9%) defined as stage 0; fifteen cases (25.86%) as stage 1; 39 cases (67.24%) were defined as stage 2. The mean age at diagnosis was 40.84±13.56 in stage 0 + stage 1 group, while it was 48.05±13.36 in the stage 2 group (p=0.06). 74.1% of the cases were women. The female/male ratio was found at 2.86. 57 out of 58 cases had a pathological diagnosis (EBUS TBNA). While PFTs values and DLCO were significantly lower at advanced stages but the same statistical significance was not identified between these values and the clinical course of the disease. As a result of the multivariate analysis, it was observed that only the presence of chest pain at admission affected the progression of the disease in the follow-up period.

Conclusion: Sarcoidosis is a multi-systemic disease and there is no clear finding for predicting the poor prognosis of the disease. We conclude that chest pain symptom at admission is valuable predictive finding and can be used as a clue for the progression at follow-up.

Keywords: Sarcoidosis, prognosis, progression, EBUS TBNA

ÖZ

Amaç: Sarkoidozun doğal seyri heterojendir. Bu hastalığın seyrini ve özelliklerini aylar/yıllar içinde öngörebilecek net bir belirteç yoktur. Başvuru sırasında bir tahmin parametresi belirlemek için hastalarımızın verilerini analiz etmeyi amaçladık.

Yöntem: 01.01.2015-31.12.2020 tarihleri arasında sarkoidoz tanısıyla takipte olan hastalar çalışma grubumuzu oluşturdu. Hastaların başvuru grafileri dahil Scadding evreleme sistemi ile evrelendi. Klinik-laboratuvar-radyolojik parametrelerin en az ikisinde düzelme veya bozulma sarkoidozda gerileme, stabil hastalık, progresyon veya relaps olduğunu gösterir.

Bulgular: Çalışmaya dahil ettiğimiz 4 vaka (%6,9) evre 0, 15 olgu (%25,86) evre 1; 39 olgu (%67,24) evre 2 olarak tanımlandı. Tanı yaşı ortalaması evre 0 + evre 1 grubunda 40,84±13,56, evre 2 grubunda 48,05±13,36 idi (p=0,06). Vakaların %74,1'i kadındı. Kadın/erkek oranı 2,86 olarak bulundu. 58 olgunun 57'sinde patolojik tanı vardı. Kullanılan yöntem Endobronşial ultrasonografi eşliğinde transbronşial iğne aspirasyonu idi (EBUS TBNA). Solunum fonksiyon testleri (SFT) ve karbonmonoksit difüzyon testi (DLCO) ileri evrelerdeki hastalarda anlamlı olarak daha düşük iken, bu testlerin sonuçları ile hastalığın klinik seyri arasında aynı istatistiksel anlamlılık saptanmadı. Çok değişkenli analiz sonucunda takip döneminde sadece başvuru anında göğüs ağrısının varlığının hastalığın progresyonunu etkilediği görüldü.

Sonuç: Sarkoidoz multisistemik bir hastalıktır ve hastalığın kötü prognozunu öngörmek için net bir bulgu yoktur. Başvurudaki göğüs ağrısı semptomunun değerli bir prediktif bulgu olduğunu ve takipteki progresyon için bir ipucu olarak kullanılabileceğini düşünüyoruz.

Anahtar Kelimeler: Sarkoidoz, prognoz, progresyon, EBUS TBNA

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*Corresponding Author: Deniz ÇELİK, Alanya Alaaddin Keykubat University, Medical Faculty, Department of Pulmonology, Alanya, Antalya, Turkey, +905524036040, deniz.celik@alanya.edu.tr

ORCİD: 0000-0003-4634-205X

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INTRODUCTION

Sarcoidosis is a multi-systemic granulomatous disease of unknown etiology, with initial findings and disease course that are highly heterogeneous [1]. Sarcoidosis mostly affects people between the ages of 20-60 and is observed 3 to 4 times more often in white people compared to black people. The most common symptoms of patients with sarcoidosis are cough and dyspnea followed by nonspecific symptoms such as chest pain, myalgia, joint pain and fever [2]. There is no current specific diagnostic test for sarcoidosis, but the combination of three criteria is sufficient for a sarcoidosis diagnosis: the compatible clinical radiological appearance, evidence of noncaseating granulomas, and the exclusion of other similar presentations or histopathological diseases [3]. Sarcoidosis is staged as five stages based on the Posterior Anterior Chest Radiography (CXR) [4].

The natural course of sarcoidosis is heterogeneous and spontaneous, while regression of the disease is observed in approximately one out of every three patients. But some patients have a progressive or fibrotic disease. There is no clear marker that can predict the course of this disease and its characteristics over months and years [1, 3].

We aimed to retrospectively analyze whether there is a possibility for identifying an estimation parameter between the admission and the course of the disease.

MATERIALS and METHODS

Study population

The study center is a tertiary chest diseases hospital. The patients in the study were in routine follow-up with the diagnosis of sarcoidosis between January 1st 2015 and December 31st 2020. The patients were staged by the Scadding staging based on CXR. All patients had thorax high-resolution computerized tomography (HRCT), blood count, biochemistry examinations, pulmonary function tests (PFTs) results, diffusing capacity of the lungs for carbon monoxide (DLCO), serum angiotensin-converting enzyme (ACE), urine tests, tuberculin skin tests (TST), and 24-hour urine calcium values at the time of diagnosis. An induration diameter over 5 mm in the TST test was considered positive. The study was approved by the Health Science University Keçiören Training and Research Hospital, Clinical Studies Ethic Committee (2012-KAEK-15/2395).

Diagnosis of Sarcoidosis

There is currently no specific test for the diagnosis of sarcoidosis. The diagnosis relies on the combination of three criteria, namely a compatible clinical-radiological presentation, pathological evidence of noncaseating granuloma, and exclusion of other disorders with similar presentation or histopathology [3].

Staging

The sarcoidosis cases were staged with the Scadding staging system based on CXR.

Stage 0: Normal chest radiography,

Stage 1: Bilateral hilar lymphadenopathy (BHL) and normal lung parenchyma,

Stage 2: BHL + Pulmonary interstitial infiltrates,

Stage 3: Pulmonary infiltrates without lymphadenopaty

Stage 4: Pulmonary fibrosis [4].

Clinical descriptions of response in the follow-up period

Clinical response: The total recovery or partial regression in the findings of pulmonary or extrapulmonary involvements, with or without treatment.

Laboratory response: Improvements in serum ACE level, 24-hour urine calcium level, biochemical values and decreases in sedimentation levels, improvements in forced vital capacity (FVC) (10%), and/or diffusing capacity of the lungs for carbon monoxide (DLCO) (15%).

Radiological response: Total or partial regression of findings in CXR or HRCT [5].

Complete remission: Total clinical and radiological response with or without treatment.

Relapse: After initial remission or in the tapering phase of treatment with prednisone or equivalent at doses < 20 mg/day [6].

Sarcoidosis activity

The activity of sarcoidosis is traditionally measured in two ways: using tests indicative of active granulomatous inflammation and assessing clinical deterioration in organ function [7]. Improvements in at least two of the clinical-laboratory-radiological response parameters indicate total or partial regression of sarcoidosis. Relapse, or progression in at least two of the clinical-laboratory-radiological parameters called the progression of the disease activity. The stability of the findings was defined as the stability of sarcoidosis.

Statistical analyzes

For the distribution of all continuous variables, the Kolmogorov-Smirnov or Shapiro-Wilk test, coefficient of variation value, skewness-kurtosis values, histogram, and detrended plot graphs were examined. If the data was nominal, it was shown as n /%, whereas if it was ordinal or numerical and not normally distributed, it was shown as median/ min-max; in numerical and normally distributed data, it was shown as mean±SD. Categorical data of the patient group was evaluated with the chi-square or Fisher test accordingly. As for numerical data, if there were two groups, it was evaluated with the Student T-test or the Mann Whitney U test; if there were more than two groups, it was evaluated with ANOVA or Kruskal Wallis. The Cochrane test was used for connected data with more than two groups. The SPSS version 22 was used as the statistics program and values with a p-value smaller than 0.05 were considered statistically significant.

RESULTS

All patients staging was performed by the Scadding staging system. Four cases (6.9%) were defined as stage 0; fifteen cases (25.86%) as stage 1; 39 cases (67.24%) were defined as stage 2. The mean age at diagnosis was 40.84±13.56 in stage 0 + stage 1 group, while it was 48.05±13.36 in the stage 2 group, and there was no difference between the two groups (p=0.06). 74.1% of our patients were women. The female/male ratio was found to be 2.86. Some 57 out of 58 cases had a pathological diagnosis. The main diagnostic method was endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (n=42, 72.4%). There was no statistical difference between smoking (p=0.183) and the initial Scadding stage (p=0.823) between the clinical courses. The demographic data and characteristics are shown in Table 1.

In the stage 2 sarcoidosis patients' follow-up, we observed a markedly clinical heterogeneity in terms of both regression and progression (p<0.0001). It was observed that patients who received treatment for sarcoidosis were at an advanced stage. There was no relationship between the stages and extrathoracic involvements or calcium metabolic disorder (Table 1).

The most common symptoms at admission were cough (n=44, 75.9%) followed by dyspnea (n=34, 58.6%). When the course of the disease and the symptoms at admission were examined, the presence of sputum and chest pain were statistically significant and they were associated with poor clinical prognosis (p=0.001 and p=0.002, respectively) (Table 2).

The patients' follow-up period was a minimum of 2 years and the average follow-up period was 5.24±3.97 (2-16) years. We found that a longer duration of the follow-up period was associated with an increased rate of progression (p=0.007). The difference between the stage at the diagnosis and the retrospective Scadding staging system was evaluated with the Cochran analyze and there was no significant difference (p=0.083).

In the follow-up period, 3 patients, whose initial stage was stage 2, were progressed to stage 4 (n=1) and stage 3 (n=2). We found that receiving sarcoidosis treatments were associated with having progressive diseases (p<0.0001), but the patients who received treatment were in advanced stages (p=0.006) (Table 2).

While PFTs values (Forced vital capacity (FVC), Forced Expiratory Volume in the first second (FEV1), FEV1/FVC ratio) and DLCO were significantly lower in advanced-stage patients, the same statistical significance was not identified between these values and the clinical course of the sarcoidosis (Table 2).

Forty-two patients' Transthoracic Doppler

Table 1. Demographic, clinical and diagnostic characteristics.

		Study population (n=58)	Stage 0 + Stage 1 (n=19, 32.8%)	Stage 2 (n=39, 67.2%)	p-value
Age at the diagnosis (mean±SD)		45.68±13.74	40.84±13.56	48.05±13.36	p=0.06
Gender	Male	15 (25.9%)	7 (36.8%)	8 (20.5%)	p=0.183
	Female	43(74.1%)	12 (63.2%)	31 (79.5 %)	
Smoking	Never smoked	34 (58.6%)	11 (57.9%)	23 (59%)	p=0.133
	Quitted	18 (31%)	4 (21.1%)	14 (35.9%)	
	Still smoking	6 (10.3 %)	4 (21.1%)	2 (5.1%)	
Time until diagnosis (month)		4.22±3.42	3.1±1.88	4.76±3.86	p=0.119
Duration of follow-up (year)		5.24±3.97	3.78±2.12	5.94±4.46	p=0.153
Diagnostic methods	Transbronchial parenchymal biopsy by FOB	5 (8.6%)	1 (5.3%)	4 (10.3%)	p=0.950
	EBUS TBNA for mediastinal LAP	42 (72.4%)	14 (73.7%)	28 (71.8%)	
	Mediastinoscopy	2 (3.4%)	1 (5.3%)	1 (2.6%)	
	Extrathoracic LAP biopsy	3 (5.2%)	1 (5.3%)	2 (5.1%)	
	Skin biopsy	2 (3.4%)	1 (5.3%)	1 (2.6%)	
	Clinical and radiological diagnosis	1 (1.7%)	0 (0%)	1 (2.6 %)	
	Transthoracic biopsy with Thorax CT	1 (1.7%)	0 (0%)	1 (2.6%)	
	Bronchial mucosa biopsy by FOB	2 (3.4%)	1 (5.3%)	1 (2.6%)	
Treatment	Received	24 (41.4%)	3 (15.8%)	21 (53.8%)	p=0.006
	Not received	34 (58.6%)	16 (84.2%)	18 (46.2%)	
Clinical Follow-up	Stable	32 (55.2%)	18 (94.7%)	14 (35.9%)	p<0.0001
	Regression	16 (27.6%)	1 (5.3%)	15 (38.5%)	
	Progression	10 (17.2%)	0 (0%)	10 (25.6%)	
Skin Involvement	Present	12 (20.7%)	6 (31.6%)	6 (15.4%)	p=0.153
	Not present	46 (79.3%)	16 (68.4%)	33 (84.6%)	
Ocular Involvement	Present	4 (6.9%)	0 (0%)	4 (10.3%)	p=0.148
	Not present	54 (93.1%)	19 (100%)	35 (89.7%)	
Calcium metabolism disorder	Present	7 (12.1%)	1 (5.3%)	6 (15.4%)	p=0.267
	Not present	51 (87.9%)	18 (94.7%)	33 (84.6%)	
FVC (Forced Vital Capacity)		2.84±0.76	3.29±0.84	2.62±0.62	p=0.001
FEV_1		2.40±0.73	2.88±0.77	2.17±0.59	p<0.0001
FEV_1/FVC		80.24±8.23	83.68±6.27	78.56±8.62	p=0.025
Pulmonary Function Tests results	Obstruction	10 (17.2%)	2 (10.5%)	8 (20.5%)	p=0.171
	Restriction	8 (13.8%)	2 (10.5%)	6 (15.4%)	
	Mixt	5 (8.6%)	0 (0%)	5 (12.8%)	
	Normal	35 (60.3%)	15 (79%)	20 (51.3%)	
DLCO (%)		91.50±18.69	106.73±11.13	84.07±17.10	p<0.0001
Transthoracic Doppler Echocardiography	Present	42 (72.41%)	11 (26.2%)	31 (73.8%)	p=0.033 p=0.885
	EF:	60.95±4.07	63.18±2.85	60.16±4.18	
	sPAP:	21.83±7.51	21.54±7.18	21.93±7.74	

FOB: Fiberoptic Bronchoscopy

EBUS TBNA: Endobronchial Ultrasonography Transbronchial Needle Aspiration

LAP: Lymphadenopathy

Thorax CT: Thorax Computerized Tomography

FEV1: Forced Expiratory Volume in the first second

DLCO: Diffusing capacity of the lungs for carbon monoxide

EF: Left ventricular systolic ejection fraction

sPAP: Systolic pulmonary artery pressure

Table 2. Symptoms at admission, treatment status and PFTs.

			Study population (n=58)	Stable Disease (n=32, 55.2%)	Regressed Disease (n=16, 27.6%)	Progressed disease (n=10, 17.2%)	p-value
Symptoms at admission	Shortness of breath	Present	34(58.6%)	16 (47.1%)	9 (26.5%)	9 (26.5%)	p=0.079
		Not present	24 (41.4%)	16 (66.7	7 (29.2%)	1 (4.2%)	
	Cough	Present	44 (75.9%)	23 (71.9%)	12 (75%)	9 (90%)	p=0.503
		Not present	14 (24.1%)	9 (28.1%)	4 (25%)	1 (10%)	
	Sputum	Present	8 (13.8%)	1 (3.1%)	2 (12.5%)	5 (50%)	p=0.001
		Not present	50 (86.2%)	31 (96.9%)	14 (87.5%)	5 (50%)	
	Chest Pain	Present	9 (15.5%)	4 (12.5%)	0 (0%)	5 (50%)	p=0.002
		Not present	49 (84.5%)	28 (87.5%)	16 (100%)	5 (50%)	
	Fever	Present	7 (12.1%)	4 (12.5%)	0 (0%)	3 (30%)	p=0.073
		Not present	51 (87.9%)	28 (87.5%)	16 (100%)	7 (70%)	
	Myalgia	Present	13 (22.4%)	7 (21.9%)	2 (12.5%)	4 (40%)	p=0.261
		Not present	45 (77.6%)	25 (78.1%)	14 (87.5%)	6 (60%)	
	Arthralgia	Present	9 (15.5%)	5 (15.6%)	1 (6.3%)	3 (30%)	p=0.266
		Not present	49 (84.5%)	27 (84.4%)	15 (93.8%)	7 (70%)	
Clinical follow-up status	Receiving treatment		24	4	11	9	p<0.0001
	Not receiving treatment		34	28	5	1	
PFTs findings	FVC		2.84±0.76	2.92±0.82	2.72±0.72	2.77±0.64	p=0.674
	FEV1		2.40±0.73	2.52±0.79	2.22±0.61	2.30±0.72	p=0.381
	FEV1/FVC		80.24±8.23	81.75±8.26	78.56±9.06	78.1±6.27	p=0.304
PFT results	Obstruction		10 (17.2%)	5 (15.6%)	4 (25%)	1 (10%)	p=0.307
	Restriction		8 (13.8%)	4 (12.5%)	4 (25%)	0 (0%)	
	Mixt		5 (8.6%)	3 (9.4%)	0 (0%)	2 (20%)	
	Normal		35 (60.3%)	20 (62.5%)	8 (50%)	7 (70%)	
DLCO (%)			91.50±18.69	97.34±16.78	90.5±16.14	74.4±18.96	p=0.002

FVC: Forced Vital Capacity

FEV1: Forced Expiratory Volume in the first second

PFTs: Pulmonary Function Tests

DLCO: Diffusing capacity of the lungs for carbon monoxide

Echocardiography (TTE) records were available at the time of diagnosis (n=42, 72.41%). The left ventricular systolic ejection fraction (EF) value was 60.95±4.07 and the systolic pulmonary artery pressure (sPAP) was 21.83±7.51. A negative and significant correlation was found between advanced stage and systolic EF (p=0.033) (Table 1). In follow-up, there was no relationship between the course of the disease and the initial EF and sPAP values (p=0.780 and p=0.833, respectively).

We compared laboratory test results with the clinical course. We found that presentation with high serum ACE and high 24-hour urine calcium values (hypercalciuria) were associated with progressed disease (p=0.013 and p=0.046; respectively) (Table 3).

As a result of the multivariate analysis, only the presence of chest pain at admission affected the progression of sarcoidosis in the follow-up period (odds ratio [OR]=50.94, 95% confidence interval [CI] 1.593–1628.685, p=0.026).

DISCUSSION

Sarcoidosis is more common in women aged between 20 and 60 [2, 8, 9, 10, 11]. In this study, the mean age at diagnosis was 45.68±13.74 years, and most of the patients were female (74.1%). ACCESS study female/male ratio was 1.77 [2], while in this study it was higher (2.86).

In a study by Voortmann et al., it was found that virtually all patients had organ-related or non-specific/non-organ-related symptoms. In this study, very nearly all patients had at least one symptom [12]. The most common presenting symptoms in previous studies were cough and dyspnea [5, 9, 13]. The most common symptoms

Table 3. Laboratory results at the diagnosis.

		Study population (n=58)	Stable disease (n=32, 55.2%)	Regressed disease (n=16, 27.6%)	Progressed disease (n=10, 17.2%)	p-value
White Blood Cell**		6.61 (3.08-17.46)	6.73 (4.47-17.46)	6.60 (4-13.9)	6.45 (3.08-9.6)	p=0.799
Neutrophil count **		4.11 (2.11-15.14)	4.33 (2.41-15.14)	3.79 (2.14-8.77)	3.9 (2.11-6.1)	p=0.686
Lymphocyte count **		1.56 (0.48-4.31)	1.64 (0.50-4.31)	2.73 (1.46-7.75)	1.45 (0.48-2.88)	p=0.708
Hemoglobin*		13.67±1.66	13.94±1.73	13.64±1.53	12.85±1.54	p=0.198
Anemia		5 (%8.6)	2 (%6.3)	1 (%6.3)	2 (% 20)	p=0.485
Normal		45 (%77.6)	24 (%75)	14 (%87.4)	7 (%70)	
Polycythemia		8 (%13.8)	6 (%18.7)	1 (%6.3)	1 (%10)	
Thrombocyte **		269.5 (104-700)	290.5 (172-486)	267 (159-421)	278 (104-700)	p=0.906
Blood Urea Nitrogen**		11.9 (6-27)	11.5 (6-27)	13.7 (6-17)	11.35 (8-24.9)	p=0.964
Creatinine*		0.80±0.13	0.82±0.12	0.74±0.07	0.82±0.18	p=0.083
Uric acid*		5.28±1.36	5.40±1.40	5.18±1.31	5.06±1.40	p=0.737
Albumin**		41.5 (32.9-51)	42.05 (32.9-50.9)	40.7 (35.4-46.7)	42.3 (33-51)	p=0.731
Alanine aminotransferase**		19.5 (10-70)	21.5 (12-70)	18.5 (10-48)	17.5 (10-30)	p=0.344
Aspartate aminotransferase*		22.06±6.64	22.03±6.67	22.75±6.27	21.1±7.62	p=0.831
Alkaline phosphatase*		79.31±24.05	78.43±24.34	77.37±20.27	85.2±29.85	p=0.696
Calcium (serum)**		9.5 (7.47-12.5)	9.5 (7.47-10.6)	9.45 (9-10.38)	9.40 (9-12.5)	p=0.928
C Reactive Protein**		6 (0.27-96)	5.8 (0.81-82.4)	5.6 (0.27-96)	6.85 (1.2-23)	p=0.620
Sedimentation **		22.5 (5-84)	20 (5-73)	25.5 (5-84)	23.5 (9-61)	p=0.327
Serum-angiotensin converting enzyme**		77 (18-165)	62.5 (21-165)	84 (64-161)	95 (18-136)	p=0.013
24-hour urine calcium *		167.3±108.2	145.62±65.77	164.1±125.8	241.9±158.05	p=0.046
Tuberculin Skin Test (mm) ***	Positive	4 (6.9%)	3 (9.4%)	0 (0%)	1 (10%)	p=0.440
	Negative	54 (93.1%)	29 (90.6%)	16 (100%)	9 (90%)	

* Analyzed with ANOVA and shown with mean±SD

** Analyzed by Kruskal-Wallis and shown with median (min-max)

*** Analyzed with Chi-square and represented as n (%)

in this study were cough and dyspnea too. While there was an expectation of spontaneous remission and good prognosis in cases with erythema nodosum, BHL, polyarthralgia and fever at the time of diagnosis [14], we did not find any clear information on which presenting symptoms were associated with good clinical course, remission and progression in the literature. Belhomme et al. examined the relationship between dyspnea and relapse in their studies, but they found no significant relationship [15]. Nath et al. found that only the presence of fatigue was associated with relapse [16]. In this study, we found that patients who had sputum and chest pain at the time of presenting progressed more normally in their subsequent follow-up. After multivariate analysis, we found that the initial presence of chest pain was associated with progression (odds ratio [OR]=50.94, 95% confidence interval [CI] 1.593–1628.685, p=0.026).

It is a recognized fact that patients with sarcoidosis smoke less than the general population [10]. In our study, 34 (58.6%) of our patients had never smoked and this is consistent with the literature. While smoking was not found to be associated with the stage of sarcoidosis in one study [17], it was found in another study that ex-smokers or current smokers were diagnosed at a later stage [18]. In our findings, there was no significant relationship between smoking and both the initial stage (p=0.183), and the subsequent clinical course (p=0.823).

Wirnsberger et al. found the initial symptom duration until the diagnosis of sarcoidosis was between 0 and 3 months for 25% of cases and 3 to 6 months for 17.6% of cases in their study [19]. We found a shorter initial symptom duration of 4.22±3.42 months until the diagnosis. We also examined the relationship between the duration of the initial symptoms and both the

stage of sarcoidosis and the clinical course of the disease in the follow-up. There was no significant relationship between the duration of the initial symptoms and the stage or the clinical course.

EBUS TBNA is significantly superior to the transbronchial lung biopsy as a pathological diagnosis method in pulmonary sarcoidosis [20]. While the most commonly used invasive method for the diagnosis of sarcoidosis was transbronchial biopsy with FOB, endobronchial biopsy, and conventional TBNA in previous studies [5, 16], Abakay et al. reported that they used the mediastinoscopy for diagnosis in their study [21]. The most frequently used invasive method in this study was EBUS TBNA (n=42, 72.4%).

The skin is the most common extrathoracic involvement in many studies [5, 6, 13,19]. Skin involvement [Lupus pernio (n=1) and Erythema Nodosum (n=11), Total (n=12, 20.7%)] was the most common extrathoracic involvement in our study as well.

The rate of patients who needed treatment was similar to the literature (n=24, 41.4%) [5]. In some studies, it was inferred that corticosteroid therapy is a predisposing cause of disease relapse [22,23]. In their study, Rodrigues et al. stated that patients who needed treatment at the diagnosis period and whose symptom durations were long, may be associated with relapse [6]. We found a relationship between treatment needs and progressive disease with relapses. In addition, we found that the patients with a high initial stage at the time of diagnosis had more treatment needs (p=0.006). In addition, we found that these patients were more progressed during the follow-up (p<0.0001), therefore we assume that these patients may be phenotypically inclined to the sarcoidosis that requires treatment at the diagnosis period, as stated in the study of Rodrigues, et al. [6].

The spirometric data in this study is similar to those in previous studies [6]. PFTs and DLCO test values are lower in patients with advanced stages of sarcoidosis [5]. Similar to these studies, we found that the initial PFTs and diffusion values were lower in the stage 2 group with lung involvement according to Scadding staging (for FVC, FEV1, FEV1/FVC, DLCO, respectively; p=0.001, p<0.0001, p=0.025, p<0.0001). Niksarlioglu et al. analyzed relapse and related factors, and found that patients with low DLCO values had more relapses [11]. We analyzed the initial PFTs and DLCO values and the course of the disease in the follow-up, only the patients with low initial DLCO values were progressed in the follow-up (p=0.002).

When the results of transthoracic echocardiography were examined in the literature, there was a positive relationship between low EF, high sPAP values and poor clinical prognosis [24]. In our study, we found that the initial EF value was lower in stage 2 cases (p=0.033). In clinical follow-up, we could not find a relationship between the course of the disease and the initial EF and sPAP values. Abnormal calcium metabolism was associated with acute disease and with relapse [6,25]. Similarly, Niksarlioglu et al. observed relapses more frequently in patients with hypercalciuria [11]. As a result of our study, we found that patients with hypercalciuria progressed more in clinical follow-up (p=0.046). In previous studies, a significant relationship was observed between high serum ACE level and relapse and clinical course [15]. However, Nath et al. did not find any relationship between serum ACE levels and relapse in their study [16]. We found that the patients with initial high serum ACE values progressed more frequently in follow-up (p=0.013).

Limitations

The foremost limitation of this study is its single-center and retrospective design. Additionally, it study did not comprise stage 3 and 4 patients. Although the follow-up period of our patients was comparatively long, it was heterogeneous (between 2 years and 16 years).

CONCLUSION

Sarcoidosis is a multi-systemic disease and defined as stable, regressed and progressed, according to the clinical course. There is no clear finding for predicting the poor prognosis of the disease in follow-up. We conclude that presentation with sputum and chest pain symptoms, advanced initial stage, low diffusion test values, high serum ACE and high 24-hour urine calcium values, may be associated with poor clinical prognosis. After

multivariate analyses, we conclude that chest pain symptoms at admission consist in valuable predictive findings and can be used as a clue for the progression at follow-up.

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Assessment of Tp-E Interval, Tp-E/Qt, Tp-E/Qtc Ratios in Thalassemia Major Patients

Talasemi Major Hastalarında Tp-E Intervali ve Tp-E/Qt, Tp-E/Qtc Oranlarının Değerlendirilmesi

Zehra Erkal[1]*

1.Antalya Training and Research Hospital Cardiology Department, Antalya, Turkey

ABSTRACT

Aim: Thalassemia major (TM) is a genetic hemoglobinopathy that causes chronic hemolytic anemia. Repeated blood transfusions are needed for treatment. Iron accumulation is used to predict the risk of ventricular arrhythmia. We designed this study to compare the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio, which are the novel and reliable predictors that show ventricular repolarization, between the TM patients and healthy control group.

Method: We included 97 TM patients who presented to our outpatient clinic for routine cardiac check-up from March 2019 to June 2020 and 90 healthy volunteers. In addition to the demographic and echocardiographic findings, patients' electrocardiograms (ECG) were retrospectively analyzed. Their serum ferritin, C reactive protein (CRP) levels and neutrophil to lymphocyte ratios were recorded and compared.

Result: The Tp-e interval was 80 msn (60.0-80.0) in the group of thalassemia major patients whereas it was 60 msn (50.0-70.0) (p<0.001) in the control group. The Tp-e/QT ratio was 0.200 (0.160-0.225) in the TM group while it was 0.175(0.150-0.210) in the control group (p=0.014). The Tp-e/QTc ratio was 0.180 (0.130-0.190) in the TM group while it was 0.150 (0.130-0.180) in the control group (p=0.035). No correlation was found between their serum ferritin levels and ECG parameters.

Conclusion: Prolonged Tp-e interval, Tp-e/QT ve Tp-e/QTc ratios on the ECG in TM patients are associated with impaired ventricular repolarization due to excessive cardiac iron deposition and ventricular arrhythmias. These simple but reliable parameters can be used to predict the risk of arrhythmia.

Key Words:Arrhythmia, electrocardiography, thalassemia

ÖZ

Amaç: Talasemi majör (TM), kronik hemolitik anemiye sebep olan genetik bir hemoglobinopatidir. Tedavisinde tekrarlayan kan transfüzyonları gereklidir. Transfüzyonlara bağlı miyokardda biriken demir, kardiyomiyopati ve ventriküler aritmi gelişimine neden olur. Özellikle hayatı tehdit edebilecek ventriküler aritmi gelişme riskini öngörmek klinik açıdan çok önemlidir ve bu amaçla birçok parametre kullanılmıştır. Biz ventriküler repolarizasyonu gösteren, yeni ve güvenilir prediktörler olan Tp-e intervali, Tp-e/QT ve Tp-e/QTc oranını TM hastalarında ve sağlıklı kontrol grubunda karşılaştırmak amacıyla bu çalışmayı planladık.

Yöntem: Çalışmamıza Mart 2019- Haziran 2020 yılları arasında polikliniğimize rutin kardiyak kontrol amacıyla gelen 97 TM hastası ve 90 tane sağlıklı gönüllü kontrol grubu dahil edildi. Demografik ve ekokardiyografik bulgularına ek olarak retrospektif olarak hastaların elektrokardiyografileri (EKG) incelendi. Serum ferritin, C reaktif protein (CRP)düzeyleri ve nötrofil lenfosit oranları kaydedildi ve karşılaştırıldı. Yine hastalar aldıkları şelasyon tedavilerine göre sınıflandırılarak EKG parametreleri arasındaki fark açısından karşılaştırıldı.

Bulgular: Talasemi majör hasta grubunda Tp-e intervali 80 msn (60.0-80.0) iken kontrol grubunda 60 msn (50.0-70.0) (p<0.001), Tp-e/QT oranı TM grubunda 0.200 (0.160-0.225) iken kontrol grubunda 0.175(0.150-0.210) (p:0.014), Tp-e/QTc oranı TM grubunda 0.180 (0.130-0.190) iken kontrol grubunda 0.150 (0.130-0.180) (p:0.035) tespit edildi. Serum ferritin düzeyi ile EKG parametreleri arasında korelasyon izlenmedi.

Sonuç: Talasemi majör hastalarında EKG de artmış Tp-e intervali, Tp-e/QT ve Tp-e/QTc oranları, artmış kardiyak demir depolanmasına bağlı oluşan ventriküler repolarizasyon bozuklukları ve ventriküler aritmiler ile ilişkilidir. Aritmi gelişme riskini öngörmede bu basit ama güvenilir parametreler kullanılabilir.

Anahtar Kelimeler: Aritmi, elektrokardiyografi, talasemi

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*Corresponding Author: Zehra ERKAL, Antalya Training and Research Hospital, Department of Cardiology, Antalya, Turkey, +905056715846, zehraerkalkard@hotmail.com

ORCİD: 0000-0003-3950-2502

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INTRODUCTION

Thalassemia Major (TM) is a genetic hemoglobin disorder characterized by the reduction or complete impairment of the synthesis of the globin chains, required for the hemoglobin structure. It leads to chronic hemolytic anemia due to ineffective erythropoiesis [1]. Long term and repeated blood transfusions are given for its treatment; as a result of these, iron accumulates in the heart, liver and endocrine glands due to hemolysis and increased intestinal absorption [2].

In addition to iron deposition, a combination of inflammatory and immunogenetic factors lead to the impairment of cardiac functions. Cardiomyopathy that develops due to iron overload and arrhythmia are the most important causes of mortality in these patients. Arrhythmias and sudden cardiac death can even be observed before the symptoms and signs of heart failure present [3].

Several parameters that can be used to predict the risk of ventricular arrhythmias, which may cause sudden cardiac death, can be checked through the use of surface electrocardiography (ECG). These parameters are called ventricular repolarization markers (VPM). They include QT interval, corrected QT interval (QTc), QT dispersion (QTd), Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio (4). Out of these parameters, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios are the novel and reliable markers that best demonstrate ventricular repolarization [4].

The purpose of our study was to compare the new reliable predictors that show ventricular polarization between the TM patients and healthy control group, in contrast with the conventional parameter on the ECG, and to assess if they are significant to predict the risk of arrhythmia in TM patients.

MATERIALS and METHOD

We included 97 patients who presented to the cardiology department from March 2019 to June 2020 for routine cardiac examination and follow-up, who did not have any cardiac complaints and were followed up after they had been diagnosed with thalassemia major. The thalassemia major patients in our study received 2 to 6 blood transfusions per month, and cardiology consultation was requested twice a year. Ninety healthy volunteers were included in the control group. This was a retrospective study, thus the hospital records of the patients and control group were analyzed retrospectively. Their personal (age, sex) and medical histories (the chelation therapies they received), laboratory parameters (hemogram, neutrophil to lymphocyte ratio, liver enzymes, kidney function tests, serum ferritin and C reactive protein level), electrocardiographic (heart rate, QT, QTc, Tp-e interval, Tpe/QT ratio, Tp-e/QTc ratio) and echocardiographic findings, were all obtained from their records, recorded and compared with those of the healthy control group.

Approval was obtained from the local ethic committee. Patients who had a severe valvular disease, coronary artery disease and heart failure, atrial fibrillation, malignancies or severe pulmonary diseases, pacemaker, and those that took any medication that might affect the ECG, were excluded from the study.

ELECTROCARDIOGRAPHY

The AECG recorder (Nihon Kohden, Tokyo, Japan) was set at the speed of 50 mm/s paper and 10 mm/mV voltage was used. The maximum and minimum QT and Tp–e intervals were performed by two cardiologists who were blinded to the patient data. QT and Tp–e intervals were measured manually with calipers and magnifying glass to reduce the error rate. Subjects with U waves on their ECGs were excluded from the study. The QT interval was measured from the beginning of the QRS complex to the end of the T wave and corrected for heart rate using the Bazett formulation: $QTc=QT\sqrt{}$ (R–R interval) [5]. Maximum (QTmax) and minimum (QTmin) QT-wave durations were defined as the longest and shortest measurable QT-wave durations, respectively, in any lead. Accordingly, corrected QT dispersion (QTcd) was calculated as the difference between maximal and minimal QTc intervals. Tp–e interval was defined as the interval between the peak and the end of T wave. Measurements of Tp–e interval were performed from precordial leads [6]. The Tp–e/QT and Tp–e/QTc ratios were calculated from these measurements.

ECHOCARDIOGRAPHY

Echocardiographic measurements of the patients were analyzed by an experienced cardiologist in accordance with the American Society of Echocardiography (ASE) guidelines. A Vivid–7 (GE Vingmed, Horten, Norway) device was used for the examination and the left ventricular ejection fraction was calculated by using the modified Simpson's method.

STATISTICAL ANALYSIS

The data obtained from the study was recorded in the SPSS 24.0 (Armonk, NY: IBM Corp.) software. Among the continuous variables, those with normal distribution were presented as mean ± standard deviation, those with normal distribution were presented as median (quartiles), while categorical variables were expressed as numbers and percentages. Conformity of continuous variables with normal distribution was examined by Kolmogorov-Smirnov test. Student-t test was used for normally distributed parameters and Mann-Whitney U test was used for non-normally distributed parameters for comparisons between groups. The Chi-square test was used in the analysis of categorical variables. Correlation analyses for ferritin, CRP (mg/L), N/L ratio were performed using Pearson or spearman tests. P values of <0.05 were considered statistically significant.

RESULTS

The mean age of the patients in the thalassemia major group was 28.0 (24.0-37.0) while it was 32.0 (23.7-39) in the control group, which were similar (p=0.257). The hemoglobin level was 9.2 g/dl (8.6-9.6) in the TM group while it was 14.0g/dl (13.0-15.1) in the control group (p<0.001). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were 27.0 U/L (19.0-44.0) and 41.0 U/L (32.0-72.0), respectively, in the TM group while they were 29.2 U/L (20.9-46.0) and 44.0 U/L (31.0-76.0), respectively, in the control group (p=0.440 and p=0.226, respectively). Serum creatine level was 0.72 mg/dl (0.5-0.9) in the TM group while it was 0.78 mg/dl (0.6-0.9) in the control group (p:0.552). Left ventricular ejection fraction was 65.0 (65.0-65.0) in the TM group and 65.0 (65.0-65.0) in the control group (p=0.660). Intraventricular septum diameter was 10.0 mm (9.0-11.0) in TM group and 11.0 mm (9.0-11.0) in control group (p=0.234). Left ventricular diastolic dysfunction was 36% in TM group and 44.4% in control group (p=0.075). Prevalence of left ventricular hypertrophy was 12.4%in TM group and 22.2% in control group (p=0.083) (Table 1).

Table 1. Comparison of laboratory and echocardiographic findings between thalassemia major group ve control group

Variable	Thalassemia Group (n=97)	Control Group (n=90)	p value
Hemoglobin, g/dL	9.2 (8.6-9.6)	14.0 (13.0-15.1)	<0.001
ALT (U/L)	27.0 (19.0-44.0)	29.2 (20.9-46.0)	0.440
AST (U/L)	41.0 (32.0-72.0)	44.0 (31.0-76.0)	0.226
Creatinine, mg/dL	0.72 (0.5-0.9)	0.78 (0.6-0.9)	0.552
LVEF, %	65. 0 (65.0-65.0)	65.0 (65.0-65.0)	0.660
IVSD (mm)	10.0 (9.0-11.0)	11.0 (9.0-11.0)	0.234
LVDD, % (n)	36 (35)	44.4 (40)	0.075
LVH	12.4 (12)	22.2 (20)	0.083

(which show a normal distribution mean ± SD, not show a normal distribution median (25th and 75th percentile) and percentage for categorical variables), (ALT; Alanine aminotransferase, AST; Aspartate aminotransferase, IVSD ;Intraventricular septum diameter, LVDD ;left ventricular diastolic dysfunction, LVEF; left ventricular ejection fraction)

Table 2 shows the comparison between the ECG parameters of both groups. The heart rate was 83.0 (75.0-88.5) in the TM group while it was 77.5 (70.0-93.2) in the control group. No significant difference was found between two groups (p=0.152). QTc was 420.4+-24.9 ms in the TM group and 395.2+- 30.3 ms (p<0.001) in the control group; QT was 360.0 ms (340.0-380.0) in the TM group and 350.0 ms (320.0-360.0) in the control group (p<0.001). Tp-e interval was 80.0ms (60.0-80.0) in the TM group and 60.0 ms (50.0-70.0) in the control group (p<0.001); Tp-e/QT ratio was 0.200 (0.160-0.225) in the TM group and 0.175 (0.150-0.210) in the control group (p=0.014); Tp-e/QTc ratio was 0.180 (0.130-0.190) in the TM group and 0.150 (0.130-0.180) in the control group (p=0.035).

Figure 1 shows the significant prolongation of Tp-e, QT, QTc intervals in the TM group compared to the control group. Figure 2 demonstrates the significant increase in the Tp-e/ QT and Tp-e/QTc ratios in the TM group compared to the control group.

As shown in Table 3, no significant correlation was found between the electrocardiographic parameters (QTc, QT, Tp-e, Tp-e/QT, Tp-e/QTc) and serum ferritin, C reactive protein (CRP) and neutrophil to lymphocyte ratio (N/L).

Table 2. Comparison of age and electrocardiographic findings between the thalassemia major group and control group

Variable	Thalassemia Group(n=97)	Control Group (n=90)	p value
Age, years	28.0 (24.0-37.0)	32.0 (23.7-39.0)	0.257
Heart Rate, (beat/min)	83.0 (75.0-88.5)	77.5 (70.0-93.2)	0.152
QTc, ms	420.4 ± 24.9	395.2 ± 30.3	<0.001
QT, ms	360.0 (340.0-380.0)	350.0 (320.0-360.0)	<0.001
Tp-e	80.0 (60.0-80.0)	60.0 (50.0-70.0)	<0.001
Tp-e/QT	0.200 (0.160-0.225)	0.175 (0.150-0.210)	0.014
Tp-e/QTc	0.180 (0.130-0.190)	0.150 (0.130-0.180)	0.035

(which show a normal distribution mean ± SD, not show a normal distribution median (25th and 75th. percentile) and percentage for categorical variables), QT; QT interval, QTc; Corrected QT, Tp-e; Tp-e interval,

Table 3. The correlation between TnI, CRP, N/L ratio and ECG parameters (QTc, QT, Tp-e, Tp-e/QT, Tp-e/QTc)

	Ferritin	CRP, mg/L	N/L ratio
QTc, ms			
Correlation coefficient	0.012	-0.023	-0.071
P value	0.909	0.819	0.511
QT, ms			
Correlation coefficient	-0.119	-0.026	-0.063
P value	0.250	0.799	0.562
Tp-e			
Correlation coefficient	0.147	-0.068	0.041
P value	0.152	0.509	0.704
Tp-e/QT			
Correlation coefficient	0.173	-0.021	0.047
P value	0.092	0.838	0.665
Tp-e/QTc			
Correlation coefficient	0.127	-0.039	0.063
P value	0.217	0.707	0.561

CRP: C reactive protein, (N/L: Neutrophil to Lymphocyte ratio)
QT; QT interval, QTc; Corrected QT, Tp-e; Tp-e interval

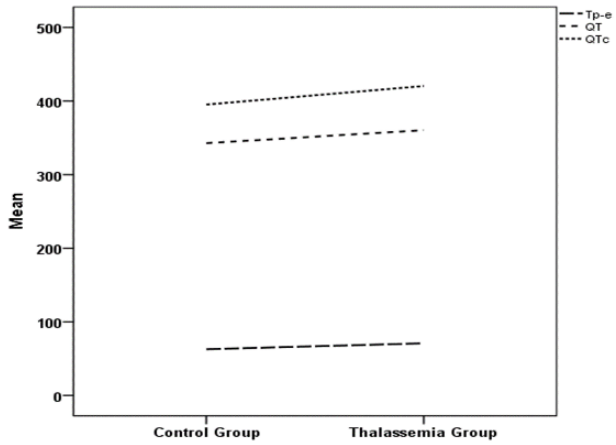

Figure 1. Tp e interval, QT and QTc increased significantly in the thalassemia major patients compared to the control group.

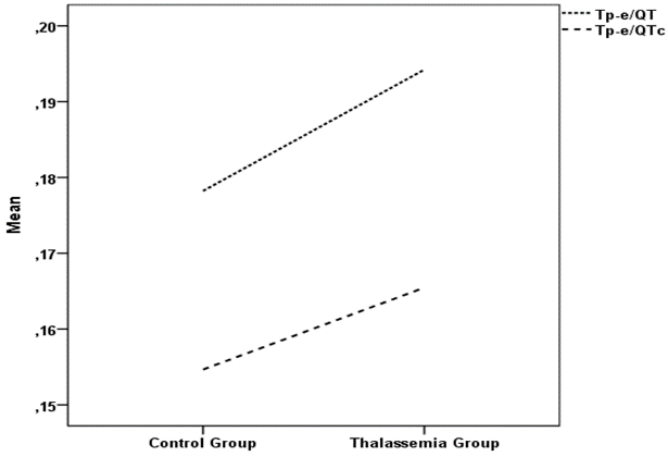

Figure 2. Tp e/QT and Tp e/QTc ratios were found to increase significantly in the thalassemia major group compared to the control group.

DISCUSSION

Our study revealed that the Tp-e interval, Tp-e/QT and Tp-e/QTc ratios increased in the TM patients compared to the healthy control group. These findings suggested that the TM patients had ventricular repolarization abnormalities. Moreover, no correlation was found between this increase and the serum ferritin, C reactive protein level and neutrophil to lymphocyte ratio. The patients were also compared as regards the ECG parameters according to the chelation therapies they received whereas no difference was found between the groups.

Continuous and repeated blood transfusion is essential for the treatment of TM patients. Repeated transfusion results in hemolysis and increased intestinal iron absorption, leading

to iron overload. Iron starts to accumulate in parenchymal tissues especially heart, liver and endocrine glands, within one year following the start of regular blood transfusion. If the iron binding capacity of transferrin is exceeded, a very toxic and free form of iron that is not bound on transferrin is formed. Free iron catalyzes the formation of hydroxyl radicals. These radicals attack proteins, lipids and DNA. As a result, cell death and fibrosis occur [7]. Moreover, iron causes a toxic effect on the endocrine glands and leads to the development of diabetes mellitus (DM). The calcium metabolism is impaired and the synthesis of the growth hormones and sex steroids is also impaired. Ultimately, all these events result in cardiac dysfunction [8].

Excessive iron accumulation in patients with thalassemia major inhibits sodium channels rapidly at cellular level, blocks the calcium releasing ryanodine channels and leads to modifications in sarcoplasmic reticulum, due to oxidative stress. All these events cause electrophysiological changes in cells and impairment of myocardial repolarization [9-10].

The most important causes of mortality and morbidity among patients with thalassemia major include cardiac involvement and associated heart failure as well as life-threatening severe ventricular arrhythmias [11-12]. Due to iron overload, first myocardial electrical conductivity is delayed or blocked and then myocardial contractility is impaired. This means that electrical activity is impaired in TM patients before heart failure develops [13]. Studies including TM patients showed that iron accumulation in the myocardium was not homogenous and it occurred earlier, especially in the free wall and interventricular septum. Such patch-like non-homogenous accumulation may be the reason for early involvement of the conduction system and higher incidence of arrhythmias among young patients [14]. Due to all these reasons, questions as to how the risk of arrhythmia can be distinguished among TM patients without any evidence of cardiac disease, and how these patients can be diagnosed early, are still important matters of debate.

Increased dispersion in ventricular repolarization is associated with life-threatening ventricular arrhythmias [13]. There are several parameters that show ventricular repolarization on the ECG. Several studies demonstrated that parameters such as QT interval, QTc interval, QT dispersion, JT dispersion increased in TM patients, which might be associated with serum ferritin level [15-17]. Similarly, increased QRS duration and presence of fragmented QRS in TM patients may be associated with increased arrhythmic events and mortality as shown in some studies [18-19]. Many ECG parameters have been used as the predictors of arrhythmia and supported by studies. There are no studies reported in the literature which used Tp-e interval, Tp-e/QT and Tp-e/QTc ratios that have been debated recently and show the transmural distribution of repolarization in TM patients.

Ventricular repolarization ends first in the epicardial cells. Action potential in the midmyocardial M cells is longer than the one in the other myocardial cells. The peak of the T wave shows the end of the epicardial action potential. The final point of the T wave shows the end of the midmyocardial action potential. In light of this information, the Tp-e interval, which is the distance between the peak point of the T wave and its last point, shows the transmural distribution of repolarization. Prolongation of this interval is associated with the risk of ventricular arrhythmia and sudden cardiac death [20]. As the Tp-e interval is affected by heart rate and body weight, Tp-e/QT and Tp-e/QTc ratios are the most precise indexes that show ventricular repolarization [21]. Several studies have demonstrated the association between these parameters and SCD and ventricular arrhythmia in different patient groups, however there is no data regarding TM patients.

In many cardiac and non-cardiac diseases, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios are used as the predictors of arrhythmia. In some studies, the patient group that had aortic stenosis was found to have markedly prolonged Tp-e interval, Tp-e/QT and Tp-e/QTc ratios, compared to the control group, and these parameters increased in parallel to the increase in the severity of aortic stenosis [22]. MVP patients were found to have prolonged Tp-e interval, Tp-e/QT and Tp-e/QTc ratios, which correlated with the increased rate of mitral

regurgitation [23]. These indexes were found to increase in the hyperthrophic cardiomyopathy patients compared to the control group [24]. They were also found to increase in patients with slow coronary flow compared to the control group [25]. All these changes increase the risk of ventricular arrhythmia in these patient groups. In conclusion, these studies have demonstrated that the ECG parameters could be used to predict life-threatening arrhythmias in different patient groups.

In our study, the Tp-e interval, Tp-e/QT and Tp-e/QTc ratios in the TM patient group were markedly prolonged compared to the healthy control group. These patients are very prone to the development of ventricular arrhythmia and must be followed-up more closely for life-threatening arrhythmias.

Studies in the literature that were conducted on TM patients reported a correlation between ventricular repolarization parameters and high serum ferritin level, and concluded that elevated serum ferritin level indicated excessive iron accumulation in the heart [25]. In our study, however, no association with serum ferritin level was found. This may be explained by the fact that the spot measurement of serum ferritin level did not show cardiac iron accumulation [24]. As we highlighted above, due to the patch-like accumulation of iron in the myocardium, arrhythmias may develop without high ferritin level as the conductor system is affected.

The basic cause of cardiac problems in thalassemia major patients is iron overload and MRI is the golden standard to show the myocardial iron accumulation [25]. In particular, the T2* value of <10 that can be shown via MRI indicates a severe myocardial iron overload [21]. However, for technical and cost reasons, it may be difficult to access MRI in different centers. In our study, we did not compare the ECG parameters and the T2* value by using MRI, which constitutes one of its limitations.

Anemia is a condition that can affect ECG parameters. However, in our study, we think that iron accumulation in the myocardium due to recurrent blood transfusions was primarily responsible for the increased frequency of ventricular arrhythmias, in thalassemia patients.

Ajibare AO et al. support our finding in the article titled “Assessment of ventricular repolarization in sickle cell anemia patients: The role of QTc interval, Tp-e interval and Tp-e/QTc ration and its gender implication”. In this study recruiting patients with sickle cell anemia who were compared with the healthy control group, there was a significant difference in hemoglobin values between the groups. Here, too, the researchers associated changes in ECG parameters with myocardial iron load (26).

The findings of our study demonstrated that simple but reliable parameters that can be analyzed via non-invasive, cost-effective and easily accessible methods such as ECG, increased statistically significantly in the TM patients for whom ventricular arrhythmias were an important cause of mortality, compared to the control group.

Limitations

There were certain limitations in our study. We had a low number of patients and arrhythmias that could develop in the long term could not be demonstrated, as they were not followed up for a long term. Moreover, as mentioned above, MRI and T2* value were not used for technical reasons, availability and cost constraints. In our study, thalassemia patients and healthy control group were compared and a difference in hemoglobin values was detected between these groups. We know that anemia affects ECG parameters, but our primary hypothesis was the development of ventricular repolarization disorder due to myocardial iron deposition. The inability to make this distinction clearly was one of the limitations of our study.

Conclusion

Simple but reliable parameters such as Tp-e interval, Tp-e/QT and Tp-e/QTc ratios that could be found through electrocardiography, increased significantly among the TM patients compared to the control group. This was associated with impaired ventricular repolarization due to cardiac iron overload. The risk of arrhythmia can be predicted via the analysis of these parameters when patients do not present any cardiac manifestations, and patients who are found to have an increase in these parameters can be

examined and followed up for arrhythmias.

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The Effects of Tumor Localization on Small Cell Lung Cancer and its Association With Prognosis

Tümör Lokalizasyonunun Küçük Hücre Akciğer Kanseri Üzerine Etkileri ve Prognoz İle İlişkisi

Sertan Bulut[1]*, Deniz Çelik[2]

1.University of Health Sciences Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Department of Pulmonology, Ankara, Turkey
2.Alanya Alaaddin Keykubat University, Medical Faculty, Department of Pulmonology, Alanya, Antalya, Turkey

ABSTRACT

Introduction: Lung cancer is classified as small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), both as pathological subtypes. SCLC is associated with a significantly short life expectancy, and it constitutes 10-15% of all lung cancers. Previous studies showed that lung cancer is mostly dominated by the upper lobe and is more common in the right lung than in the left. The principle aim of this study is to analyze the localization of the tumor in the right and left lung in aggressive and malignant SCLC patients by comparing it with determinants such as anatomical features, demographic features, laboratory features, including the association with peripheral-central localizations, especially overall survival.

Methods: There were four hundred forty-six lung cancer patients diagnosed in a chest diseases clinic in a tertiary training and research hospital between 2014-03-31 and 2020-03-31. Of these, twenty percent (n=90) were diagnosed as SCLC. Among ninety patients, six were excluded from the study due to incomplete medical SCLC records, and finally, eighty-four patients with SCLC were included in the study.

Results: We classified eighty-four patients into two groups as right and left lung localized SCLC and analyzed all the data. We found that the left lung tumor group had the more extensive-stage disease and had significantly high CRP levels (p=0.027, p=0.045, respectively). When we analyzed the data, such as demographic characteristics, diagnostic methods, overall survival, treatment characteristics, stage characteristics, anatomical features of the right and left tumor groups, we found that there were no significant differences. We used univariate and then multivariate analysis for survival. We found that being sixty-five years old and over (p=0.014), high CRP levels (p=0.016), having centrally localized tumors (p=0.01), having poor performance status (p<0.0001), and having no treatment for primary cancer (p=0.001) were associated with worse survival.

Conclusion: Primary treatment of SCLC patients should start promptly. We found that the central location of the tumor as anatomical localization may be associated with worse survival and that the left lung tumor group had the more extensive-stage disease, with significantly high CRP levels. Being sixty-five years old and over, high CRP levels, having poor performance status and having no treatment for primary cancer, were all significantly associated with worse survival.

Keywords: Small-cell lung cancer (SCLC), survival, tumor localization, prognosis

ÖZ

Amaç: Akciğer kanseri, patolojik alt tipler olarak küçük hücreli dışı akciğer kanseri (KHDAK) ve küçük hücreli akciğer kanseri (KHAK) olarak sınıflandırılır. KHAK, önemli ölçüde kısa bir yaşam beklentisi ile ilişkilidir ve tüm akciğer kanserlerinin %10-15'ini oluşturur. Önceki çalışmalar, akciğer kanserinin çoğunlukla üst lobun baskın olduğunu ve sağ akciğerde sola göre daha yaygın olduğunu gösterdi. Bu çalışmanın temel amacı, agresif ve malign KHAK hastalarında tümörün sağ ve sol akciğerdeki lokalizasyonunu anatomik özellikler, demografik özellikler, laboratuvar özellikleri gibi belirleyicilerle karşılaştırarak periferik-merkezi yerleşimlerle ilişkisini de içerecek şekilde analiz etmek ve özellikle de sağkalımı değerlendirmektir.

Metot: Bir üçüncü basamak eğitim ve araştırma hastanesinde göğüs hastalıkları kliniğinde 31.03.2014-31.03.2020 tarihleri arasında tanı almış 446 akciğer kanseri hastası tespit edildi. Bunların %20'si (n=90) KHAK tanısı aldı. Doksan hastadan altı tanesi eksik tıbbi kayıtları nedeniyle çalışma dışı bırakıldı ve son olarak KHAK'lı 84 hasta çalışmaya dahil edildi.

Bulgular: 84 hastamızı sağ ve sol akciğerde lokalize KHAK olarak iki ana gruba ayırdık ve tüm verileri analiz ettik. Sol akciğer tümörü grubunun daha yaygın evreli hastalığa sahip olduğunu ve anlamlı derecede yüksek CRP düzeylerine sahip olduğunu bulduk (sırasıyla p=0.027, p=0.045). Sağ ve sol tümör gruplarının demografik özellikleri, tanı yöntemleri, genel sağkalım, tedavi özellikleri, evre özellikleri, anatomik özellikleri gibi verileri analiz ettiğimizde istatistiksel olarak anlamlı bir fark olmadığını gördük. Tüm verilerimizin sağkalım açısından önce tek değişkenli analiz, ardından çok değişkenli analiz ile analiz edilmesi sonucunda; 65 yaş ve üzeri (p=0.014), CRP yüksekliği (p=0.016), santral yerleşimli tümör varlığı (p=0.01), performans düşüklüğü (p<0.0001) ve primer tedaviyi almayan kanser durumu (p=0.001) daha kötü sağkalım ile ilişkilendirildi.

Sonuç: KHAK hastalarının ilk tedavisi hemen başlanmalıdır. Anatomik lokalizasyon olarak tümörün merkezi yerleşiminin daha kötü sağkalım ile ilişkili olabileceğini bulduk. Ayrıca sol akciğer tümörü grubunun daha yaygın evreli hastalığa sahip olduğunu ve CRP düzeylerinin anlamlı derecede yüksek olduğunu bulduk. Altmışbeş yaş ve üstü olmak, yüksek CRP düzeyleri, düşük performans durumuna sahip olmak ve primer kanser tedavisi görmemek, daha kötü sağkalım ile anlamlı olarak ilişkiliydi.

Anahtar sözcükler: Küçük hücreli akciğer kanseri, sağkalım, tümör lokalizasyonu, prognoz

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*Corresponding Author: Sertan BULUT. University of Health Sciences Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Department of Pulmonology, Ankara, Turkey Turkey, +905415545649, drsertanbulut@hotmail.com

ORCİD: 0000-0003-1267-3440

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INTRODUCTION

Lung cancer is classified as small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), both as pathological subtypes [1]. SCLC is associated with a significantly short life expectancy and constitutes 10 to 15% of all lung cancers [2]. It has a short tumor doubling time and is highly invasive [1]. SCLC is more sensitive to chemotherapy and radiation but its prognosis is the poorest: the overall survival rate for five years is only 5 to 15% [3]. While NSCLC types are examined in four stages with the TNM Classification of Malignant Tumours (TNM) [4], SCLC is typically evaluated into two main categories: limited-stage and extensive-stage. In parallel with the developments in SCLC treatment since the 1970s, there have been improvements in the overall survival rate [5].

It has been inferred from previous studies that lung cancer is mostly dominated by the upper lobe and is more common in the right lung than the left [6,7]. Atypical malignancy localizations, such as the trachea, have also been reported in the literature [8]. No statistical association was found between the anatomical localization of the tumor on the right lung or the left lung and the survival of the patient in SCLC, in the previously analyzed limited data [6,9]. There exists varying reports regarding the association between localization of the tumor (central or peripheral tumor) and survival, in SCLC [3,10,11].

The principal aim of this study was to analyze the localization of the tumor in the right and left lung in aggressive and malignant SCLC cases, by comparing it with variables such as anatomical features, demographic features, laboratory features, including the association with peripheral-central localizations, and in particular with overall survival. In addition, we aimed to analyze the prognostic factors related to survival.

MATERIAL AND METHOD

Study population

There were four hundred forty-six lung cancer patients diagnosed in a chest diseases clinic in a tertiary training and research hospital, between March 31st, 2014 and March 31st, 2020. Of these patients, 33% (n=148) were diagnosed as squamous cell lung carcinoma, 32% (n=142) were diagnosed as adenocarcinoma, 8% (n=36) were diagnosed as NOS (not otherwise specified), 7% (n=30) were diagnosed as other primary lung cancers and finally, 20% (n=90) were diagnosed as SCLC. Among ninety patients, 6 were excluded from the study as a result of incomplete medical records so that at the final onset of the study, 84 patients with SCLC were included (Figure 1).

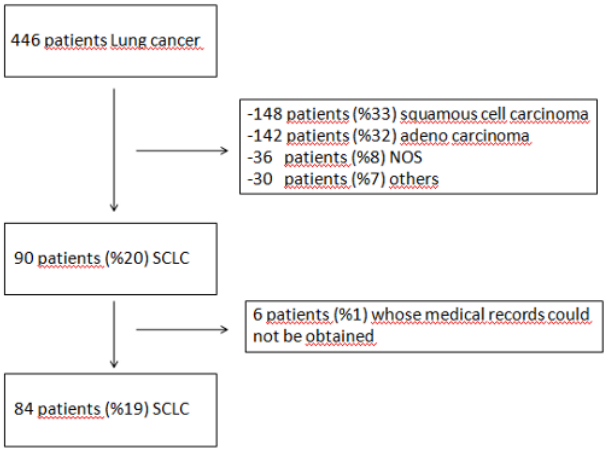

Figure 1. Patients' flowchart

As recommended by the guidelines, follow-ups were performed with Thorax CT and/or PET-CT every 3 months for the first 2 years, every 6 months for 2 to 4 years, and once a year for more than 4 years. The data of the cases in our study is right-stopped data ending on March 31st, 2020 (our last patient date). As of the end of our study, 18 patients were still alive and those were followed for at least one year. When all cases (n=84) were included, our median follow-up was 8.05 months (0.2-70 months).

All patients were over 18 years old, with a pathological diagnosis of SCLC, with complete radiological PET-CT examination and medical records. The treatment schemes of 67 patients who received treatment were reviewed. Cisplatin/Carboplatin and Etoposide treatment followed by curative radiotherapy (n=16) were applied to all limited-stage cases. Cisplatin/Carboplatin and Etoposide treatment were applied to all cases with extensive stage.

Design

The SCLC patients were divided into two main

groups in terms of anatomical localization (Figure 2: right and left lung tumors). For these two groups, demographic characteristics, accompanying diseases, radiological features, treatment features, laboratory parameters, TNM staging features, and limited and extensive stages (the Eighth Edition Lung Cancer Stage Classification), were analyzed. In addition, the presence of peripheral tumors and central tumors in these two groups was also examined. All variables were examined, and statistical significance was checked. Survival analyses were also conducted.

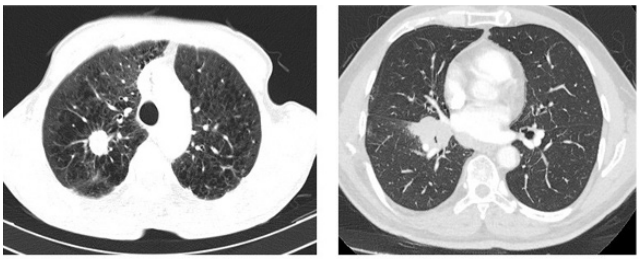

Figure 2. Peripheral and central SCLC

At the time of diagnosis, all cases underwent PET-CT scans and Cranial MRI examinations. Staging, mediastinal lymph node involvement (N1-2-3) and evaluation of metastases were performed with PET-CT. The presence of brain metastases in all cases was evaluated with Cranial MRI. The staging was performed both according to the TNM system and according to limited disease-extensive disease staging.

Definitions

The definitions of the limited and extensive stages were made in line with "The Veterans' Administration Lung Study Group (VALSG) stage classification". This widely accepted classification for SCLC is still used. "VALSG defines limited-stage (LS) as a disease confined to a single hemithorax, including contralateral mediastinal and ipsilateral supraclavicular lymph nodes if all disease can be safely encompassed in a radiation port area. Extensive stage (ES) is defined as a disease that cannot be classified as limited, including malignant pleural or pericardial effusions and hematogenous metastases" [5].

For the definitions of the locations, "central tumor location was defined as within 2 cm of the proximal bronchial tree, heart, great vessels, trachea, or other mediastinal structures" [10]. Tumors outside this definition were defined as peripheral tumors [10] [Figure 2]. Peripheral-central tumor distinctions of all patients were made with Thorax CT.

Statistical analysis

For the distribution of all continuous variable values, the Kolmogorov-Smirnov or Shapiro-Wilk test, coefficient of variation value, Skewness-Kurtosis values, histogram and detrended plot graphs, were examined. Categorical nominal data were indicated as n/%. When the data was ordinal or numeric but not normally distributed, the median was indicated as /min-max and it was indicated as mean/sd for numerical and normally distributed data. In our study group, which we divided into right lung tumor and left lung tumor, categorical data was evaluated with the Chi-square or Fisher test, where appropriate, and numerical data was evaluated with Student's t-test or Mann-Whitney-U test, as appropriate. Survival analyzes were performed with univariate survival analyzes such as the Tiger Meier test, Log Rank test, and multivariate survival analysis in the form of a Cox regression model. The SPSS (Statistical Package for the Social Sciences) statistical software package (version 22) was used and values with a p-value <0.05 were considered statistically significant. The study was approved by the institutional education board of our hospital (date: 2021-06-17 and number: 730)

RESULTS

In this study, among eighty-four SCLC patients, seventy-two were male (85.7%). The mean age at diagnosis was 65.27±9.75. We classified patients into two main groups: 54 patients (64%) with right lung tumor and 30 patients (36%) with left lung tumor (Table 1). A Chi-square test was used for these two groups and it was found that left lung tumors were mostly in the extensive stage of the disease (p=0.027). However, we found that there was no significant difference between the two groups in terms of age, gender, smoking characteristics, performance status, treatments received, overall survival, diagnostic methods and survival status (Table 1).

Fiberoptic bronchoscopy (FOB) was found to be

Table 1. Demographic and basal features

	Total n=84 (100%) n (%)	Right Lung SCLC n=54 (64%) n (%)	Left Lung SCLC n=30 (36%) n (%)	p-value
Age, median (range)	65.50 (41-87)	65.50 (41-87)	65.50 (48-86)	p=0.46
Sex				p=0.85
Male	72 (85.7%)	46 (85.2%)	26 (86.7%)	
Female	12 (14.3%)	8 (14.8%)	4 (13.3%)	
Smoking (at the time of diagnosis)				p=0.69
Nonsmoker	10 (11.9%)	6 (11.1%)	4 (13.3%)	
Quit	62 (73.8%)	39 (72.2%)	23(76.7%)	
Still smoking	12 (14.3%)	9 (16.7%)	3 (10%)	
Smoking (pack/year) (mean±SD)	33.07±19.34	33.33±19.75	32.6±18.91	p=0.86
ECOG				p=0.94
ECOG 0	7 (8.3%)	5 (9.3%)	2 (6.7%)	
ECOG 1	20 (23.8%)	13 (24.1%)	7 (23.3%)	
ECOG 2	25 (29.8%)	17 (31.5%)	8 (26.7%)	
ECOG 3	16 (19%)	10 (18.5%)	6 (20%)	
ECOG 4	16 (19%)	9 (16.7%)	7 (23.3%)	
Treatment				p=0.49
Only CT	51 (60.7%)	35 (64.8%)	16 (53.3%)	
Curative CRT	16 (19%)	10 (18.5%)	6 (20%)	
Supportive Treatments	17 (20.2%)	9 (16.7%)	8 (26.7%)	
Palliative RT				p=0.93
Received	20 (23.8%)	13 (24.1%)	7 (23.3%)	
Did not receive	64 (76.2%)	41 (75.9%)	23 (76.7%)	
PCI				p=0.25
Received	20 (23.8%)	15 (27.8%)	5 (16.7%)	
Did not receive	64 (76.2%)	39 (72.2%)	25 (83.3%)	
Median overall survival (month)	8.05 (0.2-70)	8.55 (0.20-70)	6.65 (0.3-41)	p=0.76
Survival status				p=0.81
Exitus	66 (78.6%)	42 (77.8%)	24 (80%)	
Survived	18 (21.4%)	12 (22.2%)	6 (20%)	
Diagnostic methods				p=0.15
FOB	59 (70.2%)	42 (78.8%)	17 (56.7%)	
EBUS-TBNA	12 (14.3%)	5 (9.3%)	7 (23.3%)	
TTNB	11 (13.1%)	6 (11.1%)	5 (16.7%)	
Extra thoracic lymph node biopsy	1 (1.2%)	1 (1.9%)	0 (0%)	
Pleural fluid biopsy	1 (1.2%)	0 (0%)	1 (3.3%)	

ECOG: Eastern Cooperative Oncology Group, FOB: Fiber optic bronchoscopy, EBUS-TBNA: Endobronchial ultrasonography- Transbronchial needle aspiration, TTNB: Transthoracic needle biopsy, CT: Chemotherapy, CRT: Chemoradiotherapy, PCI: Prophylactic cranial irradiation

the most common diagnostic method performed on 59 patients (70.2%). Anatomical locations and stage features are shown in Table 2. In the right and left lung tumor groups, there were 79 patients with centrally localized tumors (94%) and 5 patients with peripherally localized tumors (6%). When patients were examined in terms of the TNM classification, limited disease and extensive disease, it was observed that 52.4% (n=44) of patients were in T4, 72.6% (n=61) of patients were in N3, 57.1% (n=48) of patients were in M1c and, 76.2% (n=64) of patients were in extensive-stage. In right and left lung tumor groups, there was no statistical significance in terms of central-peripheral status, tumor size and stage characteristics (Table 2). When the comorbidities and metastasis conditions (Table 3) and laboratory characteristics (Table 4) in the right and left lung tumor groups were examined, it was observed that only the CRP level was statistically significantly higher in the left tumor group (p=0.045).

Table 2. Anatomical localization and stage features

TNM and Tumor localization	Total n=84 (100%) n (%)	Right Lung SCLC n=54 (64%) n (%)	Left Lung SCLC n=30 (36%) n (%)	p-value
Localization				
Central	79 (94%)	52 (96.3%)	27 (90%)	p=0.243
Peripheral	5 (6%)	2 (3.7%)	3(10%)	
Tumor size (cm)	6.5 (2.2-10.9)	6.4 (2.2-10.9)	6.75 (2.2-10.5)	p=0.98
Tumor				
T1	4 (4.8%)	1 (1.9%)	3 (10%)	
T2	18 (21.4%)	13 (24.1%)	5 (16.7%)	p=0.346
T3	18 (21.4%)	11 (20.4%)	7 (23.3%)	
T4	44 (52.4%)	29 (53.7%)	15 (50%)	
Node				
N1	3 (3.6%)	3 (5.6%)	0 (0%)	p=0.182
N2	20 (23.8%)	15 (27.8%)	5 (16.7%)	
N3	61 (72.6%)	36 (66.7%)	25 (83.3%)	
Metastasis				
M0	26 (31%)	18 (33.3%)	8(26.7%)	
M1a	8 (9.5%)	5 (9.3%)	3 (10%)	p=0.274
M1b	2 (2.4%)	0 (0%)	2 (6.7%)	
M1c	48 (57.1%)	31 (57.4%)	17 (56.7%)	
Stage				
Limited	20 (23.8%)	17 (31.5%)	3 (10%)	p=0.027
Extended	67 (76.2%)	37 (68.5%)	27 (90%)	

Table 3. Comorbid diseases and localizations of metastasis

	Total n=84 (100%) n (%)	Right Lung SCLC n=54 (64%) n (%)	Left Lung SCLC n=30 (36%) n (%)	p-value
Chronic obstructive pulmonary disease	34 (40.5%)	21 (61.8%)	13 (38.2%)	p=0.69
Diabetes Mellitus	9 (10.7%)	4 (44.4%)	5 (55.6%)	p=0.18
Hypertension	34 (40.5%)	22 (64.7%)	12 (35.3%)	p=0.94
Atherosclerotic heart disease	10 (11.9%)	7 (70%)	3 (30%)	p=0.68
Brain metastasis	14 (16.7%)	9 (64.3%)	4 (35.7%)	p=1
Bone metastasis	41 (48.8%)	24 (58.5%)	17 (41.5%)	p=0.28
Liver metastasis	27 (32.1%)	17 (63%)	10 (37%)	p=0.86
Adrenal metastasis	21 (25%)	11 (52.4%)	10 (47.6%)	p=0.18
Lung metastasis	22 (26.7%)	14 (63.6%)	8 (36.4%)	p=0.94
Intraabdominal lymphatic metastasis	12 (14.3%)	10 (83.3%)	2 (16.7%)	p=0.13
Pancreas metastasis	5 (6%)	2 (40%)	3 (60%)	p=0.24
Spleen metastasis	1 (1.2%)	0 (0%)	1 (100%)	p=0.17
Skin metastasis	4 (4.8%)	1 (25%)	3 (75%)	p=0.09

As shown in Table 5, among the study group, 76.2% (n=64) patients had extensive disease and 23.8% (n=20) had limited disease. The extensive disease median overall survival value was 5.7 months (4.446-6.954) and the limited disease median overall survival value was 13.3 months (0.000-28.675) (respectively, p<0.0001, log-rank). We analyzed patients in terms of survival characteristics. Firstly, the data was evaluated with the univariate Kaplan Meier test and the Log Rank test (Figure 3 and 4). As a result, being 65 years or older, having a central tumor, having an extensive stage, having a high-performance status, not receiving treatment for the primary disease, not receiving PCI (prophylactic cranial irradiation), high CRP levels were found to be

Table 4. Laboratory features

Variables	Total n=84 mean (min-max)	Right Lung SCLC n=54 (64%) mean (min-max	Left Lung SCLC n=30 (36%) mean (min-max)	p-value
WBC (x10^3/µL)	9.14 (4.5-18.8)	9.11 (4.76-18.8)	10.02 (4.5-15.5)	p=0.68
Neutrophil (x10^3/µL)	6.15 (1.7-14.64)	5.46 (2.74-14.64)	6.67 (1.7-12.46)	p=0.23
Lymphocyte (x10^3/µL)	1.98 (0.49-5.35)	1.96 (0.49-5.35)	2.08 (0.7-3.59)	p=0.23
NLR	3.07 (0.81-17.4)	2.73 (0.95-11.06)	3.75 (0.81-17.4)	p=0.12
Hemoglobin (g/dL)	13.59±1.93	13.73±1.98	13.35±1.84	p=0.38
Thrombocyte (x10^3/µL)	288 (48.4-1187)	277 (48.4-1187)	300 (145-464)	p=0.72
Creatinine (mg/dL)	0.84 (0.53-1.77)	0.85 (0.59-1.51)	0.83 (0.53-1.77)	p=0.93
Uric Acid (mg/dL)	5.2 (1.5-10.3)	5.2 (2.7-8.8)	5.3 (1.5-10.3)	p=0.70
Albumin (g/L)	38.6 (4.37-48)	39.4 (4.8-48)	37.05 (4.37-43)	p=0.08
AST (IU/L)	22.5 (8-147)	23 (8-147)	21.5 (10-120)	p=0.54
ALT (IU/L)	22 (6-176)	22 (6-176)	21.5 (6-64)	p=0.20
LDH (IU/L)	268 (136-1687)	268 (136-1202)	266 (148-1687)	p=0.44
CRP (mg/L)	20.5 (1-232.1)	12.5 (1-203.5)	24.1 (4.2-232.1)	p=0.045
Sedimentation (mm/hour)	39 (1-120)	39 (1-104)	38 (15-120)	p=0.33

WBC: White blood cell count, NLR: The neutrophil-to-lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase,CRP: C-reactive protein

Table 5. Overall survival analysis of variables with univariate log-rank test and multivariate cox regression model

Variables	n	Median Overall survival (month)	Univariate analysis p-value	Multivariat analysis HR	Multivariat Analysis (95%CI)	Multivariate analysis (p-value)
Age			p=0.016			
<65 years	44	10.7		ref	ref	
≥65 years	40	5.5		1.93	1.140-3.266	p=0.014
Gender			p=0.333			
Male	72	7		-	-	-
Female	12	9.1				
Right or Left Lung			p=0.790			
Right	54	8.6		-	-	-
Left	30	6.5				
Central/peripheral			p=0.010			
Peripheral	5	27.2		ref	ref	p=0.010
Central	79	7		0.068	0.009-0.526	
Disease status			p<0.0001			
Limited	20	13.3		ref	ref	p=0.103
Extensive	64	5.7		1.859	0.882-3.919	
Performance Status			p<0.0001			
ECOG 0-1	27	16.7		ref	ref	p<0.0001
ECOG 2-4	57	5.2		4.660	2.284-9.507	
Treatment status			p<0.0001			
Treated	67	10.2		ref	ref	p=0.001
Non treated	17	1.6		2.928	1.511-5.674	
PCI			p<0.001			
Yes	20	13.3		ref	ref	p=0.883
No	64	5.7		1.058	0.500-2.236	
CRP			p=0.032			
Normal	13	12.1		ref	ref	p=0.016
High (>5 mg/L)	71	6.5		2.631	1.201-5.763	
LDH			p=0.066			
Normal	34	9.1		ref	ref	p=0.100
High (>248 IU/L)	50	6		1.569	0.917-2.686	

ECOG: Eastern Cooperative Oncology Group, PCI: Prophylactic cranial irradiation, LDH: Lactate dehydrogenase, CRP: C-reactive protein

significantly associated with poor prognosis. When these results were analyzed with a multivariate cox regression model afterward, only being 65 years or older (p=0.014), having a central tumor at the time of diagnosis (p=0.01), poor performance status (p<0.0001), not receiving treatment (p=0.001) and high CRP levels (p=0.016) were observed to be significantly associated with poor prognosis.

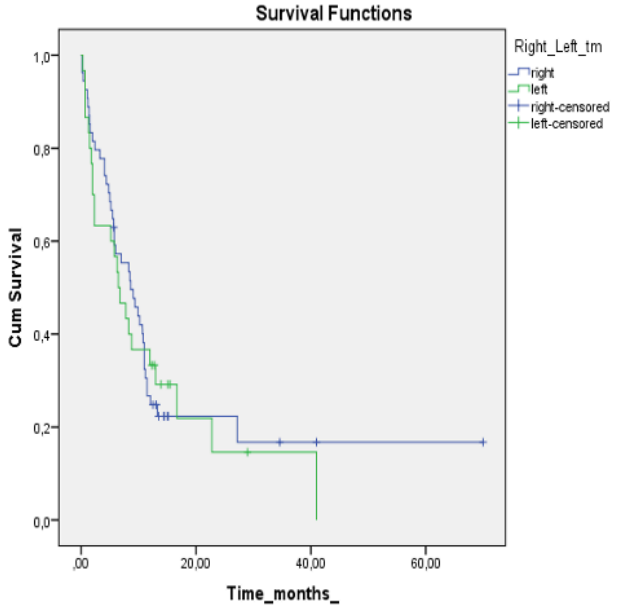

Figure 3. Survival analysis of right and left lung tumor localization with Kaplan-Meier analyze

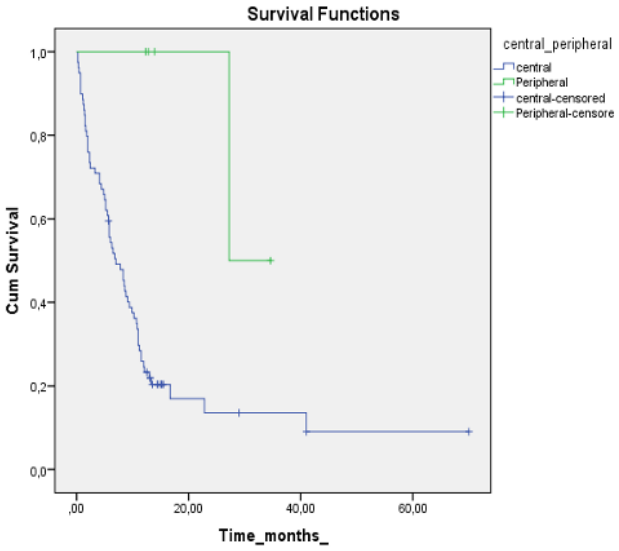

Figure 4. Survival analysis of central and peripheral lung tumor localization with Kaplan-Meier analyze

As a summary, we classified our 84 patients into two main groups as right and left lung localized SCLC and analyzed all the data. We found that the left lung tumor group had the more extensive-stage disease and had significantly high CRP levels (p=0.027, p=0.045, respectively). When we analyzed the data such as demographic characteristics, diagnosis methods, overall survival, treatment characteristics, stage characteristics, anatomical features of the right and left tumor groups, we found that there were no statistically significant differences. As a result of analyzing all our data in terms of survival, with firstly univariate analysis and then with multivariate analysis, we found that being 65 years old and over (p=0.014), high CRP levels (p=0.016), having centrally localized tumors (p=0.01), having poor performance status (p<0.0001), and having no treatment for primary cancer (p=0.001), were associated with worse survival.

DISCUSSION

In previous studies, the median age was 62 years in SCLC patients and 39% were 65 years old and over [12]. In another study, the median age was found as 72 years [11]. In our study, the median age was found to be 65.5 (41-87) consistent with the literature.

Wang et al. evaluated 106 292 SCLC patients and found the median overall survival rate to be seven months [13]. We found the overall survival rate at 8.05 months. Tas et al. found in their study that being older is an independent, poor prognostic factor [14]. When Kanaji et al. evaluated the patient group as the old and young groups, they found that there was no statistical significance in terms of overall survival [11]. In our study, while there was no association between age and right and left lung tumor groups, age was found to be an independent risk factor for survival in the univariate and multivariate analyzes performed for the 65 years old and older group (HR=1.930, p=0.014, Cox model).

The SCLC is more common in males [6,11,15] and this was the case in our study as well. There are studies in which being male was associated with poor survival [9,16] or there was no association between survival and gender [3]. We found no associations between gender and survival.

In the study by Wang et al., primary lesions in the right lung were observed in 126 patients (61.46%), while 79 (38.54%) had primary lesions in the left lung [17]. In another study, Sahmoun et al. also found that the tumors located on the right

lung were common (63%) in the SCLC group [15]. Mennecier et al. found that 53% of patients with SCLC had it on the right-side [18]. In our study, the rate of right-sided tumors (64%) was found to be similar to this previously reported data.

In earlier studies of SCLC, it was found that the right or left localization of the tumor was not associated with survival [6,9]. In our study, we also found no association between right or left localization and survival.

There are studies about the effect of having a peripheral tumor on the prognosis in patients with SCLC. The patients were classified into central and peripheral tumor groups but the results have been inconsistent. In one study, there was no significant prognostic association observed [10] yet in another, peripheral tumors were associated with a poor prognosis [3]. Kanaji et al. for their part found that peripheral tumors were associated with a good prognosis [11]. In our study, the tumors which were centrally located were found to be an independent poor prognostic factor, with the multivariate cox model performed (p=0.01).

Performance status at the time of diagnosis in SCLC patients was usually found poor. Kanaji et al. found that 25% of the patients were Eastern Cooperative Oncology Group (ECOG) class 2 and above, at the time of diagnosis [11]. Le et al. found that 41% of the patients were ECOG class 2 and above at the time of diagnosis [12]. In our study, 67% of the patients were ECOG class 2 and above. Poor performance status was associated with poor survival in SCLC patients in these and other studies [11,12,16]. In our study, poor performance status was found to be an independent risk factor, as a result of the multivariate analysis made with the Cox regression model (HR=4.66, p<0.0001).

In their analysis, Kanaji et al. found that the most commonly used diagnostic procedure was fiberoptic bronchoscopy (68%) [11]. In our study, fiberoptic bronchoscopy was indeed the most commonly used diagnostic method similar to the previous data (70.2%).

The treatment modalities of SCLC were examined in previous studies and approximately 80% of the patients had chemotherapy (CT), or radiotherapy (RT) or chemoradiotherapy (CRT), or Surgery. Approximately 20% of the patients had only the best supportive treatment [6,11]. Median overall survival (OS) with current treatments in SCLC is approximately 20 months for limited-stage (LS) SCLC patients, while it is 8-12 months for extensive-stage (ES) SCLS patients [19].

In our patients, the rates were similar in terms of treatment, 80.7% of them received primary cancer treatment for SCLC, while 19.3% did not. We found the median overall survival to be 13.3 months for our LS-SCLC patients and 5.7 months for our ES-SCLC patients. In this study, consistent with the literature data, primary cancer treatment was found to be associated with better survival (multivariate cox model, p=0.001).

The rate of brain metastasis is found at least 7% at the time of diagnosis [6] but it may increase to approximately 60% in the course of the disease [5]. PCI treatment can reduce the rate of brain metastases by 25% in the course of the disease and increase survival in LS-SCLC patients [20]. PCI treatment can be planned for LS-SCLC and ES-SCLC patients following systemic treatment [5]. In our study, the brain metastasis rate was 16.7% at the time of diagnosis and the number of patients who received PCI was 23.8%. We found that receiving PCI treatment was not statistically significant in terms of overall survival, with the multivariate cox model used.

There is currently no serum biomarker available for the diagnosis of primary SCLC [16]. However, some serum biomarkers are known prognostic factors in SCLC. The high LDH levels were associated with poor prognosis in previous studies [17,21]. Also, high CRP levels at the time of diagnosis were associated with poor overall survival in SCLC [22]. In our study, we analyzed the C reactive protein (CRP) and Lactate dehydrogenase (LDH) levels. High CRP levels were found to be a significantly poor prognostic factor (p=0.024, in the multivariate Cox model). LDH levels were found high in patients who had a worse prognosis, but it was not statistically significant (p=0.082, in the multivariate Cox model).

In our study, we found that there was no significant difference between CRP values and having a central/peripheral tumor and receiving primary malignancy treatment (p>0.05).

Limitations: This study was performed on data from a single-center and this is the main limitation. This study design was cross-sectional, retrospective and comprised patients diagnosed in the last six years and their number was comparatively low, which is our second limitation. The retrospective design was our third limitation.

CONCLUSION

Primary treatment for SCLC patients should start promptly. We found that the central location of the tumor may be associated with worse survival and that the left lung tumor group had the more extensive-stage disease, with significantly high CRP levels. Being 65 years old and over, high CRP levels, having poor performance status and having no treatment for primary cancer, were all significantly associated with worse survival.

CRP elevation was found to be significant among the poor prognostic factors in the univariate (Kaplan-Meier test) analysis and then in the multivariate analysis of our data (cox regression analysis) (p=0.016). Likewise, the presence of a central tumor, poor performance status of the patient and not receiving treatment, were found to be additional poor prognostic factors (p=0.010, p<0.0001, and p=0.001, respectively). These results were found to be compatible with the literature. They also reveal that there is no bias in the selection of the population of our study and the results of the analyzes are compatible with the literature. In addition, we think that if the patients are found to have these poor prognostic criteria at the time of diagnosis, it may be necessary to start the treatment as soon as possible.

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Predictive Value of Carbohydrate Antigen-125 in Determining the Left Ventricular Diastolic Dysfunction

Sol Ventrikül Diyastolik Disfonksiyonunun Belirlenmesinde Karbonhidrat Antijeni-125'in Tahmini Değeri

Nazım Kankılıç[1*]

1.Department of Cardiovascular Surgery, Medical School of Harran University, Şanlıurfa/Turkey

ABSTRACT

Aim: Carbohydrate antigen-125 (CA-125) is a well-known marker for mesenchymal cell activation. It is being investigated as a predictive marker for cardiac pathologies due to pericardial or pleural mesenchymal cell activation. In this study, the relationship between left ventricular diastolic diameter (LVDd) and ejection fraction (EF) and serum CA-125 levels was investigated.

Material and Method: Thirty-eight patients who underwent coronary artery bypass graft operation were included in the study. LVDd and EF values were calculated. Routine blood parameters and serum CA-125 levels were obtained from blood samples. Patients were divided into groups according to LVDd (LVDd <50mm vs. ≥50mm) and EF (EF <50% vs. EF≥50%).

Results: Among the low (<50%) and high (≥50%) EF groups, serum neutrophil, mean platelet volume (MPV), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), troponin-I, triglyceride, and very low-density lipoprotein (VLDL) levels were statistically different ($p<0.05$). However, no statistical difference was observed between the low (<50mm) and high (≥50mm) LVDd groups in other blood parameters except for serum CA-125 levels ($p>0.05$). Higher serum CA-125 levels were obtained in patients with a high left ventricular diastolic diameter (≥50mm) ($p<0.05$). In addition, CA-125 was found to be an important predictor of left ventricular diastolic diameter with an optimal cut-off value of 0.644 kU/L (60% sensitivity and 78.3% specificity).

Conclusion: According to our results, increased serum CA-125 level is an independent predictor of higher LVDd and may be a good indicator of left ventricular functions.

Keywords: CA-125, left ventricle diastolic dimension, ejection fraction.

ÖZ

Amaç: Karbonhidrat antijeni-125 (CA-125), mezenkimal hücre aktivasyonu için iyi bilinen bir belirteçtir. Perikardiyal veya plevral mezenkimal hücre aktivasyonuna bağlı kardiyak patolojiler için öngörücü bir belirteç olarak araştırılmaktadır. Bu çalışmada sol ventrikül diyastolik çapı (LVDd) ve ejeksiyon fraksiyonu (EF) ile serum CA-125 seviyeleri arasındaki ilişki araştırıldı.

Gereç ve Yöntem: Koroner arter baypas greft operasyonu uygulanan 38 hasta çalışmaya dahil edildi. LVDd ve EF değerleri hesaplandı. Kan örneklerinden rutin kan parametreleri ve serum CA-125 seviyeleri elde edildi. Hastalar LVDd (LVDd <50mm vs. ≥50mm) ve EF'ye (EF <%50 vs. EF≥%50) göre gruplara ayrıldı.

Bulgular: Düşük (<%50) ve yüksek (≥ %50) EF grupları arasında serum nötrofil, ortalama trombosit hacmi (MPV), laktat dehidrogenaz (LDH), aspartat aminotransferaz (AST), troponin-I, trigliserit ve çok düşük yoğunluklu lipoprotein (VLDL) düzeyleri istatistiksel olarak farklıydı ($p<0.05$). Ancak düşük (<50mm) ve yüksek (≥50mm) LVDd grupları arasında serum CA-125 düzeyleri dışında diğer kan parametrelerinde istatistiksel fark gözlenmedi ($p>0.05$). Sol ventrikül diyastolik çapı yüksek (≥50mm) olan hastalarda serumda daha yüksek CA-125 seviyeleri elde edildi ($p<0.05$). Ayrıca, CA-125, 0,644 kU/L'lik optimal cut-off değeri (%60 duyarlılık ve %78,3 özgüllük) ile sol ventrikül diyastolik çapının belirlenmesinde önemli bir öngörücü belirteç olarak bulundu.

Sonuç: Sonuçlarımıza göre artmış serum CA-125 düzeyinin daha yüksek LVDd için bağımsız bir öngörücü olduğu ve sol ventrikül fonksiyonlarının iyi bir göstergesi olabileceği görülmektedir.

Anahtar Kelimeler: CA-125, sol ventrikül diyastol sonu çapı, ejeksiyon fraksiyonu.

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*Corresponding Author: Nazım KANKILIÇ, Department of Cardiovascular Surgery, Medical School of Harran University, Şanlıurfa/TURKEY, Turkey, +905078097687, nfkan82@gmail.com

ORCİD: 0000-0001-7111-7503

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INTRODUCTION

Myocardial infarction and similar pathologies cause complex alterations in the ventricular structure. Subsequent neurohormonal activations lead to deterioration of ventricular functions by stimulating ventricular remodeling. In the myocardial area where infarctions exist along with an abnormal dilation and tissue weakening, hypertrophication of normal myocardial areas and dilations can be detected [1]. Early diagnosis of left ventricular failure is crucial for managing patients who develop myocardial infarction and coronary artery disease. Thus, determining the predictive data for left ventricular remodeling and diagnosing maladies with non-invasive, simple and reliable methods, along with an efficient treatment, are also crucial.

Carbohydrate antigen-125 (CA-125) is a glycoprotein spotted on ovarian tumor cells which is used to diagnose and follow-up patients with ovarian cancer [2,3]. CA-125 synthesis is not only limited to ovarian cancer. It is also secreted from fetal coelomic epithelial derivatives and mesothelial cells such as endometrium, fallopian tube, peritoneum and pleural pericardium [4]. High CA-125 levels have been determined in heart failure patients [2, 5-7] and elevated CA-125 levels were found to be associated with functional capacity in cardiac insufficiency [5].

In this study, the relationship between serum CA-125 levels and left ventricular functions consisting of left ventricular diastolic diameter (LVDd) and ejection fraction (EF), was investigated in coronary artery bypass graft surgery patients.

MATERIAL and METOD

Ethics and Patient Selection

After designation of study steps, ethical approval was obtained from the local ethical committee (Date 07.06.2021, Session No. 11 and Decision No. 11- HRU/21.11.11) and written informed consent from the patients. Thirty-eight patients who had coronary bypass operation were included to the study. Patients with advanced heart failure (EF<30), concomitant heart valve disease, chronic kidney disease, chronic liver disease, systemic inflammatory disease, chronic obstructive pulmonary disease and malignancy, were excluded from the study.

Transthoracic Echocardiography and CA-125 Measurements

The standard echocardiographic (Vivid S6, GE Vingmed Ultrasound, Horten, Norway) examinations were made by single cardiologist with 2.5–5 MHz probes. Measurements were retrieved by long axis and apical 4 spaces with standard criteria. The modified Simpson method was used for calculation of ejection fraction (EF). Cardiac chamber sizes and other echocardiographic parameters were detected according to previous guidelines [8].

Blood samples was taken from patients and placed in sterile anticoagulant tubes. The tubes were delivered to the laboratory by maintaining the cold chain. Blood samples were centrifuged at 4 000 rpm for 10 minutes. Supernatant plasma was taken into Eppendorf tubes and stored at -80°C. Plasma samples were studied with Human Carbohydrate Antigen-125 (CA-125) ELISA Kit. Results were recorded as kU/L units. Patients were divided into two groups according to EF values (EF< %50 vs. EF≥ %50) and Left ventricular end-diastolic dimension (LVDd) (< 50mm vs. ≥ 50mm) similarly as described in previous studies [9]. Obtained blood parameters and plasma CA-125 levels were compared in each group.

Statistical Analyze

All statistical analyses were calculated by the SPSS 22.0 for Windows. The normal distribution was determined by the Kolmogorov-Smirnov test and histogram. Non-parametric tests were used for calculations. The continuous variables were expressed as median (min-max). The categorical variables were expressed as n (%). The differences of continuous variables were calculated by the Mann Whitney-U test and the Wilcoxon test was used for repeated measures. The Chi-Square test was used to determine the difference between groups of categorical variables. ROC analysis is done for the effect of CA-125 on LVDd measurement and also cut-off point was calculated. $p<0.05$ were considered as statistically significant.

RESULTS

There is no significant difference between LVDd (LVDd < 50mm vs. ≥ 50mm) and EF (EF < 50% vs. EF ≥ 50%) groups in regards of demographic variables, except hypertension. Arterial blood pressure was high in low LVDd group (< 50 mm) (p: 0.006) (Table-1). The mean ages were found to be similar in for all groups (Table-2). Serum neutrophil values were statistically high in low EF group when compare with high EF [(median (min-max): 5.84 (3.8-9.62) vs. 5.07 (2.46-7.55)] (p: 0.048). Mean platelet value (MPV) is higher in low EF group [(median (min-max): 9.17 (7.06-10.27) vs. 7.77 (0-12.4)] (p: 0.040). Similarly lactate dehydrogenase (LDH), aspartate transaminase (AST), troponin-I levels were statistically higher in low EF group (p<0.05). Oppositely triglyceride and VLDL levels were significantly higher in high EF group. Other complete blood counting parameters were statistically not significant between groups (p>0,05) (Table-2). There was no difference in according to blood tests between LVDd groups (< 50mm vs. ≥ 50mm) except CA-125 levels. Incremental CA-125 values were found in high LVDd (≥ 50mm) group when compare with low LVDd (< 50mm) group (p: 0.032). The comparison of CA-125 levels was demonstrated in Figure-1-A and Figure-1-B in regards of LVDd and EF.

The receiver operator characteristic (ROC) curve analysis revealed that the optimal cut-off point 0.644 kU/L of CA-125 level shows 60% (32.9%-82.5%) sensitivity and 78.3% (55.8%-91.7%) specificity (Figure-2) for predicting the disrupted LVDd (≥50mm) [p=0.032 and AUC=0.709 (0.539-0.879; 95%CI].

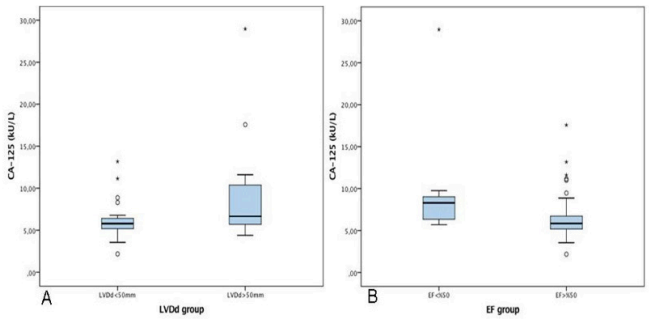
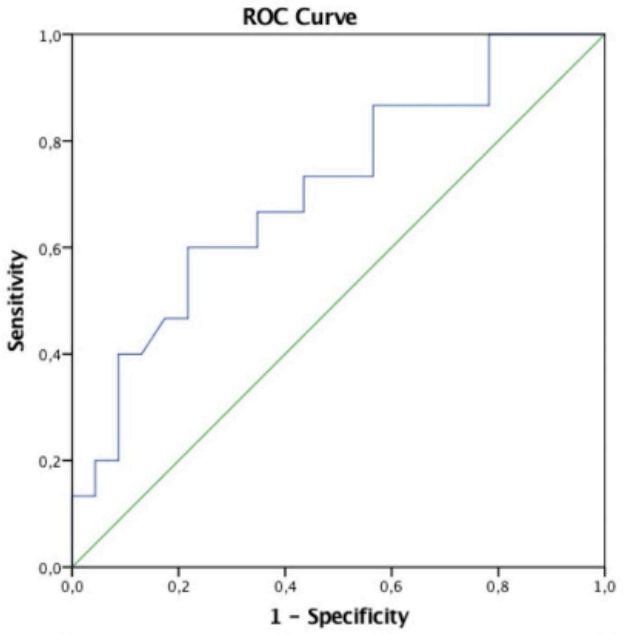


Figure 1. Comparison of CA-125 levels between groups. A= Box-plot graphic of Left Ventricular end-diastolic dimension (LVDd) group. B= Box-plot graphic of ejection fraction (EF) groups.



Area Under Curve

Test Result Variable	Area	Asymptomatic 95% Confidence Interval Lower Bound	Upper Bound
CA-125	0.709	0.539	0.879

Figure 2. ROC curve analyze of CA-125 levels for predicting LVDd (optimal cut-off value of 0.644 kU/L with 60% sensitivity and 78.3% specificity)

DISCUSSION

Serum CA-125 is a biomarker for ovarian carcinomas with peritoneal involvement for decades [10]. CA-125 is a high molecular weight glycoprotein that is similar to mucin and highly detected in disorders with peritoneal irritation. It is released by mesenchymal cells and thus the elevation of this marker is also detected in other sites which include mesenchymal cells, such as pericardium and pleura [11]. Therefore, higher CA-125 levels are detected in pelvic inflammatory disease, cirrhosis with peritoneal acid, and also congestive cardiac failure that have deteriorated with pleural and pericardial effusion [11,12]. After detection of CA-125 expression at epicardial tissue, increased levels of this marker were observed in cardiac pathologies [12]. The first findings of blood cancer markers were reported by Nagele et al. in chronic heart failure patients with heart transplantation and they were first to describe the relationship between heart

Table-1. Comparison of the demographic variances in regards of Left Ventricular end-diastolic dimension (LVDd) and ejection fraction (EF) groups.

		LVDd group		p	EF group		p
		LVDd<50mm	LVDd≥50mm		EF<%50	EF≥%50	
Gender	Female	6 (60%)	4 (40%)	1.000	3 (30%)	7 (70%)	0.351
	Male	17 (60.7%)	11 (39.3%)		4 (14.3%)	24 (85.7%)	
Age		65 (40-77)	61 (48-73)	0.559	58 (48-73)	65 (40-77)	0.692
Smoking	Absent	17 (68%)	8 (32%)	0.191	4 (16%)	21 (%84)	0.672
	Present	6 (46.2%)	7 (53.8%)		3 (23.1%)	10 (76.9%)	
Hypertension	Absent	8 (40%)	12 (60%)	0.006	4 (20%)	16 (80%)	1.000
	Present	15 (83.3%)	3 (16.7%)		3 (16.7%)	15 (83.3%)	
Diabetes mellitus	Absent	14 (56%)	11 (44%)	0.429	4 (16%)	21 (84%)	0.672
	Present	9 (69.2%)	4 (30.8%)		3 (23.1%)	10 (76.9%)	

*Chi-square test

Table-2. Comparison of the blood parameters in regards of Left Ventricular end-diastolic dimension (LVDd) and ejection fraction (EF) groups. (RBC: Red blood cell, WBC: White blood cell, RDW: Red cell distribution width, CA-125: Carbohydrate antigen-125, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, WBC: White Blood Cell, VLDL: Very Low-density lipoprotein, AST: Aspartate transaminase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, PLT: Platelet)

		Total	LVDd group		p*	EF group		p*
			LVDd<50mm	LVDd≥50mm		EF<%50	EF≥%50	
			Median (min-max)			Median (min-max)		
Age (at diagnosis)		63 (40-77)	65 (40-77)	61 (48-73)	0.559	58 (48-73)	65 (40-77)	0.692
Complete blood count	RBC(×10⁶/mm3)	5.01 (2.78-5.71)	5.02 (4.3-5.71)	4.99 (2.78-5.38)	0.226	4.85 (3.92-5.28)	5.02 (2.78-5.71)	0.266
	Hemoglobin (g/dL)	13.1 (9.72-16.2)	13.3 (10.6-16.2)	13.1 (9.72-15.9)	0.378	13.1 (10-14)	13.1 (9.72-16.2)	0.522
	Hematocrit (%)	40.15 (30.8-49)	40.6 (33.9-49)	39.5 (30.8-48)	0.250	39.7 (31.4-43.9)	40.5 (30.8-49)	0.486
	WBC (×10³/mm3)	8.55 (4.56-12.8)	8.58 (4.56-12.8)	8.52 (6.45-11.7)	0.633	9.43 (6.01-12.8)	8.42 (4.56-12.3)	0.127
	Neutrophil (×10³/mm3)	5.16 (2.46-9.62)	4.98 (2.46-9.62)	5.48 (3.25-7.54)	0.124	5.84 (3.8-9.62)	5.07 (2.46-7.55)	0.048**
	Lymphocyte (×10³/mm3)	2.19 (1.02-6.34)	2.2 (1.19-6.34)	2.17 (1.02-4.33)	0.601	2.26 (1.02-3.18)	2.17 (1.19-6.34)	0.925
	Monocyte (×10³/mm3)	0.53 (0.23-1.11)	0.52 (0.3-0.98)	0.54 (0.23-1.11)	0.929	0.56 (0.23-0.91)	0.52 (0.32-1.11)	0.778
	Basophil (×10³/mm3)	0.07 (0.04-0.13)	0.06 (0.04-0.12)	0.07 (0.05-0.13)	0.521	0.07 (0.06-0.1)	0.07 (0.04-0.13)	0.283
	Eosinophil (×10³/mm3)	0.15 (0-0.87)	0.14 (0-0.51)	0.15 (0.01-0.87)	0.940	0.14 (0.01-0.87)	0.15 (0-0.51)	0.970
	PLT (×10³/mm3)	234.5 (152-376)	229 (152-376)	258 (164-372)	0.580	229 (173-372)	240 (152-376)	0.970
	Mean platelet volume (MPV) (fL)	7.87 (0-12.4)	8 (6.57-11)	7.73 (0-12.4)	0.411	9.17 (7.06-10.27)	7.77 (0-12.4)	0.040**
	RDW (fL)	15.15 (12.33-30.7)	15.3 (12.33-30.7)	14.9 (12.78-18.5)	0.238	15.1 (12.33-15.4)	15.2 (12.91-30.7)	0.152
	Neutrophil/Lymphocyte ratio	2.36 (0.78-7.01)	2.17 (0.78-4.25)	2.6 (1.37-7.01)	0.179	2.35 (1.75-7.01)	2.37 (0.78-4.21)	0.292
	Monocyte/Lymphocyte ratio	0.26 (0.07-0.82)	0.26 (0.1-0.66)	0.25 (0.07-0.82)	0.799	0.28 (0.07-0.82)	0.25 (0.1-0.66)	0.692
Laboratory Results	Albumin (g/dL)	3.6 (1.9-4.1)	3.5 (1.9-4.1)	3.6 (2.2-3.8)	0.810	3.79 (1.9-4.1)	3.6 (2.9-4.1)	0.296
	Urea (mg/dL)	36.5 (23-73)	38 (26-60)	35 (23-73)	0.869	38 (30-73)	35 (23-60)	0.235
	Creatinine (mg/dL)	0.85 (0.69-2.33)	0.84 (0.72-1.63)	0.88 (0.69-2.33)	0.940	0.83 (0.69-2.33)	0.86 (0.72-1.63)	0.807
	Na (mEq/dL)	136 (133-141)	136 (133-141)	136 (133-140)	0.762	136 (133-140)	136 (133-141)	0.924
	K (mEq/dL)	4.05 (3.3-5.3)	4 (3.3-5.2)	4.1 (3.6-5.3)	0.177	4.1 (3.9-4.6)	4 (3.3-5.3)	0.416
	Ca (mEq/dL)	9 (7.5-10)	9 (8.1-10)	9.2 (7.5-9.7)	0.242	9.2 (7.5-9.5)	9 (8.1-10)	0.720
	LDH (U/L)	214.5 (132-998)	199 (132-998)	217 (153-679)	0.446	350 (217-998)	207 (132-423)	0.004**
	ALT (U/L)	20.5 (7-91)	20 (10-91)	21 (7-55)	0.676	27 (9-55)	20 (7-91)	0.749
	AST (U/L)	22 (10-174)	24 (10-72)	19 (11-174)	0.169	35 (19-174)	21 (10-72)	0.026**
	Triglyceride (mg/dL)	184.5 (50-721)	195 (93-721)	158 (50-584)	0.226	118 (63-155)	197 (50-721)	0.003**
	Cholesterol (mg/dL)	182 (102-253)	184 (119-248)	172 (102-253)	0.455	198 (102-248)	180 (109-253)	1.000
	HDL (mg/dL)	31 (15-54)	31 (15-54)	31 (16-43)	0.952	34 (16-54)	30 (15-41)	0.059
	LDL (mg/dL)	110.8 (21.6-400)	111.8 (38.6-400)	109.8 (21.6-400)	0.550	125.4 (51-184)	105 (21.6-400)	0.777
	VLDL (mg/dL)	38.6 (10-144)	41.2 (18.6-144)	31.6 (10-116.8)	0.174	23.6 (12.6-31)	41.2 (10-144)	0.003**
	CK-MB (ng/mL)	1.95 (0.7-93.6)	1.7 (0.8-25.1)	2 (0.7-93.6)	0.570	1.7 (0.8-93.6)	2 (0.7-25.1)	0.572
	Troponin-I (ug/L)	0.03 (0-40.38)	0.03 (0-6.72)	0.02 (0-40.38)	0.880	0.45 (0.01-40.38)	0.02 (0-6.72)	0.013**
	Sedimentation Rate	16.5 (3-39)	14 (3-39)	19 (5-39)	0.146	26 (11-39)	15 (3-39)	0.137
	CA-125 (kU/L)	6 (2.17-28.96)	5.79 (2.17-13.17)	6.66 (4.39-28.96)	0.032**	8.3 (5.7-28.96)	5.84 (2.17-17.57)	0.062

*Mann-Whitney-U test, **p<0.05 is statistically significant

functions and serum CA-125 levels [13]. Initial studies reported a faint relation between right ventricle functions and serum CA-125 levels, and insignificant prediction power of serum CA-125 levels for left cardiac functional changes [14]. However, conflicting results were reported in further studies. Varol et al. found that the levels of CA-125 were increased in patients suffering from heart failure with advanced pericardial effusion, in comparison to those suffering from heart failure with not-so-advanced pericardial effusion [7]. Turk et al. showed more pronounced CA-125 levels in patients with heart failure and pleural effusion [15]. D'Aloia et al. detected higher levels of serum CA-125 in heart failure patients with pleural, peritoneal, and pericardial effusion and advanced heart failure patients without effusion [16]. In another study, a relation was described between heart failure functional class and serum CA-125 [5]. Seo et al. detected higher levels of CA-125 in 65% of heart failure patients with different etiologies [17]. They found increased levels of CA-125 in patients with more effusion and echocardiographically witnessed that levels of CA-125 decreased and/or came down to normal levels, following decreased and/or disappeared effusion level. In the same study, they painted the pericardial autopsy material with anti-CA-125 and meaningfully detected higher levels of serum and pericardial CA-125 in anti-CA-125 positive patients. Judging from these results, they commented that CA-125 is a pericardial fluid producer. Kouris et al. evaluated the relationship between heart failure functional classes and tumor markers [6]. They found higher levels of CA-125 in patients with heart failure. At the same time, they observed elevated levels of CA-125 in correlation with functional class. They could not detect any relationship between CA-125 and left ventricular EF, EDV (end-diastolic volume) and the medical treatment provided. Battaloğlu et al. studied the effectiveness of plasma CA-125 and carcinoembryonic antigen (CEA) values in patients that underwent cardiopulmonary bypass surgery. They formed two groups: on-pump and off-pump. They could not find a meaningful difference in levels of CEA in any of the groups. But CA 125 values elevated significantly both on-pump and off-pump groups. They commented that cardiopulmonary bypass caused elevated levels of serum CA-125 [18]. Durak – Nalbantic et al. found that serum CA-125 levels were higher in patients with pleural or pericardial fluid [19]. Vizzardi et al. found that elevated serum CA-125 levels were an effective long-term prognostic marker in patients with mild-to-moderate heart failure, in patients with cardiovascular events [20]. Rong X et al. detected that elevated serum CA-125 levels could help to predict short-term cardiac insufficiency in patients with coronary artery disease [21]. Li J. et al. showed that increased perioperative serum CA-125 levels were an independent predictor of worse clinical outcomes at the one-year follow-up, after off-pump coronary artery bypass surgery [22]. In all of these studies, increased serum CA-125 levels were associated with heart failure.

Changes in cardiac workload alter left ventricular dimensions through adaptive remodeling of the myocardium. Therefore, end-diastolic volumes are considered to be a determinant of remodeling and a good indicator of functional capacity [23]. In patients with heart failure, left ventricular systolic and diastolic cavity dilations are signs of deterioration of ventricular functions and have a significant effect on mortality. Studies have shown that left ventricular dilation is one of the markers of cardiac dysfunction. Increased left ventricular cavity sizes aggravate mortality rates. A positive correlation is observed between patients with high LVDd values and mortality in patients with similar comorbidities [24].

We found incremental CA-125 values in patients with LVDd≥50mm. Furthermore, our results showed that CA-125 levels (optimal cut-off point of 0.644 kU/L) indicate disrupted LVDd with 60% sensitivity and 78.3% specificity. The relationship between LVDd - which is a predictable parameter of left ventricular dysfunction - and CA-125 values were evaluated. The increase in ventricular size and decrease in functional capacity at the end of diastole has been observed to increase CA-125 levels. These results suggest that CA-125 values above a certain level may indicate remodeling and related left ventricular enlargement.

Limitations

The first limitation is the low number of patients participating in our research. The second limitation is that plasma CA-125 levels are not compared

with healthy individuals. Finally, CA-125 values were not studied in pericardial fluid and pericardial tissue samples, as was done in some previous studies.

CONCLUSION

Our results indicated that increased CA-125 level is an independent predictor for higher LVDd. Moreover, screening of serum CA-125 levels can be useful for left ventricular diastolic dimension with an acceptable sensitivity and specificity. Increased levels of CA-125 may be one of the serious markers of left ventricular dysfunction and cardiac remodeling. Studies with larger patient groups are thought to provide a more detailed understanding of CA-125 and ventricular functions.

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ORCID and Author Contributions: NK (0000-0001-7111-7503): Concept and design, materials, practices, data collection and processing, interpretation, literature search, writing, critical review.

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RESEARCH ARTICLE

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Detection of intestinal parasites by different methods in our type 2 diabetic patients

Tip 2 diyabetik hastalarımızda farklı metotlarla intestinal parazitlerin tespiti

Müge Özsan Yılmaz[1*]

1.Hatay Mustafa Kemal University Faculty of Medicine, Endocrinology and Metabolism Department, Hatay, Turkey

ABSTRACT

Aim: Long term persistently high blood glucose levels result in various complications and conditions in diabetic patients. One of them is gastrointestinal disorders and the other is increased risk of infectious diseases like parasitosis. The aim of the study is to demonstrate of intestinal parasites with various techniques in diabetic patients and **confirm of the frequency of the parasites.**

Methods: A total of 65 patients with type 2 Diabetes Mellitus were included in the study. Laboratory tests were done and gastrointestinal symptoms were recorded. Fecal specimens were evaluated with direct microscopy, Kinyoun acid-fast staining method, trichrome staining method and antigen screening test.

Results: Of the patients included in the study 31 were male and 34 were female. While 53.8% of the patients had no chronic complications of diabetes, 33.8% had multiple complications. Thirty (46.2%) patients had gastrointestinal complaints. Examination of stool samples revealed G. intestinalis in two patients (3.07%) , C. parvum in three patients (4.6%), and G. intestinalis + E. histolytica in six patients (9.2%) by RAT. No association was found between the existence of parasite determined by RAT and any of the patient characteristics of age, sex, duration of diabetes, and dyspeptic complaints (p-values are 0.27; 0.14; 0.90; 0.68, respectively).

Conclusion: This is the first study to explore the prevalence rate of parasitosis detected by RAT in patients with diabetes. In this study, we also compared different parasite detection methods in this patient population and showed that RAT is a more sensitive method.

Keywords: Type 2 Diabetes Mellitus, Parasitic Intestinal Diseases, Gastrointestinal Disorders, antigen, microscopy

ÖZ

Amaç: Uzun süreli kalıcı yüksek kan şekeri seviyeleri diyabetik hastalarda çeşitli olumsuz sonuçlara yol açar. Bunlardan bir tanesi gastrointestinal bozukluklar ve bir diğeri de parazitozlar gibi enfeksiyöz hastalıklardaki risk artışıdır. Bu çalışmanın amacı diyabetik hastalarda bağırsak parazitlerinin çeşitli tekniklerle gösterilmesi ve sıklığının belirlenmesidir.

Yöntemler: Çalışmaya 65 tip 2 diyabet hastası dahil edildi. Rutin laboratuvar testleri yapıldı ve semptomları kaydedildi. Fekal örneklerde direkt mikroskopi, Kinyoun asit fast boyama, trikrom boyama, hızlı antijen tarama(HAT) teknikleriyle intestinal parazit arandı.

Bulgular: Çalışmaya dahil edilen hastaların 31' i erkek, 34'ü kadın cinsiyette idi. Hastaların %53.8'inde diyabetin kronik komplikasyonu mevcut olmayıp, %33.8'inde çoklu komplikasyon mevcuttu. Otuz (%46,2) hastada gastrointestinal şikayetler tespit edildi. Dışkı örneklerinin incelenmesinde HAT ile iki hastada (%3.07) G. intestinalis, üç hastada (%4.6) C. parvum ve altı hastada (%9.2) G. intestinalis + E. histolytica tespit edildi. HAT ile belirlenen parazit varlığı ile yaş, cinsiyet, diyabet süresi ve dispeptik şikayetler gibi hasta özelliklerinden herhangi biri arasında ilişki bulunmadı (p değerleri sırasıyla 0,27; 0,14; 0,90; 0,68'dir).

Sonuç: Bu çalışma diyabetik hastalarda HAT ile parazitoz prevalansını araştıran ilk çalışmadır. Ayrıca bu çalışmada bu hasta popülasyonunda farklı parazit tespit yöntemlerini de karşılaştırdık ve HAT'ın daha sensitif bir yöntem olduğunu gösterdik.

Anahtar kelimeler: Tip 2 Diabetes Mellitus, parazitik bağırsak hastalıkları, gastrointestinal hastalıklar, antijen, mikroskopİ

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*Corresponding Author: Müge ÖZSAN YILMAZ, Hatay Mustafa Kemal University Faculty of Medicine, Endocrinology and Metabolism Department, Hatay, Turkey, +903262291000, mozsan@mku.edu.tr

ORCİD: 0000-0001-8346-8941

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Introduction

Diabetes mellitus is a chronic disorder of carbohydrate, lipid and protein metabolism which may result from a total or partial deficiency of insulin or resistance against insulin action in peripheral tissues. Long term persistently high blood glucose levels result in various complications. Furthermore, in diabetic patients, the frequency of gastrointestinal (GI) symptoms is increased. Although the exact pathogenesis of diabetes related GI disease is not known clearly, it is thought that the underlying gastroparesis, depression, and anxiety disorders may induce these symptoms [1]. It was concluded that poor glycemic control might increase the frequency of these symptoms in various studies, albeit with conflicting results [2].

Diabetes mellitus increases the risk of infections. Neutrophil chemotaxis, adherence of neutrophil to the vascular endothelium, phagocytosis, intracellular bactericidal activity, opsonization, and cellular immunity are suppressed in case of persistent hyperglycemia [3]. Because of these disturbances diabetes may acceptable as immunodeficiency condition. Immundeficient patients are more susceptible to infections with opportunistic parasites such as Entamoeba histolytica, Cryptosporidium parvum, and Giardia intestinalis. Host-parasite interactions and a decline in or loss of host's resistance to parasites play a role in the transformation of parasites to the pathogen status or increase in their pathogenicity [4].

Amebiasis remains a significant health problem for developing countries [5]. Humans are infected by two species of Entamoeba, which are morphologically indistinguishable. These are infective E.histolytica and nonpathogen E. dispar. The differential diagnosis for E.histolytica and E. dispar can be achieved by the detection of specific antigens.

Cryptosporidium species are one of the commonly detected parasites in humans, domestic animals, and wild vertebrates [6]. While cryptosporidiosis causes mild diarrhea in immunocompetent individuals, it can cause life-threatening severe diarrhea and respiratory system infection in immunocompromised patients [7].

G. intestinalis is one of the leading culprits of endemic and epidemic diarrheas globally. The prevalence of giardiasis varies between 1.9% – 37.7% in studies conducted in Turkey [8,9]. Giardiasis, which might be seen in acute and chronic forms, could be asymptomatic and also cause life-threatening diarrhea.

Several studies were published as to the diagnosis of intestinal parasites in various patient groups in our country [4,10-12]. To the best of our knowledge, there is no study in the literature studying prevalence rates of amebiasis, giardiasis, and cryptosporidiosis by Rapid Antigen Test (RAT) in diabetic subjects. Hence, we aimed to investigate frequencies of amebiasis, giardiasis, and cryptosporidiosis in diabetic patients by means of an antigen screening test and to study whether there is an association between these parasites and diabetic gastrointestinal complaints. We also planned to compare the rate of parasite presence by different laboratory techniques.

Methods

A total of 65 patients with Type 2 Diabetes Mellitus and aged 18 to 65 who were assessed at adult Endocrinology and Metabolism outpatient clinic between January and June 2016 were included in this prospective study. An informed consent form was signed by all patients who were eligible for the study and wished to participate. The patients who have any gastrointestinal malignancy and immunosuppressive condition history or presence of clinically significant chronic disease other than diabetes mellitus were excluded. Age, gender, and concomitant diseases of the patients were recorded.

Serum glucose, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium (Na), potassium (K), hemoglobin A1c (HbA1c) and complete blood count (CBC) were measured in all participants. CBC tests were done with Mindray BC 6000 (Mindray Co., Shenzhen, China) a haematology device. Biochemistry parameters (Glucose, creatinin, AST, ALT, Na, K, Albumin, Calcium, Phosphorus, Magnesium, Total cholesterol, HDL cholesterol, LDL cholesterol, Triglyceride) were studied by spectrophotometric method in Siemens Advia 1800 biochemistry autoanalyzer (Siemens, Germany) and HbA1c

levels were studied by HPLC (High Performance Liquid Chromatography).

Patients were questioned in detail in terms of chronic complications of diabetes and the findings were supported by hospital records. Patients for whom appropriate and sufficient information could not be obtained from their anamnesis and records were screened for chronic complications. For this purpose, fundus examination was done for diabetic retinopathy, sensory examination evaluation of orthostatic hypotension for diabetic neuropathy, microalbumin level in 24-hour urine and GFR calculation for diabetic nephropathy, detailed cardiac examination, Doppler USG for carotid and peripheral arteries, and angiographic examinations were performed when necessary.

Patients were questioned regarding gastrointestinal symptoms such as postprandial fullness, early satiety, epigastric pain, epigastric burning, diarrhea, constipation for the last three months. If the patient had at least one of these symptoms, it was deemed that the patients had dyspepsia. Fecal specimens collected from 65 patients were brought to the Parasitology Laboratory in which direct microscopy results were obtained by precipitation with native, Lugol's iodine and formalin ethyl acetate techniques by a consultant parasitologist. Samples were also examined for intestinal parasites using Kinyoun acid-fast staining method, trichrome staining method, and antigen screening test.

1-Kinyoun Acid-Fast Staining Method: Smears were prepared from the collected stool samples and allowed to dry. Then, they were fixed in pure methanol for one minute. The smears were stained with Kinyoun carbol fuchsin for five minutes and then shaken with 50% alcohol. After that, the specimens were washed with tap water and held in a chalet containing 1% sulfuric acid for two minutes and then washed in the tap water again. After leaving for one minute in the methylene blue-containing chalet, they were washed with the tap water, then dried and examined via 100X objective of a microscope [13].

2-Conventional Trichrome Staining Method: Stool samples were spread on the slides. After the edges of slides began to dry, they were held in the Schaudinn fixative at least half an hour. Respectively, they were left in 70% ethyl alcohol for five minutes, in iodine solution of D'Antoni for three minutes, in two chalets containing 70% ethyl alcohol for two and five minutes, and in trichrome staining solution for eight minutes. Then, excess dye on the slides was removed. They were soaked three times in 90% acid-alcohol and shaken in two chalets containing 95% ethyl alcohol. The slides were held in two chalets containing carbol-xylene for two and five minutes, in two chalets containing xylene for two and five minutes, and then they were allowed to dry.

3-RIDA Quick Cryptosporidium / Giardia / Entamoeba Combicasette antigen test (R-Biopharm AG, Germany) was used as an antigen screening test. The rapid antigen test (RAT) is a one-step immunochromatographic lateral flow test. The specific antibodies themselves directed against each parasite bind to green (Entamoeba specific), red (Giardia specific), or blue (Cryptosporidia specific) latex particles. Other antibodies specific to these three pathogens bind firmly to the membrane. The stool sample is suspended in the extraction buffer and then precipitates. Clear supernatant part of the sample is placed on the test area.

Ethics committee approval of the study was obtained from Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine Clinical Research Ethics Committee with the decision number 131, dated 17.11.2015.

Statistical analysis

Data were recorded to SPSS 21 System with double check and analyzed using SPSS 21 with 95% confidence. After evaluating normality with Shapiro Wilk test, Student-t test was used for normally distributed data and Mann Whitney U test was used for data not normally distributed. In categorical data, chi-square tests were used. The significance limit for all tests was set at 0.05. ROC analysis was performed to evaluate whether there would be parasitosis according to the WBC value. The performance of the assay was calculated by the area under the curve (AUC) sensitivity and specificity values. In addition, PPV (positive predictive value), NPV(negative predictive value), Sen (Sensitivity) and Spe (Specifity) values were calculated for RAT when direct microscopy was

accepted as gold standard.

Results

Sixty-five patients with type 2 Diabetes Mellitus were included in the study. Of all participants, 47.7% (n=31) were males, and 52.3% (n=34) were females. The mean age of the patients was 51.5 ± 12.3 years. 53.8% of the patients had hypertension and 52.3% had hyperlipidemia. The median duration of diabetes mellitus diagnosis was 7 (1-20) years. While 53.8% of the patients had no chronic complications of diabetes, 33.8% had multiple complications. Thirty (46.2%) patients had gastrointestinal complaints, of which nineteen (n=19) had dyspepsia and the rest had constipation or diarrhea. The frequency of gastrointestinal complaints was 44.1% (n=15) in women and 45.1% (n=14) in men (p=0.87).

Examination of stool samples revealed C. parvum in one patient (1.5%) by Kinyoun method, G. intestinalis + E. histolytica in six patients (9.2%) by trichrom method, G. intestinalis in seven patients (10.7%) by direct microscopy, G. intestinalis in two patients (3.07%) , C. parvum in three patients (4.6%), and G. intestinalis + E. histolytica in six patients (9.2%) by RAT. No association was found between the existence of parasite determined by RAT and any of the patient characteristics of age, sex, duration of diabetes, and dyspeptic complaints (p-values are 0.27, 0.14, 0.90, 0.68, respectively). No association was found between HbA1c and other biochemical parameters and the existence of parasite (Table 1). There was not an association between the presence of parasite and hemoglobin, eosinophil, and lymphocyte counts (p>0.05). The association between the number of white blood cells (WBC) and the existence of parasites was not statistically significant. However, the frequency of parasite positivity increased as the number of WBCs decreased (Table 1). The area under the curve (AUC) was calculated as 0.711 and p=0.023 in the ROC analysis based on the presence or absence of parasites for the WBCs. The cut-off value for the WBCs was calculated as 6860 /μL with 66% sensitivity and 77% specificity (Figure 1).

No significant association between the parasite positivity and diabetic complications such as diabetic neuropathy, retinopathy, coronary artery disease, cerebrovascular disease and comorbidities was found, either (p>0.05) (Table 2).

When the RAT was compared with other methods in terms of parasite evaluation, the samples deemed as negative by direct microscopy was negative in 91.4% of the samples studied with RAT method, as well. All samples that were considered as positive by direct microscopy were also found to be positive with RAT (Table 3).

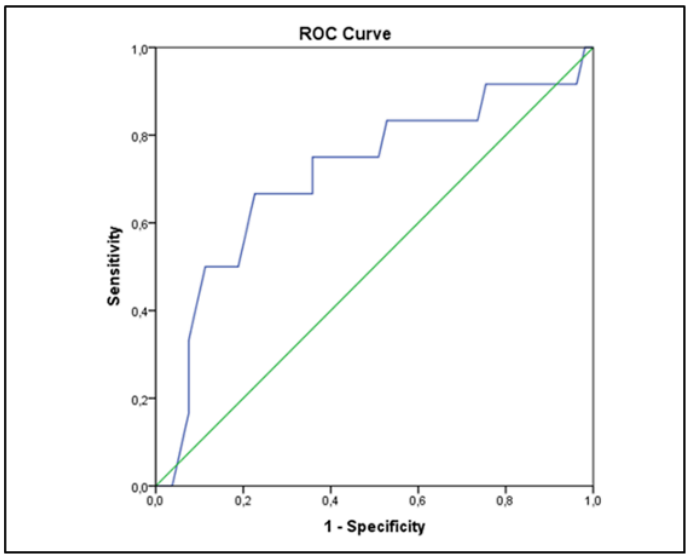

Figure 1. Association between existence of parasites and white blood cell count

Discussion

As the number of people with diabetes increases rapidly the associated complications of diabetes will increase inevitably. In the long term, diabetes leads to chronic complications including various gastrointestinal symptoms in which neuropathy is an important causative factor. The prevalence of these symptoms varies according to ethnic groups and the type of diabetes [1]. While it has been reported that gastric emptying is delayed in 25-55% of type 1 diabetic patients, and in 30% of type 2 diabetic patients, the prevalence of gastroparesis in the community has been reported to be approximately 5% in Type 1 diabetes and 1% in Type 2 diabetes [14]. In our study, 46.2% of diabetic patients had gastrointestinal symptoms, most common of which were dyspepsia and constipation/diarrhea. Gastrointestinal complaints related to diabetes are known to be more prevalent among women. The reason for this difference could

Table1. Association between existence of parasites and biochemical and hemogram results

	Parasite (+)*			Parasite (-)*			p
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	
A1C (%)	8.97±2.24	8.80	6.4-16.4	8.85±1.34	8.80	6.8-11.5	0.899
Glucose (mg/dL)	198.81±79.84	193.00	87-391	176.83±84.49	145.00	100-400	0.290
Creatinin (mg/dL)	0.82±0.14	0.79	0.56-1.39	0.97±0.26	0.90	0.56-1.39	0.029
LDL-chol (mg/dL)	118.58±63.33	104.00	7-363	91.92±42.38	89.50	7-163	0.099
HDL-chol (mg/dL)	41.88±16.61	41.00	13-129	37.83±8.93	40.50	19-51	0.388
Total chol (mg/dL)	209.24±110.08	188.00	78-838	243.42±190.63	192.00	144-838	0.806
Triglyceride (mg/dL)	192.11±144.05	157.00	49-846	218.08±179.2	163.00	68-711	0.919
AST (U/L)	22.21±12.48	18.00	9-67	21.67±5.66	22.00	11-31	0.330
ALT(U/L)	23.79±13.1	17.00	7-60	24.58±7.9	26.00	13-38	0.466
Na (mmol/L)	137.53±2.4	138.00	132-141	136.33±1.72	137.00	134-139	0.058
K (mmol/L)	4.54±0.44	4.40	3.6-5.5	4.45±0.38	4.45	3.6-4.9	0.568
Albumin (g/dL)	3.64±0.25	3.60	3.2-4.3	3.7±0.29	3.75	3.2-4.3	0.388
Ca (mg/dL)	8.97±0.37	9.10	8.4-10.4	9.11±0.51	9.10	8.5-10.4	0.490
P (mg/dL)	3.74±0.62	3.70	2.4-5.2	3.85±0.71	3.66	3-5.2	0.965
Mg (mg/dL)	1.84±0.26	1.80	1.4-2.72	1.84±0.13	1.80	1.56-2.05	0.413
WBC /µL	7191.33±2041.92	6595.00	5200-12070	8669.02±2134.01	8150.00	4400-12970	0.023
Eosinophil /µL	186.67±130.55	160.00	0-450	236.79±170.05	190.00	0-660	0.462
Lymphocyte/µL	2324.17±883.4	2405.00	950-3590	2790.94±1094.55	2830.00	70-6490	0.148
Platelet /µL	255.83±52.82	249.50	176-344	292.62±96.6	265.00	150-554	0.374

*with Rapid Antigen Test, SD: Standard deviation, Min: Minimum, Max: Maximum, LDL-chol: Low density lipoprotein cholesterol, HDL-chol: High density lipoprotein cholesterol, Total chol:Total cholesterol, AST: Alanine aminotranspherase, AST: Aspartate aminotranspherase, Na:Sodium, K:potassium, P:Phosfor, Mg:Magnesium, WBC: White Blood Cell, p:Statistical significance for Student-t and Mann-Whitney U tests, p≤0,05

Table 2. Association between existence of parasites and comorbidity, complications

Comorbidity / Complications		n/ percent	Parasite (-)*	Parasite (+)*	p
Hypertension	(-)	n	24	6	0.767
		%	80.0	20.0	
	(+)	n	29	6	
		%	82.9	17.1	
Dislipidemia	(-)	n	24	7	0.414
		%	77.4	22.6	
	(+)	n	29	5	
		%	85.3	14.7	
Complications	(-)	n	29	6	0.263
		%	82.9	17.1	
	Neuropathy	n	3	0	
		%	100.0	0.0	
	Retinopathy	n	0	1	
		%	0.0	100.0	
	Coronary arter disease	n	2	0	
		%	100.0	0.0	
	Cerebrovascular disease	n	1	1	
		%	50.0	50.0	
	Multiple complications	n	18	4	
			81.8	18.2	

Table 3. Association between rapid antigen test and the other tests

Comorbidity / Complications		n/ percent	Parasite (-)*	Parasite (+)*	p
Kinyoun	Negative	n	53	11	0.185
		%	82.8%	17.2%	
	C. parvum	n	0	1	
		%	0,0%	100,0%	
Trichrom	Negative	n	53	6	0.001
		%	89.8%	10.2%	
	G. Intestinalis + E. histolytica	n	0	6	
		%	0.0%	100.0%	
Direct microscopy	Negative	n	53	5	0,001
		%	91.4%	8.6%	
	G. Intestinalis	n	0	7	
			0.0%	100.0%	

*with Rapid Antigen Test, PPV=0.58, NPV=1.00, Sen=1.00 and Spe=0.91 for RAT, PPV: Positive predictive value, NPV: Negative predictive value, Sen: Sensitivity, Spe: Spesifity, RAT:Rapid Antigen Test, C. parvum: Cryptosporodium parvum, G. Intestinalis: Giardia intestinalis, E. histolytica: Entamoeba histolytica n: Number of patients, p:Statistical significance for Chi-square test, p≤0,05

not be explained clearly yet, but it is associated with a high prevalence of abdominal bloating/ fullness in women [15]. However, our results revealed that the prevalence of these complaints was similar between females and males (44.1%; 45.1%, respectively).

Although the entire pathogenetic process of gastrointestinal complications of diabetes mellitus is not well understood; gastroparesis, depression, and anxiety disorders may impact these symptoms. The effect of poorly controlled diabetes on these symptoms is not clear. However, it is known that the level of glycemic control affects gastric emptying [1]. Persistent poor glycemic control may lead to damage to the vagus nerve, and autonomic neuropathy in diabetic patients. This process usually takes about ten years [16]. Poor glycemic control can shorten this duration. However, it is controversial whether it increases symptoms [1,2]. Although the median duration of diabetes was seven years in our patients, higher HbA1c mean value could explain the more frequent gastrointestinal symptoms in our study population.

The pathogenesis of functional gastrointestinal disorders is poorly understood in healthy population as well as in diabetic patients, however, factors such as prolonged gastric emptying, tenderness in stomach tension, and infiltration of the duodenum with inflammatory cells might impact pathogenesis [17,18].

Chronic dyspeptic complaints can be observed following bowel infections. Many pathogens including G. intestinalis were held responsible for the development of these complaints [19]. While E. histolytica causes acute abdominal pain and diarrhea, it may also give rise to abscess formation throughout the body, especially in the liver. C. parvum may present as a diarrheal illness in immunocompromised individuals [4,5]. In our study, we did not show any association between the presence of any of the parasites studied and the symptoms such as dyspepsia, constipation, and diarrhea. This may be in part due to the small number of participants in this study.

Parasitic diseases still pose a significant health problem for underdeveloped and developing countries. These diseases are among the important causes of the morbidity and the mortality in these regions. For example; every year, 50 million people in the world are infected with amebiasis, only 10% of them are symptomatic and 100 000 people die [5]. In Turkey, intestinal parasitosis is common in regions where infrastructure problems could not be solved, and compliance with personal hygiene is poor.

Diabetes increases the risk of various infections. Hyperglycemia and hyperglycemia-induced reduction in immune response, vascular insufficiency, peripheral and autonomic neuropathy, colonization of skin and mucosa with some microorganisms are among the causes of this predisposition. Hyperglycemia affects chemotaxis of neutrophils, adherence to vascular endothelium, phagocytosis, intracellular bactericidal activity, opsonization, and cellular immunity favorably [3]. Immunosuppressed patients are more likely to be infected with opportunistic parasites such as E. histolytica, C. parvum, and G. intestinalis. Host-parasite associations and decrease or complete loss of host resistance to parasites play a role in the transformation of parasites into a pathogen or increased pathogenicity [4]. Our results demonstrated that as the number of WBCs, which is an indicator of the host's reaction to parasites, was lower than approximately 7000/μL, the prevalence of parasitosis increased.

There are various studies in the literature reporting the prevalence of different parasites in diabetic patients. In a study of 100 diabetic patients from Egypt, G. intestinalis was detected in 22%, E. histolytica in 7% and C. parvum in 5% of the patients [20]. In another study involving more patients, the prevalence of C. parvum was reported as 8.4% [21]. In another study, the prevalence of G. intestinalis was 13%, while E. histolytica was seen in 1% [22]. In a study conducted in our country, the prevalence of G. intestinalis in diabetic patients was found to be 15% [23]. In our study, the prevalence of all parasites combined was 16.9% studied by RAT, which had the highest sensitivity among the techniques we utilized. The prevalence rates of parasites in our study were 4.6% for C. parvum and 3% for G. intestinalis. The prevalence of G. intestinalis was less than other studies reported in the literature, for which a relatively small sample size of our study could

account. In our research, while E. histolytica was not seen alone, the prevalence of it with G. intestinalis was 9.2%. The prevalence of multiple parasitic infestations was higher in our study, as in other studies [21,22].

Uyar and Taylan Ozkan reported that the diagnosis of G. intestinalis and other protozoa was usually made by direct microscopic examination and it was a cheap technique [24]. However, they stated that the microscopic examination, especially by augmentation methods, was demanding and required experienced staff, and intensive work. On the contrary, antigen detection methods (Direct fluorescent antibody-DFA, enzyme immunoassay-EIA, rapid antigen tests-RAT) are useful in the diagnosis of protozoa because they are rapid and do not require experienced staff [24].

Aziz et al. emphasized that immunological methods such as DFA were more sensitive, useful, faster, and cost-effective than traditional microscopic techniques in the diagnosis of G. intestinalis [25]. Also evident in our patient group, RATs can provide a practical, early, and safe diagnosis for immunocompromised patients in centers that do not have adequate laboratory equipment and experienced staff.

Limitations of the Study:

Despite the interesting findings, the main and the first limitation of our study was the sample size. The sample size available was small. If we had a larger number of patients, we could have divided them into subgroups according to the characteristics of the patients especially for diabetic neuropathy existence. We could obtain more significant results in these subgroups in terms of parasitosis. Second we did not have a control group to account for the prevalence of parasitosis in the general population in our region. In addition, we did not use any objective measure to diagnose specific types of diabetic gastrointestinal complications such as gastric emptying study.

Conclusion

Since cellular immunity is defective in diabetic patients it has been assumed that frequency of parasitic infestations might increase among diabetic patients, which is confirmed in some but not all studies. Our results revealed a similar frequency of intestinal parasitic infections reported in the literature; however, it seems that the most sensitive method to detect these infections is antigen screening test. With such easy to use tests, diabetic patients can easily be screened with this regard. Hence, we can distinguish gastrointestinal symptoms related to diabetic intestinal autonomous neuropathy from those related to intestinal parasites. Parasitosis such as E. histolytica, C. parvum, G. intestinalis may have an effect on gastrointestinal problems in diabetic patients, but large sample studies are required to demonstrate these associations.

Although we have some limitations in this study on the other hand it has some strength as well. This is the first study to explore the prevalence rate of parasitosis detected by RAT in diabetic patients. Furthermore, we also compared different parasite detection laboratory methods in this patient population.

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Validation and Efficiency of a Scoring System Used in the Differentiation of Uncomplicated Appendicitis

Komplike Olmayan Apandisit Ayırımında Kullanılan Bir Puanlama Sisteminin Geçerliliği ve Etkinliği

Mehmet Kubat [1*], Serdar Şahin[2]

1.Department of General Surgery, Alanya Training and Research Hospital, Alanya, Turkey
2.Department of General Surgery, Ahi Evran University, Kırşehir, Turkey

ABSTRACT

Objective: Various parameters are used to differentiate between complicated and uncomplicated appendicitis cases, and scoring systems are even created where these parameters are used together. The aim of this study was to evaluate the effectiveness of one of these scoring systems by external validation.
Methodology: Retrospective evaluation was performed on the clinical, radiological and laboratory findings of patients who underwent an appendectomy between January 2018 and January 2021. Scoring was performed using the previously described scoring systems for each patient considered to have acute appendicitis as a result of imaging. They were divided into complicated appendicitis and uncomplicated appendicitis groups, according to clinical and pathological evaluation results.
Results: While evaluating 425 patients, ultrasonography was used in 48% and tomography in 52% of the patients. Significant effectiveness of the score of ≤6 was observed in the group using tomography (p<0.001, AUC: 0.838, Sensitivity 83.3%, positive predictive value 50.8%, specificity 84.3%, negative predictive value 96.3%). Significant effectiveness of the score of ≤5 was observed in the ultrasonography group (p<0.001, AUC: 0.790, Sensitivity 85.7%, positive predictive value 39.0%, specificity 72.2%, negative predictive value 96.1%).
Conclusion: The scoring system created for the selection of uncomplicated appendicitis cases has been shown to be effective and has been externally validated. Since each of the parameters used in the scoring system has higher efficiency than its independent effectiveness, scoring systems that evaluate clinical, radiological and laboratory variables together, give better results in clinical practice.

Keywords: Acute appendicitis, Complicated appendicitis, Uncomplicated appendicitis, Scoring system, Ultrasonography, Tomography

ÖZ

Amaç: Komplike-komplike olmayan apandisit vakalarını ayırt etmek için çeşitli parametreler kullanılmakta ve hatta bu parametrelerin birlikte kullanıldığı skorlama sistemleri oluşturulmaktadır. Bu çalışmanın amacı, bu puanlama sistemlerinden birinin etkinliğini dış doğrulama ile değerlendirmektir.
Yöntemler: Ocak 2018-Ocak 2021 tarihleri arasında apendektomi yapılan hastaların klinik, radyolojik ve laboratuvar bulguları retrospektif olarak değerlendirildi. Görüntüleme sonucunda akut apandisit düşünülen her hasta için daha önce tanımlanan skorlama sistemleri kullanılarak skorlama yapıldı. Klinik ve patolojik değerlendirme sonuçlarına göre komplike apandisit ve komplike olmayan apandisit gruplarına ayrıldılar.
Bulgular: 425 hasta değerlendirilirken hastaların %48'inde ultrasonografi, %52'sinde tomografi kullanıldı. Tomografi kullanan grupta ≤6 puanın anlamlı etkinliği gözlendi (p<0,001, EAA: 0.838, Duyarlılık %83,3, pozitif öngörü değeri %50,8, özgüllük %84,3, negatif öngörü değeri %96,3). Ultrasonografi grubunda ≤5 skorunun anlamlı etkinliği gözlendi (p<0,001, EAA: 0.790, Duyarlılık %85,7, pozitif prediktif değer %39,0, spesifisite %72,2, negatif prediktif değer %96,1).
Sonuç: Komplike olmayan apandisit vakalarının seçimi için oluşturulan puanlama sisteminin etkili olduğu gösterilmiştir ve harici olarak doğrulanmıştır. Skorlama sisteminde kullanılan parametrelerin her biri bağımsız etkinliğinden daha yüksek verimliliğe sahip olduğundan; klinik, radyolojik ve laboratuvar değişkenlerini bir arada değerlendiren skorlama sistemleri klinik uygulamada daha iyi sonuçlar vermektedir.

Anahtar Kelimeler: Akut apandisit, Komplike apandisit, Komplike olmayan apandisit, Skorlama sistemi, Ultrasonografi, Tomografi

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*Corresponding Author: Mehmet KUBAT, Department of General Surgery, Alanya Training and Research Hospital, 07400, Alanya/Antalya, Turkey, +905332342155, dr.m.kubat@gmail.com

ORCİD: 0000-0002-3422-194X

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INTRODUCTION

The usability of medical and minimally invasive treatment methods is being evaluated even in some diseases where surgery is preferred as the gold standard in the treatment [1,2]. One of these diseases is acute appendicitis (AA), which is one of the most common causes of emergency surgery in the adult patient group [3]. Perforation, gangrene and abscess are observed in some of the AA cases, and these cases are defined as complicated appendicitis [4]. The distinction between complicated acute appendicitis (CAA) and uncomplicated acute appendicitis (UCAA) gains importance, in particular in the planning of non-surgical treatment. There have been studies showing the success of conservative treatment in selected UCAA cases [5]. The selection criteria and treatment plans of the patient group should be more clearly defined, therefore it is necessary to achieve selectivity where the specificity is higher for the UCAA. The effectiveness of many clinical, laboratory and radiological parameters has been and is still being evaluated to be used in the differentiation of CAA/UCAA [6-9]. It has been stated that this distinction cannot reach a sufficient level with the use of imaging methods alone [10].

Scoring systems can prevent the low efficiency obtained when the parameters are evaluated alone. For this reason, they are quite frequently used in the healthcare system [11]. Evaluating the increasing numbers of parameters together increases the precision of the result. The scoring systems created by using the clinical, laboratory and radiological results of the patients were evaluated and the results were used in the differentiation of UCAA [12,13].

The aim of our study was to evaluate the usability and effectiveness of a scoring system designed to differentiate UCAA cases by using clinical, radiological and laboratory parameters in our patient group.

METHODOLOGY

A retrospective evaluation was performed on the files of patients (≥18 years) who underwent an appendectomy with the pre-diagnosis of acute appendicitis, from January 2018 to January 2021, at the Alanya Training and Research Hospital. Patient information, medical history, clinical findings, laboratory findings and pathology results were recorded.

While forming the study group, attention was paid to the fact that radiological examination was performed in the preoperative period, AA results were obtained via this imaging, and the laboratory and clinical results used in the study in the preoperative period were fully recorded. Patients with additional diseases that may have affected laboratory and/or clinical results, such as chronic inflammatory diseases (Crohn Disease, Familial Mediterranean Fever, Kawasaki disease, rheumatoid arthritis, systemic lupus erythematosus etc.) and hematological malignancies (leukemias etc.) that change CRP and WBC levels and pregnant patients, were all excluded from the study.

Patients were divided into ultrasonography (USG) group (Grp-USG) and computerized tomography (CT) group (Grp-CT) according to the imaging method used during diagnosis, and the study continued separately with these two groups. At the study center, there was no programmed approach that could affect the selection of imaging method at admission. The preferred imaging method in the center where the study was conducted is determined by emergency specialists according to the criteria of accessibility, cost and reliability. Those who carried out the study had no influence on this selection. According to the scoring system created by Atema et al.[13], scoring was performed on age, body temperature, duration of symptoms, leukocyte count (WBC), C-reactive protein level (CRP), Periappendiceal fluid on imaging, and Appendicolith on imaging criteria in Grp-USG patients (USG-Score - maximum 19 points) and on Age, Body temperature, Duration of symptoms, WBC, CRP, Extra-luminal free air on imaging, Periappendiceal fluid on imaging, and Appendicolith on imaging criteria in Grp-CT patients (CT-Score - maximum 22 points). (Table 1) As stated in the original article, a CT-Score of 6 or less and a USG-Score of 5 or less were considered to indicate UCAA. The efficacy of the scoring systems was compared with the final pathological outcome (CAA/UCAA) according to these cut-off points. The main purpose of the

scoring systems was to detect UCAA cases with greater precision.

All data collection and analysis were carried out with the approval of the Ethics Committee of Alaaddin Keykubat University (approval date/no: 13.01.2021/01-14). The study protocol confirmed the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in the approval by the ethics committee.

Statistical method: mean, standard deviation, median, minimum, maximum value frequency and percentage were used for descriptive statistics. The distribution of variables was checked using the Kolmogorov-Simirnov test. The Mann-Whitney U test was used for the comparison of quantitative data. The Chi-Square test was used for the comparison of the comparison of qualitative data. ROC analysis was used to show the effect level. Logistic Regression was used to show the effect level. The SPSS version 27.0 (IBM SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

RESULTS

The study commenced with 599 patients who underwent an appendectomy. Forty-three patients for whom no imaging method was used during diagnosis, fifty-five patients who were not diagnosed with acute appendicitis by imaging and eight patients whose laboratory results could not be accessed, were all excluded from the study group. Twenty patients who were diagnosed with non-acute appendicitis in the clinical and pathological examination or who underwent appendectomy in addition to the original disease, and forty-six patients who were not diagnosed with acute appendicitis in the pathological examination (negative appendectomy), were also excluded from the study.

The study resumed with the remaining 425 patients. Of the patients participating in the study, 64.9% (n=276) were male and 35.1% (n=149) were female. The mean age was 33.29±13.02 years. 48% (n=204) of the patients were evaluated by USG and 52% by CT (n=221). The study continued separately in these two groups. These two groups were divided into two subgroups, according to whether the patients were UCAA or CCAA, as a result of pathological evaluation and they were compared with each other (Table 2).

Table 1. Scoring system based on clinical and imaging features for both computerized tomography (CT) and ultrasonography (USG)

		Clinical and CT features	Clinical and USG features
Age≥45 years		2 points	2 points
Body temperature	≤37.0	0 point	0 point
	37.1-37.9	2 points	2 points
	≥38.0	4 points	4 points
Duration of symptoms ≥48 h		2 points	2 points
Leukocyte >13 × 10^9/l			2 points
C-reactive protein (mg/l)	≤50	0 point	0 point
	51-100	2 points	4 points
	>100	3 points	5 points
Extra-luminal free air on imaging		5 points	-
Periappendiceal fluid on imaging		2 points	2 points
Appendicolith on imaging		2 points	2 points
Maximum score		22 points	19 points

In patients evaluated by the scoring system using CT results (Grp-CT), in the CAA subgroup, Appendicolith on imaging (p=0.017), Periappendiceal fluid on imaging (p<0.001), Extra-luminal free air on imaging (p<0.001), Duration of symptoms ≥48 h (p<0.001) and Body temperature (p<0.001) were significantly higher compared to UCAA subgroup, and CRP was significantly higher (p<0.001). In the CAA subgroup, CT-Score (p<0.001) and the proportion of patients with a CT-Score >6 (p<0.001) was significantly higher compared to the UCAA subgroup (Table 2).

In patients evaluated by the scoring system using USG results (Grp-USG), in the CAA subgroup, Periappendiceal fluid on imaging (p<0.001), Duration of symptoms ≥48 h (p<0.001) and Body temperature (p<0.001) were significantly higher compared to UCAA subgroup, and CRP was significantly higher (p<0.001). In the CAA subgroup, USG-Score (p<0.001) and the proportion of patients with a USG-Score >5 (p<0.001) was significantly higher compared to the UCAA subgroup (Table 2).

In Grp-CT, in univariate model for CAA-UCAA differentiation, Body temperature (p<0.001), Appendicolith on imaging (p=0.019), Periappendiceal fluid on imaging (p<0.001), Duration of symptoms ≥48 h (p<0.001) and WBC (p=0.038), CRP (p<0.001), CT-Score (p<0.001)

showed significant efficacy. Age (p=0.001), body temperature (p<0.001), periappendiceal fluid on imaging (p=0.001), duration of symptoms ≥48 h (p<0.001), CRP(p<0.001), and USG-Score (p<0.001) showed significant efficacy in univariate model for CAA-UCAA differentiation, in Grp-USG (Table 3).

As a result of the Roc analysis, a significant (p<0.001, AUC: 0.923) CT-Score and a significant (p<0.001, AUC: 0.838) cut-off value of CT-Score ≤6 were observed in Grp-CT in the differentiation of CAA-UCAA. Sensitivity was 83.3%, positive predictive value (PPV) was 50.8%, specificity was 84.3%, and negative predictive value (NPV) was 96.3% (Table 4).

In Grp-USG, significant effectiveness of USG-Score (p<0.001, AUC: 0.867) and significant (p<0.001, AUC: 0.790) cut-off value of USG-Score ≤5 was observed in the differentiation of CAA-UCAA. Sensitivity was 85.7%, PPV was 39.0%, specificity was 72.2%, and NPV was 96.1% (Table 4).

DISCUSSION

In this study, external validation was performed on a scoring system based on clinical, laboratory and imaging results in the preoperative period, to differentiate between CAA and UCAA, in order to evaluate its effectiveness [13]. An important part of the recent studies on AA in the literature is related to the conservative treatment of UCAA cases. Therefore, preoperative differentiation of UCAA cases gains importance. In this study, the rate of CAA was 16.7% and this was consistent with the literature [14,15].

Although radiological evaluations maintain their importance in the diagnosis of AA, studies have shown that only 14.0% of cases classified as UCAA in the evaluation by CT are actually CAA [15]. In patients who were considered to be UCAA as a result of evaluation with CT alone, there was a 2% increase in the risk of perforation for every 1 hour delayed in surgery, while this was associated with only a 5% increase at the end of the 7th hour in patients with low scores, when evaluated with the Atema's scoring system [15]. Yeh et al. state that this delay caused by the diagnosis-surgery interval in the hospital setting is not a risk factor for CAA [16].

Existing scoring systems such as the Alvarado scoring or the Appendicitis inflammatory response scoring (AIRS) are used to differentiate acute appendicitis cases from other abdominal pathologies, rather than to differentiate CAA and UCAA. It has been stated that AIRS may be effective in predicting the severity of appendicitis, but the Alvarado scoring is far from effective [17]. For their part, Kose et al. deemed that the effectiveness of clinical evidence-weighted scoring systems is debatable [18]. It was stated that diagnostic scoring systems could not reach the desired level of effectiveness when used in differentiation of severity [19].

Atema et al. used clinical, laboratory and imaging results to differentiate between CAA and UCAA in their scoring system presented in their study. This study included two different models using USG or CT results based on imaging method preferences [13]. The difference in these scoring systems, which are actually similar to each other, is that the presence of free air is also a parameter in imaging in Grp-CT and the score value is given according to CRP levels. A score of 5/19 and below was accepted as significant in the scoring system designed with USG results for UCAA differentiation. In the scoring system designed with CT results, this value was accepted as 6/22 and below because it is an extra parameter [13].

When a new forecasting model is introduced, it should be evaluated in the quality-safety-efficiency triangle. For this reason, it is important to externally validate the model in cohorts with different characteristics, than the cohort with which it was created [20]. Scoring system by Atema et al., on which our study is based, is also created in a limited number of patient groups in a limited area, like many other scoring systems and nomograms. Although statistical significance and internal validation have been performed, such scientific interpretations need to be tested in larger populations and different regions to demonstrate their usability. Geerdink et al. performed external validation of the model using USG results [14]. Our study presented the external validation of both the model using USG results and the model using CT results. In the original study, c-index values were

Tablo 2. Comparison of parameters in uncomplicated acute appendicitis (UCAA) and complicated acute appendicitis (CAA) subgroups when computerized tomography (CT) and ultrasonography (USG) groups were separated

		Group evaluated by CT			Group evaluated by USG		
		UCAA	CAA	p	UCAA	CAA	p
		Mean±sd / n (%)	Mean±sd / n (%)		Mean±sd / n (%)	Mean±sd / n (%)	
Age	<45 years	152 (82.16%)	26 (72.22%)	0.168[x]	140 (82.84%)	23 (65.71%)	0.021[x]
	≥45 years	33 (17.84%)	10 (27.78%)		29 (17.16%)	12 (34.29%)	
Sex	Male	123 (66.49%)	25 (69.44%)	0.730[x]	105 (62.13%)	23 (65.71%)	0.690[x]
	Female	62 (33.51%)	11 (30.56%)		64 (37.87%)	12 (34.29%)	
Appendicolith	(-)	155 (83.78%)	24 (66.67%)	0.017[x]	153 (90.53%)	29 (82.86%)	0.183[x]
	(+)	30 (16.22%)	12 (33.33%)		16 (9.47%)	6 (17.14%)	
Periappendiceal fluid	(-)	153 (82.70%)	8 (22.22%)	<0.001[x]	109 (64.50%)	12 (34.29%)	<0.001[x]
	(+)	32 (17.30%)	28 (77.78%)		60 (35.50%)	23 (65.71%)	
Extra-luminal free air	(-)	185 (100.00%)	28 (77.78%)	<0.001[x]			
	(+)	0 (0.00%)	8 (22.22%)				
Duration of Symptoms ≥48h	(-)	129 (69.73%)	8 (22.22%)	<0.001[x]	117 (69.23%)	10 (28.57%)	<0.001[x]
	(+)	56 (30.27%)	28 (77.78%)		52 (30.77%)	25 (71.43%)	
Body Temp.	≤ 37	139 (75.14%)	15 (41.67%)	<0.001[x]	134 (79.29%)	14 (40.00%)	<0.001[x]
	37.1-37.9	34 (18.38%)	12 (33.33%)		30 (17.75%)	13 (37.14%)	
	≥ 38	12 (6.49%)	9 (25.00%)		5 (2.96%)	8 (22.86%)	
WBC (109/l)	<13	69 (37.30%)	9 (25.00%)	0.158[x]	81 (47.93%)	14 (40.00%)	0.392[x]
	≥13	116 (62.70%)	27 (75.00%)		88 (52.07%)	21 (60.00%)	
CRP (mg/l)		28.72 ± 42.42	109.25 ± 90.69	<0.001[m]	22.34 ± 34.52	60.91 ± 58.14	<0.001[m]
CRP (mg/l)	≤ 50	148 (80.00%)	13 (36.11%)	<0.001[x]	147 (86.98%)	17 (48.57%)	<0.001[x]
	51-100	21 (11.35%)	7 (19.44%)		11 (6.51%)	9 (25.71%)	
	>100	16 (8.65%)	16 (44.44%)		11 (6.51%)	9 (25.71%)	
CT-Score		4.00 ± 2.73	10.33 ± 3.68	<0.001[x]			
CT-Score	≤6	156 (84.32%)	6 (16.67%)	<0.001[x]			
	>6	29 (15.68%)	30 (83.33%)				
USG-Score					3.95 ± 2.73	8.91 ± 3.43	<0.001[x]
USG-Score	≤5				122 (72.19%)	5 (14.29%)	<0.001[x]
	>5				47 (27.81%)	30 (85.71%)	

Table abbreviations: X Chi-Square test, m Mann-Whitney U test , Temp.: Temperature, CRP: c-reactive protein, WBC: leukocyte

Table 3. Univariate and multivariate analysis of the groups evaluated by computerized tomography (CT) and ultrasonography (USG)

	Group evaluated by CT						Group evaluated by USG					
	Univariate Model			Multivariate Model			Univariate Model			Multivariate Model		
	OR	% 95 CI	p	OR	% 95 CI	p	OR	% 95 CI	p	OR	% 95 CI	p
Age	1.014	0.986-1.042	0.337				1.044	1.017-1.071	0.001			
Sex	0.873	0.403-1.889	0.730				0.856	0.399-1.838	0.690			
Body Temperature	3.537	1.988-6.291	<0.001				4.348	2.155 8.775	<0.001			
Appendicolith	2.583	1.166-5.724	0.019				1.978	0.714-5.480	0.189			
Periappendiceal fluid	16.734	6.988-40.073	<0.001				3.482	1.619-7.488	0.001			
Dur. of Symptoms ≥48 h	8.062	3.460-18.789	<0.001	3.140	1.042-9.462	0.042	5.625	2.520-12.554	<0.001	3.513	1.279-9.647	0.015
Leukocyte	1.094	1.005-1.191					1.040	0.951-1.137	0.387			
C-reactive protein	1.019	1.012-1.026	<0.001	0.038			1.018	1.010-1.026	<0.001			
CT-Score	1.781	1.493-2.124	<0.001	1.677	1.388-2.025	<0.001						
USG-Score							1.608	1.385-1.867	<0.001	1.583	1.339-1.873	<0.001

0.82 for the scoring system using USG results and 0.88 for the scoring system using CT results [13]. In the external validation study by Geerdink et al., the c-index values for the scoring system using USG results were 0.83 [14]. In our study, we found the c-index values to be 0.87 for the scoring system using USG results and 0.92 for the scoring system using CT results.

Table 4. ROC Analyses of the groups evaluated by USG and computerized tomography (CT)

	Group evaluated by USG			Group evaluated by CT		
	AUC	95% CI	p	AUC	95% CI	p
USG-Score ≤5	0.790	0.711-0.869	<0.001			
USG-Score	0.867	0.805-0.928	<0.001			
C-reactive protein	0.710	0.610-0.811	<0.001	0.840	0.774-0.906	<0.001
Leukocyte	0.546	0.449-0.643	0.391	0.595	0.495-0.695	
CT-Score ≤6				0.838	0.762-0.915	<0.001
CT-Score				0.923	0.884-0.963	<0.001

Within the score limits specified by Atema et al., the NPV was 94.7% for CAA in Grp-CT and 97.1% for CAA in Grp-USG [13]. In the validation study conducted by Geerdink et al., a NPV of 93.8% was achieved in Grp-USG [14]. In our study, 162 of 222 patients evaluated by CT had a score of 6 or lower, and 6 of them had CAA. The NPV was 96.3%. Of the 204 patients evaluated by USG, 127 had a score of 5 or lower, and 5 of them had CAA. The NPV was 96.1%.

Despite high NPV results, in Grp-USG, 2.5% of patients who had CAA according to the pathological evaluation were misclassified as UCAA and 23.0% of patients who had UCAA according to the pathological evaluation were misclassified as CAA by the scoring system. In Grp-CT, 2.7% of patients who had CAA according to the pathological evaluation were misclassified as UCAA and 13.1% of patients who had UCAA according to the pathological evaluation were misclassified as CAA by the scoring system. Due to the selective design of scoring systems, especially on UCAA patients, the false positive (complicated) rate is high.

In another model presented by Kim et al. to differentiate CAA-UCAA, CT results and percentage of segmented neutrophil were used. This model was considered as effective with AUC of 0.81, NPV of 0.81 [12]. In the scoring systems that formed the basis of our study, clinical, laboratory and radiological results were evaluated together and the effectiveness was found to be higher. We think that adding clinical parameters to the evaluations will result in a more personalized evaluation, without any additional costs. The most important reason why we achieved a higher NPV in this study was that the study in which the scoring was presented and the alternative disease group included in the validation study were not included in our study, since the diagnosis of AA was confirmed pathologically, while the patient groups were being prepared.

In another study, Eddema et al. created a model with logistic regression equation [21]. In a study externally validating this model, it is stated that the scoring system is effective, but this level of effectiveness is close to CRP. Therefore, the usability of this model, which requires an advanced mathematical equation, is not considered to be advantageous [22]. The greatest advantage of the scoring system created by Atema et al., which we used in our study, is that it leads to a decision with a simple calculation and evaluation.

The efficacy of many laboratory results alone in the CAA-UCAA differentiation was evaluated. In a study by Şengül et al., WBC and neutrophil count (NEU) seem to be significant in the diagnosis of CAA [9]. However, in this study, instead of comparing the CAA-UCAA groups, the groups were compared with negative appendectomy. In another study, WBC was found to be effective in diagnosing acute appendicitis, but insufficient in predicting CAA [8]. In our study, we found that WBC did not differ significantly between groups (AUC: 0.549, AUC: 0.595). In the external validation study by Gerrdink et al. [14], we saw that they reached a similar result with AUC of 0.55.

CRP level in CAA-UCAA differentiation was also examined and it was found to be significant as a result [6]. We found it similarly significant and observed that it correlated with the severity of inflammation. Although there are publications

stating that CRP is not sufficient in this differentiation [7].

In our study, we found that the scoring system created with CT had a higher AUC and was more effective compared to the scoring system created with USG. It is a known fact that CT is a more effective method in the diagnosis of AA compared to USG [23]. All of the imaging method parameters used in the scoring systems created in the study by Atema et al. are effective in differentiating CAA and UCAA [13]. Similarly, we observed the effectiveness of many of the parameters in our study. However, there was no significant difference between the CAA-UCAA groups for the "Appendicolith on imaging" parameter in Grp-USG (p=0.183).

Our study has a few limitations. First of all, the data were obtained retrospectively from the hospital data processing system. CT and USG evaluations were performed by different physicians. Results that were not mentioned in the reports were accepted as “nonexistent” because a standard imaging form was not used. Another limitation stems from the definition of CAA. There are publications stating that gangrenous appendicitis is not complicated appendicitis and can be treated like simple appendicitis [24]. In our study, cases that were determined to be gangrenous and perforated as a result of clinical evaluation and pathological examination were accepted as CAA.

Conclusion: Neither radiological imaging nor laboratory results alone can reach the desired level of effectiveness in the differentiation of CAA-UCAA. It would be more accurate to evaluate patients by an integrated approach. We have seen that the scoring systems created for this purpose are more effective compared to all other parameters. Being easily applicable and calculable is the reason for preference for scoring systems in clinical practice. It can be thought that acute appendicitis cases for which conservative treatment is planned can be selected more confidently with the help of these scoring systems. In the CAA-UCAA distinction, the scoring system prepared using CT gives better results than the one prepared using USG.

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The Protective Effects of Beta Glucan Against Experimental Renal Ischemia Reperfusion Injury

Beta Glukanin Deneysel Böbrek İskemi Reperfüzyon Hasarina Karşi Koruyucu Etkileri

Ayşegül Mavi Bulut[1], Ferhat Şirinyıldız[2]*, Cenk Orak[2], Gökhan Cesur[2]

1.Physiology (Medicine) Department, Aydin Adnan Menderes University, Health Science Institute, Aydin, Turkey
2.Physiology Department, Aydin Adnan Menderes University, Faculty of Medicine, Aydin, Turkey

ABSTRACT

Aim: This study aimed to investigate the possible protective effects of beta-glucan against oxidative stress caused by ischemia and reperfusion injury in kidney tissue.
Materials and methods: In the study, 30 male Wistar albino rats weighing 300-350g were used (n=10). Rats were randomly grouped into three groups of Sham control, ischemia reperfusion group (IR), ischemia reperfusion + beta glucan group (IR + BG). Sham group had left nephrectomy, the right kidney taken for histopathologic and biochemical examination. After left nephrectomy in IR group, ischemia procedure was applied for 45 minutes via nontraumatic microvascular clamp, then reperfusion was applied for 60 minutes in the right kidney. In the IR+BG group, rats were administered 100 mg/kg beta glucan via gastric gavage for 10 days. Reperfusion was applied for 60 minutes after 45 minutes of ischemia to the right kidney under anesthesia.
Results: As a result of biochemical examination MDA values showed a significant increase in IR group compared to Sham group (p<0,05). In IR+BG group, there was a significant decrease compared to IR group (p<0,05). Tissue MPO values in IR group showed a significant increase compared to Sham group, whereas in the IR+BG group there was not a significant decrease. Also, there was not a significant difference in tissue catalase levels. Tissue GSH values showed a significant decrease in IR group compared to Sham group (p<0,05). In the IR+BG group a significant increase was found compared to IR group (p<0,05). Less damage has been revealed in the IR+BG group compared to IR group in histopathologic examination.
Conclusion: All these data show that beta glucan may have an antioxidant effect on renal ischemia reperfusion injury.

Keywords: Antioxidant, Beta glucan, İschemia, Kidney, Reperfusion

ÖZ

Amaç: Bu çalışma, böbrek dokusunda iskemi ve reperfüzyon hasarının neden olduğu oksidatif strese karşı beta glukanın olası koruyucu etkilerini araştırmayı amaçlamaktadır.
Materyal ve metod: Çalışmada 300-350 gr ağırlığında 30 adet erkek Wistar albino sıçan kullanıldı (n=10). Sıçanlar rastgele Sham kontrol, iskemi reperfüzyon grubu (İR), iskemi reperfüzyon + beta glukan grubu (IR + BG) olmak üzere üç gruba ayrıldı. Sham grubuna sol nefrektomi yapıldı, sağ böbrek histopatolojik ve biyokimyasal inceleme için alındı. İR grubunda sol nefrektomi sonrası travmatik olmayan mikrovasküler klemp ile 45 dakika iskemi prosedürü uygulandı, ardından sağ böbrekte 60 dakika reperfüzyon uygulandı. IR+BG grubunda, sıçanlara 10 gün süreyle 100 mg/kg beta glukan gastrik gavaj yoluyla uygulandı. Anestezi altında sağ böbreğe 45 dakikalık iskemi sonrası 60 dakika reperfüzyon uygulandı.
Bulgular: Biyokimyasal inceleme sonucunda MDA değerleri IR grubunda Sham grubuna göre anlamlı artış gösterdi (p<0,05). IR+BG grubunda IR grubuna göre anlamlı azalma oldu (p<0,05). IR grubunda doku MPO değerlerinde Sham grubuna göre anlamlı bir artış görülürken, IR+BG grubunda anlamlı bir azalma olmadı. Ayrıca doku katalaz seviyelerinde de anlamlı bir fark yoktu. Doku GSH değerleri IR grubunda Sham grubuna göre anlamlı düşüş gösterdi (p<0,05). IR+BG grubunda IR grubuna göre anlamlı artış bulundu (p<0,05). Histopatolojik incelemede IR+BG grubunda IR grubuna göre daha az hasar saptandı.
Sonuç: Tüm bu veriler, beta glukanın renal iskemi reperfüzyon hasarı üzerinde antioksidan etkiye sahip olabileceğini göstermektedir.

Anahtar Kelimeler: Antioksidan, Beta glukan, İskemi, Böbrek, Reperfüzyon

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*Corresponding Author: Ferhat ŞİRİNYILDIZ, Physiology Department, Aydin Adnan Menderes University, Faculty of Medicine, Aydın, Turkey, +905076627799, ferhat.sirinyildiz@gmail.com

ORCİD: 0000-0001-8800-9787

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INTRODUCTION

Ischemia is an oxygen deprivation caused by decreased arterial and venous blood flow. Interruption of blood flow to the tissue decreases cellular oxidative phosphorylation, adenosine triphosphate (ATP) and phosphocreatine [1]. During ischemia and reperfusion, oxidative stress damage occurs with decreased ATP, increased intracellular calcium, increased activity of protease and phosphatase that cause degradation of membrane phospholipids and in particular, releasing reactive oxygen species [1,2]. The severity of ischemic damage is split into two categories, reversible and irreversible ischemic injury. Cellular functions are conducted by aerobic mechanism due to oxygen and high energy phosphate bonds in normoxia. In hypoxia, ATP stores are depleted and ATP production cannot be produced, therefore structural disorders occur in the cell. Increase in membrane permeability results in morphological deterioration [3]. Reperfusion is the re-oxygenation of tissue by re-flowing blood to ischemic tissue. The arrival of oxygenated blood into the tissue initiates a process that leads to more damage for tissue than the ischemic period [2]. In the ischemic period, metabolic and structural changes in the cell (such as increase in proinflammatory cytokines and leukocyte adhesion molecules, decrease in antioxidant enzymes) make the cell vulnerable to damage during the reperfusion period. Membrane lipids, proteins, nucleic acids and DNA molecules are the cellular structures that are most susceptible to reperfusion injury [4].

Beta glucans are carbohydrates composed of glucose chains found in the cell walls of yeast, bacteria, fungus and grains. They consist of 1,3 1,4 1,6 chain glycopyrrolate units. Beta glucan, which has the most biological effects, is obtained from baker's yeast - Saccharomyces cerevisiae [5]. Beta glucans strengthen the immunity by activating the macrophage and complement system when taken from outside and have effects on natural and adaptive immunity [6]. Beta glucan has been described as a potent immunostimulatory with no toxic effects or adverse effects, as well as antioxidant and organ protective properties [7]. The determination of possible positive results of beta glucan in the treatment of renal ischemic injuries will appear as an added value on antioxidant treatment area. As a result of further studies on the subject, multidisciplinary approaches are expected to be developed and a useful scientific study for humanity will be put forward.

The aim of this study was to investigate the protective effects of beta glucan on renal ischemia reperfusion injury. Since a study investigating the effects of beta glucan on renal ischemia reperfusion injury has not been found in the literature, therefore the results of this study will be a reference for further studies.

MATERIALS AND METHODS

This experimental study was carried out in Aydın Adnan Menderes University, Faculty of Medicine, Department of Physiology, with 30 male Wistar rats weighing 300-350g. The decision of the ethics committee was approved by the decision of 64583101/2015/099 Animal Experiments Local Ethics Committee dated 14 august 2015 and numbered 64583101. Rats were kept in a circadian rhythm of 12 hours a night, 12 hours a day, at a temperature of 22±2ºC and a humidity of 45-50%. Standard pellet feed and drinking water were used in the diet of the rats. In the experimental groups, 30 male Wistar albino rats were randomly divided into 3 groups (n=10). Right kidneys were analyzed in histology and biochemistry laboratories.

Sham Control Group: Left nephrectomy was applied at the end of the experiment without any application.

Ischemia-Reperfusion (IR) Group: The left kidneys were removed by nephrectomy at the end of the experiment without any application, the right kidney was exposed to ischemia with a nontraumatic microvascular clamp for 45 minutes, followed by 60 minutes of reperfusion [8 9].

Beta-Glucan + Ischemia-Reperfusion (IR+BG) Group: The group administered beta-glucan per oral (p.o.) once a day by the gastric gavage method for 10 days. After left nephrectomy on the day of the experiment, the right kidney was exposed to ischemia for 45 minutes with a nontraumatic microvascular clamp, followed by 60 minutes of reperfusion.

Beta Glucan Administration: Beta glucan dosage

was 100 mg/kg/day to rats in the IR+BG group [8-10-11]. Beta glucan 50 mg capsule Imuneks® (Gensenta Pharmaceutical I.C) was dissolved in drinking water and applied with intragastric gavage [12-13].

Ischemia-Reperfusion Induction: 50 mg/kg ketamine and 10 mg/kg xylazine were administered to the rats that were not fed 24 hours before the experiment day of ischemia-reperfusion. The midabdominal region of the rats was incised, the left kidneys were removed by nephrectomy and the right kidneys were clamped at the level of the hilus with a nontraumatic microvascular clamp and exposed to ischemia for 45 minutes. After 45 minutes, the nontraumatic microvascular clamp was removed and 60 minutes of reperfusion was achieved. 0,09% saline water was administered to prevent dehydration during the operation.

Tissue Collection: The rats were sacrificed under anesthesia with cervical dislocation after the kidney tissues were collected. Tissues were separated and stored at -80ºC for biochemical analysis and in 10% formaldehyde solution for histology examination.

Biochemical Analysis of Kidney Tissue Samples: Homogenization of tissues: after the kidney tissues in the experimental group and the control group were weighed and homogenized separately with the 'Ultra Turnax, IKA-WERKE, Germany' brand tissue homogenizer. Afterwards, PBS (phosphate buffer saline) was added for the calculation of MDA (Cat. No: K739, BioVision®, Milpitas, CA, United States), MPO (Cat. No: K744, BioVision®, Milpitas, CA, United States), CAT (Cat. No: K773, BioVision®, Milpitas, CA, United States) and GSH (Cat. No: K264, BioVision®, Milpitas, CA, United States) activities. [14,15]. The tissue homogenates were centrifuged at 1500 rotational speed (rpm) for 15 minutes at 40C. Supernatants were stored for analysis at -80oC. ELISA method 'Diagnostic Automation, Inc./ELx800TM brand model has been used.

Histological Analysis of Kidney Tissue Samples: Kidney tissues were kept in 10% formaldehyde until the day of examination. Tissue samples using routine histological follow-up method were embedded in paraffin and sections of 5 µm were cut with microtome (HistoPlusTM Specimen). The preparations stained using the hematoxylin eosin staining technique were covered with entellan. Histological examination was taken with the "Olympus DP20 Digital camera" mounted on the "Olympus B*51" microscope at the light microscope level.

Statistical analysis: Statistical analysis of all data obtained was made using Graphpad Prism® 6 package program. In the Kolmogorov Smirnov test, the data showed a normal distribution. Statistical evaluation between groups was made using the Mann Whitney U test. A p value of <0.05 was considered statistically significant.

RESULTS

Biochemical Results

MDA, the final product of lipid peroxidation, was 12.81±0.2578 nmol/mg in the Sham group; 14.53±0.3000 nmol/mg in the IR group; in the IR+BG group, it was measured as 13.46±0.3157 nmol/mg. When the Sham group and the IR group were compared; MDA value increased significantly in the IR group compared to the Sham group ($p<0.05$). The IR+BG group has a significantly lower MDA value compared to the IR group ($p<0.05$).

MPO values in Sham group were 8.643±0.4565 nmol/mg; 12.78±0.8489 nmol/mg in the IR group; It was measured as 11.86±0.6620 nmol/mg in the IR+BG group. When the Sham group and the IR group are compared; The MPO level was significantly decreased in the Sham group compared to the IR group ($p<0.05$). MPO values decreased in the IR+BG group compared to the IR group but did not make a significant difference ($p>0.05$).

Measured catalase levels, Sham group 2.456±0.2225 nmol/mg, IR group 2.453±0.2334 nmol/mg, IR+BG group 2.825±0.2413 nmol/mg. There was no significant difference between the Sham group and the IR group in terms of measured catalase values ($p>0.05$). No significant difference was found between the IR group and the IR+BG group ($p>0.05$).

Glutathione levels were 17.46±0.4148 nmol/mg in the Sham group, 7.466 ± 0.4884 nmol/mg in the IR group, and 8.879±0.3216 nmol/mg in the IR+BG

group. When the measured GSH levels were compared with the Sham group and the IR group, a significant decrease was observed in the IR group ($p<0.05$). When the IR group and the IR+BG group were compared, a significant increase was observed in the IR+BG group compared to the IR group ($p<0.05$).

All measured values are shown in detail in Table 1.

Table 1. Tissue MDA, MPO, CAT and GSH Values.

	Sham	IR	IR+BG
MDA (nmol/mg)	12,81±0,2578	14,53±0,3000*	13,46±0,3157†
MPO (nmol/mg)	8,643±0,4565	12,78±0,8489*	11,86±0,6620
CAT (nmol/mg)	2,456±0,2225	2,453±0,2334	2,825±0,2413
GSH (nmol/mg)	17,46±0,4148	7,466±0,4884*	8,879±0,3216†

* For IR group compared to Sham group: p≤0.001

† For IR+BG group compared to IR group: p≤0.05

Histological Results

Cortical degeneration, glomerular degeneration, tubular damage, medulla degeneration and congestion in kidney tissues were evaluated. Histological scoring was evaluated as 0: no damage, 1: mild, 2: moderate and 3: extensive damage. Mild cortical degeneration and mild glomerular smallness were observed in the Sham group (figure 1), moderate cortical, medullary, tubular and glomerular degeneration and congestion were detected in the IR group (figure 2), mild cortical and medullary degeneration and mild tubular degeneration were observed in the IR + BG group (figure 3). Detailed scoring of all groups is shown in Table 2.

Table 2. Histological Scores

	Sham	IR	IR+BG
Congestion	0	2	0
Cortical Degeneration	1	2	1
Gromerular Degeneration	1	1	0
Tubular Damage	0	2	1
Medulla Degeneration	0	2	1

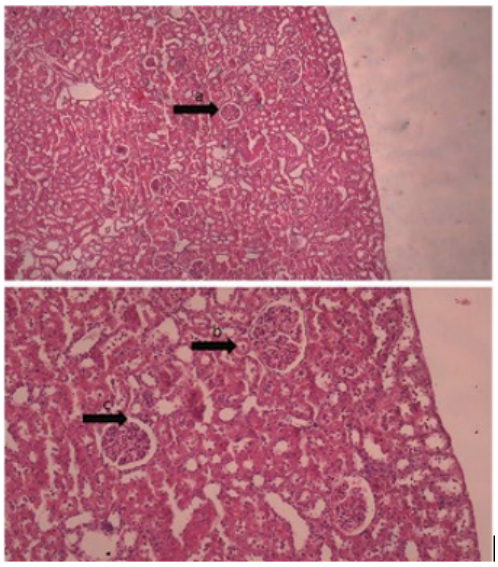

Figure 1. Sham group histopathological sample: kidney morphological structures are preserved a:glomerule (40X,H&E), b:distal tubule (100X,H&E), c:Bowman's capsule (100X,H&E).

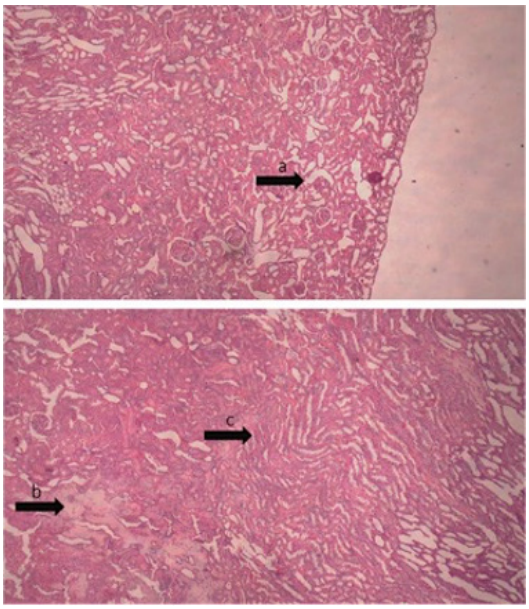

Figure 2. IR group histopathological sample (40X, H&E); Moderate morphological degeneration is observed in the kidney. a:disruption in glomerular integrity, b:ischemic focus, c:medullary degeneration.

DISCUSSION

Beta glucans became an important subject of research in recent years and significant beneficial results have been obtained. Numerous studies showed that beta glucans have beneficial effects on human health against a number of diseases, such as cancer, infection, wound healing and others [16]. Clinical studies on beta glucan have also been increasing in recent years and it is being used in many supportive treatments

[17]. We investigated the possible effects of beta glucan administration as pre-treatment like various studies performed by other researchers [18,19]. Renal ischemia can be observed in clinical situations such as kidney transplantation, partial nephrectomy, sepsis, cardio-pulmonary bypass, various urological procedures and hydronephrosis. As a result of studies on kidney, the critical time period determined for permanent damage was determined to be 30 minutes [20]. Mitochondrial disorders are irreversible after approximately 30-40 minutes of ischemia [21]. In our study rats were exposed to ischemia for 45 minutes, with irreversible damage. Rats were applied reperfusion for 60 minutes after ischemia and histological and biochemical results supported by previous research [8,9].

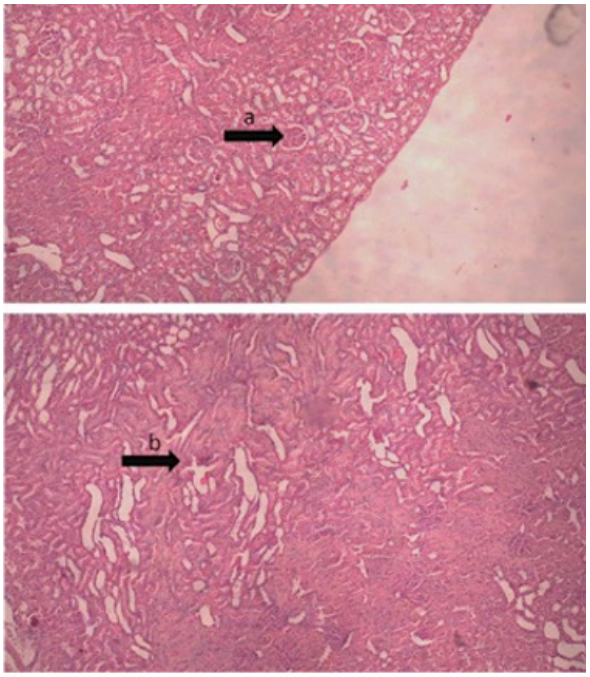

Figure 3. IR+BG group histopathological sample (40X,H&E); Glomerular structures are largely preserved by observing low-level degeneration areas in the morphological structure. a:glomerulus, b:medullary degeneration.

The dosage of beta glucan is specified as 40-3000 mg per day, which is accepted by the FDA on the GRAS category and 2-6 mg/kg of body weight has been considered [12]. Suzuki et al. reported that beta glucan should be applied over 80 mg doses and should be applied for 5-10 days [13]. Amany et al. and Alkhalidi et al. applied the beta glucan the dose of 100 mg/kg by oral administration [10,11]. In our study we also applied beta glucan orally and the dose was 100 mg/kg as well. We investigated pretreatment effects of beta glucan for 10 days, as per Yücel et al. and Çetin [8,19].

Beta glucan shows its antioxidant effects as a powerfully intracellular reactive oxygen species scavenger and has a protective effect on oxidative damage, by suppressing lipid peroxidation [22]. In a study by Şener et al. [6] it was shown the beta glucan prevents the increase of MDA, the final product of lipid peroxidation in tissue. In our study, tissue MDA values increased significantly in the IR group compared to the Sham group and decreased significantly in the IR+BG group compared to the IR group. These results show that beta glucan can have protective effects on oxidative damage. Toklu et al. [23] studied the effects of beta glucan on kidney injury and they found significantly decreased MDA values in tissue, as we have. MPO is an enzyme localized in leukocytes and is considered to be an indicator of neutrophil infiltration [23]. In our study, tissue MPO values in the IR group showed a significant increase compared to the Sham group, whereas in the IR+BG group there was not a significant decrease. MPO values decreasing but not with a significant difference may be due to the rats' count of group numerically. Erkol et al.'s study-on beta glucan as both prophylactic and therapeutic and it was found that beta glucan administration in the postoperative group decreased MPO, while in the prophylactic group did not provide a significant reduction for MPO [24]. MPO values not significantly decreasing may be the result of the administration of beta glucan prophylactically in our study.

Catalase, an enzyme which is found in high rates in kidney and blood, allows hydrogen peroxide to hydrolyze [25]. In our study, there was not a significant difference in tissue catalase levels. İlhan et al. [26] and Rausher et al. [25] also studied oxidative damage and could not find any significant change on CAT activity. Catalase may affect by the administration of the duration and dosage of the antioxidant substance.

Glutathione is a protective component against oxidative damage [27]. In our study, tissue GSH values showed a significant decrease in the IR group compared to the Sham group ($p<0,05$). In the IR+BG group a significant increase was found

compared to the IR group (p<0,05). Şener et al. [5], Erkol et al. [27], Toklu et al. [23] studied beta glucan and they found high GSH values, as we did.

In our study, less damage was revealed in the IR+BG group compared to the IR group in the histopathologic scores. Bedirli et al. [2] reported in their study that beta glucan provided healing histopathological on congestion, hemorrhage and infiltration. Şener et al. [4] reported the histopathological on interstitial inflammatory infiltration, glomerular necrosis and Bowman's capsule degeneration, were decreased significantly.

Limitations: The limitations of the study can be listed as follows: there are dietary and digestive system differences between rats and humans, therefore the absorption of beta glucan may cause differences. Rats are fed with a single type of food, so the effects of beta glucan on humans may vary as a result of nutritional diversity and substance interactions. Finally, the long-term effects of beta glucan may need to be investigated: the effects in different forms (encapsulated, ready-made liquid form), different administration forms (intraperitoneal), different durations (acute, subchronic and chronic) and different doses (low, optimal, high) should be investigated in further studies.

CONCLUSION

Considering its proven safety and low toxicity, beta glucan administration has increased in recent years and its effectiveness has been demonstrated with different experimental methods. The antioxidant effects of beta glucan decreased lipid peroxidation and accordingly, tissue MDA levels changed significantly in our study. MPO which is responsible for neutrophil infiltration, also decreased in the beta glucan group. In addition, positive changes were observed of histological examinations in the beta glucan group. It is shown that beta glucan prevents cortical, medullary and tubular damage histopathological, after renal ischemia reperfusion injury. All this data shows that beta glucan may have an antioxidant effect on renal ischemia reperfusion injury. The effects of clinical studies on different experimental models need to be investigated.

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RESEARCH ARTICLE

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Diagnosis and treatment of acute pulmonary embolism: A single center experience

Akut pulmoner emboli tanı ve tedavisi: Tek merkez deneyimi

Ayşe Ertekin[1*], Aydın Balcı[2], Erhan Bozkurt[3], Emre Atay[4], Ramazan Sami Aktaş[5]

1.Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Emergency Medicine, Afyonkarahisar, Turkey
2.Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Chest Diseases, Afyonkarahisar, Turkey
3.Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Internal Medicine, Afyonkarahisar, Turkey
4.Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Anatomy, Afyonkarahisar, Turkey
5.Van Yüzüncü Yıl University, Faculty of Medicine, Department of Emergency Medicine, Van, Turkey

ABSTRACT

Aim: Pulmonary embolism is a potentially life-threatening cardiovascular disease frequently encountered in emergency departments. The computed tomography pulmonary angiography is the imaging modality of choice in the diagnosis of pulmonary embolism. This study aimed to examine the effects of clinical findings and treatment methods on prognosis and mortality by examining patients diagnosed with acute pulmonary embolism in the emergency department.
Methods: In this retrospective cohort study, records of patients with acute pulmonary embolism were accessed from the archive. Patients' age, gender, medical complaints, co-morbidities, the treatment method applied to the patients, and the clinical outcomes of the patients were analyzed. The statistical distribution of the patients' demographic and clinical information was calculated.
Results: The most common complaint of 206 patients with acute pulmonary embolism was dyspnea. 25.7% patients had massive pulmonary embolism. The blood d-dimer, lactate and troponin T levels of patients with massive pulmonary embolism were found to be higher than patients with sub-massive pulmonary embolism. Thrombolytic therapy was administered to 6.8% of acute pulmonary embolism patients and it was found to be a method that had a statistically positive effect on survival. D-dimer, white blood cell, neutrophil, blood urea nitrogen, lactate and troponin T values were found to be higher in mortal patients. It was determined that 13.1% of the patients died.
Conclusion: The sooner the early diagnosis of acute pulmonary embolism, which can be mortal in the emergency department, is made and the treatment is started, the mortality rate will decrease significantly.

Keywords: pulmonary embolism, thrombolytic therapy, emergency department.

ÖZ

Amaç: Pulmoner emboli, acil servislerde sıklıkla karşılaşılan, potansiyel olarak yaşamı tehdit eden bir kardiyovasküler hastalıktır. Bilgisayarlı tomografi pulmoner anjiyografi, pulmoner emboli tanısında tercih edilen görüntüleme yöntemidir. Bu çalışmada, acil serviste akut pulmoner emboli tanısı konulan hastaları inceleyerek klinik bulguların ve tedavi yöntemlerinin prognoz ve mortalite üzerine etkilerini incelemeyi amaçladık.
Yöntem: Bu retrospektif kohort çalışmada akut pulmoner emboli hastalarının kayıtlarına arşivden ulaşıldı. Hastaların yaşı, cinsiyeti, tıbbi şikayetleri, ek hastalıkları, hastalara uygulanan tedavi yöntemi ve hastaların klinik sonuçları analiz edildi. Hastaların demografik ve klinik bilgilerinin istatistiksel dağılımı hesaplandı.
Bulgular: Akut pulmoner embolili 206 hastanın en sık şikayeti nefes darlığıydı. Hastaların %25.7'sinde masif pulmoner emboli vardı. Masif pulmoner emboli hastalarında kan d-dimer, laktat ve troponin T düzeyleri submasif pulmoner emboli hastalarına göre daha yüksek bulundu. Akut pulmoner emboli hastalarının %6.8'ine trombolitik tedavi uygulanmış ve sağ kalımı istatistiksel olarak olumlu etkileyen bir yöntem olduğu saptanmıştır. Mortal hastalarda d-dimer, beyaz küre, nötrofil, kan üre nitrojen, laktat ve troponin T değerleri daha yüksek bulundu. Hastaların %13.1'inin hayatını kaybettiği belirlendi.
Sonuç: Acil serviste ölümcül olabilen akut pulmoner emboli ne kadar erken teşhis edilir ve tedavisine başlanırsa mortalite oranı önemli ölçüde azalacaktır.

Anahtar Kelimeler: pulmoner emboli, trombolitik tedavi, acil servis.

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*Corresponding Author: Ayşe ERTEKİN, Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Emergency Medicine, Afyonkarahisar, Turkey, +905063698159, doktorayse6@yahoo.com

ORCİD: 0000-0002-9947-9917

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INTRODUCTION

Pulmonary embolism (PE) is a potentially life-threatening cardiovascular disease frequently encountered in emergency departments (EDs) [1]. Venous thromboembolism (VTE) is the third most common acute cardiovascular syndrome after myocardial infarction and stroke, manifesting clinically as deep vein thrombosis (DVT) or acute PE with its most dangerous complication [2]. The incidence of PE is 39-115/100 000 people and it. PE causes 300 000 deaths annually in the United States. Although PE is diagnosed in only 35% of suspected PE cases in EDs, the mortality rate is 10% [3].

PE risk factors may be related to both genetic and acquired risk factors, although the former's risk factors are less common. As acquired risk factors, we may include recent hospitalization history, previous surgical intervention, immobilization, cancer (20% VTE risk), hormone and steroid therapy (risk 2-3 times higher); pregnancy should also be considered [4]. However, it has been shown that 30% of patients with PE do not have any risk factors [3].

Clinical suspicion is important in the diagnosis of PE. In cases with risk factors such as immobility, cancer, previous trauma and major surgery, PE should be suspected in the presence of complaints such as sudden onset of shortness of breath, chest pain, syncope or hemoptysis [5]. Modified Genova and Wells scoring systems are most commonly used among clinical prediction scoring systems [6]. It is recommended to use the d-dimer test to exclude PE in cases with low and moderate probability predictive scoring. The computed tomography pulmonary angiography (CTPA) is the imaging modality of choice for imaging the pulmonary vessels in cases with suspected PE [7]. Transthoracic echocardiography (TTE) and CTPA are important in rapid diagnosis in hemodynamically unstable cases. Anticoagulant treatment should be started while waiting for diagnostic test results in suspected cases of PE with high and moderate clinical probability. Hypoxemia is frequently seen in severe PE cases and oxygen support is applied in cases with oxygen saturation values of less than 90%. The first treatment option in high-risk PE cases is reperfusion therapy and mostly systemic thrombolytic therapy [8]. The main indication for thrombolytic therapy is massive PE with persistent hypotension, unrelated to cardiogenic shock and/or another cause (such as sepsis, hypovolemia, new-onset arrhythmia) [9].

Massive PE presents with acute right ventricular failure accompanied by hypotension, shock, or cardiopulmonary arrest. Patients with syncope, severe hypoxemia, cardiac arrest, or undergoing cardiopulmonary resuscitation, should be evaluated for massive PTE. In sub-massive PE, there are signs of right ventricular dysfunction detected on echocardiography (ECO) despite normal systemic blood pressure [9].

Due to the incidence of acute PE and the high mortality rate, rapid identification and accurate risk stratification of patients with acute PE, play an important role in treatment. In this study, it was aimed to examine the effects of clinical findings and treatment methods on prognosis and mortality, by examining patients diagnosed with acute PE in the ED.

METHODS

This retrospective cohort study was approved by the Ethical Committee of Afyonkarahisar Health Science University, Faculty of Medicine (2021/344 on 04/06/2021). Patients (18-99 years old) diagnosed with acute PE in the ED of Afyonkarahisar Health Science University Faculty of Medicine between 01.08.2016 and 01.01.2021, based on clinical, laboratory and radiological findings, were retrospectively accessed from the archive. The patients' age, gender, medical complaints, co-morbidities, the treatment method applied and the clinical outcomes were analyzed. Patients diagnosed with PE according to clinical, laboratory and CTPA results were included in the study. The statistical distribution of the patients' demographic and clinical information was calculated. Patients with suspected pulmonary embolism but not diagnosed with PE were excluded from the study.

Statistical analysis

Statistical analyzes of the study were performed using the SPSS software version 22.0. The distribution of data was analyzed with the

Kolmogorov-Smirnov test. Data groups that did not show homogeneous distribution as a result of the evaluation were evaluated using the Mann-Whitney U test. Values with $p<0.05$ were considered statistically significant. All values were expressed as mean ± standard deviation (mean ± sd).

RESULTS

In our study, it was determined that 14.6% (n=206) of 1414 patients admitted to the ED with the suspicion of PE were diagnosed with acute PE according to clinical, laboratory findings and CTPA reports. 51.9% (n=107) of the PE patients were female and 48.1% (n=99) were male patients, and the mean age was 64.94±15.85 years. PE was detected in 114 patients of advanced age (>65 years). The most common clinical presentations were dyspnea 90.8% (n=187), chest pain 20.4% (n=42), hemoptysis 5.3% (n=11), syncope 4.4% (n=9), flank pain 1.5% (n=3) and cough 0.9% (n=2). When comorbid diseases of patients with pulmonary embolism were examined, it was found that malignancy (27.2%) was the most common comorbidity in patients (Table 1). In this study, it was found that 5.8% (12) patients had a previous history of PE, 3.9% (8) patients had a previous history of DVT, and 0.5% (1) patient had a heterozygous methylenetetrahydrofolate reductase (Mthfr) gene mutation. When the clinical findings were evaluated, tachycardia was detected in 24.8% (n=51), hypotension in 21.8% (45), atrial fibrillation in 6.3% (n=13) and fever in 1.5% (n=3) of the patients. Lung cancer constituted 34% of malignancy patients. There were 44 (21.4%) patients with a surgical history and 32 (15.5%) patients with a history of immobilization.

DVT was detected in lower extremity venous doppler ultrasonography, performed in 39 (61.9%) of 63 patients examined for DVT. Right ventricular dysfunction was detected in 39.4% (n=26) of 66 patients who underwent ECO in the ED, and left atrial thrombus was observed in 1 patient.

PE rates in low, moderate and high probability groups, respectively; Wells (Canadian) PE was found to be 34%, 64.5%, and 1.5% in the clinical prediction scoring method, and 9.2%, 84.5%, and 6.3% in the Modified Geneva scoring method. As a result of clinical findings, d-dimer and CTPA, 153 (74.3%) patients had sub-massive PE and 53 (25.7%) massive PE (Figure 1).

Table 1. Comorbid diseases of patients with pulmonary embolism

Comorbid Diseases	%	n	Comorbid Diseases	%	n
Malignancy	27.2	56	Chronic renal failure	2.4	5
Chronic pulmonary disease	23.8	49	Immune thrombocytopenic purpura	0.9	2
Hypertension	17.9	37	Cerebral vein thrombosis	0.5	1
Coronary artery disease	12.1	25			
Diabetes	11.7	24			
Neurological diseases	7.8	16			
Congestive heart failure	6.3	13			

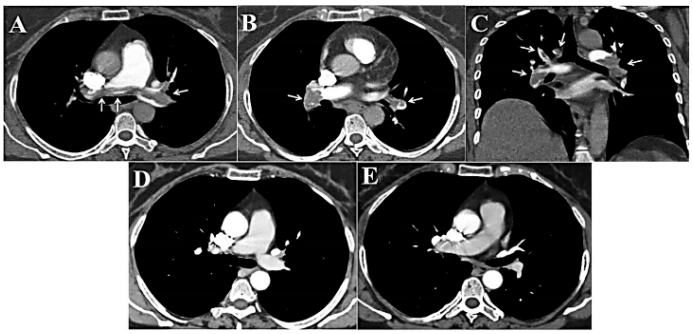

Figure 1. 63-year-old female patient. Axial (A, B) and coronal (C) pulmonary CT Angiography images reveal bilateral massive pulmonary embolism extending from the carina to both main pulmonary arteries (arrows). Follow-up axial CT angiography images (D, E) show completely resorption of bilateral massive pulmonary embolism.

It was determined that 14 (6.8%) patients were treated with thrombolytic therapy and 192 (93.2%) patients were treated with anticoagulant drug therapy. When evaluated according to the treatment groups, it was determined that the application of thrombolytic treatment to massive PE patients had a better effect on healing the patients. Thrombolytic therapy was found to be a method that had a statistically positive effect on survival ($p<0.001$). No patient who underwent pulmonary embolectomy or percutaneous catheter intervention was found in our study.

The mean hospital stay was 7.94±8.54 days. When the patient outcomes were evaluated, it was determined that 42 (20.4%) patients were admitted to the intensive care unit and 27 (13.1%)

patients died. In the evaluation of survival-mortality in massive and sub-massive PE groups, the discharge frequency of massive PE patients was found to be higher than that of sub-massive PE patients (p= 0.002). Age, d-dimer, white blood cell (WBC), neutrophil, blood urea nitrogen (BUN), lactate and troponin T values were found to be higher in patients who died than those who survived (respectively p= 0.001, 0.037, 0.003, 0.008, 0.001, 0.03, 0.001).

It was determined that patients with sub-massive PE had a statistically longer hospital stay than patients with massive PE (p=0.04). Blood d-dimer, lactate, and troponin T values were found to be higher in patients with massive PE than in patients with sub-massive PE (0.001, 0.032, 0.011, respectively), (Table 2).

DISCUSSION

PE clinical findings and non-invasive diagnostic methods are not 100% diagnostic. In order to exclude and diagnose PE, it is recommended to evaluate patients together with anamnesis, physical examination, laboratory results, lower extremity doppler ultrasonography, radiological imaging, and non-invasive diagnostic methods [10]. In this study, PE was diagnosed in 14.6% of 1414 patients based on clinical suspicion and radiological imaging results.

PE is more common in women over the age of 50 [11]. In this study, 51.9% (n=107) of the PE patients were female and 48.1% (n=99) were male patients, and the mean age was 64.94±15.85 years. In this study, the incidence in women was

Table 2. Age, hospitalization period and blood test results of patients diagnosed with massive and sub-massive pulmonary embolism

	Massive PE (n= 53)		Sub-massive PE (n=153)		Total (n=206)		p value
	Mean±SD	Median (Max-Min)	Mean±SD	Median (Max-Min)	Mean±SD	Median (Max-Min)	
Age (year)	65.06±15.65	66.00 (92.00-25.00)	64.90±15.98	67.00 (91.00-24.00)	64.94±15.85	67.00 (92.00-24.00)	.950
Hospitalization period (day)	7.08±9.34	5.00 (47.00-0.00)	8.25±8.24	6.00 (54.00-0.00)	7.94±8.54	6.00 (54.00-0.00)	.040
d-dimer (ng/mL)	9.27±9.63	6.18 (38.60-0.00)	3.96±4.55	2.90 (34.00-0.30)	5.54±6.88	3.55 (38.60-0.00)	<.001
WBC (10^3/UL)	14.37±17.55	11.96 (134.00-2.27)	11.49±4.89	10.90 (24.34-0.48)	12.24±9.93	11.27 (134.00-0.48)	.378
Neutrophil (10^3/UL)	7.83±6.56	6.22 (30.17-0.86)	13.39±54.28	7.03 (660.00-0.06)	11.92±46.72	6.65 (660.00-0.06)	.988
Lymphocyte (10^3/UL)	1.88±1.66	1.32 (9.16-0.23)	1.47±0.87	1.28 (4.71-0.19)	1.58±1.14	1.30 (9.16-0.19)	.294
NLR	7.82±6.55	6.22 (30.17-0.86)	13.31±53.92	7.02 (660-0.06)	11.88±46.49	6.65 (660-0.06)	.351
Thrombocyte (10^3/UL)	221.42±78.64	212.00 (492.00-74.00)	237.68±115.19	225.00 (592.00-0.01)	233.43±106.91	218.00 (592.00-0.01)	.466
Hemoglobin (g/dL)	15.02±14.97	13.00 (121.10-8.90)	13.58±10.56	12.90 (139.00-6.40)	13.95±11.85	12.90 (139.00-6.40)	.472
CRP (mg/dL)	8.62±9.74	5.00 (40.30-0.63)	7.21±7.55	4.90 (38.50-0.18)	7.58±8.18	5.00 (40.30-0.18)	.424
Creatinine (mg/dL)	1.07±0.84	0.88 (6.40-0.34)	1.90±12.26	0.80 (151.00-0.25)	1.68±10.55	0.82 (151.00-0.25)	.069
BUN (mg/dL)	46.38±25.79	40.80 (168.20-4.60)	46.88±27.08	40.30 (166.20-13.30)	46.75±26.69	40.60 (168.20-4.60)	.738
pH	7.17±1.28	7.45 (7.59-0.77)	7.35±0.80	7.45 (7.70-0.43)	7.30±0.95	7.45 (7.70-0.43)	.445
Lactate (mg/dL)	25.66±24.08	16.00 (123.00-3.00)	16.42±7.57	15.00 (65.00-6.00)	18.83±14.43	16.00 (123.00-3.00)	.032
hs-Troponin T (ng/mL)	0.17±0.76	0.04 (5.14-0.00)	0.05±0.09	0.02 (0.90-0.00)	0.08±0.39	0.03 (5.14-0.00)	.011

PE: Pulmonary embolism, WBC: white blood cell, CRP: C-Reaktif Protein, NLR: neutrophil/lymphocyte ratio, BUN: blood urea nitrogen, SD: standard deviation.

similar to the literature [11] but the incidence was higher in the advanced age group (>65 years), with a rate of 55.34%. Similar to the study conducted by Sevim et al., in our study PE patients applied to the ED with the most common complaints of dyspnea (90.8%) and chest pain (20.4%) [10]. Similar to the studies [5,10] 24.8% of our PE patients had tachycardia.

The presence of predisposing factors increases clinical suspicion. The most common predisposing factors are long-term immobilization, previous history of VTE, surgery and malignant diseases [10]. In our cases, which were included in our study, the most common predisposing factors were found to be malignancy (27.2%), surgery (21.4%) and immobilization (15.5%) in line with the literature. In our study, DVT was detected in most of the patients (61.9%) who underwent lower extremity venous doppler ultrasonography. Malignancies increase the risk of VTE by 6 times, and 20% of VTE cases constitute patients with malignancy [12]. In our study, 26.6% of the patients with DVT had a history of malignancy.

VTE is multifactorial and associated with acquired and hereditary conditions. Individuals with inherited causes of thrombophilia are at increased risk of thrombosis, but most of these individuals do not develop thrombosis [13]. In our study, heterozygous Mthfr gene mutation was detected in only one patient and the diagnosis of pulmonary embolism occurred on the basis of hereditary thrombophilia, similar to the literature.

ECO is valuable in deciding the cases that need thrombolytic therapy and embolectomy, since it provides information about right ventricular functions and provides a rapid risk analysis [14]. In a study, ECO performed in 43 (55.1%) of the patients revealed increased pulmonary artery pressure (PAP) in 95.3% of the patients [11]. In our study, it was determined that right ventricular dysfunction was detected in 39.4% (n=26) patients and PAP elevation was observed in 56.1% (n=37) patients of 66 patients who underwent ECO in the ED.

Massive PE causes tachycardia, hypotension, cerebral perfusion disorder and syncope, which is caused by the left ventricular dysfunction due to acute right ventricular failure. Hypotension develops due to occlusion of the main pulmonary artery by thromboembolism [15]. In a study of 560 syncope patients, PE was diagnosed in 17.3% and PE in the main pulmonary artery was detected in 41.7%. In our study, PE was detected in syncope patients with a lower rate of 4.4%, and similar to the literature, it was determined that 33.3% had embolism in the main pulmonary artery [5].

In the literature, neutrophil/lymphocyte ratio (NLR) and high troponin were evaluated as mortality indicators in PE patients [1,16]. In a study designed by Jia et al., NLR, platelet/lymphocyte ratio, d-dimer, troponin I and NT-ProBNP values were found to be significantly higher in patients with right ventricular dysfunction in acute PE patients in the ED [1]. In a study conducted by Çil et al., although the mean troponin and the mean NLR value were higher in bilateral PE patients than in unilateral PE patients, no statistically significant difference was found [16]. In our study, d-dimer, lactate and troponin T values were found to be higher in patients with massive PE than in patients with sub-massive PE, but no statistically significant difference was found in NLR between these two groups. In addition, patients with a mortal course were found to have higher d-dimer, WBC, neutrophil, BUN, lactate and troponin T values, than those who survived.

PE treatment is carried out according to the risk of mortality. Undoubtedly, reperfusion treatments should be applied in a patient presenting with shock and hypotension. Thrombolytic therapy can be applied to patients who present with shock and hypotension in emergency departments or who are diagnosed with perioperative PE. Thrombolytic therapy is preferred because it has a quick effect, can be applied in a short time and has a short half-life [17]. In our study, although 93.2% of patients were treated with anticoagulant drugs, 11% (n=21) patients died. As we mentioned in our results, this study supports that thrombolytic therapy has a statistically positive effect on survival. Due to the frequency and high mortality rate of acute PE, rapid identification of patients and accurate risk stratification play an important role in its management. About 11% of patients with acute PE die suddenly [1]. In our study, 4.4% of the acute PE patients detected died on the same day.

The present study has some limitations. Due to the retrospective nature of the study and the change in the hospital file system before 2016, patient information was not available. In addition, our research was constrained as a result of its single center nature.

CONCLUSION

The most common ED admission clinic in acute PE patients was found to be dyspnea. D-dimer, lactate and troponin T values were higher in patients with massive PE (25.7%) than in patients with sub-massive PE (74.3%). We believe that this can strengthen our hand in the diagnosis of embolism by evaluating troponin and lactate increases together with d-dimer in patients with whom we suspect PE. In addition, d-dimer, WBC, neutrophil, BUN, lactate and troponin T values were found to be higher in patients who died, than in patients who survived. Thrombolytic therapy was found to be a method that had a statistically positive effect on survival. Our results showed us that the sooner the early diagnosis of acute PE, which can be fatal in the ED, is made and the treatment is started, the more the mortality rates decrease significantly.

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NTNG2 Mutation: A candidate gene for a new brain-skin disorder with early neuropsychiatric manifestation? An analysis based on 3000 patients

NTNG2 Mutasyonu: Erken nöropsikiyatrik manifestasyonlu yeni bir beyin-cilt hastalığı için aday bir gen mi? 3000 hasta üzerinden bir analiz.

Burak Yuluğ[1], Akif Ayaz[2]*

1.Department of Neurology, Alaaddin Keykubat University Faculty of Medicine, Alanya, Turkey
2.Department of Medical Genetics, Istanbul Medipol University Faculty of Medicine, Istanbul, Turkey

ABSTRACT

Aim: In this study, the relationship between genetic analysis and exome sequencing and clinical and neuroimaging findings of four patients from the same family was investigated by analyzing a clinical and genetic (WES) database containing more than 3000 patients.
Methods: We analyzed the WES data of approximately 3000 patients performed in our center in terms of NTNG2 biallelic mutations. In addition, MR imaging findings were investigated.
Results: We found four patients with the same mutation in the NTNG2 gene, presenting with similar clinical and neuroimaging findings. As a result of filtering, the c242G>A variant was determined in the NTNG2 gene. In addition, mild to severe brain parenchymal volume loss and frontal and temporal lobe atrophy were seen in cases 1, 2, and 4 on axial T2-weighted MRI.
Conclusion: The current study has similar phenotypic and genotypic features and is a very rare report showing NTNG2 mutation in this context. Existing clinical data are important in choosing NTNG2 gene-related neuropsychiatric disorders as a future treatment target.

Keywords: Netrin-g2; Synapse formation; Phenotype; WES analysis; Schizophrenia; Neuropsychiatric Disease

ÖZ

Amaç: Bu çalışmada 3000'den fazla hastayı içeren klinik ve genetik (WES) veri tabanını analiz ederek aynı aileden dört hastanın genetik analizi ve ekzom dizilimi ile klinik ve nörogörüntüleme bulguları arasındaki ilişki araştırılmıştır.
Yöntem: Merkezimizde 3000 hastanın WES verileri NTNG2 bialelik mutasyonları açısından incelendi. Ayrıca MR görüntüleme bulguları araştırıldı.
Bulgular: NTNG2 geninde aynı mutasyona sahip, benzer klinik ve nörogörüntüleme bulguları ile başvuran dört hasta bulundu. Filtreleme sonucunda NTNG2 geninde c.242G>A varyantı belirlendi. Ayrıca aksiyel T2 ağırlıklı MRG'de vaka 1, 2 ve 4'te hafif ila şiddetli beyin parankimal hacim kaybı ve frontal ve temporal lob atrofisi görüldü.
Sonuç: Mevcut çalışma benzer fenotipik ve genotipik özelliklere sahip olup bu bağlamda NTNG2 mutasyonunu gösteren çok nadir bir rapordur. Mevcut klinik data NTNG2 geniyle ilişkili nöropsikiyatrik bozukluklarda gelecekteki bir tedavi hedefi olarak seçilmesinde öneme sahiptir.

Anahtar Kelimeler: Netrin-g2, Sinaps oluşumu; Fenotip; WES analizi; Şizofreni; Nöropsikiyatrik hastalık

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*Corresponding Author: Akif AYAZ, Department of Medical Genetics, Istanbul Medipol University Faculty of Medicine, Istanbul, Turkey. +902164448544, aayaz@medipol.edu.tr

ORCID: 0000-0001-6930-7148

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INTRODUCTION

Netrin-g2 (Ntng2) also called laminet-2, a vertebrate-specific axon guidance molecule that belongs to the Netrin-G subfamily, binds to the plasma membrane through a glycosyl phosphatidylinositol (GPI) anchor [1,2,3]. The netrin-G1 (*Ntng1*) and *Ntng2* genes are expressed in the mouse brain in a complementary manner in the dorsal thalamus, olfactory bulb and the cerebral cortex, respectively [1,3]. Several studies have shown that NTNG2 can regulate synapse formation and promote neurite outgrowth [4, 5]. Also, its ligand, NetrinG2 ligand (NGL-2), supports presynaptic differentiation in cultured neurons probably via netrin-G2 [5]. Various expression studies of NTNG2 have reported its possible association with many phenotypes [1,7]. Recently, Zhang et al. reported that abnormal expression of Netrin-g2 and its receptor is associated with impaired memory, learning, and abnormal acoustic startle response in transgenic mice [6]. In their interesting paper, the authors have stated that Netrin-G2 and netrin-G2 ligand are both required for normal auditory responsiveness. On the other hand, abnormal expression levels, have also been reported to be associated with schizophrenia and bipolar disorder in human patients [7]. Also, single nucleotide polymorphisms (SNPs) in the genes for *NTNG1* and *NTNG2* have been reported to be associated with schizophrenia [8,9]. It has been reported that possible candidate genes for schizophrenia might have a role in synapse formation, functioning and plasticity [10,11]. Despite these promising studies suggesting the role of the *NTNG2* gene in the pathophysiology of schizophrenia, more detailed studies are needed to understand the specific symptoms of schizophrenia and bipolar disorder (BPD) (i.e., cognitive symptoms). Based on analysis of more than 3000 patients, in the current paper, we aimed to present the clinical and neuroimaging findings and results of whole exome sequencing of four patients belonging to the same family and present with severe psychomotor retardation. With this report, we hope to provide important informative data for the clinical findings caused by the *NTNG2*gene which could have therapeutic implications in the near future.

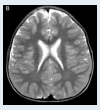
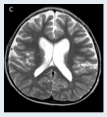
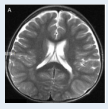
Clinical Presentation

A five-year-old boy (Case-1) was admitted to our department due to severe motor retardation and mutism. The patient has never walked and was not able to sit without support at five-year-old. Since he had respiratory distress immediately after delivery, he remained in the incubator with appropriate respiratory support for 2 days. In his detailed history, his parents have noticed that he suffered from hypotonia first time when he was four-month-old. At his current physical examination bi-temporal narrowing, bilateral strabismus, triangular face, skin hyperelasticity, hirsutism on arms and back, muscular hypotonia and hypoactive deep tendon reflex were present. He had also prominent torticollis, right SCM contraction without any contracture. Dysmorphic facial findings were mild and there was no abnormality in hand, foot and chest examination (Table 1). Cranial Magnetic Resonance Imaging (MRI) showed that the depth of the cerebral sulcus is slightly increased in the frontotemporal region indicating to an underlying mild cerebral atrophy (Figure 2). In his detailed family history, the parents have reported that they have first cousin relationship and the patient has also a sister who have similar clinical findings (Table 1). The second case was his sister (Case-II), who was eight years old and has never been able to speak and walk. Her clinical findings which were associated with significant general atrophy in the frontotemporal region (Figure 2) have been summarized in Table 1. Interestingly, there were similar findings in both cousins, fifteen-month-old (Case-III) male and eleven-year-old male (Case-IV), and there was also a first cousin relationship between their parents. Eleven year-old male presented with muscle atrophy and contracture and he has never been able to walk and speak. He had also bilateral undescended testis story, hirsutism, oculomotor apraxia, hypochromic microcytic anemia, patent ductus arteriosus and patent foramen ovale on echocardiography. In the cranial MRI taken at the age of three years, a slight increase in the CSF distances was observed in the anterior temporal lobe (Figure 2) and the frontal lobe. Accordingly, his cranial MRI revealed slight frontotemporal atrophy (Figure 2). Fifteen-month-old male patient showed mild facial dysmorphic findings such as the prominent forehead, synophrys and bilateral infraorbital creases, skin hyperelasticity

and prominent axial hypotonia. In his actual examination, the patient was not able to sit and to speak. Myotonic discharges have been observed on electromyography evaluation. Unfortunately, the MRI data was not available for this patient.

Shortly, after we have obtained the signed release from the patients, here we present four patients with *Ntng2* mutation who presented with similar clinical findings as well as a progressive cerebral atrophy pattern (Table 1 and Figure 2).

Table 1. Clinical, radiological and genetic findings of patients

		Case I	Case II	Case III	Case IV
Age		5 yo	8 yo	15 mo	11 yo
Gender		M	F	M	M
Onset of clinical findings		4 mo	4-6 mo	3-4 mo	4-6 mo
Neurological findings	Hypotonia	+	+	+	+
	Unsupported seating	-	-	-	-
	Walking	-	-	-	-
	Strabismus	+	-	-	-
	Speech	-	-	-	-
	Contracture	-	-	-	+
	Oculomotor apraxia	Unknown	Unknown	Unknown	+
Non-neurological findings	Skin hyperelasticity	+	+	+	+
	Intestinal motility disorder	-	+	-	-
	Cryptorchidism	-		-	-
	Hirsutism	+	-	-	+
	Hypochromic microcytic anemia	-	-	-	+
Cranial MR findings		Cerebral Atrophy 	Cerebral Atrophy 	NA	Cerebral Atrophy 
EMG		NA	NA	Myotonic discharge	Normal
Echo		NA	NA	NA	PDA
WES Results		Homozygous c.242G>A NTNG2	Homozygous c.242G>A NTNG2	Homozygous c.242G>A NTNG2	Homozygous c.242G>A NTNG2

NA: Not available, PDA: Patent Ductus Arteriosus

Clinical, radiological and genetic findings of patients at different age groups. Please see common neurological and non-neurological findings in the table highlighted in red.

MATERIAL AND METHODS

We analyzed the WES data of approximately 3000 patients performed in our center in terms of *NTNG2* biallelic mutations. In this context, peripheral blood samples were collected at the Istanbul Medipol University and genomic DNA was isolated using standard protocols. Whole-exome sequencing was performed with the Illumina Nextera and with Illumina Nextseq 500 platform. Alignment to the reference genomes (hg19 for human) was performed using Burrows-Wheeler Aligner (BWA). We applied the following additional filters; the minimum read depth:10, the minimum base quality:20, the minimum of alternative allele frequency: %20. The identified variants were functionally annotated using ANNOVAR. We excluded from further analysis variants in non-coding regions, synonymous variants and variants present in highly repetitive regions. Detected variant in *NTNG2* was confirmed by Sanger Squencing with ABI 3130xl (Figure 1C). Written consent form was obtained from the parents of patients.

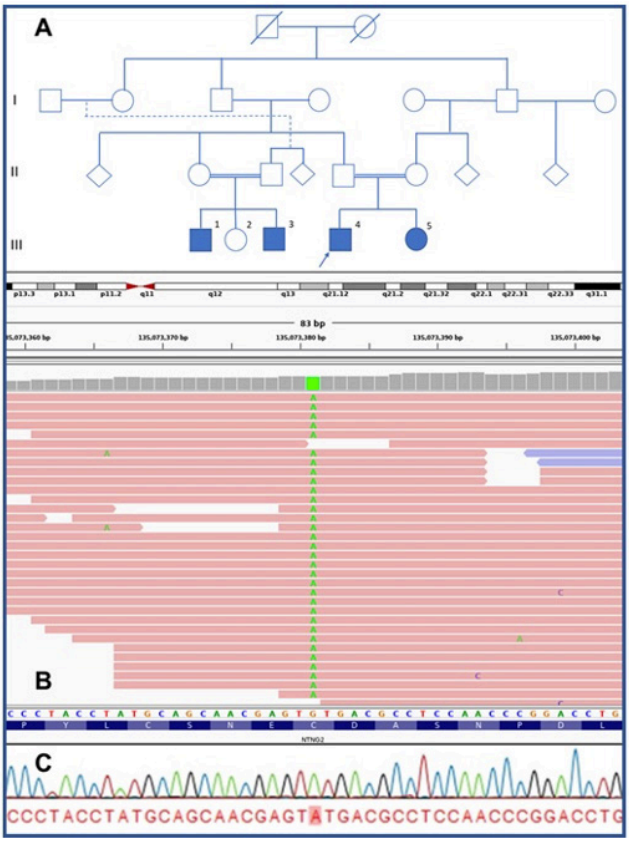


Figure 1. A. Affected cases in the family are shown with III-1, III-3, III-4 and III-5 in pedigree. B. IGV images of III-4 showing the homozygous G> A change C. Sanger sequencing of case III-4 supporting IGV image.

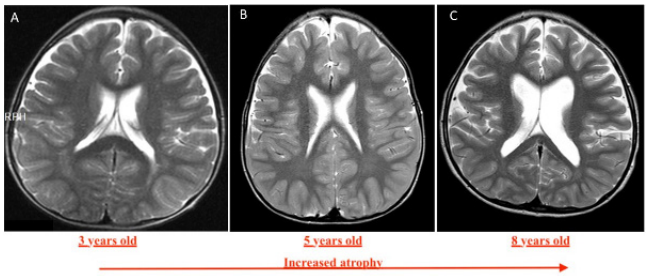


Figure 2. A. Cranial MR images of case III-1, at 3 years old, showing enlargement of CSF distances in the temporal lobe anterior. B. Cranial MRI images of case III-4 showing slightly increased in the frontotemporal region which could indicate to an underlying mildly cerebral atrophy (at 5 years old) C. Cranial MRI images of case III-5 showing significant general atrophy especially in frontotemporal region and dilated lateral ventricles (at 8 years old).

MRI: MR imaging was performed on 1.5-T MRI scanner (Magnetom Avanto, 18 channels, Siemens Medical Solutions, Erlangen, Germany) with a matrix head coil used as both transmitter and receiver. T1W, T2W, diffusion-weighted, and HEMO sequences were obtained in axial plane with 5 mm slice thickness and 30% interslice gap. For dedicated study, inversion recovery (IR) oblique coronal images (TE: 51, TR: 3500, FOV: 250 mm, slice thickness: 2 mm) and oblique coronal T2W images (TR: 4000, TE: 101, FOV: 230, slice thickness: 2 mm) covering the whole brain were acquired. The images were assessed for cortical atrophy, loss of defined morphologic structure of any specific region, increased T2W signal and decreased T1W signal. The diagnosis of the atrophy was made if there was evidence of signal abnormality of the specific region. Raters were blinded to the clinical information and each other's results.

RESULTS

In evaluating approx. 3000 patients WES data, we have found four patients from the same family who have the same mutation in *NTNG2* gene and present with similar clinical and neuroimaging findings: A 5-year-old male patient. There was no variant which might be enough to explain his clinical findings. Thus, we included other affected three family members to WES study and matched the homozygous common variants in all 4 patients. As a result of our filtering we have determined c.242G> A variant in *NTNG2* gene. We identified this variant as a heterozygote by sanger sequencing in the parents of patients and in a healthy sibling. In addition, sanger confirmations of this variant were performed in patient DNAs. (Figure 1C)

MRI: Axial T2 weighted MRI showed mild to severe brain parenchymal volume loss and frontal and temporal lobe atrophy in case 1, 2 and 4. (Figure 2).

DISCUSSION

Studies evaluating available NTNG2 data have reported that the NTNG2 gene promotes presynaptic differentiation in neurons co-cultured with its ligand (NGL-2) [5]. These findings were in accordance with expression studies, revealing that NTNG2 and its receptor have been associated with impaired memory and learning in schizophrenia and bipolar disorder [6,7]. Wei G. et al. reported that KDM5C mutations regulate Netrin G2 and suppress neurite growth in Neuro2a cells [12] . In the light of these findings, it is not unreasonable to assume that the most likely mechanism to explain our patient's findings might be the impaired synaptogenesis which is one of the important components of brain development, especially when it comes to neurogenesis and migration. It is well-known that synaptogenesis involves the formation and elimination of synapses over time while the failure of this process may cause progressive clinical and neurobiological deterioration in various neuropsychiatric disorders. Here, we present clinical findings and the whole exome sequencing results of four patients who had similar clinical findings such as severe hypotonia, intellectual disability, motor retardation and skin hyperelasticity. Despite these similar presentations, the patients differed in terms of some clinical features which are summarized in Table 1. Radiologically, although there was no significant difference in any of the MRI atrophy parameters in the first years of life between the subjects, there was a trend towards an atrophy (i.e., increased extra-axial cerebrospinal fluid distance in frontotemporal region and decreased periventricular white matter volume in bi-frontoparietal region) in the following years (5-10-year-old) suggesting that there could be an underlying progressive neurodegenerative process. (Figure 2). Importantly, we detected homozygous c.242G>A (p.Cys81Tyr) variant on

NTNG2 gene which is not observed in WES data of approximately 3000 other patients that we have analyzed before. It should be noted that there was no problem in IGV images and the images were found to be normal in terms of reading depth and base quality (Figure 1B). Also, sanger squencing of this region was performed. This variant has not identified in gnomAD, exac and iranome databases. According to ACMG, it has PM1, PM2, PP5, PP2 and PP3 criteria and is classified as pathogenic. In silico analysis tools (MutationTaster, FATHMM, FATHMM-MKL, MetaSVM, MetaIR), all of them, were classified "damaging" or "disease causing". The variant of DANN score, located in highly conserved region, is 0.9973, and GERP score is 5. SIFT and Provean, which are two of mostly used functional in slico tools were classified the variant we detected as damaging (Table 2).

Clinical Databases	Clinvar	Pathogenic
	HGMD	Disease-causing mutations
	ACMG classification	Pathogenic (PM1, PM2, PP5, PP2, PP3)
Allel frequency	gnomAD exomes	--
	gnomAD genomes	--
	Iranome	--
	In house database	--
In silico predicton database	Mutation Taster	Disease causing
	FATHMM	Damaging
	FATHMM-MKL	Damaging
	MetaSVM	Damaging
	MetaIR	Damaging
Functional Database	SIFT	Damaging
	Provean	Damaging
DANN Score		0.9973
GERP Score		5

In addition, segregation of the variant in family members were compatible with autosomal recessive inheritance pattern. The strength of our present report is that although some studies on NTNG2 have been done at the molecular level, clinical findings are still very inconclusive. In light of current information, there are very few records on NTNG2 in HGMD. Taken together, with this current article, we aimed to clarify the clinical manifestations caused by *NTNG2* mutations in humans and evaluate if the *NTNG2* may be a good candidate gene for a new brain-skin disorder characterized with hypotonia, intellectual disability, cerebral atrophy and skin hyperelasticity. Except of one patient all MRI findings were available which were taken at different time points which can be considered as a major weakness in this study. Although we are aware that longitudinal MRI data gathered from each patient would provide a more reliable data, we were curious to see if the cross-sectional neuroimaging data differed between different age groups which could indicate to an underlying progressive neurodegenerative process. To this respect, instead of waiting for each patient's neuroimaging data, which is time-consuming, we prefered to compare the imaging data between patients in a time-dependent manner. Not surprisingly, we have revealed that these patients not only presented with similar atrophic regions in the MRI but also showed a progressive atrophy pattern which was associated with increased age. In order to accurately describe the progressive pathology, and overcome common problems of cross-sectional data we are aware of the fact that the emphasis of this study should be placed on longitudinal neuroimaging data (serial correlations, time-dependent interindividual variability). Despite this limitation our current findings provide first preliminary evidence for the neuropathophysiology of NTGN2 mutation. In addition, since the embryonic ectodermal germ layer contribute to central nervous system and skin organ systems, and many brain-skin disorders are strongly correlated with neurobehavioral impairment (i.e., Von Recklinghausen's disease) it is not surprising that our patients have been presented with common skin and central nervous system findings. Although there is still no evidence for the existence of NTGN2 expression in the skin tissue further studies should evaluate whether NTNG2 is involved during the embryonic ectodermal germ layer development. Given the neuromorphological evidence in our study, it is not unreasonable to assume that NTNG2 might play a critical role in schizophrenia which has been suggested to be a neurodevelopment disorder while frontal-lobe-related executive dysfunction and cognitive failure is usually noted during the course of schizophrenia [13]. Here it is interesting to notice that recent studies indicated that executive dysfunction was especially present in parents with a positive family history of schizophrenia while schizophrenia diagnosis in the family predicted

impaired performance on executive function in healthy relatives suggesting that hypofrontality may represent a genetic endophenotype for schizophrenia [14,15]. Accordingly, recent SNPs and haplotype studies have confirmed that there is a significant association between NTNG2 and schizophrenia [8]. Considering the anatomic and functional significance of the frontal cortex in the pathogenesis of schizophrenia [16], defects in any of the structures which are involved in intrinsic and extrinsic functional connectivity (i.e., DLPF circuit) might be related to the negative symptomology of schizophrenia such as the dysfunction of the attention and executive function [17]. In this context, the potential disturbance of NTN2 gene regulation at the transcriptional level might suggest a molecular contribution by netrin-G gene(s) to the disrupted higher-order brain functions in schizophrenia. It should be also noted that recent experimental studies have suggested that attention and cognitive deficits in schizophrenia might be related to impaired sensorimotor filtering [18, 19]. For instance, Nishumara et al have revealed that Ntng2 mutant mice showed altered NMDA receptor-mediated electrophysiologic responses in brain slices demonstrating that netrin family proteins are critical for NMDA receptor function, lending further support to altered NMDA neurotransmission hypothesis for schizophrenia [19]. Although we consider our findings to be significant confirmation of results by pooling data from multiple cohorts would be required. Moreover, further well-designed clinical neuroimaging studies (i.e Magnetic Resonance Spectroscopy) with larger number of human subjects in combined with relevant Induced Pluripotent Stem cell (IPS) culture studies would be logical steps to understand the pathophysiology of the underlying progressive cerebral atrophy. Although we are aware that the present clinical and neuroimaging data are not conclusive and need to be strengthened, we believe that its novelty (this is the first demonstration that NTNG2 phenotype is associated with common neuropsychiatric in all patients) deserves to be brought to the attention of the neuropsychiatry and neurogenetic community. The clinical presentation of *Ntng2* mutation reported here may even be considered as a future treatment target in *Ntng2* gene related neuropsychiatric disorders.

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Clinical And Radiological Results of Ludloff Medial Open Reduction Technique in Patients Wıth Developmental Hip Dysplasia

Ludloff Medial Açık Redüksiyon Uygulanan Gelişimsel Kalça Displazili Hastaların Klinik Ve Radyolojik Sonuçları

Sedat Demir[1]*, Baki Volkan Çetin[1], Ahmet Yiğit Kaptan[1], Emrah Vatansever[1], Mehmet Ok[1], Mehmet Akif Altay[1]

1.Harran University, Faculty of Medicine, Department of Orthopedics and Traumatology, Şanlıurfa, Turkey

ABSTRACT

Aim: The aim of this study was to evaluate the clinical and radiological results of Ludloff medial open reduction surgery in patients with the developmental of hip dysplasia, younger than 18 months old.

Methods: The radiological and clinical results of 35 patients (49 hips), younger than 18 months of age treated with Ludloff medial approach due to DDH between the years 2013 and 2020 were retrospectively evaluated. Preoperative, final control acetabular index angles and medial apertures were measured according to the McCay criteria, Tönnis classification, Kalamchi-MacEwen classification, IHDI classification and Severin classification were analysed.

Results: At the last control, the youngest age was 27 months, the oldest was 88 months and the mean age was 43.90 ± 14.17 months. The follow-up period was performed at a minimum age of 12 months, a maximum age of 72 months, and the mean follow-up period was 24.81 ± 17.17 months. According to the Tönnis classification, 40 hips were Tönnis classification type 1 (81.63%), 4 hips were Type 2 (8.16%), 3 hips were Type 3 (6.12%) and 2 hips were Type 4 (4.08%) in the follow-up visit. According to McCay clinical evaluation criteria, 38 hips (79.59%) were grade 1 which equates to excellent results. Grade 0 (no necrosis) was detected in 38 (77.55%) of 49 hips according to the Kalamchi and MacEwen AVN clinical evaluation criteria. According to the Severin classification, type 1 results were observed in 32 (65.31%) of 49 hips, type 2 in 9 hips (18.37%), type 3 in 1 hip (2.04%) and type 4 in 7 hips (14.29%). The mean CE angle was found to be 18.56 ± 9.93. Additional surgical intervention was required in 8 hips of 6 patients.

Conclusion: Clinically and radiologically satisfactory results were obtained in DDH patients with Ludloff medial open reduction technique, below the age of 18 months.

Key words: Developmental hip dysplasia, open reduction and avascular necrosis.

ÖZ

Amaç: Bu çalışmanın amacı, 18 aylıktan küçük, gelişimsel kalça displazisi olan hastalarda Ludloff medial açık redüksiyon cerrahisinin klinik ve radyolojik sonuçlarını değerlendirmektir.

Yöntem: 2013-2020 yılları arasında GKD nedeniyle Ludloff medial yaklaşımı ile tedavi edilen 18 aylıktan küçük 35 hastanın (49 kalça) radyolojik ve klinik sonuçları retrospektif olarak değerlendirildi. Ameliyat öncesi, son kontrol asetabular indeks açıları ve medial açıklıklar McCay kriterlerine göre ölçüldü, Tonnis sınıflaması, Kalamchi-MacEwen sınıflaması, IHDI sınıflaması ve Severin sınıflaması analiz edildi.

Bulgular: Son kontrolde en genç 27 ay, en yaşlı 88 ay ve ortalama yaş 43.90 ± 14.17 ay idi. Takip süresi minimum 12 ay, maksimum yaş 72 ay ve ortalama takip süresi 24.81 ± 17.17 ay idi. Tönnis sınıflamasına göre 40 kalça Tönnis sınıflama tip 1 (%81,63), 4 kalça Tip 2 (%8,16), 3 kalça Tip 3 (%6,12) ve 2 kalça Tip 4 (%4,08) idi. McCay klinik değerlendirme kriterlerine göre 38 kalça (%79.59) derece 1 idi ve bu da mükemmel sonuçlara tekabül ediyordu. Kalamchi ve MacEwen AVN klinik değerlendirme kriterlerine göre 49 kalçanın 38'inde (%77,55) derece 0 (nekroz yok) saptandı. Severin sınıflamasına göre; 49 kalçanın 32'sinde (%65.31) tip 1, 9 kalçada tip 2 (%18.37), 1 kalçada tip 3 (%2.04) ve 7 kalçada tip 4 (%14.29) tespit edildi. Ortalama CE açısı 18,56 ± 9,93 olarak bulundu. 6 hastanın 8 kalçasına ek cerrahi müdahale gerekti.

Sonuç: Ludloff medial açık redüksiyon tekniği ile 18 aydan küçük GKD hastalarında klinik ve radyolojik olarak tatmin edici sonuçlar elde edildi.

Anahtar kelimeler: Gelişimsel kalça displazisi, açık redüksiyon ve avasküler nekroz.

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*Corresponding Author: Sedat DEMİR, Harran University, Faculty of Medicine, Department of Orthopedics and Traumatology, Sanliurfa, Turkey, +905531615668, sdtdmr1987@gmail.com

ORCİD: 0000-0002-5663-2328

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Introduction

Developmental hip dysplasia (DDH) is a vigorous disease in which the structures that compose the hip joint, which are normal during their intrauterine formation, subsequently and for various reasons show structural deterioration [1]. The main goal in DDH treatment is to ensure the concentric reduction of the hip joint as soon as possible and to provide interaction between the proximal femur and the acetabulum [2]. It has been reported that the acetabulum has the ability to develop over many years when appropriate contact is provided between the femoral head and acetabulum [3].

Treatment steps to be applied to the patient includes a process starting from dynamic (Pavlik bandage) or static (such as abduction orthosis, Frejka pillow, etc.) orthoses, to closed reduction, medial or anterior open reduction and pelvic or femoral osteotomy. The age and clinical condition of the patients and the experience of the clinician should be taken into consideration, before selecting treatment options.

Medial open reduction for DDH was described by Ludloff in 1908. The medial approach with the Ludloff technique requires minimal soft tissue dissection, low blood loss and provides direct access to all inferomedial structures that prevent reduction. However, the Ludloff technique requires precision and focus due to the risk of injury to the medial circumflex artery and restricted the hip joint vision [4].

As the diagnosis is delayed, the joint remodelling ability and treatment success decreases, causing complications, and the risk of developing degenerative joint disease increases. The significance of providing the patient with a lifelong, painless and functional hip joint is early diagnosis and treatment [2].

In this study, we aimed to evaluate the clinical and radiological results of the Ludloff medical open reduction surgery in patients with developmental hip dysplasia younger than 18 months old.

Patients and methods

The radiological and clinical results of the patients who underwent open reduction surgery using the Ludloff medial approach technique due to DDH, between 2013 - 2020 in the Harran University, Faculty of Medicine, Orthopedics and Traumatology Clinic, were retrospectively evaluated.

Patient files were scanned and those who underwent medical open reduction surgery at the age of 18 months and younger, were included in the study. Patients who were older than 18 months at the time of surgery, had teratological dislocation and did not show up for regular follow-ups, were excluded.

Radiographic evaluation of the patients were done with preoperative and final visit, direct pelvic radiographs. Acetabular index angles and medial apertures were measured on the radiographs. The Tönnis and IHDI classifications were used for radiological staging. Additionally, acetabular coverage was evaluated with the Severin classification and the requirements for secondary acetabular intervention were determined. Pain and range of motion were evaluated using the Mc Cay clinical evaluation criteria. Kalamchi-MacEwen classification was used to evaluate patients according to a radiologic avascular necrosis, during the final visit.

Tönnis Classification System: The Tönnis classification was used for arthrographic staging preoperatively and during surgery. The hips are classified according to Tönnis's Rating: accordingly, grade 1 defines acetabular shallowness, grade 2 subluxation, grade 3 dislocation and grade 4 defines high dislocation [5,6].

IHDI classification: A new radiographic classification system has been developed by the International Hip Dysplasia Institute (IHDI), which uses the centrum of the proximal femoral metaphysis as a reference point. Grade 1 represents the mildest hip dislocation, whilst Grade 4 refers to the worst hip dislocation. The IHDI classification gives more effective and accurate results than the Tönnis classification in patients without femoral head ossification [7].

The clinical results of our patients were analyzed according to the McCay clinical evaluation criteria [8]. As for the Kalamchi-MacEwen classification, it divides AVN cases into four groups, thereby

focusing on growth plate involvement [9].

Severin evaluation system: This test is an evaluation system based on the CE angle. The CE angle is normally between 15-25 °. This angle is less than 15 ° in acetabular dysplasia [10]. This angle is considered to be 19 ° and above between the ages of 6-13, and 25 ° and above in patients older than 14 years of age [11]. The head center cannot be evaluated completely in children younger than 5 years, therefore although the diagnostic value of CE angle is higher at the age of 5 years and older [12]. However, some studies used the Severin radiological evaluation criteria in patients under 5 years of age [13,14]. Severin's radiological evaluation criteria were used in this study, with reference to the studies in the literature.

Surgical technique: Patients were positioned in supine position. Arthrography was performed under fluoroscopy and the femoral head-acetabulum relationship and capsule were evaluated. According to the arthrography results, 4 cm incision was made parallel and 1 cm distal to the groin crease, starting from the adhesion site of the adductor longus tendon in patients who could not achieve stable concentric reduction with closed methods. Thereafter, tenotomy was performed, 2 cm distal to the insertion of the adductor longus with electrocautery. Consequently, an iliopsoas tenotomy was performed using the cleavage between the adductor longus-pectineus (in superior of the adductor longus) to find the iliopsoas. Subsequently iliopsoas tenotomy, the capsule was exposed and opened in a T shape. Ligamentum teres and transverse acetabular ligament were excised, and the intra-articular pulvinar was removed. The hip was shortened without suturing the capsule. At the end of the operation, the incision was sutured in layers. Wound dressings were applied. The patient was taken to the plaster table with his reduction preserved. A pelvipedal cast was applied in the human position (Figure 1.) [15].

Results

Forty-nine hips of thirty-five patients were included in this study. The youngest age at the last visit was 27 months and the oldest was 88 months old. The mean age was 43.90 ± 14.17 months. The follow-up period was minimum 12, maximum 72 months, and the mean follow-up period was 24.81 ± 17.17 months. The youngest age at time of operation was 5 months, the oldest was 18 months and the mean age at the time of operation was 13.61 ± 2.80 months. The rate of using the Pavlik bandage was found in only 1 (0.35%) patients. It was observed that two (0.7%) of the patients had previously undergone closed reduction. No infection was found in any of the patients. One patient (2.85%) had a femur fracture during pelvipedal casting. Twenty-six (74.28%) of the patients used postoperative abduction devices, while nine (25.72%) did not (Table 1).

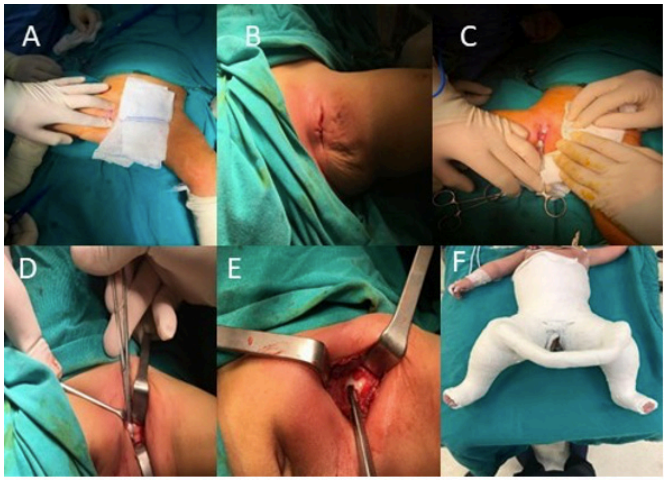

Figure 1. Surgical incision (A, B) Adductor longus view after the fascia is opened (C) Iliopsoas musculotendinous junction (D) Opening the joint capsule in "T" shape, view of acetabulum and femoral head after excision of ligamentum teres and pulvinar (E) Pelvipedal cast (F)

Table 1. Demographics of the patients

		Mean±Std	Min-Max
Age at last follow-up (month)	Female (n:30)	43,43±14,79	27-88
	Male (n:5)	44,22±10,98	29-55
	Total (n:35)	43,90±14,17	27-88
Age at operation (month)	Female (n:30)	13,58±2,55	5-18,00
	Male (n:5)	14,96±1,07	9-16,13
	Total (n:35)	13,61±2,80	5-18,00
Follow-up duration	Female (n:30)	24,75±17,61	12-40
	Male (n:5)	23,61±12,03	12-72
	Total (n:35)	24,81±17,17	12-72

The mean preoperative Acetabular Index angle of 35 patients was found to be 37.19 ± 4.23. The mean Acetabular Index angle at the last controls was 25.84 ± 6.42, and the repeated angular values over these periods showed a statistically significant change (t: 4.967; p: 0.013). The mean

preoperative medial aperture (mm) of 35 patients (49 hips) was 8.56 ± 2.69, while the mean medial aperture (mm) of 35 patients (49 hips) in the last controls was 0.97 ± 0.76, and the repeated angular values over these periods, statistically showed significant change (t = 3,871; p: 0,006).

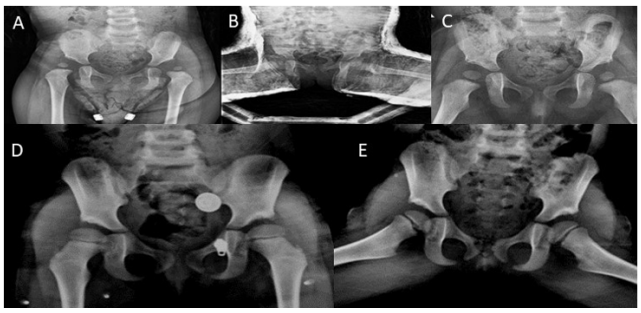

Figure 2. 16 month old female patient preoperative AP radiography (A) Postoperative AP radiography after bilateral Ludloff medial approach technique (B) Postoperative 3rd month AP radiography (C) Postoperative 28 month AP (D) and frog leg (E) radiography

The preoperative radiologic evaluation according to the Tönnis classification revealed 4 hips were type 2 (8.16%), 25 hips were type 3 (51.02%) and 20 hips were type 4 (40.82%) DDH. At the final follow-up, 40 hips were type 1 (81.63%), 4 hips were type 2 (8.16%), 3 hips were type 3 (6.12%) and 2 hips were type 4 (4.08%). A statistically significant difference was established between the preoperative Tönnis classification and the last visit according to the chi-square analysis (χ^2: 9.119 p: 0.035) (Table 2.).

Table 2. Tönnis classification

	Tönnis classification	n	%	Chi-square (χ^2)	P value
Preoperative	Type 2	4	8,16	9,119	0,035**
	Type 3	25	51,02		
	Type 4	20	40,82		
Final follow-up	Type 1	40	81,63		
	Type 2	4	8,16		
	Type 3	3	6,12		
	Type4	2	4,08		

Preoperative radiologic evaluation according to the IHDI classification revealed 3 hips were type 2 (%6.12), 30 hips were type 3 (%61.22), 16 hips were type 4 (%32.65). At the final follow-up, 40 hips were type 1 (%81.63), 6 hips were type 2 (%12.24), 3 hips were type 3 (%6.12) (Table 3). A statistically significant deviation was found between the preoperative IHDI classification and the last control IHDI classification according to the chi-square analysis (χ^2: 8,478 p: 0.018).

Table 3. IHDI classification

	IHDI	n	%	Chi-square (χ^2)	P value
Preoperative	Type 2	3	6,12	8,478	0,018**
	Type 3	30	61,22		
	Type 4	16	32,65		
Final follow-up	Type 1	40	81,63		
	Type 2	6	12,24		
	Type 3	3	6,12		

According to the McCay clinical evaluation criteria of the patients in the study, 38 hips (79.59%) were Grade 1 (excellent), 3 hips (%6.12) were grade 2 (good), 2 hips (4.08%) were grade 3 (moderate) and 6 hips (%12.24) were Grade 4 (poor) (Table 4).

Table 4. McCay classification

	n	%
Grade 1 (excellent)	38	79,59
Grade 2 (good)	3	6,12
Grade 3 (moderate)	2	4,08
Grade 4 (poor)	6	12,24

The rates of AVN in our cases were evaluated according to the Kalamchi-MacEwen classification. According to the Kalamchi-MacEwen AVN clinical evaluation criteria, 38 (77.55%) of the hips were grade 0 (no necrosis), 9 hips (18.37%) were grade 1, 1 hip (2.04%) was grade 2 and 1 hip (2.04%) was grade 3 (Table 5).

Tablo 5. Kalamchi-MacEwen classification

	n	%
Grade 0	38	77,55
Grade 1	9	18,37
Grade 2	1	2,04
Grade 3	1	2,04

The patients were also evaluated according to the Severin classification: 32 hips (65.31%) were type 1, 9 hips (18.37%) were type 2, 1 hip was type 3 (2.04%) and 7 hips (14.29%) were Type 4. The mean CE angle was found 18.56 ± 9.93. Additional surgery was required in 8 hips of 6 patients in the study, 2 patients rejected further treatment (3 hips), a Pemberton osteotomy was performed

on 4 patients (4 hips) and Salter osteotomy was performed on 1 patient (1 hip).

Discussion

In this study, low AVN rate, high functional scores and successful radiological results were obtained in the early period with the Ludloff open reduction method in DDH patients younger than 18 months. Faresetti et al. retrospectively analyzed 71 hips that they treated with medial open reduction and reported excellent results in 44 hips (76%), good results in 24 hips (17%), and moderate results in 3 hips (7%) according to the McKAy criteria after a mean follow-up of 22 years [16]. Okano et al. used the Ludloff method for 43 patients (45 hips) and reported excellent results in 35 hips (77%), good result in 1 hip (2.2%), moderate results in 3 hips (6.6%) and poor results in 4 hips (8.8%) according to the McKay criteria after a mean follow-up of 16.4 years [17].

In the present study, in accordance with the literature, grade 1 excellent results were observed in 38 hips (79.59%) according to the McCay classification. In addition, grade 2 good results were observed in 3 hips (6.12%), grade 3 moderate results in 2 hips (4.08%) and grade 4 poor results in 6 hips (12.24%). We surmise that the reason we observed a similar success rate with long-term follow-up studies in the literature is that the Ludloff method requires minimal soft tissue dissection, as well as a low AVN rate over a long term period.

AVN is the most serious complication in the long term after DDH treatment. Its frequency rates have been reported in a wide range of 0-73% in different series [3]. In a study conducted by Biçimoğlu et al., 185 hips of 143 patients were reduced with posteromedial limited open intervention and they reported that AVN was observed in 19.5% of patients who were followed up retrospectively, at an average of 7.5 years [18]. Koizumi et al. analysed the results of surgical treatment to 35 hips of 33 patients with DDH using the Ludloff's medial open approach and reported an AVN rate of 42.9% after an average follow-up of 19.4 years [19].

In the present study, AVN rates were evaluated according to the Kalamchi-MacEwen classification. Accordingly, 38 (77.55%) of the hips were grade 0 (no necrosis), 9 hips (18.37%) were grade 1, 1 hip (2.04%) was grade 2 and 1 hip (2.04%) was grade 3. AVN rates with the Ludloff method in the early period were satisfactory in the present study. However, the reason for the low AVN rate reported in this study may be the shorter follow-up period compared to other studies in the literature.

Isiklar et al. found an affiliation between the age of the child at the time of surgery and secondary surgeries they performed later in patients younger than 18 months in DDH patients, operated with the medial approach [20]. Zamzam et al. found that residual acetabular dysplasia in the patients they treated increased in children older than 12 months [21]. The most controversial age group in hip dysplasia treatment is between 15-18 months. Tümer et al. emphasized the importance of early concentric reduction and recommended monitoring of spontaneous healing in patients before early secondary bone procedures [3]. As a result, it has been seen that residual acetabular dysplasia rates can be reduced at a young age, low grade (Tönnis), low acetabular index angle before reduction, and stable concentric reduction after treatment. In our study, the mean age of patients requiring secondary surgery (10-18 months, mean: 15.7) was higher than the general average age (5-18 months, mean: 13.6). The preoperative mean acetabular index was also found to be 39 ° and Tönnis tapering average was 3.

In light of all this literature, we may infer that residual acetabular dysplasia rates can be reduced at a younger age, low grade (Tönnis), low acetabular index angle before reduction, and stable concentric reduction after treatment. Before performing such surgical interventions, planning should be made according to the Tönnis degree, acetabular index angle and the surgeon's experience and preference [22].

K. Yamada et al., reported the results of 103 patients who underwent open reduction with Ludloff's medial approach, where 115 hip joints were observed over a long-term beyond the age of maturity. According to Severin's classification, 69 hips (60.0%) considered to represent acceptable results were classified as group I or II. A total of 39 hips (33.9%) were group III and the remaining 7

hips (6.1%) were group IV. As for reoperation, 20 of 21 patients who underwent surgical reduction after the age of 12 months required additional corrective surgery during the growth period, as the hip joint tended to subluxate gradually [23].

We evaluated the patients according to the Severin classification: 32 (65.31%) of 49 hips were type 1, 9 hips (18.37%) were type 2, 1 hip (2.04%) type 3 and 7 hips (14.29%)) were Type IV. Mean CE angle was 18.56 ± 9.93. Additional surgery was required for 8 hips of 6 patients in the study. 2 patients underwent treatment rejection (3 hips), 4 patients Pemberton osteotomy (4 hips), 1 patient salter osteotomy (1 hip). Consistent with the findings in the literature, we observed that residual acetabular dysplasia rates and the need for secondary intervention increased as the age and acetabular index rate at the time of operation increased.

The limitation of the present study are the limited number of patients and a short follow-up period. With long follow-up periods, the rate of AVN, secondary acetabular dysplasia and the number of patients requiring secondary surgeries may change.

Conclusion

The Ludloff medial open reduction technique is a reliable method with low AVN rate and satisfactory clinical results, in patients with DDH younger than 18 months of age.

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Effects of LDD and CAPE administration on total antioxidant and total oxidant levels in experimental periodontitis model of rat brain

Sıçan beyninin deneysel periodontitis modelinde DDD ve KAFE uygulamasının toplam antioksidan ve toplam oksidan düzeyleri üzerine etkileri

Umut Yiğit[1*], Fatma Yeşim Kirzioğlu[2], Özlem Özmen[3], Abdülhadi Cihangir Uğuz[4]

1.Department of Periodontology, School of Dentistry, Usak University, Usak, Turkey

2.Department of Periodontology, School of Dentistry, Suleyman Demirel University, Isparta, Turkey

3.Department of Pathology, School of Veterinary Medicine, Mehmet Akif Ersoy University, Burdur, Turkey

4.Department of Biophysics, School of Medicine, Yozgat Bozok University, Yozgat, Turkey

ABSTRACT

Aim: Observing the effects of caffeic acid phenethyl ester (CAPE) and/or low dose doxycycline (LDD) on total antioxidant and oxidant status of brain in experimental periodontitis is the purpose of the study.

Methods: 48 male Wistar albino rats were designed as the following: control group (C, n=8), periodontitis + CAPE group (PC, n=10), periodontitis + LDD (PD, n=10), periodontitis + LDD + CAPE group (PCD, n=10), and periodontitis group (P, n=10). The time period for the experiment was 14 days. 10 µmol/kg/day of CAPE was administered using an intraperitoneal injection (IP). 10 mg/kg/day of LDD was administered using an oral gavage method. Histopathological changes were evaluated.

Results: Beneficial results were seen in all of the groups after LDD and/or CAPE administration on decreasing the alveolar bone loss level and oxidative stress. All of the experimental groups showed signs of periodontitis with alveolar bone loss. The P group leads with the most alveolar bone loss compared to the other periodontitis groups and the lowest group was the PC group in the periodontitis groups. The evolution of alveolar bone loss from high to low was that group P, group PD, group PCD, group PC, and group C ($P < 0.05$). However, there is no statistical difference between brain total antioxidant status and brain total oxidant status average values according to brain groups ($p > 0.05$).

Conclusion: The combination of LDD and CAPE are not significantly different when applied alone or together on oxidative status. But both of the agents have beneficial effects on reducing the oxidative stress and tissue damages.

Key words: Brain, Oxidative stress, periodontitis, total antioxidant status

ÖZ

Amaç: Deneysel periodontitis modelinde kafeik asit fenetil ester (CAPE) ve/veya düşük doz doksisiklinin (LDD) beyin total antioksidan ve oksidanlar üzerine etkisinin araştırılmasıdır.

Yöntem: 48 adet erkek Wistar albino rat, kontrol grubu (C, n=8), periodontitis + CAPE grubu (PC, n=10), periodontitis + LDD (PD, n=10), periodontitis + LDD + CAPE (PCD, n=10) ve periodontitis grubu (P, n=10) şeklinde gruplara ayrıldı. Çalışma süresi 14 gün olarak belirlendi. 10µmol/kg/gün CAPE, bir intraperitoneal enjeksiyon (İP) kullanılarak,10 mg/kg/gün LDD, oral gavaj yöntemi kullanılarak uygulandı. Değişiklikler histopatolojik olarak değerlendirildi.

Bulgular: LDD ve/veya CAPE uygulamasının tüm gruplarda oksidatif stress ve alveolar kemik kaybı şiddetinin azaltması açısından faydalı sonuçlar gösterdiği belirlendi. Deney gruplarının tamamında periodontitisin kesin bulgusu olarak alveolar kemik kaybı tespit edildi. Sadece P grubunda, diğer periodontitis gruplarına kıyasla daha fazla alveoler kemik kaybı gözlenirken, PC grubunda ise en az alveolar kemik kaybı gözlendi. Gruplar arasında alveolar kemik kaybının yüksekten düşüğe sıralaması şu şekildeydi: grup P, grup PD, grup PCD, grup PC ve grup C ($p < 0.05$). Buna ragmen beyin gruplarına göre beyin total antioksidan durumu ve beyin total oksidan durumu ortalama değerleri arasında istatistiksel olarak anlamlı bir farklılık tespit edilmedi. ($p > 0.05$).

Sonuç: LDD ve CAPE kombinasyonu, tek başına veya birlikte uygulandığında oksidatif durum ve doku hasarı üzerine istatistiksel olarak herhangi bir anlamlı farklılık göstermedi. Ancak her iki ajanın da oksidatif stresi ve doku hasarlarını azaltmada faydalı etkileri vardır.

Anahtar kelimeler: Beyin, oksidatif stres, periodontitis, toplam antioksidan seviyesi

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*Corresponding Author: Umut YİĞİT, Department of Periodontology, School of Dentistry, Usak University, Usak, Turkey, +902762212231, umut.yigit@usak.edu.tr

ORCİD: 0000-0001-8080-2932

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INTRODUCTION

Periodontitis is a chronic inflammatory disease that originates from dental plaque. It is characterized by soft and hard tissue destruction around the teeth. Many studies have discussed the possible relationship between periodontitis and several systemic diseases such as diabetes, atherosclerotic cardiovascular diseases, low birth weight, metabolic syndrome, chronic renal failure, rheumatoid arthritis and neurodegenerative diseases [1]. This is emphasized in the new classification of periodontal diseases in 2017, as the main topic of this resource is the host immune response, associated periodontitis and relationship with systemic diseases [2].

The basic stimulant of inflammatory diseases is oxidative stress and periodontitis is a type of chronic inflammatory disease that is affected from the imbalance between the oxidative and antioxidative status [3]. In the activation of the disease, periodontopathogens in periodontitis stimulate neutrophils and cause to elevate oxidative stress status, reactive oxygen (ROS) and nitrogen species (RNS), load and by this way this is called like ‘‘respiratory burst’’. Hypochlorous acid, superoxide anion, and hydrogen peroxide are the most increased reactive specieses. The antioxidant barrier may be impaired after an attack of oxidative stress and then, oxidative/nitrosative modifications of cell components may be damaged [4]. The impaired antioxidant balance causes to decrease scavenging mechanisms of free radicals and the neutralization activity. Interestingly, periodontitis showed some differences with both increase/decrease in activity of scavenging [3]. The same ROS can severely damage the structure and function of cell membranes and even oxidative damage to tissues and organs. In a physiological state, ROS occurs as a natural byproduct of normal oxygen metabolism and has important roles in cell signaling and homeostasis. However, apart from environmental stress, increased ROS production along with a reduced antioxidant defense has been suggested to play a critical role in brain damage [5]. Brain tissue is more susceptible to oxidative damage due to high polyunsaturated fat content, high oxygen consumption and insufficient antioxidants. Astrocytes supply antioxidants and free radical scavengers that protect the brain from oxidative stress [6]. For all this, host modulation therapies (HMTs) deal to inhibit or stabilize the tissue breakdown, as well as increasing the levels of regenerative or preventive responses [7].

Caffeic acid is a biologic active content of honeybee propolis which is one of the well-known host modulator agent and scavenger of free radicals. It activates the antioxidant enzymes such as superoxide dismutase and catalase against free radicals and protects tissues against lipid peroxidation (LPO) which is produced by the oxidative stress and damages the cell integrity with its flavanoid content [8,9].

Caffeic acid and its derivatives have been extensively studied in the past, showing that these chemicals have functions such as acting as antioxidants, suppressing cerebral LPO, and reducing cerebral infraction in. It has also been suggested that caffeic acid and its derivatives have therapeutic potential in the treatment of neurodegenerative diseases [5].

Today, researchers suggest using CAPE as a therapeutic agent in periodontal treatment to increase host response by its known beneficial properties such as antioxidant, anticarcinogenic, immunomodulatory and anti-inflammatory [10]. The benefits of CAPE in vivo periodontal disease models have not been investigated completely. Only one study has reported in vivo experimental periodontitis [10]. However, in vitro studies, about the relation of periodontopathogens and cellular responses in culture media have been studied in a few studies [10].

Another immunomodulatory agent is doxycycline and it is a member of the tetracycline antibiotic family [7]. Besides its anti-microbial properties, at low (subantimicrobial) doses doxycycline (LDD) has anti-inflammatory and anti-oxidant effects by the way of decreasing nuclear factor-κappaB activity [7]. Yağan et al. has emphasized the beneficial effect of LDD on the treatment of periodontitis by its antioxidative performance and collagenolytic activity [7].

The multitude of enzymatic and non-enzymatic antioxidants as well as their synergistic effects cause an interest in the evaluation of the total oxidative and antioxidative capacity. The recent

research results indicate that the antioxidant/oxidant capacity of saliva is used in the diagnosis of such systemic diseases as chronic renal disease, hypertension, chronic heart disease, or psoriasis [3]. It is therefore necessary to evaluate several parameters characterizing the total antioxidant potential of the body [3].

To date, there have been no studies investigating the efficacy of LDD combined with CAPE in the management of periodontitis and its relationship with the brain. The aim of the present study was to evaluate the effects of LDD and/or CAPE on ABL and TAS-TOS levels, in an experimental periodontitis rat model.

MATERIALS AND METHODS

Animals, Care and Nutrition

A total of forty-eight female Wistar Albino rats weighing 200±20 g were kept under laboratory conditions with a 12-hour light/dark cycle and a room temperature of 21±3ºC. Standard pellet food was used for feeding and all animals had free access to water. The study was approved by the Mehmet Akif Ersoy University Experimental Medical Research Center's Experimental Animals Ethics Committee (17.02.2021-719).

Animals and Treatment

The forty-eight rats were randomly divided into five groups. The groups were group C (n:8); control, group P (n:10); periodontitis, group PC (n:10); periodontitis administered CAPE, group PD (n:10): periodontitis administered LDD, and group PCD (n:10); periodontitis administered CAPE and LDD.

Experimental periodontitis was induced in rats under general anesthesia by the intraperitoneal injection of ketamine, (90 mg/kg of body weight) and xylazine (10 mg/kg of body weight) by placement of sterile 3–0 silk ligatures in a subgingival position around the maxillary 2nd molars in all groups for 14 days, except Group C. All rats were periodontally healthy because of the exclusion of rats with 0.5 mm periodontal probing depths. CAPE3 10 µmol/kg/day, was intraperitoneally administered [11], with LDD,4 10 mg/kg/day, being administered by oral gavage [12], over the experimental 14-day period. The ligature-induced periodontitis model, which produces plaque accumulation and allows interaction between host and bacteria in the dentogingival area, is highly reproducible and reliable [12,13]. The ligature-induced experimental periodontitis model in rats is recommended for short observation periods (≤15 days) [13].

CAPE3 10 µmol/kg/day, was intraperitoneally administered [5], with LDD4, 10 mg/kg/day, being administered orally, over the experimental 14-day period [7]. There are three ways to administer the CAPE, namely topically, orally and intraperitoneally. All of these have shown beneficial effects, however the significant positive effects was seen in the intraperitoneal applied groups, therefore we chose the intraperitoneal administration, in accordance with the literature [14]. Novel "low doses" or non-antibacterial formulations of tetracyclines, such as subantimicrobial-dose doxycycline (SDD) or low-dose doxycycline (LDD) as an adjunctive treatment of periodontal disease, have been approved by the US Food and Drug Administration and other national regulatory agencies in Canada and Europe. According to previous studies, all of the application designs were focused on oral administration [12]. On the other hand, according to our reviews of the literature, the best absorption for CAPE should be administered as i.p. and the antibiotics are generally administered as oral gavage. We believe these two methods can be applied together.

Ketamine/xylazine (60/5 mg/kg) anesthesia was used for the sacrification. The tissues were removed and divided longitudinally into two sections after the sacrification, one part for biochemical analysis (stored under -70 °C) and the other for histologic evaluation (hidden kept in formaldehyde solution).

The total antioxidant status (TAS)

The method of Erel O. was applied for the measurement of TAS supernatant fractions [15,16]. Hydroxyl radicals and similar biologic radicals were produced using this method. Hydrogen peroxide was mixed with a ferrous ion solution and this application developed a potent radical the likes of dianisidinyl radical cations in the experiment. The measurement of the material antioxidative effect was done by the hydroxyl

radicals. The sensitivity values were lower than 3%. The total antioxidant response results were recorded as nmol Trolox equivalent/mg protein.

The total oxidant status (TOS)

The method of Erel O. was applied for the measurement of TOS supernatant fractions [15,16]. The oxidants in the sample oxidized ferrous ion-o-dianisidine complex to ferric ion. This ferric ion incubates a colored complex with xylenol orange in the acidic medium and the intensity of the color that is related to the total amount of oxidant molecules was able to be measured by spectrophotometric methods. The measurement was calibrated with hydrogen peroxide and the results were presented as nmol H2O2 equivalent/ng protein. Oxidation reaction was increased due to the glycerol molecules which were too abundant in the reaction medium.

Histological examination

Firstly, the tissues were kept in 10% neutral buffered formaldehyde and were then dehydrated in alcohol and embedded in paraffin. Tissues were divided to the 4 µm sections, deparaffinized and stained with hematoxylin and eosin. The samples were analyzed with light microscopy and blindly randomized. Inflammation, oedema, congestion, degeneration, necrosis and necrobiosis were evaluated. After the results were graded, all of the groups were compared with each other.

Statistical Analysis

Analyzed was performed with the IBM SPSS V23 and compliance with normal distribution was examined using the Shapiro-Wilk test. One-way analysis of variance (ANOVA) was used in the comparison with normal distribution groups. The Tukey HSD multiple comparison test was preferred to find out from which group the significant difference originated in the analysis. Analysis results are presented as mean value and standard deviation. The significance level was taken as p <0.05.

RESULTS

All of the experimental groups showed periodontitis signs with alveolar bone loss. The P group leads the most alveolar bone loss, compared to the other periodontitis groups. The lowest group was the PC group in the periodontitis groups. The order from high to low was that group P, group PD, group PCD, group PC, and group C ($P < 0.05$) and the differences were significant. The alveolar bone loss was measured from the cementoenamel junction to the alveolar bone crest (Table 1 and Figure 1).

Table 1.Comparison of Brain TAS and TOS mean values according to groups

	Brain TAS (mmolTrolox Equıv/L)	Brain TOS (mmolTrolox Equıv/L)	ABL (mm)
Cape (n= 10)	0,64 ± 0,14	1,92 ± 0,70	0.42 ± 0.14
Dox (n= 10)	0,42 ± 0,17	2,49 ± 0,58	0.60 ± 0.12
Dox-Cape (n= 10)	0,58 ± 0,24	2,20 ± 0,72	0.56 ± 0.19
Control (n= 8)	0,58 ± 0,24	2,69 ± 0,56	0.22 ± 0.04
Perio (n= 10)	0,42 ± 0,14	2,09 ± 0,56	0.83 ± 0.24
Total (n= 48)	0,52 ± 0,21	2,27 ± 0,66	0,52± 0.14
p	0,05	0,1	

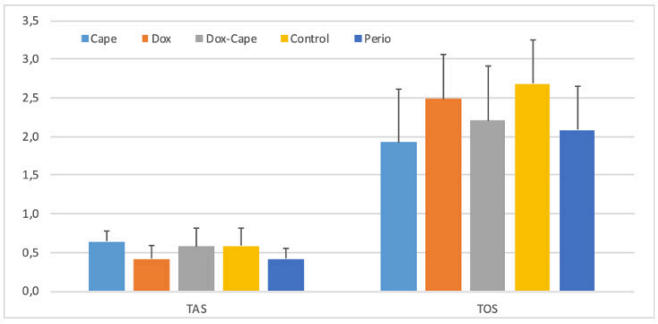

Figure 1. Mean and standard deviation graph of TAS and TOS values by groups

Biochemical Results

There was no periodontal inflammation and bone resorption in group C, where unligated animals and interdental papilla remained intact. All of the periodontitis-induced groups showed alveolar bone loss with increased oxidant activity. However, there were no statistical differences between brain TAS and brain TOS average values (p values 0.05 and 0.1, respectively). The brain TOS levels were precisely observed in the groups, as follows: the PC group was 1.92, in the PD group the level was 2,49, the level was 2.2 in the PCD group, the C group was 2.69 and the P group was 2.09 mmolTrolox Equiv/L. When the brain TAS mean values were examined by groups, the level of the group PC was 0.64 and, it was 0.52 in the

P group.

The results observed reveal that increased periodontal damage can affect periodontal tissues, alveolar bone levels and brain oxidative stress negatively.

DISCUSSION

The question of how the periodontal attachment apparatus is damaged in periodontal diseases has been discussed many times in previous studies. The most common answer is oxidative stress and its direct effect on extracellular matrix components degradation, such as collagen, elastin, proteoglycans and glycosaminoglycans (eg; hyaluronic acid) [3]. In fact, the periodontal infection can also be increased by oxidative stress and host response [3].The best evidence of this promotion is the increasing activity of nicotinamide adenine dinucleotide phosphate (NADPH) (NOX) oxidase and lysosomal enzymes, which are important in periodontal pathogens and tissue destruction because of its protection of redox stress accomplished by providing reducing equivalents to antioxidants, such as glutathione and thioredoxin [3].

There are various experimental periodontitis models In the literature [7,17]. The ligature-induced periodontitis model, which produces plaque accumulation and allows interaction between host and bacteria in the dentogingival area, is highly reproducible and reliable. The ligature-induced experimental periodontitis model in rats is recommended for short observation periods (≤15 days) [7]. Toker et al. reported that alveolar bone resorption reached a peak at 11 days and increased from 1 to 15 days in ligature-induced experimental periodontitis [17]. In the present study, experimental periodontitis was evaluated at day 14, with morphometric analysis revealing that periodontitis was successfully induced in the experiment groups.

There are a great number of studies that have shown the increased TOS levels in periodontitis. Wei et al. observed that LPO levels and TOS were higher in the periodontal region and also in serum, gingival crevicular fluid, blood and unstimulated saliva [9]. Baltacıoğlu et al. have reported similar results as the former: they showed that the increased TOS and decreased TAS, rather than LPO, had an important role in the periodontal pathology, and they also emphasized that TOS levels increase by the periodontitis levels [18]. Zhang et al. had reported the importance of saliva for diagnosis periodontal inflammation and they showed that oxidative stress and TOS are important for periodontitis progression, tissue damage and immune response [19].

CAPE is one of the effective regenerative solutions for bone loss, through its bone healing process and prevention capacity on RANKL-induced osteoclastogenesis. This property, as well as its antioxidant effects in periodontitis and bone healing, have been studied in various studies [20].

LDD is also an effective agent in periodontitis treatment, especially in preventing alveolar bone loss by way of decreasing NF-κB activity. Yağan et al. has emphasized the beneficial effect of low dose doxycycline (LDD) on the treatment of periodontitis by its antioxidative performance and collagenolytic activity [7]. Several studies have shown that LDD suppresses MMPs on the host in periodontal lesion, thereby inhibiting other components of periodontal tissues (fibronectin, proteoglycan ground substance, elastin and basement membranes) and bone resorption [12]. In addition to inhibiting MMPs, doxycycline has antioxidant effects that may be found against beneficial effects in recent studies [12]. Akamatsu et al. reported that doxycycline significantly reduced O2-, H2O2, and -OH levels in human neutrophils [21]. Recent research has focused on the role of ROS, LPO products and antioxidant systems in the periodontal pathology. These studies have reported that the level of ROS molecules with periodontitis increase and when this occurs, oxidative damage begins in the periodontal ligaments and cause osteoclastic bone resorption [12].

In this study, the CAPE induced groups (the PC and PCD group) were more successful than the other groups (the P and PD group) in reducing the alveolar bone loss. Many neuroinflammatory diseases have proven to be the underlying cause of oxidative stress associated with inflammation [6,22,23]. Researchers have reported different neurotoxic reactions and oxidative responses to

aldehydes in different regions of the brain such as the frontal and occipital lobes [6,24].

Uzar et al. reported that CAPE reduced the activities of antioxidant enzymes and malondialdehyde restriction in the cerebellum of rats exposed to methotrexate [25]. Ginis et al. reported that pretreatment with CAPE can protect brain tissue against central neurotoxicity due to ifosfamide [26]. Huang et al. reported that CAPE could provide a promising avenue for treating neurodegenerative diseases with oxidative stress acrolein, such as Alzheimer's disease [27].

MMP is a marker that arises in ischemic organs, such as heart and brain under any damage or injury, because MMPs regulate inflammation, epithelial-mesenchymal transition, cell proliferation, angiogenesis and apoptosis. Doxycycline inhibits MMPs and shows beneficial molecular effects in the brain and heart [28].

Although optimal doses of tetracyclines and drugs to the brain have been studied in experimental models for a wide variety of neurological diseases, tetracyclines, particularly minocycline, remain a concern [29]. However, inhibition of cerebral MMP-9 correlates well with drug levels measured in the brain, despite variability in drug distribution for tetracyclines. Previous studies have suggested several types of inhibition suggesting that it is linked to modulation such as gene transcription, scavenging reagent strains, or Zn2+ binding [29,30].

In this study, the increased TOS and decreased TAS levels were seen in the periodontitis group as well as brain tissues that induced periodontitis. The findings of this study demonstrate that CAPE is an effective additive agent in reducing oxidative stress, TOS versus increasing the TAS not only LDD, but also when given as a combination therapy with CAPE. But, the effects of CAPE and LDD combinations on ABL did not change so crazy in rats with ligature-induced periodontitis.

Many studies have showed that treatment with LDD or CAPE significantly reduced the inflammatory infiltration and bone resorption levels in rats [7]. In the present study, histomorphometric findings showed the lowest ABL in the PC group, when compared to the other experiment groups. ABL was not found to be different between the PD and PCD groups.

Exogenic radicals (radiation, pollution, smoking) and endogenic factors (inflammation, xenobiotic killing) may be a reason of increasing oxidative damage. [31]. Cells, cell membranes and extracellular fluids contain antioxidants and these antioxidants target and neutralize excessive and inappropriate ROS formation for improving the balance mechanism against the oxidants (e.g., chronic inflammation, cigarette smoking, and diets poor in antioxidants and/or rich in pro-oxidants [31]. The transporter in this balance mechanism is blood, through distribution of the related antioxidants to the related part of the body. The main problem is the reactions between catalytic metal ions and long-lived ROS, such as the superoxide anion or hydrogen peroxide and in this situation, plasma can break this chain and prevent more harmful effect of the ROS. Plasma can scavenge long-lived ROS, such as the superoxide anion or hydrogen peroxide, thus preventing reactions with catalytic metal ions to produce more harmful species [31]. For example, ascorbate can be turned back from oxidized ascorbic acid by plasma, so that many different compounds and systemic metabolic interactions present plasma antioxidant status [31].

Within the limitations of this study, we find that the different dose groups could not be included in the study, since there is no study in the literature on ideal dose adjustment for CAPE and LDD. Studies with different doses, durations and administration methods are needed within the limits of the study. Since our study is the first to investigate the antioxidant effect of CAPE and/or LDD on periodontal disease and its relation with the brain, there is a need for additional studies in which the effects on all periodontal tissues are examined and other host modulatory agents are compared, and dose-dependent/non-dependent and systemic effects are monitored.

CONCLUSION

The combination of drugs may be effective for anti-oxidative purposes and their different doses could be suitable for the treatment of neuronal diseases. In this study, the combination of LDD and CAPE are not significantly different when applied alone

or together on oxidative status. But both of the agents have beneficial effects on reducing the oxidative stress and tissue damages.

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CASE REPORT

OLGU SUNUMU

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Anesthesia management in Bart's syndrome: A case report

Bart's sendromunda anestezi yönetimi: Bir olgu sunumu

Faruk Cicekci[1*]

1.Department of Anesthesiology, Selcuk University, School of Medicine, Konya, Turkey

ABSTRACT

Bart's syndrome is a genetic disorder that is also associated with epidermolysis bullosa (EB), which is characterized by congenital focal absence of the skin, mechanical bullous, and nail dystrophy. We present the anesthesia management of a male neonate with congenital localized skin absence, nail dystrophy, and ear atrophy who underwent surgery due to congenital pyloric atrophy. Palliative measures were perforemed paying attention to skin lesions in areas of rich-red peeling on the hands and feet of the patient, and standard general inhalation anesthesia was administered. As far as I could research in the English literature, this case report may be the first case report to present the management of anesthesia in a patient with Bart syndrome

Keywords: Bart's syndrome; case report; congenital absence of the skin; congenital pyloric atresia; epidermolysis bullosa.

ÖZ

Bart's sendromu, derinin konjenital fokal yokluğu, mekanik büllöz ve tırnak distrofisi ile karakterize epidermolizis bülloza (EB) ile de ilişkili genetik bir hastalıktır. Konjenital pilorik atrofi nedeniyle ameliyat edilen doğuştan lokalize cilt yokluğu, tırnak distrofisi ve kulak atrofisi olan erkek yenidoğanın anestezi yönetimini sunuyoruz. Hastanın el ve ayaklarında zengin kırmızı soyma bölgelerindeki cilt lezyonlarına dikkat edilerek palyatif önlemler alındı ve standart genel inhalasyon anestezisi uygulandı. İngilizce literatürde araştırabildiğim kadarıyla bu olgu sunumu Bart sendromlu bir hastada anestezi yönetimini sunan ilk olgu sunumu olabilir.

Anahtar Kelimeler: Bart's sendromu; olgu sunumu; cildin doğuştan yokluğu; konjenital pilorik atrezi; epidermolizis bülloza.

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*Corresponding Author: Faruk ÇİÇEKÇİ, Department of Anesthesiology, Selcuk University, School of Medicine, Konya, Turkey. +905057649235, farukcicekci@yahoo.com

ORCİD: 0000-0002-3248-0745

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Introduction

Bart's syndrome is a genetic disorder that is also associated with epidermolysis bullosa (EB), which is characterized by congenital focal absence of the skin, mechanical bullous, and nail dystrophy. It was described by Bart et al. in 1966 [1]. Raw and red plaques, which are a sign of localized skin absence, appear on different parts of the patient's body. There is a sharp boundary between affected and normal skin. Any part of the skin may be affected, but the disease tends to be more common in parts of the body that are subject to friction and trauma, such as the skin around the mouth and extremities [2].

With this case report, anesthesia management in a neonate with Bart syndrome who underwent surgery with a diagnosis of congenital pyloric atresia is described.

Case Presentation

A 35-week, 1800 grams, 1-day-old male neonate was taken to surgery for pyloric atresia. A physical examination revealed that there was no skin extending from both knees on the anteromedial aspect of the lower leg to the dorsal and medial plantar directions of the feet (Figure 1). There were also similar lesions involving both elbows. A sudden transition to normal skin where the lesions ended was striking (Figure 2). In addition to the absence of skin, hypoplastic nails (Figure 3) and ear atrophy were present. No brain anomaly was detected in transfontanelle ultrasonography (USG). There was no erosion in the mouth or nasal cavity. Complete blood count, liver and kidney function tests, and electrolyte results were within normal limits. Immunohistologic and genetic linkage studies of the sample taken from the skin after birth could not be performed in the period until the surgery (within 24 hours). Hydrocortisone + mupirocin mixed pomade was applied to the patient's body before being taken to the operating table, and he was carried on a plastic pad. Thus, pathologies that could occur with the friction of his body were avoided. Electrocardiography (ECG) pallets were placed on the back of the patient because the palettes were not self-sticking, and in this way heart rate and ECG monitoring were achieved. A pulse oximeter for SpO2 was connected to the lower extremity. The cautery plate was placed on the back. Vascular access was provided through the umbilical vein. After induction, anesthesia was provided with 3 mg.kg-1 propofol, 1 mcg.kg-1 fentanyl, 0.6 mg.kg-1 rocuronium, and endotracheal intubation was provided at the appropriate time with a No.3 endotracheal tube. No intraoral lesions were observed. The endotracheal tube was fixed to the rim with a hypoallergic silk patch. Anesthesia was maintained with 40% O2 and 3.2% sevoflurane. The patient, who underwent gastrojejunostomy, was transferred to the neonatal intensive care unit (NICU) as intubated at the end of the procedure. The neonate died on the 7th postoperative day.

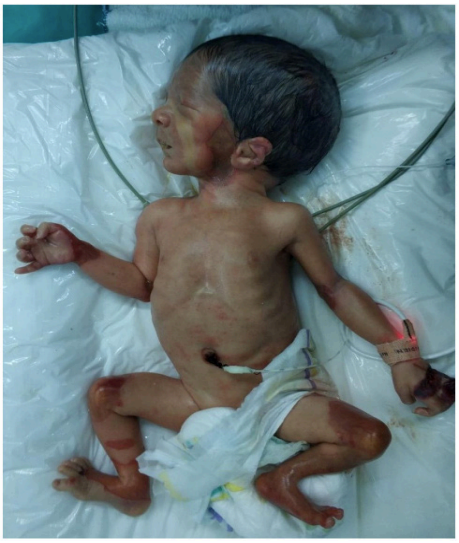

Figure 1. Absent skin, on face and neck, bilaterally on the upper and lower extremities

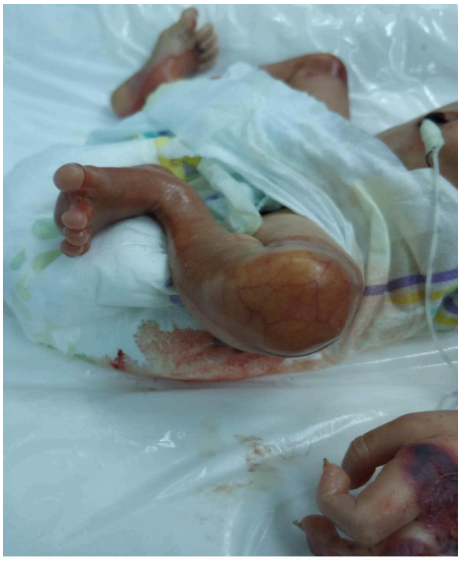

Figure 2. Sharply demarcated lesion margin.

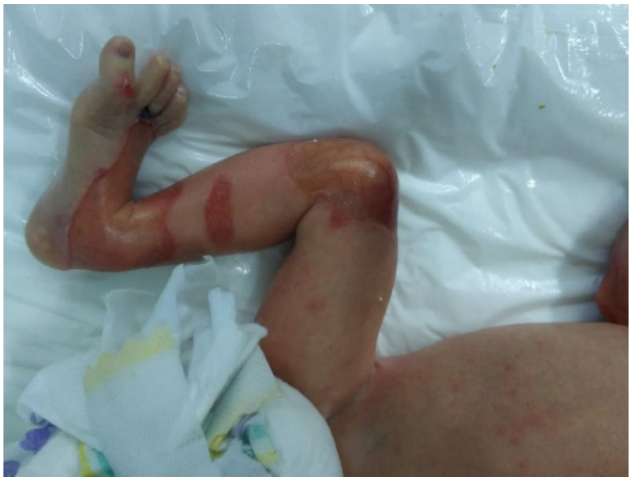

Figure 3. View of hypoplastic nails

Discussion

Bart's syndrome is known to be one of the subtypes of EB [3], which initially presents with congenital absence of skin in the lower leg and common skin, mucous membrane, and nail dystrophy [4]. Duran-McKinster et al. suggested that the congenital absence of localized skin in Bart's syndrome might follow Blaschko's lines due to physical trauma to the uterus [5]. Zelickson et al. demonstrated various abnormalities of anchorage fibrils, which are predominantly composed of VII type collagen, at the dermal-epidermal junction in Bart's syndrome [6]. The autosomal dominant inheritance of this syndrome has been demonstrated. However, some patients with unaffected parents are believed to be due to sporadic mutations [7]. Chiaverini et al.[7] reported that collagen VII gene was associated with mutations in the triple helix area in sporadic cases. This mutation can lead to Bart's syndrome, associated with the synthesis of a thermolabilin Col 7. In the present case, there was no family history of congenital localized skin absence and raised lesions. Bart's syndrome is sometimes accompanied by nail abnormalities. Our patient had a congenital localized absence of skin, involvement of raised lesions, and partial nail involvement. Bart's syndrome may also be associated with other anomalies such as pyloric atresia, primitive ear development, flattened nose, broad nasal root, and wide-set eyes [8]. There were associated findings in the present case.

Bart's syndrome has been associated with pyloric atresia [9,10]. In our case, the reason for the surgery was congenital pyloric atresia and gastrojejunostomy was performed. During the procedure, the patient was on a plastic pad and because the hydrocortisone + mupirocin mixed pomade was applied to his body, it was not possible to stick the ECG pallets, so they were placed on the patient's back. We think that the use of a cuff for pulse pressure may pose a risk because patients with Bart's syndrome are quite susceptible to skin trauma. In addition, the patches used to fix the vascular access can cause skin trauma. In the present case, an umbilical venous catheter was used for volatile anesthetics, opioid and neuromuscular blockers for anesthesia induction, and maintenance. Treatment management in Bart's syndrome is generally conservative. Treatment aims to prevent infection of the affected area, accelerate healing, and reduce the risk of scarring [11]. Close monitoring is essential for serious complications such as bleeding, infection, hypothermia, and hypoglycemia. The prognosis is good and depends on the effectiveness of the treatment. However, death occurred on the 7th postoperative day in the present case. The possible cause of sudden death in our case may have been of metabolic origins, such as hypothermia and hypoglycemia due to congenital absence of skin or concomitant infection.

Conclusion

This case report has shown that preoperative use of moisturizing + antibiotic ointments avoided possible advanced skin trauma. The key components of this case were anesthesia induction including optimal preoperative preparation and controlled induction of anesthesia. Standard general anesthesia techniques and anesthetic drugs (including sevoflurane, fentanyl, remifentanil and rocuronium) were used with success. This case report is the first on anesthetic management in Bart's syndrome in the literature.

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ORCID and Author's contributions: FÇ (0000-0002-3248-0745): Consept, Design, Data Collection, Interpretation, Literature Search, Manuscript Writing, Critical Review.

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