MEDICAL JOURNAL OF BAKIRKÖY TIP DERGİSİ

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Editorial

Dear Colleagues;

Medical Journal of Bakırköy (BMJ), the sixteen-year periodical publication of Sadi Konuk Training and Research Hospital, have successfully reached these days with your valuable contributions. By the beginning of 2020, I and my brand-new editorial team have taken over the editorship and have decided to continue our journal's publication life with a new and more contemporary approach.

The Bakırköy Medical Journal (BMJ) is currently within the scope of ESCI as well as many other major indexes. Our primary goal is to meet the Science Citation Index (SCI) criteria and be listed in that database. Aligned with this goal, we decided our journal to be published entirely in English. We rapidly formed a team and a new system to enable fast evaluation of incoming manuscripts, gain access to larger audiences, publish high quality articles and increase the number of citations. We have not only transformed the content of the journal, but also completely renewed our website, journal management system, cover page, layout of articles and publication policies.

We are well aware of the responsibility on ourselves and we will need your understanding, experience and ideas more than ever.

We are very excited by this challenge and aim to bring our journal to a new level all together.

Prof. Dr. Esra Şevketoğlu
Chief Editor

The "New" Problem of Humanity: New Coronavirus (2019-nCoV / COVID-19) Disease

İnsanlığın "Yeni" Sorunu: Yeni Koronavirüs (2019-nCoV / COVID-19) Hastalığı

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ABSTRACT

At the end of December 2019, a new respiratory virus infection was identified in Wuhan city, China, in the province of Hubei, after patients with acute severe respiratory infections showed clustering. The cases were thought that they could be related to exposure in the Huanan Seafood Market where wholesale fish and live animals are sold in this city. In January 2019, the causative agent was named 2019-nCoV (2019 novel coronavirus), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and 2019 coronavirus disease (COVID-19) by the World Health Organization (WHO).

Coronaviruses are enveloped and single-stranded RNA viruses of the Coronaviridae family and are known as "crown viruses" due to their crown-like protrusions on their outer surfaces. They can infect various species. In addition to mild upper respiratory diseases, it is the causative agent of serious acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). 2019-nCoV shows 79% similarity to SARS-CoV and means that bats such as SARS-CoV may have been the original host of this virus. The route of transmission is by respiratory droplets and direct contact. In order to prevent the spread of infection, early diagnosis, proper isolation and personal protective measures are especially important in the hospital environment. The agent uses angiotensin converting enzyme 2 (ACE2) receptor to enter the cell. The incubation period is usually 3-7 days and can extend up to 14 days. While it is more severe in upper-middle aged people, those with advanced age and additional comorbidities pose risk factors for severe disease. Adult patients have high fever, weakness and dry cough, and some have headaches and muscle pain. As the disease period progresses, shortness of breath acute respiratory distress syndrome, septic shock, metabolic acidosis, clotting disorders, and multiple organ failure may occur. In particular, children can pose an unnoticed threat in spreading the outbreak. Children are less likely than adults to have the infection as an obvious clinical status. The clinical features of the disease are milder and death has not been reported under 10 years of age. Blood count and C-reactive protein values can usually be found normal or slightly increased. In the radiological evaluation of the lung, ground glass appearance and bronchial shadows may be evident. A nucleic acid test is performed from the nose or throat swab to determine the exact cause of the disease. Adequate calorie and fluid intake and the need for oxygen should be ensured in the treatment. An effective anti-virus treatment is not yet available. However, in severe cases, interferon-α nebulization and efficacy have not been proven, lopinavir / ritonavir and chloroquine are recommended. In certain cases, corticosteroids can be used. The virus can be inactivated with disinfectants containing ethanol and chlorine. People with close contacts and suspicious exposure should be advised of 14 days of observation and isolation, starting from the last contact day with the patient infected with 2019-nCoV. Vaccine development studies for 2019-nCoV are ongoing.

Keywords: 2019-nCoV, SARS-CoV-2, COVID-19, severe acute respiratory syndrome

ÖZ

İlk olarak 2019 Aralık ayı sonunda Çin'in Hubei eyaletinde bulunan Wuhan kentinde akut ağır solunum yolu enfeksiyonu tanılı hastaların kümelenme göstermesi üzerine dikkat çeken yeni bir solunum virüs enfeksiyonu tanımlandı ve vakaların bu şehirde bulunan toptan balık ve canlı hayvan satışının yapıldığı Huanan Deniz Ürünleri Pazarı'nda maruziyetle ilişkili olabileceğini bildirdi. Ocak 2019 içinde de etken Dünya Sağlık Örgütü (DSÖ) tarafından 2019-nCoV (2019 novel coronavirus), şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) ve 2019 koronavirüs hastalığı (COVID-19) virüsü olarak adlandırıldı.

Koronavirüsler Coronaviridae ailesinin zarflı ve tek sarmallı RNA virüsleridir ve dış yüzeylerindeki taç benzeri çıkıntılarından dolayı "taç virüs" olarak bilinir. Çeşitli canlı türünü enfekte edebilirler. Hafif üst solunum yolu hastalıkları yanında ciddi akut solunum sendromu (SARS) ve Orta Doğu solunum sendromu (MERS) etkenidir. 2019-nCoV SARS-CoV'a %79 benzerlik göstermektedir ve SARS-CoV gibi yarasaların bu virüsün orijinal konağı olabileceği anlamına gelmektedir. Bulaşma yolu solunum damlacıklarıyla ve doğrudan temasla olmaktadır. Enfeksiyonun yayılmasını engellemek için erken tanısı, uygun izolasyon ve özellikle hastane ortamında kişisel koruyucu önlemler çok önemlidir. Etken hücre içine girmek için anjiotensin dönüştürücü enzim 2 (ACE2) reseptörünü kullanmaktadır. Kuluçka süresi genellikle 3-7 gündür ve 14 güne kadar uzayabilir. Daha çok orta yaş üzeri kişilerde daha ağır klinik tablo oluştururken yoğun bakıma yatırılanlar ileri yaşta ve ek hastalığı bulunanlar olmaktadır. Erişkinlerde yüksek ateş, halsizlik ve kuru öksürük, bazılarında baş ağrısı ve kas ağrısı görülür. İlerledikçe nefes darlığı akut solunum sıkıntısı sendromu, septik şok, metabolik asidoz, pıhtılaşma bozuklukları ve çoklu organ yetmezliği oluşabilir. Özellikle çocuklar, salgını yaymada farkedilmeyen tehdidi oluşturabilir. Çocuklarda enfeksiyonun aşikar hastalık oradan ortaya çıkma ihtimali erişkinlerden daha azdır; hastalığın klinik özellikleri daha hafiftir ve ölüm 10 yaş altına bildirilmemiştir. Kan sayımı ve C-reaktif protein değerleri genellikle normal ya da hafif artmış bulunabilir. Akciğer radyolojik değerlendirmesinde buzlu cam görünümü ve bronşiyal izlerde belirginleşme olabilir. Hastalığı etkeninin kesin ortaya konması için burun veya boğaz sürüntüsünden nükleik asit testi yapılır.

Tedavide yeterli kalori ve sıvı alımının sağlanmalı, oksijen ihtiyacı giderilmelidir. Etkili bir virüs karşıtı tedavisi henüz mevcut değildir; ancak ağır vakalarda interferon-α nebulizasyonu ve etkinliği kanıtlanmış olmasa da lopinavir/ritonavir ve klorokin önerilmektedir. Belirli durumlarda kortikostroidlerden yararlanılabilir. Virüs etanol ve klor içeren dezenfektanlarla inaktive edilebilir. Yakın temasları ve şüpheli maruziyeti olan kişilere, 2019-nCoV ile enfekte hastayla son temas gününden başlayarak 14 günlük gözlem ve izolasyon tavsiye edilmelidir. 2019-nCoV için aşı geliştirme çalışmaları devam etmektedir.

Anahtar kelimeler: 2019-nCoV, SARS-CoV-2, COVID-19, şiddetli akut solunum sendromu

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INTRODUCTION

On 31 December 2019, while people around the world are preparing to see off the "old" year; with the "new" coming year, they were discussing the salary increases that they will receive, the bonus to be released from the lottery, or even though it has a familiar answer, whether December 31 will be a public holiday [1].

At the same date Wuhan Municipal Health Commission in China recently reported on their local websites that a total of 27 local pneumonia cases clustered with findings of fever, breathing difficulties, and chest x-ray infiltrations, 7 of which were in serious condition in this South China City of Marine Products [2]. It was stated that all cases were thought to have viral pneumonia, and the etiology was not yet known, but the detection of the pathogen and the cause of the infection continued and patients were isolated for treatment.

The city of Wuhan, which has a population of 19 million, also known as "the city of lakes", is a megacity located in Hubei province of China [3]. In the central part of the city, there is the Huanan Seafood Market, where wholesale fish and live animals are sold, and it is a crowded shopping mall where food, domestic and a wide variety of wild animals are traded. Regarding this health problem that occurred in late December, the World Health Organization (WHO) reported that the outbreak may be related to exposure there, as some patients were vendors or dealer operators in this market [4]. A few days later, on 7 January 2020 Chinese authorities determined that these pneumonia cases were caused by an isolated "new" type of coronavirus (nCoV) [5]. WHO called this newly identified virus the 2019-nCoV (2019 novel coronavirus), as it was first detected in 2019. The virus is also described as Wuhan seafood pneumonia virus, human coronavirus 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and 2019 coronavirus disease (COVID-19) [6].

ETIOLOGY

Coronaviruses are enveloped and single-stranded RNA viruses belonging to the Coronaviridae family. Thanks to the surface proteins that appear as an extension to the outside in the form of large crown-like protrusions under electron microscope, they are named as "crown virus" in Latin [7]. They can infect humans and a wide variety of animals. The coronavirus causes infections in farm animals, birds, bats, mice and many other wild animals, and each type of virus is unique to the host where it can cause infection. Four groups of coronaviruses (Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus) have been identified, and human coronaviruses (HCoVs) belong to the first two types of coronaviruses.

Until 2019, only six coronaviruses have been identified that are known to cause respiratory diseases in humans. Among these, HCoV-229E, HCoV - OC43, HCoV - NL63 and HKU1 are known as coronaviruses with low pathogenic potential [8]. They are responsible for 10-30% of mild cases with upper respiratory diseases and rarely can cause serious infections in young children and the elderly. Severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) are zoonoses [9] that can cause serious and fatal lower respiratory tract infections in human beings and pose an important threat to public health.

2019-nCoV is the seventh member of the coronavirus family that infects humans after MERS-CoV and SARS-CoV. Sequence analysis revealed that 2019-nCoV has a typical coronavirus genome structure and is included in the Betacoronavirus family cluster, which includes SARS and MERS coronaviruses, provided that it is more similar to coronaviruses in bats [10]. Within four weeks of the first recognition of the outbreak, the new virus isolated from the airway epithelial cells of patients with pneumonia was shared with WHO using full genome sequencing, polymerase chain reaction and culture methods. With these analyzes, diagnostic tests have been designed to be used in the detection of 2019-nCoV infection in China and globally [11]. Since the virus is transmitted to a growing number of people, continuous monitoring of molecular analysis is required as new mutations may emerge

EPIDEMIOLOGY

The first coronavirus infection in the world, where sudden emergence and global epidemic threat came

to the agenda, occurred in 2003 with a species that was become known as severe acute respiratory syndrome (SARS). SARS first appeared in China as a new respiratory pathogen in 2002, spread to 29 countries, lasting a total of 9 months, causing infections in 8098 people and 774 deaths. It is thought that SARS-CoV is derived from SARS-CoV-like viruses found in horseshoe bats and probably in musk cats as an intermediate host before the virus "jumped" to the human beings [12].

The coronavirus episode, which concerned the whole world for the second time, started in Saudi Arabia in 2012 and was defined as the Middle East respiratory syndrome (MERS) [13]. As of November 2019, 2494 cases diagnosed as MERS and 858 related deaths have been recorded in 27 countries to date [14]. The data show that the MERS agent is most likely transmitted from bat coronavirus and camel is the intermediate host. Some types of coronaviruses can also cause epidemics and significant losses in farm animals.

The 2019-nCoV is similar to coronaviruses in SARS-CoV (79%) and MERS-CoV (50%) and resembling more closely coronaviruses in bats (96.3% for BatCoV RaTG13, 88% for bat-SL-CoVZC45 and bat-SL-CoVZXC21). This means that bats may be the original host of this virus. However, it is known that most bat species in Wuhan City were hibernating at the end of December 2019, the first period of the epidemic, and bats were not sold in the Wuhanan seafood market. Therefore, it is estimated that an animal sold in the seafood market in Wuhan may be an intermediate host that facilitated the emergence of this novel virus in humans [15]. Based on the analysis of glycoproteins in the capsid of the virus, it has been suggested that the snake may be the most likely animal reservoir as an intermediate host in the transition from bats to humans [16].

Although the relationship of the patients diagnosed at the beginning of the outbreak with the seafood market had been emphasized, any epidemiological connection has not been found in later cases. For this reason, it has been reported that the only source of the virus is not in this market region, but the virus probably entered the market with an intermediate host first and then spread out from there [17].
The news that the 2019-nCoV infection spread out-

side of China within three weeks after its first emergence in China began to be heard: Neighboring Thailand, Japan, and Korea were the first countries to report these cases [18,19].

The first appearance of 2019-nCoV infection has been an important issue of curiosity. According to researches, 2019-nCoV probably emerged in Wuhan on November 9, 2019 (95% confidence interval), September 25, 2019 and December 19, 2019), and Wuhan has been estimated as the main center from where 2019-nCoV outbreak has spreaded in China and elsewhere [20].

One method of determining the extent of infectivity of an infectious agent is known as the basic reproduction number (R0) The R0 value can vary with the reporting rate of the disease. After reporting that the 2019-nCoV infection can pass from person to person [21], R0 was calculated between 1.4 and 6.47 in various studies. According to the most comprehensive and up-to-date calculation available today, the doubling rate of the total number of infected people is 1.8 days [22].

Today, the main route of transmission in 2019-nCoV infection is through airborne droplets and direct contact. It has been suggested that fecal-oral transmission may occur because viral particles are detected in the stool samples of pneumonia patients with gastrointestinal symptoms [23].

Early diagnosis, proper isolation and personal protective measures are especially important in the 2019-nCoV infection. Hospital-acquired infection poses a risk to both inpatients and hospital staff. In a clinical series presenting 138 adult patients with 2019-nCoV pneumonia, it was emphasized that 41% of them, including 29% of healthcare workers, were suspected of getting the infection by nosocomial transmission [24]. People with both evident disease and asymptomatic individuals in incubation period are in critical position for preventing and controlling the outbreak because they have the potential to spread the infection [25].

PATHOGENESIS

The 2019-nCoV uses angiotensin converting enzyme 2 (ACE2) receptor-binding motif (RBM) as a receptor,

similar to that of SARS-CoV [26]. In other words, 2019-nCoV S (spike) -protein and SARS-CoV S-protein share almost the same structure in the RBM domain (27), and the ACE2 receptor region is the gate that the virus uses to enter the cell [28].

ACE2 receptors are found in the lungs mainly in type II alveolar cells. Whether the susceptibility to 2019-nCoV infection is due to individual differences in this region where the virus binds during entry into the cell has been an important subject of research. In a study in which normal lung tissue cells of eight healthy individuals were analyzed, ACE2 expressing the cell ratio was more than five times higher in a single Asian donor than white and African -American donors [29]. This means that - although more evidence is needed to reach such a conclusion - the Asian population is probably more susceptible to the 2019-nCoV infection.

On the other hand, in another study, any direct genetic evidence was not found to support the presence of ACE2 mutants resistant to coronavirus S-protein binding in different populations. Since the East Asian population has been associated with higher ACE2 expression in tissues, it has been reported that there may be different coronavirus susceptibilities or responses in different populations [30].

China has experienced twice recurring outbreaks of coronavirus (SARS-CoV and its relative SARS-CoV-2) over the past 18 years, suggesting that Asians are more susceptible to coronavirus. ACE2 expression has been studied by Chen et al using transcriptomal data from more than 1000 lung tissue samples within the scope of Cancer Genome Atlas Project, and the following data have been obtained: The expression of ACE2 on the cell surface increases with age, but it is not sex-related. Also, Asians show a similar ACE2 expression to other races. One reason for coronavirus outbreaks occurring over time in China is explained by the diversity of coronaviruses and host animals and the unique Chinese food culture [31].

CLINICAL CHARACTERISTICS

The first case series, consisting of 41 adult patients infected with 2019-nCoV, was published on January 24, 2020. While 66% of cases had a history of being in the Huanan seafood market. The median age of the patients was 49 years, and there was an underlying disease in 32% of the patients. While the main diagnosis was pneumonia in all patients, one-third of the patients were followed up in the intensive care units and six of them died. In patients with severe conditions, plasma cytokine concentrations were increased [32].

In another series [33], almost half of 425 cases were found to be adults aged 60 years and older. Infections not as highly frequent as SARS and MERS outbreaks have been identified in healthcare workers. Average incubation time was recorded as 5.2 days (95% confidence interval [CI], 4.1-7.0), and the 95th percentile of the distribution was 12.5 days and the mean hospitalization time was 12.5 days

While disease-related ICU hospitalization is required in an average of one fourth of the cases, advanced age and various comorbid conditions are factors that increase mortality [24]. Patients may also develop additional infections caused by bacteria or fungi which negatively affect prognosis [34].

In theory, the individual is susceptible to 2019-nCov infection at any age, and the average age is 5-6 decades for reported patients [23,35]. Men are more frequently affected, possibly due to higher probability of occupational exposure.

According to reported epidemiological studies, most patients have close contact with a patient with 2019-nCoV infection, or a history of travel to Wuhan City or Hubei province in China. The incubation period is usually 3-7 days and can extend up to 14 days.

In 2019-nCoV infection, the symptoms are not specific and are milder than SARS and MERS. The most common symptoms described in adults are high fever, malaise and dry cough; Upper respiratory system symptoms such as a runny nose are rare. Fever may not always be the first sign. Some patients may complain of headache and muscle pain, diarrhea may occur. More than half of the patients may develop shortness of breath within 8 days after the onset of the disease. Acute respiratory distress syndrome (ARDS) may develop, as well as septic shock,

metabolic acidosis, clotting disorders, and multiple organ failure. Some individuals, and especially children, can pass the infection without fever or symptoms and pose an unnoticed threat in spreading the outbreak

Patients may have decreased total leukocyte, lymphocyte and platelet counts, increase in C-reactive protein and muscle enzymes, and prolonged coagulation tests. D-dimer levels increase in severe disease [36].

It is recommended that all suspect patients are evaluated by chest computed tomography (CT). Chest CT examination shows multiple patchy appearances (lobular and postsegmental consolidation), ground glass changes and thickening of interlobular septa, which are typical for viral pneumonia, and known as cobblestone changes [25].

Radiological disorders in the elderly are more prominent than young patients. In some cases, viral nucleic acid testing may initially be negative. Therefore, lung imaging can be used as a pre-screening method to reveal symptomatic cases, and re-examination of nasopharyngeal swabs or sputum samples is recommended.

The nucleic acid test, performed using the fast-yielding and reliable polymerase chain reaction (PCR) method is employed to determine the disease agent precisely. Viral gene sequencing from nose or throat swabs, as well as sputum, feces or blood samples can be used for definitive identification of the disease agent [36].

THE 2019-nCoV INFECTION IN CHILDREN

Experience is limited, except for the publication of follow-ups of 28 patients reported in the literature on 2019-nCoV infection in children [37]. The main mode of transmission of the infection in children occurs mainly from a sick person who is near them In other words, there is another family member who is sick in the home of a sick child. After transmission of the infection, children are less likely to have an infection with obvious manifestations of the disease than adults. According to the analysis of case series, the clinical features of the disease are milder in children compared to adults, and death has not been report-

ed under 10 years of age. Some of the pediatric patients were diagnosed without any complaints using screening tests performed because they contacted the sick people. In symptomatic patients, familiar upper respiratory tract symptoms such as fever, weakness, dry cough, runny nose, and some nausea and vomiting were also observed.

Whole blood cell counts and C-reactive protein values may be usually within normal limits or slightly increased. In the radiological evaluation of the lung, ground glass appearance and bronchial scars may be evident. In the examination of chest CT images of 15 children aged 4-14 years diagnosed with 2019-nCoV infection, 9 patients had pulmonary signs of inflammation, usually in the form of nodular ground-glass opacities. In addition, clinical symptoms are not specific [38].

The clinical course usually takes 1-2 weeks. Although progression to pneumonia and serious cases are rarely seen, ARDS should be kept in mind in children with other serious coronavirus infections such as MERS.

Pregnancy is generally a period of increased sensitivity to viral infections. Our knowledge about coronavirus infections that occur during pregnancy is limited. The risks that pregnant women have in the 2019-nCoV outbreak have not been determined yet. Although greater number of pregnant women have not been affected in both the SARS pandemic and MERS infection, disease –related mortality rates in pregnant women were as high as 25% and 27%, respectively [39]. Hypoxemia due to severe infection in pregnant women can lead to intrauterine asphyxia and preterm labor. Fortunately, as of 04.03.2020, placentally transmitted fetal infection with SARS or MERS has not been reported yet. However, it should be taken into consideration that pregnant women may have a serious risk of developing infections during the 2019-nCoV outbreak [40]. Although a 30-hour-old newborn baby was shown to be infected with 2019-nCoV viruses which were detected in both mother and caregiver, placental transmission of the disease in newborn was not proven [41]. According to available data, it has not been clarified whether it is transmitted from mother to baby during pregnancy or with breast milk [36].

The COVID-19 (2019-nCoV Disease) Guide, prepared by the TR Scientific Committee Study of the Ministry of Health General Directorate of Public Health and last updated on March 11, 2020 is a source of information concerning case definition and management, contact tracking, infection control and isolation, patient care and treatment. It also includes information about the requirements requested from individuals who will travel to the countries where this infection was seen [42].

TREATMENT

Four principles are important in patient management: "early recognition", "early isolation", "early diagnosis" and "early treatment" [36].

Patients with mild complaints should remain isolated in their homes. As general treatment principles, supportive treatments such as providing bed rest, adequate calorie and fluid intake and meeting the need for oxygen should be implemented, and followed up closely. In cases where secondary bacterial infection cannot be excluded, antibiotics can be added to the treatment.

An effective antiviral treatment is not yet available; however, in severe cases, interferon-α nebulization and although its efficacy has not been proven, oral lopinavir / ritonavir treatment is recommended [36]. It is emphasized that antiviral therapy is useful when started in an early stage of the disease [25].

Interferon-α is a broad spectrum antiviral drug used in the treatment of HBV. Lopinavir and ritonavir are protease inhibitors used to treat human immunodeficiency virus (HIV) infection and have in vitro anti coronavirus activity.

Remdesivir is an effective adenosine analog antiviral agent for various RNA viruses (including SARS-CoV / MERS-CoV). In MERS-CoV-infected mice remdesvir has been shown to suppress the virus and improve lung tissue damage. Phase III clinical trials have been conducted with the same drug for the treatment of Ebola virus infection [43]. As a recent data, the drug has been shown to inhibit virus infection in a 2019-nCoV- sensitive human cell line (human liver cancer cells). In addition to being an antimalarial drug, chloroquine has immunoregulatory and antiviral activity. The combined use of both drugs was found to be effective in vitro against 2019-nCoV infection [44]. It should be emphasized that developments regarding the treatment of the disease are a very dynamic process.

Although not a routine practice , corticosteroids can be used in certain situations: such as ARDS, encephalitis, toxicosis, hemophagocytosis, septic shock, and prominent wheezing. Intravascular immune globulin is also used in the treatments recommended for the severe clinical entities. For respiratory support, ventilation technique and hemo (dia) filtration / plasma exchange can be applied.

Traditional Chinese medicine, arbidol and mesenchymal stem cell transplant applications are studies to be performed in near future in which some of the pediatric patients are planned to be included [45].

PREVENTION

The 2019-nCoV can be inactivated by heating for 30 minutes at 56° C and with disinfectants containing 75% ethanol and chlorine, while chlorhexidine is partly effective.

People with close contact and suspicious exposure should be advised to observe the 14-day social isolation. Period starting from the last day of the contact with 2019-nCoV-infected patients or suspected environmental exposure.

Special means of transportation should be used to transfer infected patients. Strict protection for transport personnel and disinfection for the vehicle is vital.

Medical personnel should act in accordance with appropriate personal protection, hand hygiene, ward management, environmental ventilation, object surface cleaning and disinfection, medical waste management and other hospital infection control studies based on the standard prevention protocol to minimize development of nosocomial infection.

Vaccine development studies for 2019-nCoV are ongoing. Approximately 15 potential vaccine candi-

dates are being studied by applying various technologies such as messenger RNA, DNA-based, nanoparticle, synthetic and modified virus-like particles [45].

It is within the capacity of modern medicine to carry out a systematic arrangement and preparation against the ongoing epidemic in every aspect due to the 2019-nCoV, the most current world-threatening viral infection of the twenty-first century.

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Endovascular Treatment of Intracranial Aneursyms with Flow Diverter Stents

İntrakraniyal Anevrizmaların Akım Düzenleyici Stentler ile Endovasküler Tedavisi

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ABSTRACT

Objective: We aimed to present the treatment and follow-up results of 41 patients who were treated for intracranial aneurysm with flow diverter stents.

Method: Forty-one patients (Age range 27-68 years) were treated with the flow- diverting devices during January 2010 and January 2014. Aneurysms ranged in size from small to large (1-30 mm) and include wide-necked aneurysms, multiple, saccular, blister, dissecan, fusiform and recurrent intracranial aneurysms. Control skull X-Ray Graphy was typically performed at 1, 3 and 6 months after treatment. A follow-up digital subtraction angiogram (DSA) was performed first day, 6 and 12 months after treatment.

Conclusions: Complete angiographic occlusion was achieved in 36 patients (88%) at follow-up digital subtraction angiogram. Two transient morbidities and one permanent morbidity occurred due to stent thrombosis. There was no mortality observed. Flow diverter stents are an effective tool in the treatment of large wide neck, high growth rates, and technical problematic aneurysms to treat with conventional endovascular methods.

Keywords: intracranial aneurysm, endovascular treatment, flow-diverter stenting

ÖZ

Amaç: Akım düzenleyici stentler yardımıyla intrakraniyal anevrizma tedavisi yapılan 41 hastanın tedavi ve erken dönem takip sonuçlarını sunmayı amaçladık.

Yöntem: Ocak 2010 ile Ocak 2014 arasında yaş aralığı 27-68 arasında değişen 41 intrakraniyal anevrizmalı hasta akım düzenleyici stent ile tedavileri yapıldı. Anevrizma boyutları küçük ve büyük (Aralık, 1-30 mm) olmak üzere geniş boyunlu, sakküler, fuziform, blister, dissekan ve rekürens gösteren anevrizmaları içermektedir. Tüm hastalar işlemden sonraki 1, 3 ve 6. ayında direkt kafa grafileri ve tedavinin 1. günü, 6 ve 12. ayında kontrol dijital subtraksiyon anjiyografi (DSA) incelemeleri yapılarak takip edildi.

Sonuçlar: Tedavi sonrası kontrol DSA' da 36 (%88) hastada anevrizma kesesinde tam oklüzyon izlendi. Komplikasyon olarak stent trombozuna bağlı iki hastada geçici morbidite ve bir hastada kalıcı morbidite izlendi. Mortalite izlenmedi. Akım düzenleyici stentler geniş boyunlu, yüksek büyüme oranları bulunan ve teknik problemler nedeniyle endovasküler tedavisi kısıtlı olan anevrizmaların tedavisinde etkili bir araçtır.

Anahtar kelimeler: intrakraniyal anevrizma, endovasküler tedavi, akım düzenleyici stent

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INTRODUCTION

Intracranial aneurysms which are the most frequently seen non-traumatic causes of subarachnoid hemorrhage (SAH) observed in 3.7% of retrospectively and 6% of prospectively designed angiography studies [1]. Although surgical clipping is widely used in the treatment of intracranial aneurysms, endovascular approaches provide a proper and effective alternative treatment method to surgical treatment by protecting the patient from the risks of major surgery by occluding or thrombosing the lumen of aneurysm with various techniques. Coil embolization is the most frequently used method in the endovascular treatment of intracranial aneurysms but harbours some limitations.

These limitations are mainly observed in wide-necked aneurysms, and migration of the coils to the parent artery and recanalization in the aneurysm sac after the treatment are seen [2]. Although balloon modeling, stenting and coiling methods are effective in dealing with these difficulties, treatment with the help of flow –diverter (FD) stents is the new alternative in such selected cases [3]. The aim of this study was to evaluate the early results of the reliability and efficacy of the intracranial aneurysms using FD stents.

MATERIAL and METHOD

Between January 2010 and January 2014, 41 patients with intracranial aneurysms who applied to the Interventional Neuroradiology Department with treated using a FD stents (Balt Extrusion, Montmorency, France). Our study was approved by the Ethics Committee of our Hospital on 03.31.2014 with the project number no. 2014-60 as a dissertation study. Our study population consisted of 31 (67%) female and 13 (23%) male patient with a mean age of 47.8±1.2 years (range: 27-68 years). Ten (24%) patients applied to us two weeks before our treatment with a history of SAH and 3 patients (7%) with mass effect-related symptoms.

Among twenty asymptomatic patients (48%), aneurysm was detected incidentally using computed tomography or magnetic resonance imaging techniques requested with the indication of nonspecific

complaints (mostly headache). The remaining 8 (19%) patients presented with enlargement of their aneurysms after treatment by surgical or endovascular methods.

Indications for treatment with FD stents are as follows; arterial fusiform or saccular aneurysms, giant aneurysm or aneurysms with mass effect, wide-necked aneurysms, blister-type aneurysms, small (<2 mm) aneurysms that cannot be treated with surgery or conventional endovascular treatment techniques and enlarged aneurysms developed after endovascular or surgical treatment were included in the treatment.

The mean aneurysm size was 14,3±1,4 mm (range, 1-30 mm). The aneurysms were located at the parophtalmic segment in 30 patients, at the posterior comminicating artery in 8 patients and at the anterior choroidal artery in 2 patients.

RESULTS

Technically, FD stent was successfully placed in 41 patients. In the DSA (Digital subtraction angiography) examination of the patient whose clinical picture worsened 2 hours after the procedure, the stent lumen occluded with thrombus was observed. The complete patency of the stent lumen was achieved by passing a microcatheter through the occluded lumen, and application of antiplatelet glycoprotein IIb / IIIa blocker, Tirofiban (Aggrastat) was performed. Neurological deficit was not observed in the patient after the treatment.

On the first day control DSA review,patient had thrombotic occlusion of the right ICA (Internal Carotid Artery) and stent lumen was observed and the filling of the right hemisphere was compensated with anterior and posterior communicating arteries from left ICA and posterior circulation. Upon normal neurological examination of the patient, the patient was included in the routine follow-up protocol.

The patient, who was treated with FD stent due to parophtalmic aneurysm of the left ICA, did not wake up from postprocedural anesthesia (Figure 1A-B). Thus, control DSA was performed which revealed thrombotic occlusion of the stent lumen (Figure 1C).

Figure 1A. On DSA, left ica paroftalmik giant aneurysm was showed.

Figure B. After Deployment of Flow-diverter stent, thrombosed aneurysm was showed.
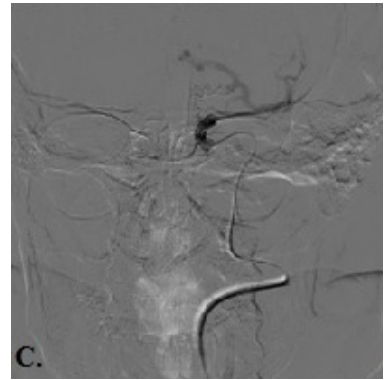
Figure 1C. On first day control DSA, Thrombotic occlusion of a FD stent was showed.
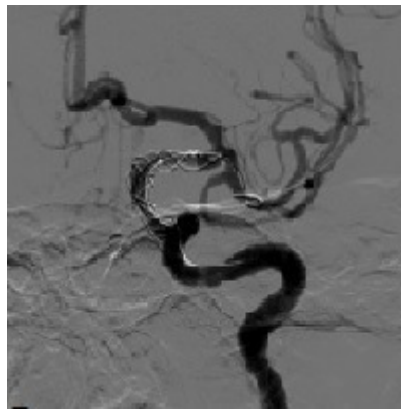
Figure 1D. Intraarterial thrombolysis was applied and a second stent was inserted through the luımen of the stent to achieve stent patency.

Then intraarterial thrombolysis was applied and a second stent was inserted through the luımen of the stent to achieve stent patency (Figure 1D). Neurological deficit was not detected in during post-treatment control ofthe patient.

In the patient, who ha a history of surgical treatment due to a bleeding basilar tip aneurysm, 50% collapse at the proximal end of the stent was observed in the control DSA performed one day after parophtalmic aneurysm of the left ICA was treated with an FD stent. This situation handle with passing through the collapsed segment of the stent with a micro guidewire, the PTA procedure was performed and the apposition of the stent to the vascular wall was ensured.

Control DSA examination performed the patient due to speech disorder and hemiparesis developed one day after the treatment, the MCA (Middle Cerebral Artery) M1 segment was found to be thrombosed starting from the distal of the stent. Occlusion of the lumen of both the stent and the artery were completely relieved as a result of mechanical thrombectomy and intraarterial Aggrastat application after negotiating of microcatheter at the thrombosed segment of the stent and MCA. Neurological deficit occurred in the patient secondary to extensive MCA infarction as detected during the control MRI examination.

The patient treated with FD stent due to left posterior communicating artery (PCoA) aneurysm on the follow up patients was re-treated using a second FD stent because of persistent filling of the aneurysm neck as observed in the control DSAs performed in the 6th and 12th months. After the second FD stent was performed, there were no filling detected in the aneurysm during follow-up examinations.

In our study, in 5 patients (12%) who were treated with FD stents, the filling of the neck of the aneurysm continued as observed in the 1st year control in DSA examinations.

DISCUSSION

Flow-diverter stents; can be used as a new option in the treatment of dissecan, fusiform, blister, wide-neck and recurrent aneurysms. The purpose of this treatment is interrupt the blood flow in the aneurysm sac and to activate the thrombosis with its flow-regulating effects. In our patient group, 88% (36/41) total occlusion in the aneurysm sac was determined in the 1st year control DSA. Also, FD stents present some specific problems in treatment. First of all, when using such materials, we encounter stent placement difficulties. In their multicenter prospective study, Byrne et al. reported procedural difficulties in 29% (n=20) their patients. These procedural difficulties are mainly; inadequate stenting in 12, inappropriate stent placement in 4, stent migration in 4, and partial, and complete thrombosis of the parent artery in 7 patients [4].

In our study, we encountered stent placement problems in a total of 4 (9.7%) patients. On the first day of control DSA, 50% collapse (2.4%) in the proximal end of the stent in 1 and stent thrombosis in 4 (9.7%) patients were observed. The vascular structure of patients complicates stent placement especially in tortuous vessels. Most of the stent placement difficulties occurred in our first case series. Accumulating experience, and information about features of the stent, and the most accurate selection of stent size is important in overcoming stent placement difficulties. When choosing the stent size, if there is a difference between the diameters of the proximal and distal parts of a artery, a stent diameter should be selected. proximal site of the artery.

When placing the stent complete appositon of the proximal end of the stent to the artery is important. In cases where the complete apposition of the FD stent to the artery can not be achieved collapse and thrombosis of the stent can be occured due to changes induced by FD stent-related flow [5]. In addition, these stents have low radial forces, so a slight collapse or insufficient opening of the distal tip can be observed when loading the stent. In cases where the distal tip of the stent does not open adequately, then distal tip patency can be provided with the help of a balloon angioplasty. As in studies with other flow-diverter stents, the probability of occlusion of the aneurysm after treatment increases over time, but the development is unpredictable [6,7].

In small series such as our study, it is difficult to determine the timing of aneurysm occlusion. Dual antiplatelet drug treatment for at least 4 months, sometimes even longer due to partial stenosis or thromboembolic events in the stent lumen increases this uncertainty.

Recurrence in aneurysm is an important problem, especially in patients undergoing coil embolization. In the literature, recurrence rates between 13% and 34% have been reported in large series after endovascular treatment [8,9]. In our study, residual neck filling was observed in aneurysms of 5 (12%) patients.

Blister-type aneurysms are difficult to treat with both surgical methods and classical endovascular methods due to their weak walls, small sizes and large necks, and atypical locations. These aneurysms have a high risk of rupture during surgery [10]. Thus, they have high morbidity and mortality rates. In our study, three of our patients with a history of subarachnoid hemorrhage caused by rupture of the blister aneurysm were treated with FD stents. These patients were treated 2 weeks after bleeding to rule out possible SAH-related complications. Any complications were not observed in the post-procedural follow-up of the patients, and occlusion of the aneurysm sacs were observed in the 1st year control DSA examinations.

Kulesar et al. treated a patient with a FD stent who had SAH due to rupture of aneurysm 20 days previously [11]. Another study conducted by Byrne et al. treated four of 10 ruptured aneurysms with FD stents within the first 30 days of SAH [4]. In addition, studies on the use of FD stents in ruptured aneurysms have been reported [12]. In our cases, 10 ruptured aneurysms were treated with FD stents 2 weeks after SAH. The main concern with the use of FD stents in ruptured aneurysms is the complications

associated with the use of dual antiplatelet drug therapy and the uncertainty of aneurysm occlusion time after treatment.

After the treatment of the ruptured aneurysms mentioned in the above studies with FD stent, no rebleeding occurred in any case, but other options should be carefully considered before using flow-diverter stents in ruptured aneurysms.

Intracranial hemorrhage can be observed after successful treatment with flow-rdiverter stents. Byrne et al. had reported a ruptured case 7 months after the treatment [4]. Furthermore, Lubicz et al. reported a ruptured case secondary to the migration of the stent into the aneurysm sac 13 days after the treatment [13].

Although the mechanism of bleeding after treatment with FDstents is not fully known, the formation of new and organized luminal thrombosis is an important risk factor that causes deterioration in the aneurysm wall structure and has been associated with aneurysm rupture. Kulcsár et al. reported that main features of ruptured aneurysms after treatment with FD stents [14]. Accordingly, large and giant aneurysms, symptomatic aneurysms recently showing growth and wall instability, saccular aneurysms with a dome / neck ratio greater than 1.6 have been reported to have significantly higher risk of rupture. Cebral et al. reported that flow –diverter stents can be increase the intracranial pressure which may cause rupture especially in large and giant aneurysms [15].

In our patient group, there were no bleeding complications observed since we performed coil embolization combining with FD stent in patients with parenchyma- embedded aneurysms

CONCLUSION

Our aim in this retrospective study is to focus on the technical difficulties encountered when using FD stents, and we wanted to share our experience about the complications of treatment. Although this treatment has its own technical difficulties, and complications in the early and mid-term follow-up. FD stents have been discovered to be promising,

especially for morphologically difficult aneurysms. With long-term follow-up monitoring, conducting further studies on the hemodynamic effects and healing reactions of this treatment will increase our knowledge.

In the literature, bleeding rates after treatment have been observed in large diameter and when the aneurysm is embedded in the parenchym. In our study, the use of FD stents with coil embolization in large diameter and parenchyma-embedded aneurysms is an important finding in our study. Another important detail is the first-day DSA should be performed. In cases where the stent patency is insufficient as revealed in the DSA performed on the 1st day after the treatment, the placement of the stent into the artery has been successfully achieved with the balloon angioplasty method and provides early intervention to thromboembolic events that may occur.

In conclusion, FD stent is an effective treatment tool for the most challenging wide-necked, giant, blister, dissecting and fusiform aneurysms, despite all FD insertion difficulties. This method will improve our major therapeutic approaches in the treatment of complex aneurysms in the future.

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Demographic Distribution and Long-Term Surgical Outcomes of Intracranial Aneurysms Operated at a Tertiary Health Institute: A Retrospective Study

Tek Referans Hastanesinin İntrakraniyal Anevrizmaların Demografik Dağılımı ve Uzun Dönem Cerrahi Sonuçları: 398 Hastanın Retrospektif Değerlendirilmesi

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ABSTRACT

Objective: *To evaluate the demographic distribution and the long-term surgical outcomes of intracranial aneurysms (IAs) at a tertiary health institute.*

Method: *I retrospectively reviewed the medical records of 398 patients with IAs who underwent surgical intervention at our tertiary health institute within 3 years, between 2011 and 2013. The demographic distribution regarding the patients' cities and their long-term surgical outcomes were evaluated.*

Results: *Sixty-one (36 females, 25 males) patients were from Istanbul. Majority (14.6%) of our patients (n=120: 71 females, 49 males) with IAs came from the Marmara region. The locations of IAs in our patients with subarachnoid hemorrhage (SAH) were antrerior communicating artery (AcoA) (n=78), middle cerebral artery (MCA) (n=74), multiple aneurysms (67), internal cerebral artery (ICA) (n=24), posterior communicating artery (PcoA) (n=13), anterior cerebral artery (ACA) (n=7), superior cerebellar artery (SCA) (n=6), and posterior cerebral artery (PCA) (n=5), whereas the locations of incidentally diagnosed IAs were MCA (45), ACoA (32), multiple (23), ICA (22), PCoA, ACA, and PCA one each artery. The mortality and morbidity rates were higher in SAH patients 16.7% - 10.6% (15% - 3% in patients with incidentally diagnosed IAs). The rate of the patients who returned to their normal daily activities was higher.*

Conclusion: *A higher rate of postoperative hydrocephalus was observed in patients with multiple aneurysms. There was no relation between sex and morbidity and mortality rates. SAH patients presented with multiple aneurysms had a higher morbidity rate. Advanced age (> 65) and MCA location were associated with a higher mortality rate, while locations of ICA (especially ophthalmic), PCoA, and ACoA were associated with a higher morbidity rate.*

Keywords: *intracranial aneurysm, demographic distribution, subarachnoid hemorrhage, prognosis, incidental aneurysm*

ÖZ

Amaç: *İntrakraniyal anevrizmaların (IA) demografik dağılımını ve uzun dönem cerrahi sonuçlarını tek referans merkezde değerlendirmektir.*

Yöntem: *2011-2013 yılları arasında 3 yıllık bir süre boyunca BRSHH hastanesinde intrakraniyal anevrizması olan 398 hastanın tıbbi kayıtları retrospektif olarak incelendi. Hastaların doğduğu şehirlerine ve ait olduğu bölgesine göre demografik dağılım ve uzun dönem cerrahi sonuçları değerlendirdik.*

Bulgular: *İstanbul'dan 61 hasta (36 kadın, 25 erkek) bizde ameliyat olurken, Marmara Bölgesinden hastalarımızın %14,6'sını oluşturup (71 kadın, 49 erkek) en fazla hasta kaynağımız olmuştur. En yaygın lokalisyon ACoA (SAK: 78, İns: 32), MCA (SAK: 74, İns: 45), İCA (SAK: 24, İns: 22), PCoA (SAK: 13, İns: 1), ACA (SAK: 7, İns: 1), PCA (SAK: 5, İns: 1), SCA (SAK: 6, İns: 0) ve Çoklu anevrizma ise (SAK: 67, İncs: 23) hastada saptandı. Mortalite oranları (% 15: % 3), morbidite oranları (% 16.7: % 10.6) ve (% 68.3: % 86.4) hastalar işlerini ve günlük aktivitelerini normale döndürdüler. Komplikasyonları ise postoperatif 58 (SAK: 50, İns: 8), hidrosefali (SAK: 15, İns: 3), postoperatif hematom (SAK: 10, İns: 3), vazospazmaya bağlı kalıcı enfarktüs (SAK: 15, İns: 3) ve jeneralize nöbetler (SAK: 8, İns: 1).*

Sonuç: *Postoperatif hidrosefali en çok SAK ile prezente olan çoklu anevrizmalı hastalarda görüldü. Cinsiyet ile ne morbidite ne de mortalite oranları arasında ilişki yoktu. Özellikle çoklu anevrizma tanısı alan SAH hastalarının morbidite oranı yüksekti. İleri yaş (>65) ve MCA yerleşimi yüksek mortalite oranı ile ilişkiliyken, İCA (özellikle paroftalmik), posterior ve anterior kommunikan arterlerinde yerleşim gösteren anevrizmalı hastalarda yüksek morbidite oranı görüldü.*

Anahtar kelimeler: *intrakraniyal anevrizma, demografik dağılım, subaraknoid kanama, prognoz, insidental anevrizma*

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INTRODUCTION

Intracranial aneurysms (IAs) are entities that occur as a result of a weakened blood vessel wall, which may be diagnosed incidentally or after an incident of subarachnoid hemorrhage (SAH). As an aneurysm increases in size, so does the risk of rupture. Aneurysms can be the result of a hereditary condition or an acquired disease. IAs are fairly common entities, particularly in hypertensive old population. The patients with unruptured IAs usually complain of nonspecific symptoms such as headache, vertigo or/ and forgetfulness. Rupturing of IAs leads to SAH which has a high propensity to permanent neurological deficits and death [1,2]. One literature review published earlier suggested that the incidence of unruptured IAs in healthy individuals can be as high as 6% [3]. Among the patients with IAs, the multiplicity rate ranges between 15% and 33% [3,4].

The factors that have an impact on the formation of multiple IAs were investigated in many previously published studies. The multiplicity of IAs are observed to be higher among female, advanced aged, and heavy smoker patients who presented with SAH [5,6]. It is suggested that some chronic factors such as chronically increased blood pressure (i.e., hypertension) can influence wall thickness of intracranial arteries. Thus, long-term increase in blood pressure leads to enlargement of the IAs and eventually, they get ruptured. Rupturing of IAs is generally associated with an acute rise in the patients' blood pressure. Initially, the patient can have a single IA or can present with multiple IAs (MIAs). IAs may present as SAH or may be diagnosed incidentally.

Despite all advancements and refinements of intensive care units, surgical tools, equipments, and micro neurosurgical techniques, aneurysmal SAH has a poor prognosis that remained relatively unaffected [7-10]. Through an exhaustive review, we found that SAH has a high mortality rate of up to 40%, while 60% of the surviving patients with SAH can have serious neurological limitations and need other individuals' support and help [7,11]. To manage IAs, good preoperative planning, fine usage of sophisticated surgical equipment, and considerable expertise are necessary. Detailed preoperative planning includes performing digital subtraction angiography (DSA) and other scanning methods such as MRI, MRA, 3D-CT, and CT. The surgical treatment of such entities can be realized only in advanced (tertiary) healthcare centers which were prepared for this challenge [7,8]. The current study aimed to investigate the demographic distribution and the long-term surgical outcomes of IAs at a single tertiary healthcare center.

MATERIALS and METHODS

The current research was retrospective in design and approved under decision 575/2016 fof the board of the medical ethics in our hospital. All patients and/or their next of kin signed written informed consent for surgical interventions and their publication.

I retrospectively reviewed medical records of 398 IA patients who were diagnosed and surgically treated at our hospital, during 3 years from 2011 to 2013. The demographic distribution according to the patients' cities of origin and the long-term surgical outcomes of IAs at a single tertiary healthcare center was discussed.

All statistical data manifested hereafter were given with the ranges within parentheses and expressed as the mean ± standard deviation values. The one-way analysis of variance (ANOVA) and the SPSS 21.0 statistical package were utilized to assess the differences among groups. Findings were consiered to be statistically significant when the p-value was less than 0.05. All p-values were presented with odds ratio (OR). ORs were presented within 95% confidence interval (CI).

Surgery

The patients were placed in supine position with the head holder in the fixation device. A craniotomy is always done on the side of the ruptured or complex, inverse projected aneurysm (in SAH/multiple IA cases). The lateral wall and roof of the orbit were drilled, and thinned using high-speed motors. Accordingly extra space is gained for more exposure of parent vessels to facilitate distal and proximal control of neurovascular structures without further need to retract the neural tissue. The anterior clinoid process can be completely drilled before duratomy step for a safer go-ahead especially in surgeries of

IAs located on ipsilateral proximal internal carotid arteries (ICAs). To prevent major traumatic pressure and infarcts, we avoid using self-retaining retractors.

To gain further space and get brain further relaxed, before beginning dissection to reach IAs, lamina terminalis was opened except for anteriorly directed anterior communicating artery (ACoA) aneurysms. Opening lamina terminalis is useful for reducing possible SAH-related hydrocephalus in the long term, but the immediate shrinking of the brain, leading to more space without retraction is a major benefit. For incidentally diagnosed IAs that did not present with a SAH, opening lamina terminalis is preferred after clipping if the drainage of the cisternal CSF was satisfactory and cistern was not swollen after SAH. In this way, the surgeon keeps the 3rd ventricular system away from unintended oozing during anatomical dissection.

A retrograde clipping model is adopted in incidentally diagnosed MIAs. That is; neurosurgeon has to start from the deeper IAs (IAs located proximally regarding vessel entry into the cranium, distally according to the surgeon). To emphasize the complete obliterating of IAs from the circulation, I strongly recommend puncturing the dome of the clipped aneurysm with a needle after clipping. Micro-Doppler is utilized to control circulation in vessels distal and proximal to the aneurysm after clipping. As a neurosurgeon, I recommend clipping all reachable IAs in a single session [7].

RESULTS

A total of 409 micro-clipping surgeries were applied to 398 (216 females and 182 males) patients with IA. IAs were diagnosed after an episode of SAH in 274 patients and IAs were incidentally diagnosed in 124 patients. The most common presenting symptoms are given in Table 1. A total of 308 patients were diagnosed with a single IA and 90 patients with MIAs. Sixty-five out of 90 multiple IA patients (72.2%) presented with 2 aneurysms (Table 2). The mean age of the whole sample was 50.4 (11-82) years. A total of 61 (36 females, 25 males) patients [15.3%] were from Istanbul. Most of our patients with IAs (n=120; 30.2%; incl. 71 female, 49 male cases) came from the Marmara region followed by; the Black Sea region (62 women, 57 men) [29.9%], Eastern Anatolia region (42 women, 38 men) [20.1%], Central Anatolia (23 women, 23 men) [11.6%], Southeastern Anatolia (10 women, 8 men) [4.5%], Mediterranean region (3 women, 2men) [1.2%], Aegean region (2 women, 2 men) [1%] and 6 patients were from abroad [1.5%] (Fig. 7). The locations of SAH in our patients were as follows: ACoA (n=78), middle cerebral artery (MCA) (n=74), multiple sites (n=67), ICA (n=24), posterior communicating artery (PCoA) (n=13), anterior cerebral artery (ACA) (n=7), superior cerebellar artery (SCA) (n=6), and posterior cerebral artery (PCA) (n=5), whereas the locations of incidentally diagnosed IAs were as follows: MCA (n=45), ACoA (n=32), multiple sites (n=23), ICA (n=22), PCoA, ACA, and PCA one on each artery. A total of 220 IAs were

Table 1. Baseline clinical and demographic characteristics of the 398 IA patients.

	Ruptured Aneurysms	Unruptured Aneurysms	All Pts
Age (years)	51.3±13.2 (11-82)	49.4±7.4 (17-64)	50.4±11.9 (11-82)
No. Of Patients	274 pts (68.8%)	274 pts (31.2%)	398 pts (100%)
Gender (F/M)	141/133	75/49	216/182
Symptoms - Headache	[Severe] 92% (n=252)	[Chronic] 63.7% (n=79)	83.2% (331/398)
- Nausea&Vomiting	57.7% (n=158)	6.5% (n=8)	41.7% (166/398)
- Impaired consciousness	44.2% (n=121)	0	30.4% (121/398)
- Vertigo	1.8% (n=5)	26.6% (n=33)	9.5% (38/398)
- Generalized seizure	8.4% (n=23)	3.2% (n=4)	6.8% (27/398)
- Hemiparesis	7.7% (n=21)	2.4% (n=3)	6.0% (24/398)
- Memory imparment	1.1% (n=3)	7.3% (n=9)	3.0% (12/398)
- Neck pain	3.3% (n=9)	0	2.2% (9/398)
- Aphasia / Dysphasia	2.9% (n=8)	0	2.0% (8/398)
- Behavioral impairment	2.2% (n=6)	0	1.5% (6/398)
- Fatigue	0	3.2% (n=4)	1.0% (4/398)
Follow-up period* (months)	41-77 (Av. 60.1±18.4)	36-76 (Av. 57.5±12.1)	39-77 (Av. 59.3±21.3)
Mean length of hospital stay (days)	9.7±8.0 (4-39)	5.6±3.5 (3-16)	8.4±7.4 (3-39)

* Follow-up periods were calculated only for patients who are still alive after treatment; pts: patients.

Table 2. Numbers of aneurysms in multiple cerebral aneurysms patients (n=90).

Numbers of Aneurysms	Ruptured Aneurysms				Unruptured Aneurysms			
	Females		Males		Females		Males	
	N	%	N	%	N	%	N	%
2	25	73.5	26	78.8	8	53.3	6	75.0
3	7	20.6	6	18.2	3	20.0	1	12.5
≥4	2	5.9	1	3.0	4	26.7	1	12.5
Total	34	100.0	33	100.0	15	100.0	8	100.0

Table 3. Co-morbidities of the all IAs patients.

Co-morbidities	Ruptured Aneurysms				Unruptured Aneurysms			
	Females		Males		Females		Males	
	N	%	N	%	N	%	N	%
Smoking	52	36.9	78	58.6	26	34.7	17	34.7
Hypertension	89	63.1	43	32.3	45	60.0	23	46.9
Coronary Artery Diseases	31	22.0	4	3.0	2	2.7	14	28.6
Diabetes Mellitus	18	12.8	6	4.5	4	5.3	18	36.7
COPD*	11	7.8	8	6.0	3	4.0	6	12.2
Thyroid Dysfunction	10	7.1	2	1.5	16	21.3	9	18.4
CVA**	7	5.0	3	2.3	5	6.7	4	8.2

*COPD: Chronic obstructive pulmonary diseases; ** CVA: Cerebrovascular accident.

detected as MIAs in 90 patients (67 with SAH and 23 incidentally diagnosed cases). The co-morbidities of all patients are given in Table 3. The respective mortality 15% vs 3%) [P=0.0002, OR 5.28 (1.85-15.09)], and morbidity rates (16.7%:vs %10.6) [P=0.027, OR 1.97 (1.0-3.8)] were as indicated and the greater proportion of incidentally diagnosed patients with single IAs returned to their normal daily activities (GOS ≥4) (86.4% vs 68.3%). The complications such as postoperative infections, hydrocephalus, hematoma, vasospasm and generalized seizures were higher in SAH patients with rates of (50:8) [P=0.001, OR 2.83 (1.48-7.06)], (17:3) [P=0.049, OR 3.07 (0.88-10.7)], (10:3) [P>0.05], (15:3) [P=0.086, OR 2.68 (0.76-9.46)], and (8:1) [P>0.05], respectively. Nine out of 17 patients with hydrocephalus had MIAs [P=0.005, OR 0.24 (0.09-0.64)]. Even though hydrocephalus was a complication seen after surgery of IA patients with SAH (n=17) and unruptured aneurysm (n=3) patients, this complication was associated with aneurysmal SAH patients especially with MIAs (P=0.049). We found out that infection rates increased coherent to Fisher grade rather than the Hunt-Hess scale (Fisher grade I and II vs Fisher grade III and IV; P=0.032).

Postoperative infections were observed in 58 of our patients where 50 patients had presented with SAH initially (P=0.001, OR 2.83). In the same period of our study 1361 patients were admitted to ICU for different causes. In the remaining 963 patients, the most common infections were pneumonia, BSI, meningitis, and UTI, respectively. This order was not the same in our aneurysm patients (in decreasing order of frequency: blood site infection (BSI), pneumonia, meningitis, surgical site infection (SSI) and urinary tract infection (UTI), respectively). In patients with SAH, multiple aneurysms and ruptured ACoA aneurysms had high infection rates (P<0.05) compared to other IAs. Advanced age and female gender (except for pneumonia and UTI), multiple aneurysms (except for meningitis), SAH presentation, increased hospitalization period, delayed surgical intervention and poor neurological status increase risks of the nosocomial infections.

In the SAH group (n=274), poor neurological grade at presentation, the presence of hematoma, and the impairment of consciousness (high Hunt-Hess grade [IV/V]) are associated with high morbidity and mortality rates; [(P<0.001, OR 0.02); (P<0.001, OR 0.07)],

[(P<0.001, OR 0.22); (P=0.001, OR 0.32)], and [(P=0.003, OR 0.35) and (P<0.001, OR 0.07)], respectively.

There was no relationship between gender of the patients and the morbidity (37 women, 23 men) and the mortality (26 women, 18 men) rates, (P=0.3, OR 0.8) and (P=0.11, OR 0.67) , respectively. Advanced age (>65 years) [16 of 59 of these patients died] (P<0.001, OR 0.24) and MCA location [23 of 109 patients with MCA aneurysms died] (P<0.001, OR 0.31) were associated with higher mortality rate while ICA location (especially location on para-ophthalmic segment) [14 of 46 patients with ICA aneurysms had GOS<3] (P=0.004, OR 0.34), posterior communicating segment location [5 out of 14 patients ICA aneurysms with GOS<3] (P=0.044, OR 0.3) and anterior communicating artery location [28 of 82 patients had ICA aneurysms with GOS<3] (P=0.0005, OR 0.37) were associated with higher morbidity rates.

Sixty-one (67.8%) patients with multiple IAs (GOS ≥4), and 233 out of 308 patients with single IA had good outcomes. Seventeen multiple and 44 single IA patients had poor outcomes (GOS ≤3) and 12 patients with multiple and 33 patients with single IAs died. The mortality and the morbidity rates were (P=0.13, OR 0.66) and (P=0.27, OR 0.75), respectively.

Seven (3 men and 4 women) SAH patients with a mean age of 59.4±5.4 (51-65) years presented with recurrent SAH. SAH in all seven patients originated from other IAs that were not found in DSA performed at first bleeding episode. The interval between the first and second SAHs ranged between 23 and 122 (average on 70) months. All seven patients were heavy smokers (more than 40 cigarettes a day) with a known hypertensive disease. Five of them presented with MIAs.

Exemplary Cases

Case 1: A 61-year-old woman brought to our Emergency Department after complaining from a severe headache followed by nausea and vomiting. The neurological examination of this hypertensive
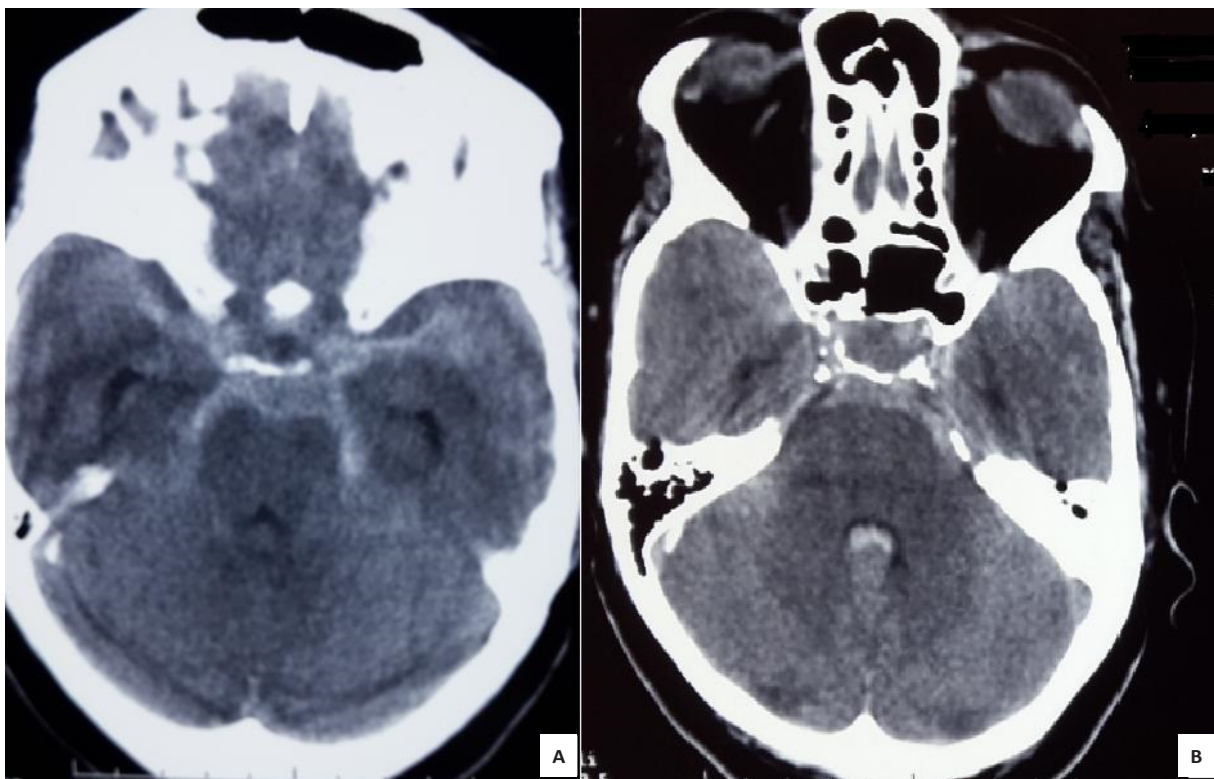
Figure 1. Preoperative cranial computerized tomography (CT) revealed subarachnoid hemorrhage (SAH) that was evaluated as grade 4 in Fisher scale and mild hydrocephalus; [A]: Perimesencephalic SAH and mild hydrocephalus are apparent in temporal horns of lateral ventricle; [B]: Fisher grade IV Intraventricular subatrachboid hemorrhage in the fourth ventricle.
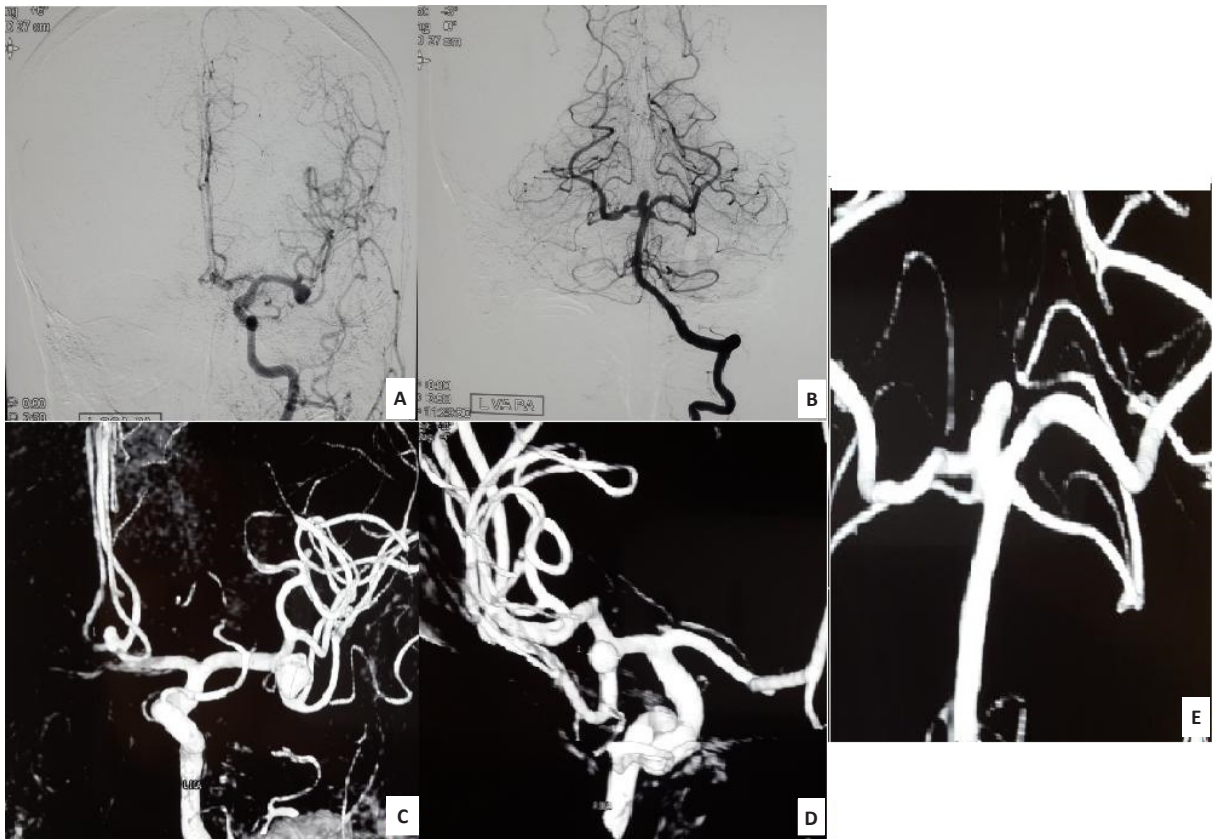
Figure 2. Preoperative DSA demonstrating a case of the multiple aneurysms of bilateral middle cerebral, anterior communicating and basilar arteries; [A]: Preoperative DSA shows left MCA aneurysm; [B]: Preoperative DSA shows basilar artery aneurysm; [C]: Preoperative three-dimensional DSA shows both left MCA and ACoA aneurysms; [D]: Preoperative three-dimensional DSA shows both right MCA and ACoA aneurysms; [E]: Preoperative three-dimensional DSA shows basilar artery aneurysm.

patient was not remarkable Except for the nuchal rigidity (++), she had no neurological deficits (Hunt-Hess grade II). Urgent brain CT demonstrated a SAH accompanied by mild hydrocephalus (Figure 1). Right femoral intraarterial DSA demonstrated MIAs of four separate IAs (Figure 2).

All IAs were successfully clipped through a left lateral supraorbital craniotomy (Figure 3). The patient fully recovered without any neurological deficit and she was discharged on the 7th postoperative day. No complications were recorded.

Case 2: A 38-year-old woman was brought to our outpatient clinics with a headache of 2 years' duration. The patient said that she became tired easily even with a moderate effort. Her neurological examination and vital signs were within normal ranges.

MIAs were detected on bilateral MCA bifurcations on brain MRI and DSA (Figure 4, 5). Both bilateral MCA IAs were successfully clipped through a right lateral supraorbital craniotomy (Figure 6). The patient fully recovered without any neurological deficit and she was discharged on the 4th postoperative day. No complications were recorded.

DISCUSSION

The advancement of all intensive care units, neurosurgical fields, and equipment types has not proportionately improved the prognosis of SAH, because morbidity and mortality rates still being at an unacceptably high levels [8,9]. Many previously published articles reported that patients with MIAs that presented with SAH had less favorable outcomes compared to cases with single aneurysms [5,6]. Even though we did not face additional surgical difficulties, our multiple IA cases were associated with a higher rate of postoperative hydrocephalus complications.

Even though our tertiary hospital is in the European side of Istanbul, 50% (n=199) of all our patients were born in the Black Sea and Eastern Anatolia regions, the regions close to the Chernobyl area. We interpreted this by one of three possibilities; 1) Environmental factors: greater number of our patients were from the regions close to the Chernobyl nuclear plant accident happened in 1986, 2) Habitual factors such as the patients' feeding pattern, or 3) The genetic nature of the disease since consanguineous marriage is common in these areas. Presently, limited evidence exists for the risk

for vascular disorders such as IAs associated with radiation exposure emitted from a nuclear plant accident 12).

In our study, we found that surgically treated unruptured aneurysms may reduce the high complication rate which was observed in SAH patients. Therefore, we preferred to operate most of the patients who were diagnosed incidentally. Unruptured IAs are serious entities that have to be treated immediately or observed regarding their size, irregularity of their shape, and the frailty index of the patients [8]. The
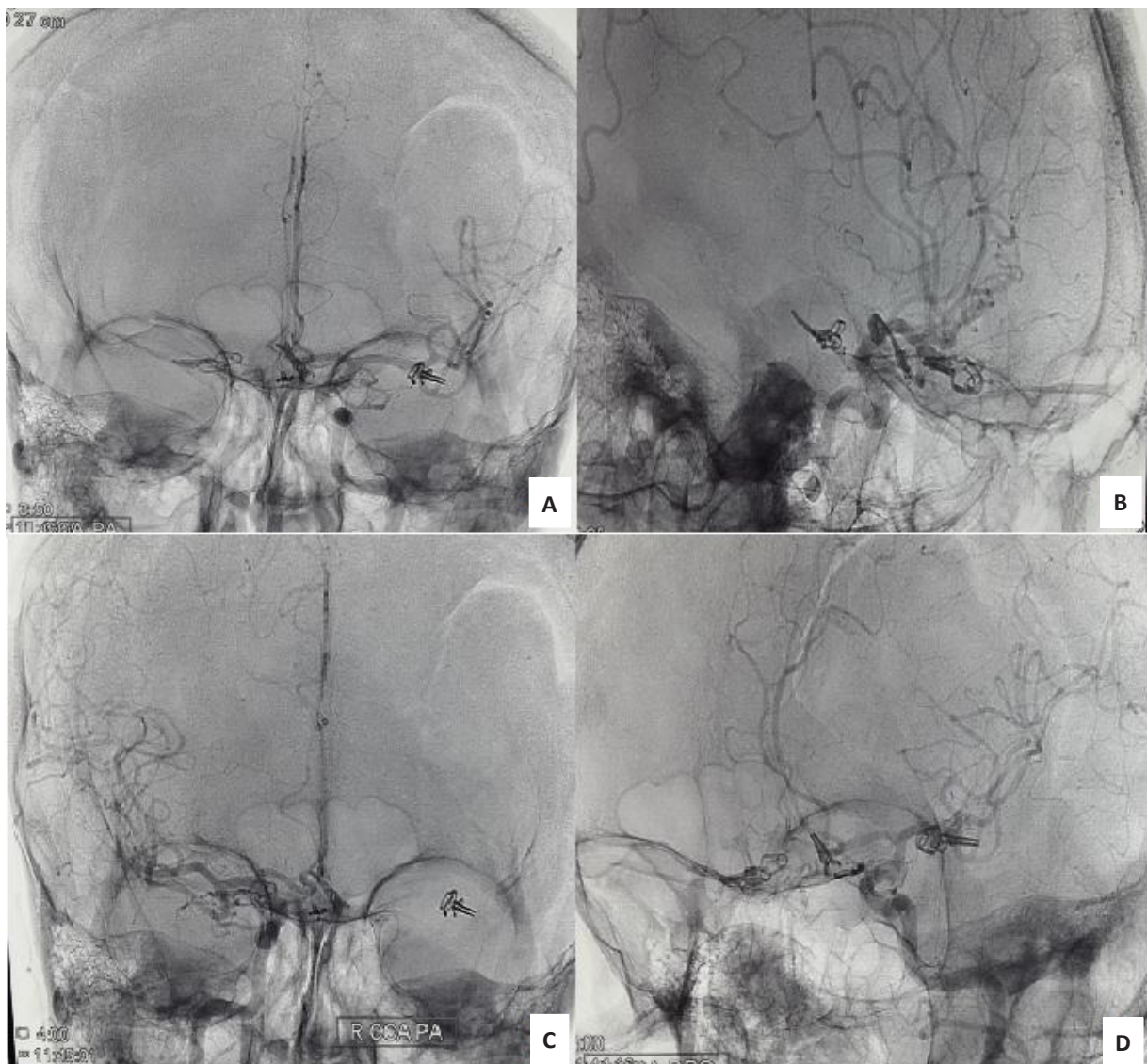
Figure 3. Early postoperative DSA demonstrates that all four aneurysms were clipped without rest; [A and C]: Anteroposterior aspect of early postoperative DSA demonstrates that all aneurysms were clipped without rest (4A: DSA image of the left Common Carotid Artery (CCA); 4C: DSA image obtained from right CCA); [B and D]: Lateral aspect of early postoperative DSA demonstrates that all aneurysms were clipped without rest (4B: DSA image of the left Common Carotid Artery (CCA); 4D: DSA image of the right CCA).
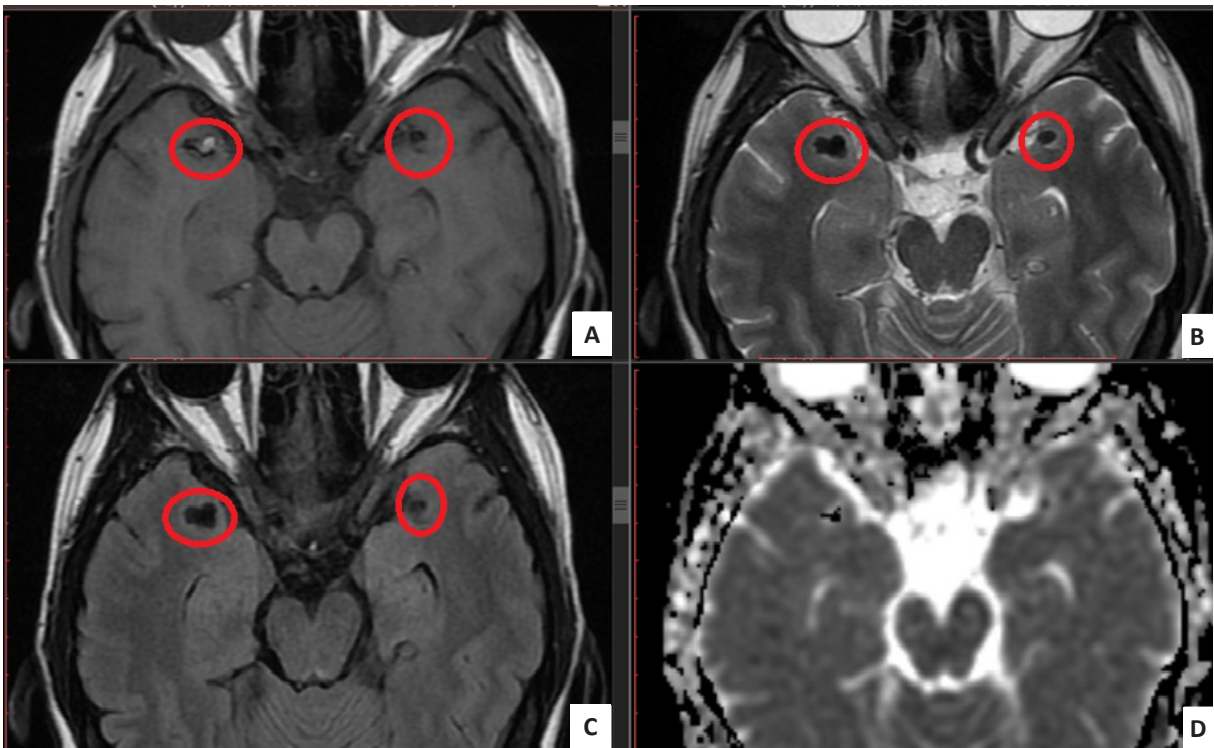
Figure 4. Preoperative magnetic resonance images (MRI) revealed bilateral middle cerebral artery aneurysms. The red cycles indicate the aneurysms; [A]: T1-weighted MRI; [B]: T2-weighted MRI; [C]: T2-flair-weighted MRI, [D]: Apparent diffusion coefficient (ADC).
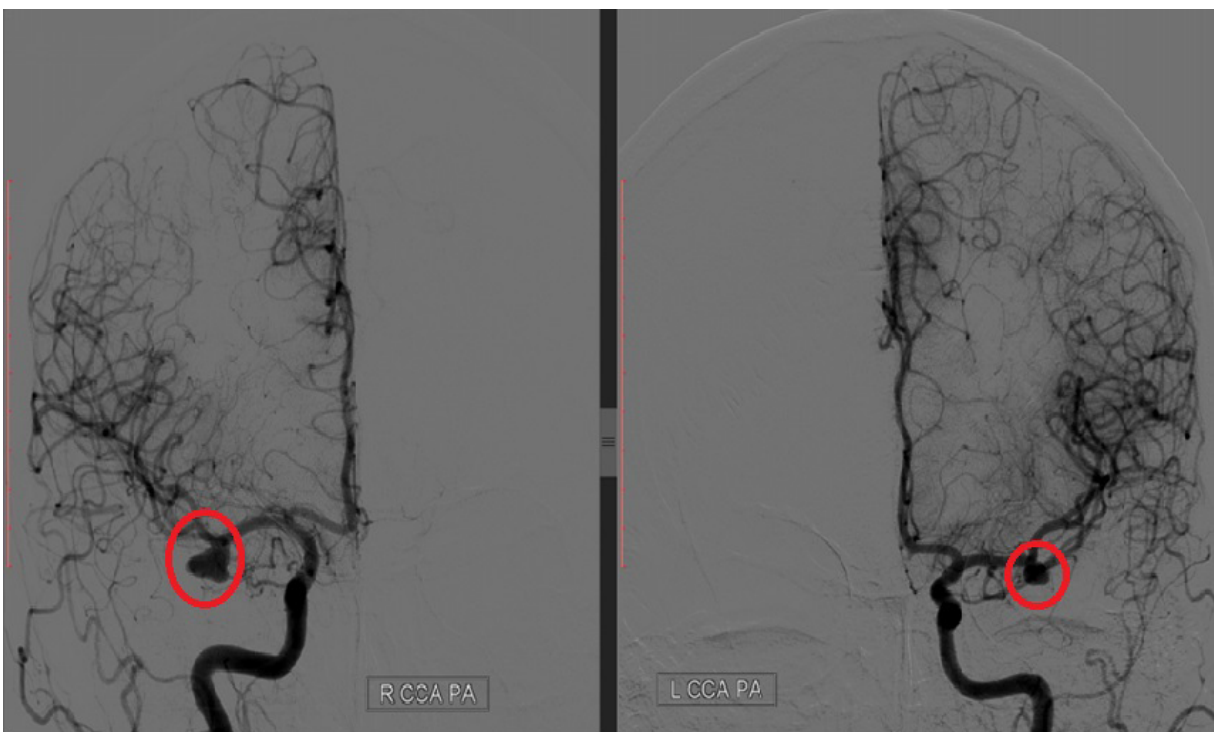
Figure 5. Preoperative DSA shows multiple aneurysms of bilateral middle cerebral artery. The red cycles indicate the aneurysms; [Right side]: Preoperative DSA shows right MCA aneurysm; [Left side]: Preoperative DSA shows left MCA aneurysm.

Figure 6. Early postoperative DSA demonstrates that all four aneurysms were clipped without rest; [A]: Coronal aspect: Rt. MCA aneurysm was clipped; [B]: Coronal aspect: Lt. MCA aneurysm was clipped; [C]: Anteroposterior aspect; [D]: Lateral aspect.

physician has to balance the rupture risk and treatment of the patients after discussing this with the patients with unruptured IAs and their first-degree relatives. Two systemic review studies have suggested that the predictors of higher risk of IAs getting ruptured includes several factors such as history of aneurysmal SAH, hypertension, and coronary artery disease, as well as many different demographic factors such as geographical region, age, aneurysm size (IAs with a diameter greater than 7 mm) and the locations of IAs on the ACoA, PCoA, and vertebrobasilar arteries [13,14]. The IAs with these factors are more fragile and have a high propensity to rupture than other IAs.

Smoking, younger age and multiplicity of IAs at the presentation are independent risk factors for recurrent SAH [7,15]. Another retrospective study found that hypertension was a serious risk factor for aneurysm regrowth or de novo aneurysm formation [15]. Several studies showed that both hypertension and smoking are risk factors for the development of IAs, presenting either incidentally or with SAH. In our series, small number of (7/274) patients presented with recurrent aneurysmal SAH which was insufficient to generalize our findings, however, our findings supported the results obtained from the literature regarding recurrent SAHs that multiple IAs, smoking, and hypertension were independent risk factors for recurrent SAH (P<0.01).

As we showed in our previously published studies [7] our findings demonstrated that presenting with poor neurological status, presence of hematoma and loss/impairment of consciousness in aneurysmal SAH patients are independent risk factors that can be associated with poor prognosis. The location of aneurysms have an impact on the prognosis of IAs. We found that patients with MCA aneurysms had a high mortality while the patients with ACoA, ICA-PCoA and paraophthalmic segment aneurysms had a high morbidity rates (GOS<3). Postoperative hydrocephalus was observed in particularly SAH group with MIAs.

In their most recent study Foreman et al. found that nosocomial infection is independently associated with delayed cerebral ischemia. They suggested that this association is hypothesized to be partly causative through the exacerbation of systemic inflammation leading to thrombosis and subsequent ischemia [16].

Marmara
F: 71; M: 49
(n=120)
[30.2 %]

Our Hospital

Black Sea
F: 62; M: 57
(n=119) [29.9%]

East Anatolia
F: 42; M: 38
(n=80) [20.1%]

Aegean
F: 2; M:2
(n=4) [1%]

Southeast Anatolia
F: 10; M: 8
(n=18) [4.5%]

Mediterranean
F: 3; M: 2
(n=5) [1.2%]

Central Anatolia
F: 23; M:23
(nş46) [11.6%]

** Foriegn Patients
F: 3; M: 3 (n=6) [1.5%]
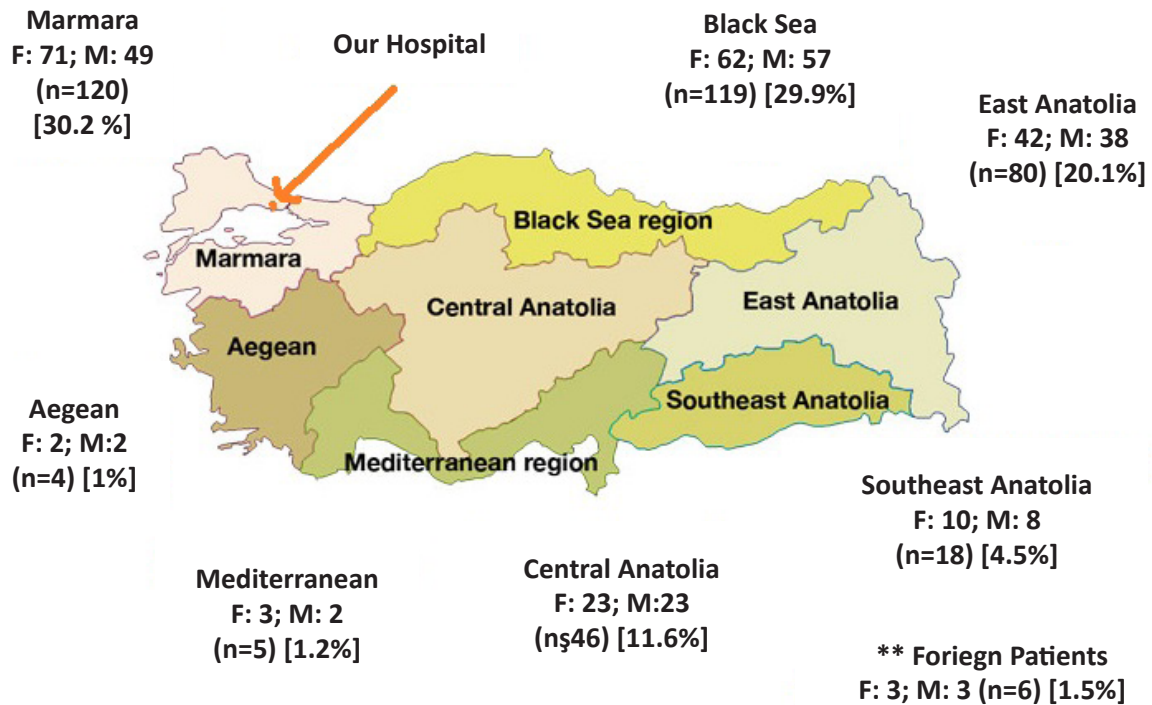
Figure 7. Demographic distribution of 398 IA patients according to geographic regions they came from.

In our series, postoperative infections observed among the patients with SAH were related to MIAs or ruptured ACoA rather than other IAs. We interpreted this by the general impairment of the immune system in the patients with SAH due to the general fatigue related to SAH itself, whereas the same impact of SAH was not observed in other neurosurgical disorders even though both groups underwent intracranial surgery and stayed longer in ICU. Regarding our results, infection rates increased coherent to Fisher grade rather than the Hunt-Hess scale. We thought this was associated with the increased amount of blood in the cisterns leading to adhesion of the brain. This adhesion may further suppress immunity in the brain. The morbidity rates (GOS <3) of SAH patients were higher especially of those diagnosed with MIAs. Even the exact mechanism is not clear, we found that SAH affected the immune state of the patients negatively.

The limitations of our study were as follows 1) the sample size was relatively small to generalize all results and findings to endemic geographic areas, 2) single healthcare institute outcomes, and 3) the retrospective design of the study. Our findings need to

be confirmed /supported by further prospective randomized studies with larger samples and longer follow-up periods so as to improve the representativeness of our findings.

CONCLUSIONS

Compared to the patients diagnosed with IAs incidentally, the patients that presented with SAH had higher morbidity and mortality rates. Even though the multiplicity of IAs at presentation did not influence surgical outcomes, a higher rate of postoperative hydrocephalus was observed in SAH patients with multiple aneurysms. There was no relationship between gender of the patients, and morbidity or mortality rates. Advanced age (>65) and MCA location of IA were associated with a higher mortality rate, while locations of IAs on ICA (especially para-ophthalmic), posterior, and anterior communicating arteries were associated with a higher morbidity rate.

Ethics Committee Approval: Secretary General of Istanbul Bakırköy Regional Public Hospitals Association Bakırköy Dr. Approval of Ethics Committee of Mazhar Osman Health and Neurological Diseases

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Analysis of Meningitis Cases in Pediatric Intensive Care Unit: 8-Year Single Center Experience

Çocuk Yoğun Bakım Ünitesinde Menenjit Olgularının Analizi: 8 Yıllık Tek Merkez Deneyimi

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ABSTRACT

Objective: *The aim of the study was to evaluate clinical features, management of intensive care treatment, complications and mortality in children with meningitis treated in pediatric intensive care unit.*
Method: *Data of 47 patients who were followed-up in the pediatric intensive care unit between January 2006 and December 2014 with the diagnosis of meningitis were retrospectively reviewed. Patients were screened for demographic features, etiological and predisposing factors, physical examination and laboratory findings, treatment, prognosis, mortality rate, acute and chronic complications, Glasgow coma scale and pediatric mortality risk score.*
Results: *The age, sex distribution, hospitalization day, and chronic disease rate of aseptic meningitis and bacterial meningitis did not differ significantly. In bacterial meningitis, S. pneumoniae was detected in 12.5% of patients and N. meningitidis in 6.2% of patients. In aseptic meningitis, invasive ventilation, inotropic use rate and pediatric mortality risk score score were significantly lower than the bacterial meningitis (p=0.011, p=0.042 and p=0.043, respectively).*
Conclusion: *Early diagnosis, initiation of appropriate antibiotic therapy, and provision of necessary life support in life-threatening complications may reduce the need for pediatric intensive care unit, morbidity and mortality in meningitis patients. We believe that multicenter and prospective studies are needed to reduce sequelae and mortality of meningitis cases observed in pediatric intensive care unit.*

Keywords: *bacterial meningitis, aseptic meningitis, mortality, pediatric intensive care unit*

ÖZ

Amaç: *Bu çalışmada çocuk yoğun bakım ünitesinde tedavi edilen menenjit tanısı almış çocuk hastaların klinik özelliklerinin, yoğun bakım tedavi yönetiminin, komplikasyonların ve mortalitenin değerlendirilmesi amaçlandı.*
Yöntem: *Çocuk yoğun bakım ünitesinde Ocak 2006 ile Aralık 2014 tarihleri arasında menenjit tanısı ile takip edilen 47 hastaya ait veriler geriye dönük olarak incelendi. Hastalar demografik özellikler, etiyolojik ve hazırlayıcı faktörler, fizik muayene ve laboratuvar bulguları, uygulanan tedavi, prognoz, mortalite oranı, akut ve kronik komplikasyonlar, Glaskow koma skalası ve pediatrik mortalite riski skorlaması açısından tarandı.*
Bulgular: *Aseptik menenjit ve bakteriyel menenjit grubunda hastaların yaşları, cinsiyet dağılımı, yatış günü, kronik hastalık oranı anlamlı farklılık göstermedi. Bakteriyel menenjitte, hastaların %12,5'inde S. pneumoniae ve %6,2'sinde N. meningitidis saptandı. Aseptik menenjit grubunda invazif ventilasyon, inotrop kullanım oranı ve pediatrik mortalite riski puanı bakteriyel menenjit grubundan anlamlı olarak daha düşüktü (sırasıyla p=0,011, p=0,042 ve p=0,043).*
Sonuç: *Erken tanı, uygun antibiyotik tedavisinin başlanması ve hayatı tehdit eden komplikasyonlarda gerekli yaşam desteğinin sağlanması menenjitli hastalarda çocuk yoğun bakım ünitesi ihtiyacını, morbidite ve mortaliteyi azaltır. Özellikle çocuk yoğun bakım ünitesinde izlenen menenjit olgularının sekel ve mortalitesinin azaltılmasına ışık tutacak çok merkezli, daha fazla sayıda hasta içeren ve prospektif tasarımlı çalışmalara ihtiyaç olduğu kanısındayız.*

Anahtar kelimeler: *anatomi, vagus siniri, karotis arter, endarterektomi, kadavra çalışması*

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INTRODUCTION

Meningitis is an acute or chronic inflammatory disease caused by various microorganisms, and involving the pia and arachnoid membranes surrounding the brain and spinal cord. The disease is characterized by cellular and biochemical changes in the cerebrospinal fluid (CSF) and neurological findings as clinical manifestations. The fetiologic actors that cause meningitis can be bacteria, viruses, fungi or parasites [1]. *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* type b were found to be the most common agents of acute bacterial meningitis in our country [2]. Bacterial meningitis is less frequently seen thanks to routine vaccination programs against *S. pneumoniae* and *H.influenzae* type B and the introduction of conjugated meningococcal vaccines. Aseptic meningitis is more common in childhood and viruses are mostly responsible for etiology [3]. In 50-80% of cases with aseptic meningitis, enteroviruses have been reported as causative agents.

Other viral agents include viruses such as herpes simplex virus, Ebstein-Barr virus, varicella zoster virus, cytomegalovirus, adenovirus, rubella, mumps virus, and measles virus [4]. Diseases that cause aseptic meningitis include tuberculosis, leptospirosis, ricketsia and brucellosis [3]. Meningitis continues to be an important health problem due to death or sequelae in children. In order to reduce the development of complications in these patients, early diagnosis and effective treatment should be initiated without wasting time [5]. Neurological or hemodynamic deterioration caused by meningitis requires close follow-up of patients in the pediatric intensive care units (PICUs) in terms of the cardiorespiratory system disorders [6]. Most of the deaths in the hospital due to meningitis occur within the first 48 hours in the PICU [7]. In our study, we aimed to evaluate the clinical features, management of intensive care treatment, complications and mortality of the patients with meningitis in pediatric patient cohort treated in PICU.

MATERIAL and METHODS

This study was conducted in accordance with the principles of Helsinki Declaration after receiving the approval of the institutional ethics committee (ethics committee research approval number and date of decision: 2015/50 - 2015/05/08), in a nine-bed highly –advanced PICU with bedside echocardiography, plasmapheresis, hemodiafiltration. Nine mechanical ventilation facilities. The data of 47 patients who were followed-up with the diagnosis of meningitis between January 2006 and December 2014 were analyzed retrospectively. The patients were evaluated in two groups as acute bacterial meningitis and aseptic meningitis. The files were scanned in terms of demographic characteristics, etiological and predisposing factors, physical examination and laboratory findings, treatment, prognosis, mortality rates, acute and chronic complications, Glaskow coma scale (GCS) and Pediatric Risk of Mortality (PRISM) scores. Diagnosis of cases with acute bacterial meningitis was made based on cerebrospinal fluid (CSF) findings (turbid appearance, protein >100 mg/dL, CSF glucose <40 mg/dL, high leukocyte count, and polymorphonuclear leukocytes> 75%) and / or isolation of the pathogenic factor in culture. The diagnosis of tuberculous meningitis was made based on the clinical course of subacute onset, the detection of 100-500/mm^3 cells in CSF (lymphocyte dominancy), increased protein levels in CSF, and acid-fast bacilli (AFB) in CSF and fasting gastric juice, growth of *Mycobacterium tuberculosis* in CSF culture or the presence of basal arachnoiditis and tuberculoma as shown radiologically by magnetic resonance imaging (MRI). Patients meeting any one and several of these criteria were evaluated as tuberculous meningitis. [8]. The diagnosis of aseptic meningitis was made when the WBC counts in CSF were above 100-500/mm^3 with lymphocytic dominancy, the CSF protein at normal or close to normal levels, and the CSF glucose levels close to half or above of the blood glucose levels measured simultaneously [8].

Average, standard deviation, median, maximum, minimum, frequency and ratio values were used in the descriptive statistics of data. The distribution of variables was checked with Kolmogorov-Smirnov test. Independent sample- t test and Mann-Whitney U test were used in the analysis of quantitative data. In the analysis of qualitative data, chi-square test and when chi-square conditions were not met Fisher test were used. Statistical Package for Social Sciences "version 22.0 (IBM Corp., Armonk, NY, USA) program was used in the analysis.

Table 1. Demographic and clinical features of patients.

	RA patients (n=50)		Bacterial Meningitis			
	Mean±SD / N (%)	Median	Mean±SD / N (%)	Median	p	m
Age	5,9±4,1	5,4	4,5±4,3	2,6	0,153	X²
					0,012	
Gender						
Male	6 (27,3%)		16 (64,0%)		0,513	m
Female	16 (72,7%)		9 (36,0%)			
Hospitalization (days)	14,3±15,9	10,5	10,0±10,8	5,0	0,939	m
PRISM score	10,9±11,1	6,0	9,5±10,7	6,0	0,673	m
GCS	10,5±3,1	11,0	10,6±3,4	10,0	0,654	X²
Chronic disease	4 (18,2%)		7 (28%)			

m: Mann-Whitney U test, X²: Chi-square test (Fischer test)
GcS: Glaskow coma score, PRISM: Pediatric risk of mortality

Table 2. Evaluation of clinical and laboratory findings of patients.

	Aseptic Meningitis		Bacterial Meningitis		
Symptoms and findings	Mean±SD / N (%)	Median	Mean±SD / N (%)	Median	p
Fire	17 (77,3%)		24 (96,0%)		0,055 X²
Headache	9 (40,9%)		11 (44,0%)		0,831 X²
Vomiting	11 (50,0%)		17 (68,0%)		0,210 X²
Fontanel bulge	3 (13,6%)		7 (28,0%)		0,230 X²
Debris	1 (4,5%)		8 (32,0%)		0,017 X²
Blurring of Consciousness	12 (54,5%)		6 (24,0%)		0,032 X²
Convsulsion	10 (45,5%)		4 (16,0%)		0,028 X²
Diarrhea	2 (9,1%)		4 (16,0%)		0,479 X²
Acute Respiratory Failure	1 (4,5%)		1 (4,0%)		1,000 X²
Nape Hardness	11 (50,0%)		12 (48,0%)		0,891 X²
Kernig positivity	4 (18,2%)		6 (24,0%)		0,627 X²
Brudzinski positivity	1 (4,5%)		3 (12,0%)		0,611 X²
Antibiotic usage	11 (50,0%)		10 (40,0%)		0,491 X²
Blood findings					
White blood cell (WBC)	14,0±8,2	13,0	21,2±12,2	22,0	0,017 m
C-reactive protein	8,6±7,0	6,5	14,6±8,5	12,0	0,008 m
Neutrophil (NEU #)	72,5±18,1	77,0	74,9±18,6	84,0	0,353 m
Lymphocyte (LYM #)	17,8±13,8	16,0	17,2±16,5	9,0	0,455 m

m: Mann-Whitney U test, X²: Chi-square test (Fischer test)

RESULTS

The demographic and clinical features of the patients are given in Table 1. A total of 47 patients were included in our study (M/F: 22/25). In the aseptic meningitis and bacterial meningitis groups, the age, days of hospitalization and rate of chronic disease did not differ significantly between groups. There was no significant difference in GKS value, fever, headache, vomiting, fontanel swelling, rash, confusion, convulsion, diarrhea, acute respiratory distress, neck stiffness ratio, Kernig and Brudzinski test positivity, and empirical antibiotic use among the groups. In addition, WBC counts, neutrophils, lymphocytes did not differ significantly between the groups. While the CRP value and CSF protein were significantly lower in the aseptic meningitis group than in the bacterial meningitis group, the percentage of lymphocytes was significantly higher (p=0.008; p=0.012 and p=0.000, respectively).

In the bacterial meningitis group, while the CSF glucose and CSF glucose / blood glucose were lower than the aseptic meningitis group, the percentage of polymorphonuclear leukocytes was significantly higher (p<0.001, p<0.001 and p<0.001, respectively)

Table 3. Evaluation of the treatment methods of patients.

	Aseptic Meningitis		Bacterial Meningitis		
Need for steroids	N	%	N	%	P
Dexamethasone	10	45,5%	12	48,0%	0,861 X^2
Need for respiratory support					
Invasive ventilation	6	27,3%	9	36,0%	0,522 X^2
CVS Inotrop	5	22,7%	7	28,0%	0,679 X^2

X^2: Chi-square test (Fischer test)
CVS: cardiovascular system

Table 4. Comparison of the groups in terms of complication and prognosis.

	Aseptic Meningitis		Bacterial Meningitis		
Acute Complication	N	%	N	%	P
Hydrocephalus	2	9,1%	1	4,0%	0,593 X^2
Convulsion	2	9,1%	3	12,0%	0,747 X^2
Abscess	1	4,5%	1	4,0%	1,000 X^2
Diabetes insipitus (DI)	6	27,3%	1	4,0%	0,025 X^2
Prognosis					
Neuromotor disorders	1	4,5%	4	16,0%	0,204 X^2
Failure of breath	1	4,5%	1	4,0%	1,000 X^2
Death	4	18,2%	1	4,0%	0,116 X^2
Full recovery	15	68,2%	18	72,0%	0,775 X^2

X^2: Chi-square test (Fischer test)

(Table 2). In the groups, ophthalmoscopic findings of the fundus, computed tomography (CT) and magnetic resonance imaging (MRI) findings obtained before lumbar puncture (LP) were comparable between groups. In bacterial meningitis, *S. pneumoniae* was determined as the causative agent in 7 (28%) patients (growth in both blood and CSF cultures in three, and only in CSF culture in one patient), while in 5 (20%) patients, *N. meningitidis* was grown both in blood and CSF cultures. In 7 (31.8%) patients with aseptic meningitis, *M. tuberculosis* was considered as the causative agent, but only in two patients it was isolated in fasting gastric juice. There was no growth in blood and CSF cultures of patients who were followed up with tuberculous meningitis. Steroid use and oxygen utilization rates did not differ between groups. Noninvasive ventilation was not used in both groups. Invasive ventilation and frequency of inotrop use and PRISM scores in the aseptic meningitis group did not differ when compared with the bacterial meningitis group (p=0.522, p=0.667

and p=0.939, respectively). Continuous renal replacement therapy (DRRT) and plasma exchange rates were similar between groups (Table 3). Any significant difference was not observed between the groups in terms of acute complications and prognosis. All of five exited patients received the diagnosis of bacterial meningitis (Table 4).

DISCUSSION

Acute meningitis is one of the most serious infections in children. The main goal in acute bacterial meningitis is to establish diagnosis at an early stage, and to start effective treatment without wasting time to prevent complications [9]. Acute meningitis has a high risk of acute complications, mortality and long-term morbidity. In the studies performed, mean ages at the time of diagnosis of acute bacterial meningitis were found to be 4.8±4.1 years by Ceyhan et al. [10] and 3.4 years by Mongelluzo et al. [11]. In our study mean ages at diagnosis in acute bacterial, and

aseptic meningitis were 4.5±4.3, and 5.9±4.1 years, in accordance with the literature, respectively. In previous studies it has been reported that central nervous system infections are more common in men. Michos et al. [13] reported M/F ratio in bacterial meningitis as 1.79, while Harald et al [14] found the M/F ratios as 1.33 in bacterial, and 1.84 in aseptic meningitis and in aseptic meningitis, respectively Şensoy et al. [12], and Ceyhan et al. [10] from our country reported M/F ratios as 2.05, and 1.55 in aseptic meningitis, respectively. In our study, the M/F ratio was 1.78 in bacterial, and 0.37, in aseptic meningitis. Our results in bacterial meningitis are consistent with the literature, while in aseptic meningitis, male patients needed intensive care treatment less than girls.

In many cases, it is difficult to differentiate between bacterial and aseptic meningitis. Accurate diagnosis cannot be made in all patients by analyzing peripheral blood and CSF (such as CSF culture, blood culture, Gram staining, PCR, latex agglutination) [14]. Therefore, many researchers have developed a bacterial meningitis scoring (BMS) system [15,16]. If peripheral blood CRP level was <2 mg/dL Harald et al. used BMS in favor of aseptic meningitis, and if CSF protein level was >100 mg/dL then they used BMS in favor of bacterial meningitis. If glucose levels in CSF were <53 mg/dL, they used BMS scale scores in favour of bacterial meningitis. As a result using BMS system they differentiated 54 of 71 patients with viral meningitis from bacterial meningitis [14]. In our study, 25 (53.2%) patients were diagnosed with bacterial meningitis and 22 (46.8%) patients with viral meningitis based on clinical findings, CSF examinations, biochemical tests, CSF, and blood cultures. In our study, CRP <2 mg/dL was detected in only three patients who were followed up due to aseptic meningitis. Based on this data, since the CRP value is increased in bacterial and aseptic meningitis it was shown that the CRP value alone cannot be used for the differentiation between both groups. In our study, in 44% of patients with purulent meningitis, there was a history of empirical antibiotic use, and only in six (24%) of 25 patients bacterial growth was detected in CSF cultures. Harald et al. found bacterial growth in CSF cultures in 14 (66.6%) of 21 bacterial meningitis patients [14]. Ceyhan et al, observed bacterial growth in CSF culture of 41 (17%) out of 243 bacterial meningitis

patients [10]. The vaccination of our patients in whom S. pneumoniae was detected as the causative pathogen was performed with 13- serotype conjugated pneumococcal vaccine (CPV) in accordance with the Ministry of Health vaccination schedule. Identification of serotypes of pneumococcal isolates is significant in terms of determining the vaccine serotypes. Surveillance studies in the pediatric age group are also important to establish the correct vaccine serotype repertoire. Therefore, we believe that the CPV content should be updated based on the results of pneumococcal serotype surveillance studies.

Acute bacterial meningitis is also an important cause of death and neurological sequela in children in our country. Early diagnosis and appropriate antibiotic selection are the most important steps of treatment. In a previous study, the rate of acute complications due to meningitis was found to be 16% [17]. In our study, acute complications developed in 44% of children diagnosed with acute meningitis. This higher rate can be explained by frequent monitorization of thigh risk patients in PICU. Experiencing a convulsive attack in the acute phase of acute bacterial meningitis increases morbidity and mortality [18]. On the other hand, it has been shown that seizures seen at first admission or appear within the first four days do not have prognostic significance [19]. In our study, convulsion was the most frequently detected acute complication. Studies have shown that in acute bacterial meningitis and tuberculous meningitis, corticosteroid treatment performed half an hour before and four days after antibiotherapy reduces mortality, neurological sequelae and hearing loss in the long run [20,21]. In our study, 23 patients received corticosteroid therapy. The use of steroids in bacterial meningitis has become controversial in the literature over time. For this reason, a standard protocol regarding steroid use was not applied in our study. None of the patients had hearing loss, but one patient had vision loss, three patients had epilepsy, and five patients had neuromotor impairment. Taşkesen et al. reported the average length of hospital stay as 10.5 days [22]. Michos et al. [13] indicated the average length of hospitalization for aseptic meningitis as four days, Şensoy et al. [12] stated the average length of hospital stay as 6.2 days for aseptic meningitis. Although there is no statistical difference between the groups in terms of length of hospital stay, it is noteworthy

that the duration of hospitalization of patients with bacterial meningitis (average 10 days) was shorter than that of patients with aseptic meningitis (average 14.3 days).

PRISM III is a scoring system in which intensive care patients are evaluated in terms of mortality. The high score is related to the mortality and morbidity rate in patients. In our study, the mean PRISM score was 9.5 in patients with bacterial meningitis and 10.9 in aseptic meningitis. Invasive device (CCRT, plasmapheresis) was used more frequently in patients with bacterial meningitis than patients with aseptic meningitis. The mortality rates range from 1.4% to 47% in different series [5,23,24]. An average mortality rate of 4.5% has been reported in developed countries [25]. Our mortality rate was 10.6% and it was thought that the causative factor might be *M. tuberculosis* in four patients and *S. pneumoniae* was detected in one patient. While the pathogen was isolated in fasting gastric juice in two patients which thought to be the cause of *M. tuberculosis,* and the clinical findings and CSF analysis of the other two patients were compatible with *M. tuberculosis* meningitis. In a retrospective cohort study conducted in PICU, Folafoluwa et al. found the mortality rate as 7 percent. Abuhandan et al. found that the mortality rate was 2.2% in meningitis patients followed up in the pediatric service [26]. Wasier et al. found mortality rate as 49%, and sequelae 48% of 49 patients with pneumococcal meningitis [27]. In our study, three patients whose general condition was very poor at the time of admission were lost as a result of brain edema and two patients died of cerebral abscess. In our study, the reason for the high mortality rate compared to developed countries can be explained by the fact that the patients with high risk and low GKS scores are being hospitalized in our PICU, the delayed diagnosis and inadequate selection of initial treatment before hospitalization of the patients in the intensive care unit. In our study, any relationship was not found between age, gender, length of PICU stay, fever, meningial findings, CSF cell count, protein height, and complication(s). In their study Singhi et al., could not find a correlation between these factors and prognosis [7]. In our study, it was found that most of the deaths of inpatients due to meningitis occurred within the first 24-48 hours of PICU hospitalization.

Limitations of the study

The limitations of our study are its retrospective design, the absence of randomization and the small number of cases. On the other hand, to our knowledge, being one of the limited number of retrospective meningitis studies in PICU is the strength of our study.

CONCLUSION

Early diagnosis, initiation of appropriate antibiotic therapy and providing necessary life support in life-threatening complications may reduce the need for PICU stay, morbidity and mortality in patients with meningitis. In cases that should be followed in PICU, rapid and multidisciplinary approach by ICU of infectious diseases and pediatric intensive care are essential for the management of possible acute and chronic complications. We believe that there is a need for prospectively designed multicentre studies performed with greater number of patients that will shed light on the reduction of sequelae and mortality of meningitis cases, especially in PICU.

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Vagus Nerve Injury During Carotid Endarterectomy: A Cadaveric Study

Karotis Endarterektomi Sırasında Oluşan Vagus Siniri Yaralanması: Kadavra Çalışması

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ABSTRACT

Objective: Vagus nerve injury is one of the most feared and highly prevalent complications of carotid endarterectomy (CEA). The aim of this study is to demonstrate the bilateral positional variations of the common carotid artery (CCA), vagus nerve and internal jugular vein (IJV) inside the carotid sheath in postmortem cadaveric specimens.
Method: Carotid endarterectomy procedure was performed bilaterally step by step in 20 cadavers and every step was photographed. Positional variations of vagus nerve, CCA and IJV inside right and left carotid sheaths were evaluated.
Results: In all dissections anatomical relations between vagus nerve and vascular structures were identified. The right vagus nerve was positioned posteriorly, medially, and anteriorly to IJV and CCA in 8 (40%), 4 (20%) and 4 (20%) of the specimens, respectively. In 2 (10%) specimens right vagus nerve was posterior to the IJV and in 2 (10) specimens' right vagus nerve was positioned posterior to the CCA. The left vagus nerve was positioned anteriorly, centrally, and posteriorly to IJV and common carotid artery in 10 (50%),2 (10%) and 5 (25%) of the specimens, respectively. In 2 (10%) specimens left vagus nerve was positioned posterior to IJV. In 1 (5%) specimen the vagus nerve was located posterior to CCA.
Conclusion: In right and left anatomical relations between vagus nerve and vascular structures, considerable asymmetry was seen in anterior and middle positioning of vagus nerve. During CEA, taking this asymmetry into consideration is important to prevent possible cranial nerve injury complications.

Keywords: anatomy, vagus nerve, carotid artery, endarterectomy, cadaveric study

ÖZ

Amaç: Vagus sinir hasarı, karotis endarterektominin (CEA) en çok korkulan ve yüksek prevalans gösteren komplikasyonlarından biridir. Bu çalışmanın amacı postmortem kadavra örneklerinde karotid kılıfın içindeki common karotid arter (CCA), vagus siniri ve internal juguler ven (IJV)'nin pozisyonel varyasyonlarını göstermektir.
Yöntem: Karotis endarterektomi işlemi 20 kadavrada bilateral olarak (40) adım adım yapıldı ve her adım fotoğraflandı. Vagus Sinirinin sağ ve sol karotis kılıflarının içinde CCA ve IJV arasındaki pozisyonel varyasyonları değerlendirildi.
Bulgular: Tüm diseksiyonlarda vagus siniri ve vasküler yapılar arasındaki anatomik ilişkiler belirlendi. Sağ vagus siniri, örneklerin 8 (%40), 4 (%20) ve 4 (%20)'ünde sırasıyla IJV ve CCA'ya göre posterior, medial ve anterior yerleşimliydi. İki (n=2/10) örnekte sağ vagus siniri IJV'ye posterior yerleşimli olup, 2 (%10) örnekte sağ vagus siniri CKA göre posterior yerleşimliydi. Sol vagus siniri, örneklerin 10 (%50), 2 (%10) ve 5 (%25)'inde sırasıyla IJV ve CKA'e göre anterior, medial ve posterior olarak yerleşimliydi. Spesimenlerin ikisinde (n=2/ %10) sol vagus siniri IJV'ye göre posterior yerleşimliydi. Bir örnekte ise (n=1/%5) vagus siniri CCA'in posteriorunda yerleşikti.
Sonuç: Vagus siniri ve vasküler yapılar arasındaki sağ ve sol anatomik ilişkilerde vagus sinirin ön ve orta konumlandırılmasında belirgin asimetri görüldü. Bu asimetriye CEA sırasında dikkat edilmesi, olası sinir yaralanmaları komplikasyonlarını önlemek için önemlidir.

Anahtar kelimeler: anatomi, vagus siniri, karotis arter, endarterektomi, kadavra çalışması

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INTRODUCTION

Stenosis caused by atherosclerotic plaques in common carotid artery (CCA) and internal carotid artery (ICA) are common findings as is the case for other vascular structures. Carotid artery stenosis are responsible for 20-25% of all ischemic strokes [1]. Although risk increases when the level of stenosis exceeds 70%, some asymptomatic stenosis may need intervention if there are accompanying factors. Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are recommended in patients with symptomatic ≥50% stenosis or asymptomatic ≥70% stenosis [1]. Carotid endarterectomy is a conventional surgical technique to prevent stroke and is performed by vascular surgeons, cardiovascular surgeons and neurosurgeons.(2) Given the stroke prevalence and the accompanying disability caused by it, the CEA technique has become very important. Although CAS was considered an alternative when it was first performed in 1994, it still hasn't become the gold standard in stroke prevention. One of the major complications of the CEA technique is the cranial nerve injury [1,3]. Cranial nerve injury following CEA varies from 5% to 50% and vagus nerve injury following CEA reported between 1.5% and 35% [4]. Especially vagus nerve and its branches (the laryngeals), and hypoglossal nerve injuries may cause debilitating clinical syndromes.

Better understanding of the anatomy of vagus nerve and related structures is crucial to minimize the risk of injury during CEA. The relation of the nerves to the carotid artery and their common variations should be also known. In this study, we have shown step by step neuroanatomy of the CEA procedure, as well as the bilateral positional variations of the CCA, vagus nerve and internal jugular vein (IJV) inside the carotid sheath in postmortem cadaveric specimens. Furthermore, CEA and endovascular treatment methods are compared considering the recent studies in the literature.

MATERIAL and METHODS

CEA procedure was performed step by step on 20 formalin-fixed adult cadaveric specimens (40 sides). The specimens after routine procedures were fixed in 10% formaldehyde solution and photographs were taken of representative cases. Cadaveric dissections were performed by K.Y at the Skullbase lab, Barrow Neurological Institute. Dissections were made under the operating microscope (Carl Zeiss surgical Microscope Meditec AG, Oberkochen, Germany) with x6 and x40 magnifications. Conventional microneurosurgical instruments were used for dissections. Positional variations of vagus nerve, carotid artery and IJV inside right and left carotid sheaths were revealed.

Surgical Technique
Patient was laid in supine position with the head turned 45 degrees contralateral to the surgical intervention site. Incision was done 2-3 cm above the clavicle anteriorly along the sternocleidomastoid muscle (SCM), superiorly until 1.5-2 cm to the mastoid tip and posteriorly below 1cm of the mandibular angle. After the skin was incised, the platysma was split parallel to the skin incision. Anterior edge of the SCM and superior edge of the omohyoid muscle were identified at this point. The tip of the angle formed by the SCM and omohyoid muscle was directed toward the carotid artery. Trachea was retracted medially and SCM laterally. Surrounding tissues were dissected after the bifurcation was identified. The carotid bifurcation was exposed between 2 cm caudal to the bifurcation and cranially to the lower border of the digastric muscle. After dissections were completed vagus nerve, CCA and IJV were identified and CEA was performed (Figures 2 and 3). Possible positions of the vagal nerve relative to CCA and IJV are shown in a scheme (Figure 1). The positions and localisation of vagus nerve was defined as follows;
- Anteriorly between ICA and IJV
- Centrally between ICA and IJV
- Posteriorly between ICA and IJV
- Posterior to ICA
- Posterior to IJV

RESULTS

The relations of vagus nerve in both sides are summarized in Figure 1 and Table 1. In all dissections anatomical relations between vagus nerve and vascular structures could be identified. In 8 (40%) specimens the right vagus nerve was positioned posteriorly to IJV and CCA. In 4 (20%) specimens' right vagus
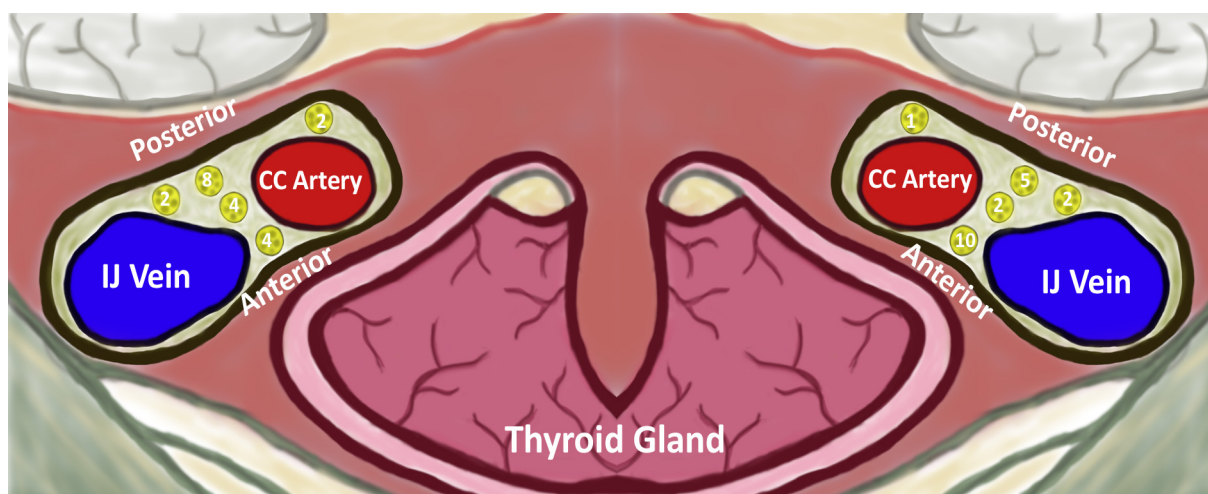
Figure 1. Schematic description of anatomical relations between vagus nerve (labelled with yellow points), common carotid artery and internal jugular vein.

Table 1. Anatomical relations between vagus nerve, common carotid artery and internal jugular vein.

Vagus Nerve	Between IJV and CCA			Posterior to IJV	Posterior to CCA
	Anterior	Middle	Posterior		
Left vagus nerve	10 (50%)	2 (10%)	5 (25%)	2 (10%)	1 (5%)
Right vagus nerve	4 (20%)	4 (20%)	8 (40%)	2 (10%)	2 (10%)

CCA: common carotid artery, IJV:ınternal jugular vein

nerve was positioned in the middle of the IJV and common carotid artery. In 4 (20%) specimens right vagus nerve was positioned anterior to IJV and CCA. In 2 (10%) specimens right vagus nerve was posterior to the IJV and in 2 (10%) specimens right vagus nerve was positioned posterior to the CCA.

The left vagus nerve was located anterior to IJV and common carotid artery in 10 (50%) specimens. The left vagus nerve was positioned in the middle of the IJV and common carotid artery in 2 (10%) specimens. In 5 (25%) specimens left vagus nerve positioned posterior to IJV and CCA. In 2 (10%) specimens left vagus nerve positioned posterior to IJV. In 1 (5%) specimen the vagus nerve was positioned posterior to CCA. In right and left side, a considerable asymmetry was seen in anterior and middle positioning of vagus nerve. and vascular structures.

DISCUSSION

Our study demonstrated that there was a considerable asymmetry between vagus nerve, CCA and IJV both at right and left sides. Carotid endarterectomy is a well-established safe procedure for treatment of carotid artery stenosis [5]. With CEA the risk of stroke and mortality could be avoided. Although CEA is regarded as a safe procedure, reported complications include cardiac and hemodynamic complications (myocardial infarction etc), central neurological complications (ischemic attack, intracerebral hemorrhage etc.) and cranial nerve injuries at surgical site. [1,5]. The injuries of cranial nerves related with CEA may be seen in hypoglossal nerve, facial nerve, vagus nerve and its branches and rarely in glosspharyngeal nerve [2,4,5]. The reported incidence of cranial nerve injury following CEA may be up to %50 which was reported differently across studies [4,5]. The most common cranial nerve injury following CEA was reported to involve hypoglossal nerve and the second is variably reported in the literature as facial nerve or vagus nerve [2-4]. Delicate dissection and prompt knowledge of cranial nerve tracts, their relations with surrounding structures and anatomical variations are the fundamental steps for preventing cranial nerve injury during CEA.
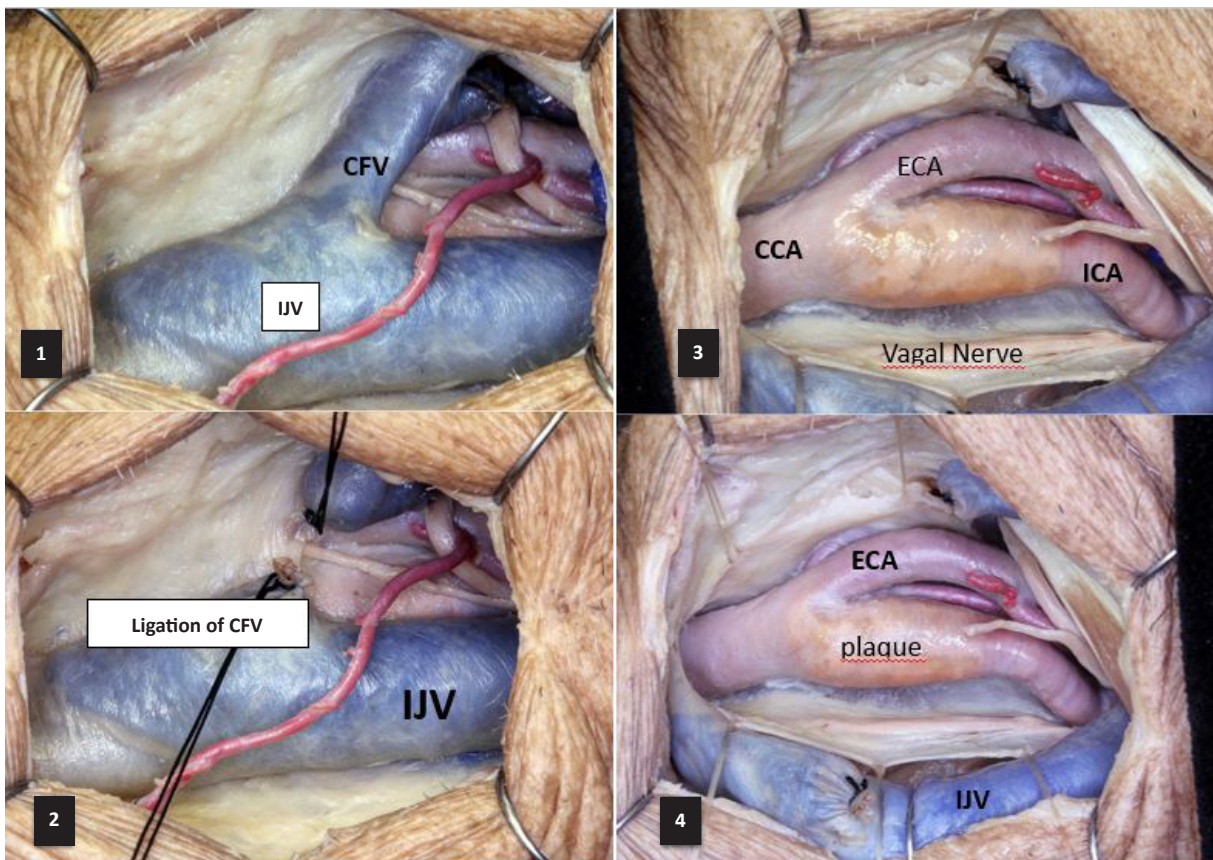
Figure 2. The dissection steps of carotid endarterectomy (continues in Figure 3).

2.1. The first encountering vessel is the internal jugular vein and branch of superior thyroid artery. This vein is located lateral to the internal carotid artery. C the common facial vein (CFV), hypoglossal nerve and its descending branch that can be sacrified.
2.2. We see the ligation of the common facial vein. The carotid artery comes into view.
2.3. After ligation of facial vein , bifurcation of common carotid artery (CCA), atheromatous plaque of internal carotid artery (ICA), External carotid artery (ECA), hypoglossal nerve, vagal nerve come into view
2.4. Closer view of the same anatomic structure seen in Figure 1.3

During the CEA, vagus nerve injury is one of the most feared and highly prevalent complication that was reported up to 35% of the cases [2,4]. Unilateral damage to vagus nerve or recurrent laryngeal nerve can be asymptomatic, however if bilateral carotid reconstruction is planned the risks become more prevalent. Direct injury to the vagus nerve or indirect injury to the recurrent laryngeal branch of the vagus nerve due to direct or retraction can cause hoarseness and loss of cough mechanism due to paralysis of the ipsilateral vocal cord. Bilateral injuries can lead to airway congestion and can be life-threatening [4]. Therefore, in a surgical procedure, it is very important to know the relation of the vagus nerve with its surroundings and its positional anatomy inside the carotid sheath. Numerous studies have been done reporting the variational anatomy of the cervical vagus nerve [6-9].

Usually vagus nerve lies between IJV and CCA inside the carotid sheath [3,10]. However vagus can be seen in anterolateral, and posterolateral to the CCA or medial to IJV. In an anatomical study Lo et al. dissected 36 cadavers to detect the course of vagus and hypoglossal nerve in 67 carotid specimens [11]. In itsmost common form, the vagus nerve was located posterior to the carotid bifurcation in 60% of the subjects. Vagus nerve was also reportedly located at posterolateral (36%), posteromedial (3%), and anterolateral to carotid bifurcation (1.5%). The relation between vagus nerve and CCA was found to be asymmetrical in 17 out of the 31 cadavers without predominance to either side [11]. In our study, it has been shown that the position of the vagus nerve showed asymmetry inside the carotid sheath on each side. We have shown that right vagus was anteriorly posi-
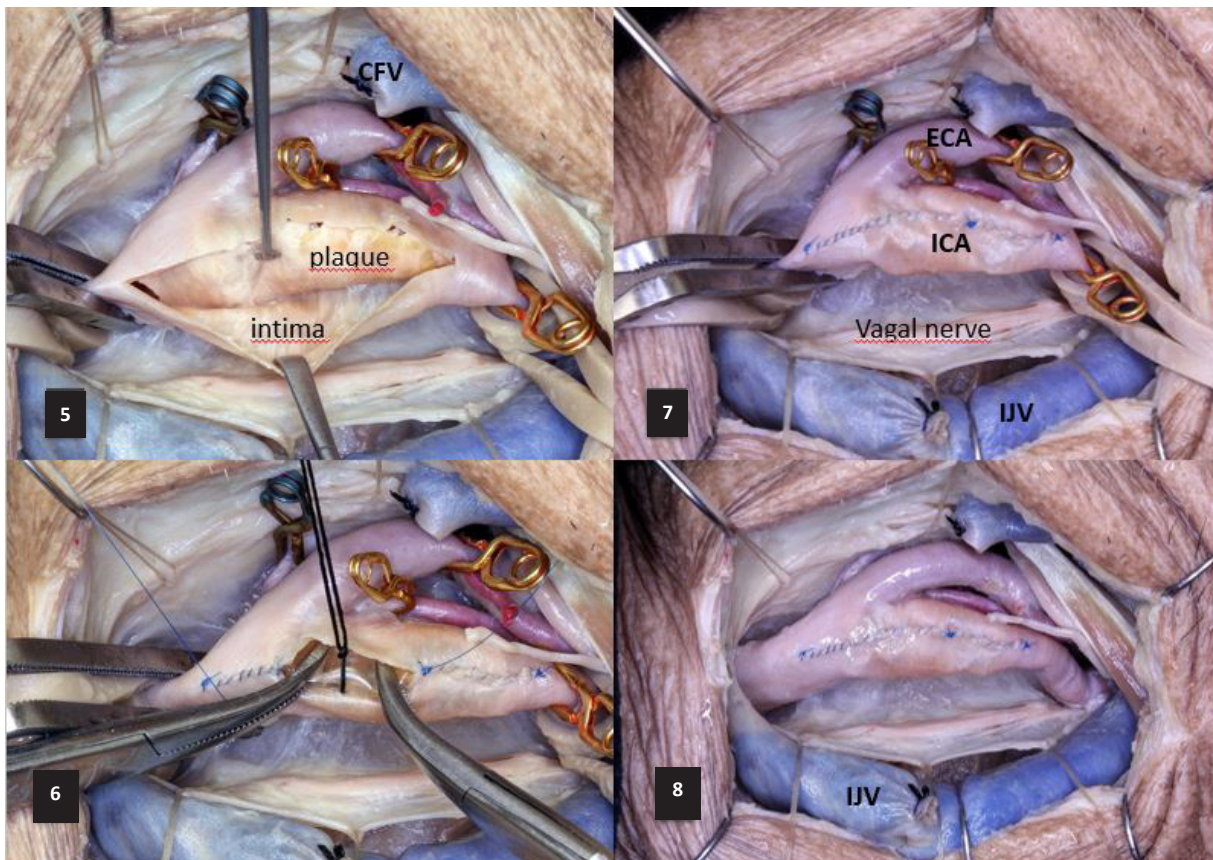
Figure 3. The dissection steps of carotid endarterectomy.

3.5. Procedure of CEA; Clipping order; ICA, CCA, ECA; Dissection of plaque from intima of ICA
3.6. Closing Stage: After the dissection of plaque, CCA and ICA are closed with 6/0 prolene sutures.
3.7. Closing stage is completed but still clipping
3.8. All Clips removed removed. Removing order: ECA , CCA, ICA

tioned closer to midline when compared with the left side and its posterior position.

The consensus on the anatomical position of the vagus nerve inside the carotid sheath is its being in-between the CCA and IJV [10]. In this study we have shown the positional variance of the vagus nerve in axial plane as anterior middle and posterior position in between the CCA and IJV and posterior to CCA or IJV. In our anatomical findings, it was observed that the left side vagus nerve was mostly localized anterior to the carotid sheath, and the right side vagus nerve was located behind the sheath. Therefore, considering these findings, it can be interpreted that a risk of direct injury to the vagus nerve or indirect injury to the recurrent laryngeal nerve is greater during a CEA procedure performed on the left side. Therefore anatomical variations should be kept in

mind while planning a procedure on this side. Classical CEA approach to the right side can be considered safer for the right side. A more lateral approach such as a retrojugular approach can be considered instead of a classical antejugular approach for a left sided procedures depending on these findings [12]. On the other hand, since the sample size is low in our study, further studies on the variations of the vagus nerve are required to show the least risky approach method for the CEA procedure. Recurrent laryngeal nerve (RLN) rooted from the vagus nerve is also at risk during CEA. Direct trauma to the RLN is unusual however, if a trauma (sharp, blunt, thermal, etc.) to the vagus nerve occurs; fibers inside the vagus nerve could be damaged. A non-recurrent laryngeal nerve which occasionally arises from the vagus nerve near the carotid bifurcation should be also kept in the mind (6%) [4,9,12].

In carotid endarterectomy staples had always been used in the treatment for carotid stenosis. However, since the treatment modalities of carotid balloon angioplasty and stenting have been developed the debate abouıt the superior treatment has arisen. There has been a number of randomized trials as well as ongoing ones to answer the question of "Will carotid stenting take the place of carotid endarterectomy?" However, the studies have been the source of more debate. It should be more appropriate at this point to suggest that studies exploring the question of the treatment method are better suited for each patient individually, rather than an end-all treatment for the carotid stenosis entity [13,14].

If the patient is symptomatic or asymtomatic, indications and treatment remain controversial. Despite that debate, CEA is still accepted to be the most efficient intervention to decrease the risk of stroke due to carotid artery stenosis [14,15].

The carotid endarterectomy is a surgical modality with the inherent risk of general anesthesia and progressive increase in operative risk on recurrent operations due to simple postoperative fibrosis. The carotid balloon angioplasty and stenting on the other hand is an operation done with local anesthesia, which inherently be better suited for patients with multiple comorbidities [14,16]. By deconstructing the two modalities down to its basics lets us see how the patient groups for the two treatments differ. Despite group randomization may be well done in a study, we could tell from certain factors which treatment protocol could be better for a specific patient. Therefore, the inclusion criteria for the studies must be well adjusted to account for the patient group that fall in the grey area between these boundaries [17,18].

It should also be kept in mind that both modalities are surgical treatment methods. In other words, the surgical expertise plays a major role in the outcome rates of both treatment methods. This phenomenon leads to a lower reproducibility in the treatment methods. The variations in the outcome rates regardless of the treatment method could lead to one option better in a one well organized randomized trial and another in the next [16,17,19].

Another important point about this treatment methods is that debate involves the asymptomatic patient group despite the level of stenosis [20]. It is important to work on the indications for each treatment depending on both the stenosis level and whether if the patient is symptomatic or not. Despite the treatment method, justifying the risk for the operation must be the principal issue. Risk- benefit assessment should be carefully done in all situations regardless of the study which brings a whole new set of variables in the design of the randomized studies. Stenting is comparably a new treatment and is highly defendant on the quality of the materials used as well [17,19]. The ongoing advances in the material engineering may prove that although stenting is doubtful in the long run, the carotid endarterectomy may not be in the same point versus stenting in the near future.

There are various mechanism of vagal nerve injury during CEA. Usually it is caused by direct trauma to the vagal nerve by retraction, stretch, dissection, excessive manipulation of the carotid sheath, especially in the posterior, misplacement of the clamps or bipolar coagulation [21].

Some specific measures are available in order to avoid vagal nerve injury Careful separation of the vagus nerve from the carotid artery in carotid dissection prevents injury to the vagus nerve during carotid clamping.The dissection also needs to be closer to CCA and IJV. Besides carotid arteries should not be overmanipulated. When applying sharp retractors, care must be given to deep surgical planes (tracheoesophageal grove) to avoid possible vagal nerve nerve and RLN injuries. You have to avoid vagal nerve injury , and be aware of applying clamps on CCA/ICA. Coagulation should be used in appropriate low setting and direct and careful coagulation have to be preferred especially when coagulating anatomical structures close to the CCA and IJV [4,5,21,22].

CONCLUSION

Our study provides a reliable anatomical knowledge on vagus nerve for CEA. A considerable asymmetry was seen in anatomical relations between vagus nerve, and vascular structures as CCA and IJV.on both sides, During surgery defined considerable asymmetry should be taken into consideration to pre-

vent possible complications. In our study right side was regarded safer than the left one in terms of vagal nerve injury.

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Original Article

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Multi-Purpose Dynamic Use of Right Subcostal Trocar in Laparoscopic Sleeve Gastrectomy: Retrospective Analysis of a Single Center Experience

Laparoskopik Sleeve Gastrektomide Sağ Subkostal Trokarın Çok Amaçlı Dinamik Kullanımı: Tek Merkez Deneyiminin Retrospektif Analizi

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ABSTRACT

Objective: It is important to prevent exploration difficulties caused by the presence of fat and hypertrophic liver in obese patients and provide a good surgical field of vision. Recently, various liver retraction techniques have been described for laparoscopic procedures. We aimed to assess outcomes of a multi-purpose dynamic use of right subcostal trocar in laparoscopic sleeve gastrectomy.

Method: All patients who underwent laparoscopic sleeve gastrectomy from January 2016 to December 2017 were determined prospectively. The data were retrospectively reviewed.

Results: Five hundred and seventy-six patients were included in the study. Average age was 38.9 years, average body weight 130.8 kg and average body mass index (BMI) 47.4 kg/m². Complications such as bleeding, leakage and stenosis were observed in 6,7 and 6 patients, respectively. There were no significant change of the serum liver enzymes in both preoperative and postoperative periods. No additional retractor was required for liver retraction in any of the cases. None of our patients experienced any complications related to the methods described in the perioperative period.

Conclusion: Right subcostal trocar in laparoscopic sleeve gastrectomy for liver retraction can be successfully used without risks of postoperative morbidity and clear inspection of the surgical field with traction of the respective area. There is a need for long-term outcomes.

Keywords: bariatric surgery, laparoscopic surgery, liver retraction, sleeve gastrectomy

ÖZ

Amaç: Obez hastalarda yağ ve hipertrofik karaciğerin varlığından kaynaklanan araştırma zorluklarını önlemek ve iyi bir görüş alanı sağlamak önemlidir. Son zamanlarda, laparoskopik prosedürler için çeşitli karaciğer retraksiyon teknikleri tanımlanmıştır. Biz, laparoskopik sleeve gastrektomide sağ subkostal trokarın çok amaçlı kullanımının sonuçlarını değerlendirmeyi amaçladık.

Yöntem: Ocak 2016 ve Aralık 2017 tarihleri arasında laparoskopik sleeve gastrektomi uygulanan tüm hastalar prospektif olarak belirlendi. Veriler geriye dönük olarak incelendi.

Bulgular: Beş yüz yetmiş altı hasta dahil edildi. Ortalama yaş 38.9 idi. Ortalama vücut ağırlığı 130.8 kg ve ortalama vücut kitle indeksi (VKİ) 47.4 kg. Kanama, kaçak ve darlık gibi komplikasyonlar sırasıyla 6,7 ve 6 hastada gözlendi. Preoperatif ve postoperatif dönemde serum karaciğer enzimlerinde anlamlı bir değişiklik olmamıştır. Hiçbir olguda karaciğer retraksiyonu için ek retraktör gerekmedi. Peroperatif dönemde tarif edilen yöntemle ilgili komplikasyon görülmedi.

Sonuç: Karaciğer retraksiyonu için laparoskopik sleeve gastrektomide sağ subkostal trokar kullanımı postoperatif morbidite riski olmadan ve ilgili alanın traksiyonu ile açık görüş başarıyla tamamlanabilir. Uzun vadeli sonuçlara ihtiyaç vardır.

Anahtar kelimeler: bariatrik cerrahi, laparoskopik cerrahi, karaciğer retraksiyonu, sleeve gastrektomi

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INTRODUCTION

Many bariatric procedures are routinely performed laparoscopically. A major challenge during surgery is the inability to achieve adequate inspection of the surgical field due to interference of the liver, especially during upper gastrointestinal surgery. It is important to overcome this challenge, as it is essential to prevent exploration difficulties caused by the presence of fat and hypertrophic liver in obese patients and provide a good field of vision. Recently, various liver retraction techniques have been described for laparoscopic procedures such as cholecystectomy and stomach resection [1]. Although mechanical retractors have traditionally been used to retract the liver, their use necessitates additional trocar entry. In response, new techniques have been developed in which the retractors are placed intracorporeally [1-4]. However, none of them has become known as a standard technique because each has advantages and disadvantages.

The aim of this study is to assess outcomes of a multi-purpose dynamic use of right subcostal trocar in laparoscopic sleeve gastrectomy (LSG) by emphasizing weight loss and complications.

MATERIALS and METHODS

The study included 576 patients with LSG performed from January 2016 to December 2017. The study was permitted by the local ethics committee. Prospectively-collected patient data were retrospectively reviewed.

Inclusion criteria were as follows:age 18 -65 years,baseline body mass index (BMI) 40 kg/m2 or BMI of 35 kg/m^2 in the presence of additional comorbidity and failure of conservative treatment for 2 years.

Preoperatively gender, age, BMI (kg/m^2) and weight (kg), duration of surgery (min), and hospitalization, and postoperative complications were collected. Follow-up of patients was performed at 1, 6, 12, months after surgery. Liver function tests were performed by measuring the levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) preoperatively and on first postoperative day. Weight loss(kg), BMI variation, percentage of excessive weight loss (EWL) and mortality were recorded.

Surgical technique

After placing the patient in the 30º reverse-Trendelenburg position, we directly inserted a 10-mm trocar approximately 10 cm below the xiphoid process and 1 cm lateral to the midline. Then we inserted four trocars (5 mm to the right subcostal, 15 mm to the right midclavicular 5 mm to the left subclavicular, and 5 mm to the left subcostal line) into the abdomen under direct vision, forming a concave cocnfiguration. By inserting a laparoscopic 5mm atraumatic grasper through the right subcostal trocar, we achieved superior traction of the stomach along the large curvature, which resulted in retraction of the liver (Figure 1). The addition of this traction maneuver mobilized greater curvature of the stomach by transecting the gastrocolic ligament and short gastric vessels. With the aid of the same instrument, we held the free side of the stomach fundus to achieve traction toward the liver and upper abdominal wall (Figure 2). With this maneuver, we achieved both retraction of the liver and exploration of posterior wall of the stomach i and also left hand of the surgeon was freed.

Figure 1. Superior traction of the stomach along the large curvature.

Figure 2. Traction of fundus and dissection of hiatus.

Under wide and clear vision, we performed hiatus dissection until the left crus was exposed and the stomach fundus was completely released. To release the distal part of stomach, we held the free side of the antrum in a similar manner and tracted it to reveal the hepatoduodenal ligament, duodenum, and distal part of the stomach. Then we mobilized the distal part of the stomach up to the pylorus (Figure 3). Under the guidance of 36-F bougie, we introduced an articulating linear cutting stapler (suture length 60 mm, staple height 4.8 mm; Endo GIATM, Covidien, Norwalk, CT, USA) starting 2 cm proximal to the pylorus. During this step we used the right subcostal trocar for liver retraction (Figure 4). After the first 2 fires, we used 3.5 mm stapler loads (EndoGIATM, Covidien, Norwalk, CT) to complete the stomach dissection along the bougie up to the angle of His. After the stomach was completely separated, we checked the stapler line and the separated omentum for hemostasis. All procedures were performed fully laparoscopically by two experienced surgeons using the same standard technique. For all techniques, anastomosis or stapler lines were checked with methylene blue to inspect anastomotic leaks.
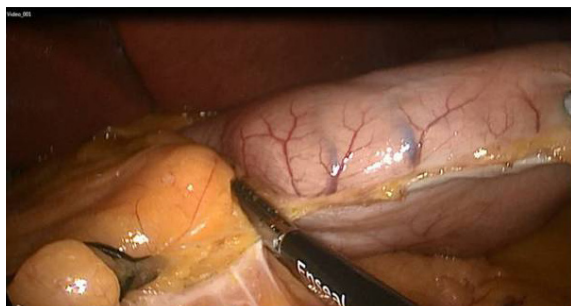
Figure 3. Traction of antrum and release of the distal stomach.

Figure 4. Retraction of the liver during stapling.

RESULTS

Of the 576 consecutive patients we examined, 437 were female (75.8%). The mean age was 38.9 years, the mean body weight 130.8 kg (range 94–240), and mean body mass index (BMI) 47.4 kg/m2 (Table 1). Mean duration of surgery was 75 minutes and hospital stay 4 days. Complications such as bleeding, leakage and stenosis are shown in Table 2.

Table 1. Demographic data in the preoperative period.

Variable	Value	(Interval)
Gender (male/female)	139/437	-
Age (years)	38,9	(19-63)
Weight (kg)	130,8	(94-240)
BMI (kg/m^2)	47,4	(40-106)

BMI: body mass index

Table 2. Surgery outcomes of patients.

Variable		Value
Operation time (minutes)		75.22±21.65
Hospital stay (days)		4.07±1.50
Complications (n)	Leak	7
	Hemorrhage	6
	Stenosis	6

BMI: body mass index

There were no significant change of the serum liver enzymes during both preoperative and postoperative periods (p>0.05) (Table 3). The mean weight loss in the postoperative one-year period was 43.8 kilograms (22-80). Postoperatively, mean BMI and EWL % values are indicated in Table 4. In 105 (87.5%) patients, we achieved satisfactory EWL % values. There was no mortality in study group.

Table 3. Preoperative and postoperative level of serum liver enzymes.

	Preoperative	Postoperative	P
ALT (IU/L)	21.8±16.7	28.2±13.7	0.84
AST (IU/L)	25.2±17.6	31.8±22.1	0.91

ALT: alanine aminotransferase, AST: aspartate aminotransferase

Table 4. Postoperative follow-up parameters.

Variable	Value
Weight loss(kg)	43.8 (22-80)
BMI (kg/m^2)	32.1 (23-55)
EWL (%)	62.9 (30-101)

BMI: body mass index, EWL: excessive weight loss

We did not require any additional retractors to assist with liver retraction during any of the operations. None of our patients experienced any complications related to the methods described in the perioperative period nor elevations in liver function parameters in the postoperative period.

DISCUSSION

Unimpeded observation of the small and large curvatures of the stomach as well as the hiatus is necessary for safe and effective performance of all bariatric procedures. For this purpose, Nathanson, fan-shaped, and snake mechanical retractors of various shapes and sizes have been used in laparoscopic upper gastrointestinal and bariatric surgeries to retract the left lobe of the liver and provide a better field of view [1]. Although mechanical excision through the subxiphoid approach provides a good visual field, it has potential side effects, including postoperative pain, wound complications, and iatrogenic liver injury [1].

Several alternative methods of laparoscopic surgery are described in the literature. In the Istanbul technique, a Penrose drain attached to two silk sutures is placed under the lateral segment of the liver to serve as a "hammock" [2]. In another technique two 4 × 4 gauze pads are folded and then threaded using a 2-0 polypropylene monofilament suture to create a makeshift traumatic support for liver suspension [3]. Although both techniques provide non-traumatic hanging of the liver, the hammock and gauze pads must be manually made, lengthening surgical time. In a technique used to hang the liver using the percutaneous method, a 15 cm Veress needle covered with a 16- to 18-French nasogastric tube or drainage tube is inserted into the abdomen from the subxiphoid area to retract liver. Although this method reduces the need for additional incision, trocars, and retractors, it fails to provide adequate retraction of a hypertrophic liver [4].

Based on our clinical experience, we developed a new method of retraction in laparoscopic sleeve gastrectomy (LSG) using a multi-purpose right subcostal trocar. Use of this method allows dynamic retraction of the liver and traction of the stomach during LSG surgery. When used with a laparoscopic 5mm atraumatic grasper, inserted in the right sub-

costal region and manipulated differently at each step of surgery, our method permits clear inspection of the hiatus.

Use of our multi-purpose subcostal trocar technique overcomes these challenges in gfavour of successful LSG surgery. One advantage is that it achieves liver retraction in patients with a BMI as high as 106 kg/m2 with severe hepatomegaly, which has resulted in successful surgery in our patients with this condition. Contrary to the results of Tamhankar et al. [5], use of our method prevents liver deterioration by achieving dynamic liver retraction via application of brief periods of pressure to different parts of the liver, which is enabled by the ability to maneuver the surgical instrument as necessitated for this reason, our patients did not experience any change in liver function, as evidenced by liver function tests performed in the early postoperative period. It facilitates manipulation of the instrument during repositioning, so any additional trocars for liver retraction are not required decreasing the risk of intraoperative complications.

In conclusion, by allowing us to achieve liver retraction at every stage of surgery, permitting clear inspection with traction of the respective area, use of our method facilitates more efficient and safe dissection and LSG surgery.

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Bone Mineral Density in Patients With Early- Onset Rheumatoid Arthritis[§]

Erken Başlangıç Romatoid Artritindeki Hastalarının Kemik Mineral Yoğunluğu

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ABSTRACT

Objective: Rheumatoid arthritis (RA) is a chronic inflammatory and destructive joint disease that affects 0.5-1% of the world's population and commonly leads to significant disability and consequent impairment of quality of life. Osteoporosis is an early and common feature in RA and occurs during the course of the disease as extra-articular manifestation of rheumatoid arthritis, which may result in increased risk of fractures, morbidity, and mortality. The aim of this study was to evaluate changes in bone mineral density in patients with early- onset rheumatoid arthritis including its correlation with disease activity.
Method: Ther study was performed with 50 patients diagnosied as early- onset rheumatoid made less than two years ago n the Private Clinic "Rheuma", who fulfilled the diagnostic criteria of American College of Rheumatology/ European League Against Rheumatism and 30 healthy volunteers as controls. Bone mineral density of these patients was measured at lumbar spine and hip by using dual energy x-ray absorptiometry scan (DEXA Stratos 800). Demographic and clinical data including age, gender, BMI, menstrual status, disease duration, laboratory tests, and disease activity scale (DAS28) scores were collected.
Results: From a total of 50 patients with RA, 36 were females and 14 were males with an overall mean age of 27-57 (33.7±7.87 years), fulfilling ACR/EULAR Criteria. The patients with RA, had osteoporosis (16%), osteopenia (65%) and normal BMD (30%) values. In the group of RA patients with osteoporosis had higher disease activity scores (DAS-28) without any statistically significant correlation compared to RA patients with normal BMD values or osteopenia.
Conclusion: Patients with RA are more likely to have bone loss compared to normal age subjects. Lower BMD values were found in patients at earlier stage of the rheumatoid arthritis with higher disease activity. Dual energy x-ray absorptiometry is an important tool to assess BMD in early RA patients.

Keywords: rheumatoid arthritis, osteoporosis, DAS-28, BMD

ÖZ

Amaç: Romatoid artrit (RA), dünyadaki popülasyonun% 0,5-1'ini etkileyen ve genellikle yaşam kalitesinde önemli bir sakatlığa ve bunun sonucunda bozulmaya neden olan kronik bir enflamatuar ve yıkıcı eklem hastalığıdır. Osteoporoz RA'da erken ve yaygın bir özelliktir. Hastalığın seyri sırasında romatoid artritin ekstra-artiküler belirtisi olarak ortaya çıkar ve bu da kırık, morbidite ve mortalite riskinde artışa neden olabilir. Bu çalışma, erken başlangıçlı romatoid artritli hastalarda hastalık aktivitesi ile korelasyonu da dahil olmak üzere kemik mineral yoğunluğu değişikliklerini değerlendirmeyi amaçlamaktadır.
Yöntem: Örnek erken başlangıçlı romatoid olan 50 hastadan oluşmaktadır. Özel Klinik "Romatoloji"de iki yıldan daha az olan artrit, Romatoloji / Amerikan Romatoloji Koleji / Romatizmaya Karşı Teşhis Kriterleri ve 30 sağlıklı gönüllü kontrolör olarak yerine getirildi. Bu hastaların kemik mineral yoğunluğu lomber omurga ve kalçada çift enerjili x-ışını absorpsiyometri taraması (DEXA Stratos 800) ile ölçüldü. Demografik ve klinik veriler yaş, cinsiyet, BKİ, adet durumu, hastalık süresi, laboratuvar testleri ve hastalık aktivite ölçeği (DAS28) gibi toplandı.
Bulgular: RA'lı toplam 50 hastadan 36'sı kadın, 14'ü ACR / EULAR kriterlerini karşılayan ortalama yaş 27-57 (33.7±7.87 yıl) idi. RA'lı hasta grubunda % 16'sında osteoporoz, %65'inde osteopeni ve %30'unda normal KMY vardı. Osteoporozlu RA hasta grubunda daha yüksek hastalık aktivite skoru (DAS-28) bulundu ve normal BMD ya da osteopeni olan RA hastalarına göre istatistiksel olarak anlamlı bir ilişki yoktu.
Sonuç: RA hastalarının normal yaştaki deneklere göre kemik kaybı yaşama olasılığı daha yüksektir. Bulgular, romatoid artritin erken evrelerinde, hastalık aktivitesi yüksek olan hastalarda düşük KMY olduğunu göstermektedir. Erken RA hastalarında KMY'yi değerlendirmek için çok önemli bir araç çift enerjili x-ışını absorpsiyometrisi olarak kabul edilir.

Anahtar kelimeler: romatoid artrit, osteoporoz, DAS-28, BMD

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory and destructive joint disease, which affects about 0.5–1% of the population in the world. It is the most common form of chronic inflammatory arthritis and in many cases it causes joint damage and physical disability. It may also result in a variety of extra-articular manifestations, such as fatigue, formation of subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities [1]. As an inflammatory disease, rheumatoid arthritis changes the biomechanical properties of bones, which leads to the alterations in bone components through the increased production of pro-inflammatory cytokines [2]. Some studies have found that disease duration, seropositivity for anti-CCP, and rheumatoid factor (RF) are associated with bone loss in RA patients [3]. Osteoporosis is an early and common feature in RA. It is present during the course of the disease as extra-articular manifestation of rheumatoid arthritis, which may lead to increased risk of fractures, morbidity, and mortality [4]. The National Osteoporosis Foundation (NOF) and International Society for Clinical Densitometry (ISCD) have recommended dual-energy x-ray absorptiometry (DEXA) testing for women, who are over 65 years old, for patients who have fractures after the age of 50 or if they suffer a fragility fracture, patients on chronic glucocorticoid therapy, and people at high risk of low bone mass, bone loss or fracture, as well as for patients with RA [5]. Several studies have found an increased risk of bone loss in patients with rheumatoid arthritis. Patients with rheumatoid arthritis are at increased risk of osteoporosis for various reasons. Thus, to contribute to knowledge development, this study aims to evaluate bone mineral density changes in patients with early -onset rheumatoid arthritis, including its correlation with DAS-28 scores.

MATERIAL and METHODS

Study Population: This research is a cross-sectional case- control study. The sample comprises of 50 patients with early- onset rheumatoid arthritis (diagnosed within less than 24 months after its onset) and 30 healthy volunteers as controls. All of these patients fulfilled the American College of Rheumatology/European League Against Rheumatism EULAR/ACR criteria for RA [6]. They were recruited in Private Clinic "Rheuma" in Kosovo. For this study, informed consent was obtained from patients included in this study. DAS-28 scores were measured in order to evaluate RA disease activity. DAS-28 scores were rated as follows: ≤2.6, disease remission; 2.6-3.2, low disease activity; 3.3-4.9 , moderate disease activity, and >5.1, severe disease activity [7]. Functional class assessment was conducted by using a validated version of the health assessment questionnaire (HAQ) [8]. BMDs were measured for all RA patients at Private Clinic "Rheuma" through dual energy x-ray absorptiometry scan (DEXA-Stratos800) at lumbar spine (L1-L4) and proximal femur. World Health Organization (WHO) was used as a basis to diagnose osteoporosis. Osteopenia is defined with BMD between -1.0 SD and -2.5 SD and osteoporosis below -2.5 SD [9]. Laboratory test were conducted, comprising of a full blood count (CBC), erythrocyte sedimentation rate (ESR, mm/hour), C-reactive protein (CRP, mg/dL), full blood chemistry, including renal and liver function tests, rheumatoid factor (RF IgM, U/L), and anticyclic citrullinated peptide (antiCCP, u/ml).

Statistical Analysis: The Statistical Program for Social Sciences (SPSS) was used to analyze the data by expressing values as mean and standard deviation. The unpaired t-test for numerical variables was used to analyze the differences between two groups. Categorical variables were analyzed using chi-square test. Spearman correlation test (r) was used for correlations. P values of >0.05, were nonsignificant if P values ware < 0.05, they were considered to be significant predictors. While P values of <0.001 denoted high degrees of significance.

RESULTS

From a total of 50 patients with RA (Group 1), 36 were females and 14 were males with a mean age of 33.7±7.87 (range, 27-57) years with a mean disease duration of 15.3±8.87 months fulfilling ACR/EULAR criteria. The healthy group of 30 controls (Group 2) comprised 21 females (70%) and 9 (30%) males, with a mean age of 37.3±6.37 (range, 25-51) years. In Group 1, 15 (30%) and in Group 2, 6 (20%) study participants were smokers. Thus, Table 1 presents demographic data, DAS-28 scores, HAQ scores, and results of laboratory tests used in the study.

Table 1. Demographic, clinical, and laboratory data of patients with RA versus healthy controls.

Variables	Ra subjects (n=50)	Controls (n=30)	P value	Significance
Age (years) mean ±SD	33.7±7.87 (27-57 years)	37.3±6.37 (25-51 years)	>0.05	Nonsignificant
Gender				
Female	36	21 (70%)	>0.05	Nonsignificant
Male	14	9 (30%)		
Smoking				
Yes	15 (30%)	6 (20%)	>0.05	Nonsignificant
No	35 (70%)	14 (80%)		
Disease duration mean ±SD and range (month)	15.3±8.87			
DAS-28Remission (≤2.4)	6/50 (12%)			
Mild disease activity (2.5-3.6)	5/50 (10%)			
Moderate disease activity (3.7-5.5)	29/50 (58%)			
Severe disease activity (>5.5)	10/50 (20%)			
HAQ				
0–1 (mild disability)	35/50 (70%)			
1–2 (moderate disability)	10/50 (20%)			
2–3 (severe disability)	5/50 (10%)			
ESR mean ±SD	61.4±27 (14-110)	10±4	<0.001	Highly Significant
CRP mean ±SD	27.3±12 (6-60)	0	<0.05	Significant

Abbreviations: RA: rheumatoid arthritis; DAS 28: Disease activity scale; HAQ: Health Assessment Questionnaire; ESR: erythrosedimentation rate; CRP: C-reactive protein; SD: standard deviation.

The findings suggest that by deploying a modified DAS-28 scale 12 % (6/50) of RA patients were considered to be in remission, while other had hlow, (6/50:12%), high (5/50:10%), moderate (29/50:58%), and high (10/50: 20%) disease activities as presented in Table 1. Based on HAQ scores, it was found that RA patients had mild (score 0-1), (35/50: 70%), moderate (1-2) 10/50 (20%), and severe (score 2-3) (5/50:10%) disabilities (Table 1). The empirical results did not reveal any statistically significant correlation between disease duration, DAS28, ESR, and BMD (p>0.05). Moreover, comparison of risk factors for osteoporosis between patients and controls did not show any statistically significant correlation (p>0.05) for the variables as age, gender, and smoking status. Yet, routine laboratory tests revealed a highly statistically significant difference in ESR (p<0.001) and CRP (p<0.05) values between two groups (Table 1). Any statistically significant differences were not found in other routine laboratory tests, such as kidney and liver function tests, and complete blood count. In the group of RA patients with osteoporosis, a higher disease activity score (DAS-28) was found still without any statistically significant correlation compared to RA patients with normal BMD values or osteopenia.

The findings indicate dthat osteoporosis was more common in RA patients who smoked (8/15 (53.3%)) in comparison to nonsmokers (6/35 (17.1%)) (Table 3). The patients with RA had osteoporosis (n=8: 16%), osteopenia (n=27: 65 %), while 15 (30 %) patients had normal BMD values. While in the healthy control group, 8 cases had osteopenia and 22 cases had normal BMD values (Figure 1). Osteoporosis at all sites was significantly more common in females than in males.

DISCUSSION

Osteoporosis is a common complication perceived in patients with RA which also affects quality of life [10]. The aim of our study was to evaluate changes in BMDs in patients with early -onset rheumatoid arthritis and its correlation with DAS28 scores. The results of our study have shown the presence of an association between RA and osteoporosis. Herein, it was found that our patients had osteoporosis (16%),

Table 2. Comparison of lumbar spine and left femur BMD values in patients with RA and healthy controls.

T score	RA patients (n=50)			Healthy Controls (n=30)		
	Normal BMD (n=15)	Osteopenia (n=27)	Osteoporosis (n=8)	Normal BMD (n=22)	Osteopenia (n=8)	Osteoporosis (n)
Lumbar spine (L1-L4)	17/50 34%	24/50 48%	9/50 16%	22/30 73.3%	8/30 26.6%	0 0%
Left femur	32/50 64%	12/50 24%	6/50 12%	29/30 96.6%	1/30 3.3	0 0%

Abbreviations: BMD: bone mineral density; RA: rheumatoid arthritis
BMD normal (T score>-1), osteopenia (T score ≤-10>-2.5), osteoporosis (T score ≤ -2.5);

Table 3. Comparison of BMD values in patients with rheumatoid arthritis with demographic data.

	RA patients (n=50)		
	Normal BMD (n=15)	Osteopenia (n=27)	Osteoporosis (n=8)
Age Mean±SD, years	30.2±5.3	38.4±7.2	45.5±12.3
Disease duration Mean+SD, months	8.6±2.8	11.3±4.6	16.2±2.8
Gender Female (n=36) Male (n=14)	8 (22.2%) 7 (50%)	22 (61.1%) 5 (35.7%)	6 (16.6%) 2 (14.2%)
Smoking Yes (15) No (35)	2 (13.3%) 17 (48.5%)	5 (33.3%) 12 (34.2%)	8 (53.3%) 6 (17.1%)
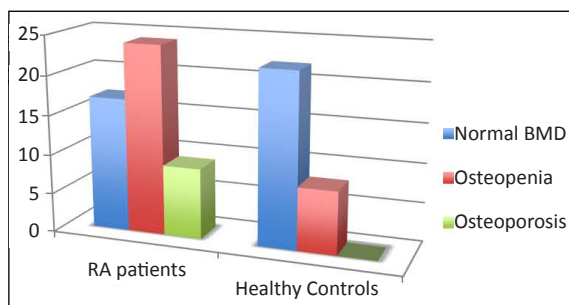
Figure 1. Comparison of BMD values in patients with RA and healthy controls.

osteopenia (65%), or normal BMD (30%) values In the healthy control group, the findings have shown that none of them had osteoporosis, while 8 patients had osteopenia, and 22 had normal BMD values. These findings are similar with the study of Brand et al, indicating higher risk of low BMD in RA patients compared to healthy controls [11]. A study from Kim et al. emphasized higher risk of osteoporotic fractures in patients with RA in all age groups in both males and females

and at various anatomical sites compared to individuals without RA [12]. Nevertheless, in our study, osteoporosis at all sites was more common in females than in males, without any statistically significant intergroup difference. Furthermore, in the study of Yoon J et al and in similar studies, gender of the patients was significantly associated with osteoporosis [13]. Spine was the most common site of osteoporosis in patients with RA with BMD of 16 %, followed by hip with BMD of 12%. The results of our study were similar to those of Güler-Yüksel et al who found that the most common site for osteoporosis in RA patients was the spine (9%), which is followed by the total hip (4%) [14]. Yoon et al. showed that osteoporosis in women with RA, younger than 60 years were more prevalent at the lumbar spine than at the femur, but the difference was not statistically significant [15]. HAQ scores in our study showed that RA patients with osteoporosis had severe disability. In their study, Sinigaglia et al found significantly higher HAQ scores in RA patients with osteoporosis (p=0.001) [16].

CONCLUSION

RA patients are more likely to have bone loss compared to normal age-matched subjects. The findings suggest that patients with lower BMD values at earlier stage of the rheumatoid arthritis had higher disease activities. Disability of patients with RA leads to limitation of physical activity, and reduces bone mineral density. All these factors cause bone loss independent of each other. A crucial tool to assess BMD in early-onset RA patients is considered to be dual energy x-ray absorptiometry.

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Clinical and Molecular Features of Our Pompe Patients: Single-Center Experience

Pompe Tanısı Alan Hastalarımızın Klinik ve Moleküler Özellikleri: Tek Merkez Deneyimi

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ABSTRACT

Introduction: Pompe disease (PD), glycogen storage disease Type II (GSD II), is an autosomal recessive inherited lysosomal storage disease caused by pathogenic variants in the GAA gene that encodes lysosomal acid α-glucosidadase (GAA) enzyme. The incidence of the disease varies from country to country. PD is mainly presents as two groups of phenotypes as infantile-onset Pompe disease (IOPD) and late-onset Pompe disease.
Objective: The aim of this study is to discuss the molecular and clinical characteristics of infantile-onset Pompe disease (IOPD) and late-onset pompe disease (LOPD) followed-up in our center.
Method: A total of 10 patients diagnosed with IOPD and 4 patients diagnosed with LOPD in Izmir Dr. Behcet Uz Pediatric Health and Diseases and Surgery Training and Research Hospital Pediatric Metabolism Unit between 06.01.2015 and 06.01. 2019 were included in the study. The patients' demographic characteristics, clinical findings at the time of diagnosis and during the folllow-up period, biochemical findings, muscle biopsy data, results of enzymatic analyses and molecular-genetic characteristics were recorded retrospectively.
Results: A total of 10 patients were included in the study. 7 patients were diagnosed with IOPD and 3 patients with LOPD. The median follow-up period of all patients was 26 months (range: 6-42 months). The c.896 C> T (8/32, 25%) is detected as the most common variant. 1237G>T (p.Asp413Tyr), c.2019 C>A (p.Asn673Lys), c.418A>T (p.Asn140Tyr) variants were detected for the first time.
Conclusion: Pompe disease is one of the most important congenital metabolic diseases in which early diagnosis and treatment are of great importance. Despite the significant improvement in disease prognosis with the introduction of enzyme replacement therapy, there are still patients with poor prognosis despite early diagnosis. Phenotype-genotype studies are crucial in this respect.

Keywords: Pompe disease, hypertrophic cardiomyopathy, hypotonicity

ÖZ

Giriş: Pompe hastalığı (PD), glikojen depo hastalığı Tip II (GSD II), lizozomal acidα-glucosidadase (GAA) enzimini kodlayan GAA genindeki patojenik varyantlar sonucu ortaya çıkan otozomal resesif kalıtımlı lizozomal depo hastalığıdır. Hastalığın sıklığı ülkeden ülkeye değişmektedir. Temel olarak erken başlangıçlı pompe hastalığı (IOPD) ve geç başlangıçlı pompe hastalığı (LOPD) olmak üzere iki gruba ayrılır.
Amaç: Çalışmamız, merkezimizde izlenen LOPD hem IOPD hastalarının moleküler ve klinik özelliklerinin tartışılmasını amaçlamaktadır.
Yöntem: Çalışmamıza 01.06.2015-01.06.2019 tarihleri arasında İzmir Dr.Behçet Uz Çocuk Sağlığı ve Hastalıkları ve Cerrahisi Eğitim Araştırma Hastanesi Çocuk Metabolizma Ünitesi'nde IOPD hastalığı tanısı alan toplam 10 hasta ve LOPD tanısı alan 4 hasta dahil edilmiştir. Hastaların retrospektif olarak demografik özellikleri, tanı anındaki ve izlem sırasındaki klinik bulguları, biyokimyasal bulguları, kas biyopsisi verileri, enzimatik analiz sonuçları ve moleküler-genetik özellikleri kayıt altına alındı.
Bulgular: Çalışmamıza toplam 10 hasta dahil edilmiştir. 7 hasta IOPD, 3 hasta LOPD tanısı almıştır. Tüm hastaların izlem süresi median 26 ay (range: 6-42 ay) olarak saptanmıştır. En sık görülen varyant c.896 C>T (8/32, %25) olarak saptanmıştır. 1237G>T (p.Asp413Tyr), c.2019 C>A (p.Asn673Lys), c.418A>T (p.Asn140Tyr) varyantları ilk kez saptanmıştır.
Sonuç: Pompe hastalığı erken tanı ve sonuç olarak tedavinin büyük önem taşıdığı doğumsal metabolik hastalıkların başında gelmektedir. Enzim replasman tedavisinin kullanıma girmesi ile hastalık prognozunda belirgin düzelme olmakla birlikte erken tanıya rağmen halen prognozu kötü giden hastalar bulunmaktadır. Fenotip-genotip çalışmaları bu açıdan önem taşımaktadır.

Anahtar kelimeler: Pompe hastalığı, hipertrofik kardiyomyopati, hipotonisite

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INTRODUCTION

Pompe disease (PD), or glycogen storage disease Type II (GSD II), is an autosomal recessive inherited lysosomal storage disease caused by pathogenic variants in the GAA gene that encodes llysosomal acidα-glucosidadase (GAA) enzyme [1]. The GAA gene is a typical housekeeping gene expressed in all cell types. Pathogenic variants in the GAA gene are present in all cell types, but some organs and functions are affected more strongly. Skeletal muscle and heart muscle are the primarily affected tissues [2].

The prevalence of PD varies in different ethnic groups according to clinical forms. The incidence of rapidly progressive infantile-onset pompe disease (IOPD) was 1/138000 in Caucasian race and 1/30000 in Taiwan [3]. The clinical classification of PD is based on the age and progression of the disease. PD is presented in two main groups as infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD). Classical IOPD or rapidly progressive IOPD is a progressive disease presenting within the first few days to several weeks of life with severe cardiomyopathy, respiratory failure and death in the first few years of life. Non-classical IOPD occurs in the first year of life and cardiomyopathy is milder compared to classical IOPD. However, muscle weakness is significant and in untreated cases respiratory failure occurs in early childhood [3,4]. The 28% of PD cases were IOPD and 85% of them were shown to be classical IOPD [5]. Clinical findings of Pompe disease develops due to GAA activity decreasing to less than 30% [1]. Classical IOPD occurs when enzyme activity is less than 1% of normal [6]. LOPD occurs after infantile period; while onset of the clinical findings may vary from the first to the sixth decades of life [7]. Clinical presentation in LOPD can be seen as limb-girdle muscular dystrophy or severe respiratory muscle weakness that require treatment with mechanical ventilation. Heart muscle is rarely affected in this group [8].

In 2006, enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase (rhGAA; alglucosidase alfa©; Myozyme©, Lumizyme©, Genzyme Corporation, Cambridge, MA) was introduced. Although the natural course of the disease changes with ERT; 51% of patients become ventilator dependent before age 3 [9]. The effective dose of ERT remains controversial. There is information in the literature on the use and efficacy of doses ranging from 20 mg / kg / every other week (eow) to 40 mg / kg / week [9,10]. There are many conditions that influence the efficacy of ERT other than its dosage, but one of them is undoubtedly the cross-reacting immunologic material (CRIM). It is known that CRIM-negative patients demonstrate much weaker response to ERT compared to CRIM-positive patients [11-14].However, the fact that CRIM is not available in all centers and that the results come from overseas centers pose significant difficulties in the decision-making process.

The aim of this study is to discuss clinical follow-up, molecular genetic characteristics and phenotype-genotype relationships of 10 patients with IOPD and LOPD.

MATERIALS and METHODS

Patient Selection

A total of 7 patients diagnosed with IOPD and 3 patients with LOPD in Izmir Dr. Behcet Uz Pediatric Health and Diseases and Surgery Training and Research Hospital Pediatric Metabolism Unit between 06.01.2015 and 06.01. 2019 were included in the study. The patients' demographic characteristics, clinical findings at the time of diagnosis and over the folllow-up period, biochemical findings, results of enzymatic and molecular-genetic analysis were recorded retrospectively.

Lysosomal acid α-glucosidadase (GAA) measurement

Lysosomal acidα-glucosidadase activity was measured with UHPLC MS/MS method (Orsini JJ) in dry blood and leukocytes (Waters Acquity ™ UPLC I-Class system). The substrate was provided by CDC [15].

GAA mutation analysis

GAA mutation analyses were performed in 10 patients with highly suspected PD. DNA was extracted from 2 ml EDTA containing peripheral blood samples using QIAamp DNA Mini Kit in accordance with the manifacturer's instructions. The full coding sequen-

ces of the GAA gene (NCBI: NT024871) were amplified and sequenced. The most likely disease-causing variants, identified by data analysis, were confirmed using Sanger sequencing method. Segregation analysis was then performed.

RESULTS

Demographic Findings and Clinical Features

The clinical characteristics of our patients are summarized in Table 1. A total of 10 patients were included in the study. Seven patients were diagnosed with IOPD and 3 patients with LOPD. The median follow-up period of all patients was 26 months (range: 6-42 months). Clinical, laboratory and genotypic features of our patients are summarized in Table 1. Most (80%) of the patients were male (8/10) and 20% of them were female (2/10). The median age of onset of symptoms was 3.6 months (range: 0-12 months) in IOPD patients. Hypotonicity was the most common symptom (5/7; 83%), followed by respiratory distress (5/7, 83%). Cardiomyopathy (6/7; 85%) and hypotonicity (6/7; 85%) were the most common findings at presentation. Arrhythmia was seen in 66% of our patients (4/7). Two IOPD patients were diagnosed during the postnatal evaluation due to sibling history; one IOPD patient was diagnosed incidentally after detection of hypertrophic cardiomyopathy (HCM) and elevated muscle enzymes in the evaluation for congenital metabolic diseases during his admission with hemolytic anemia. Five of our 7 IOPD patients had been investigated for spinal muscular atrophy (SMA) before investigation for Pompe disease.

The median age of onset of LOPD patients was 8 years (1-23 years). The most common initial symptom was muscle weakness (4/4; 100%) followed by fatigue (3/4; 75%). None of our LOPD patients required the use of wheelchairs or invasive or noninvasive mechanical ventilators during follow-up. During the follow-up of our LOPD patients in different clinics, 3 patients were seen to have been followed up with a preliminary diagnosis of limb-girdle muscular dystrophy.

GAA activity measurement and Creatine Kinase values

GAA activites, analyzed from the dry blood samples of patients diagnosed with IOPD and LOPD, were determined as 0.12± 0.16 nmol/ml/hour (N: 1.1-4.02) and 0.51± 0.93 nmol/ml/hour, respectively. A statistically significant difference was found between the GAA activities of LOPD and IOPD patients (Table 2).

Serum creatine kinase (CK) levels were found to be high in all of our patients. Mean serum CK levels were 463± 45.6 in IOPD and 521± 59.3 IU/l (N: <175) in LOPD patients. No statistically significant difference was found between LOPD and IOPD patients.

GAA mutations

Pathogenic GAA variants detected in our patients were studied as 20 alleles in total from 10 patients listed in Table 3. In 80% (8/10) of our patients, kinship was found between parents. Patient 2-3, and patient 5-6 were siblings. Homozygous pathogenic variant was detected in 8 patients and compound

Table 1. Clinical feaures of patients.

Patient	Gender	Age at onset	Age at diagnosis	Cardiomyopathy		Dysrithmia	Hypotonicity	Muscle weakness	Disease classification	Survival Time	Current Age
				Hypertrophic	Dilated						
1	Male	0 months	3 months	+	-	+	+	-	IOPD	8 months	-
2	Male	4 months	12 months	+	-	-	+	-	IOPD	12 months	-
3	Male	0 months	0 months	+	-	-	+	-	IOPD	-	4 years
4	Male	2 months	2 months	+	-	+	-	-	IOPD	-	3.5 years
5	Male	0 months	6 months	+	-	+	+	-	IOPD	9 months	-
6	Male	2 months	6 months	-	-	-	-	-	IOPD	-	13 months
7	Female	0 months	1 month	-	+	+	+	-	IOPD	-	8 months
8	Male	5 years	9 years	+	-	+	-	+	LOPD	-	13 years
9	Female	23 years	24years	-	-	-	-	+	LOPD	-	26 years
10	Male	8 years	17 years	-	-	-	-	+	LOPD	-	19 years

Table 2. Molecular genetic findings of patients .

Patient	Allele 1	Location	Allele 2	Location	Variant classification	CPK at diagnosis (IU/L) (N:<175)	GAA enzyme activity (nmol/ml/saat) (N:1.-4.02)
1	c.896 T>C p.(Leu299Arg)	Exon 5	c.896 T>C p.(Leu299Arg)	Exon 5	B (Potentially less severe)	345	0,24
2	c.258dup p.(Asn87GlnfsX9)	Exon 2	c.258dup p.(Asn87GlnfsX9)	Exon 2	A (very severe)	521	0,11
3	c.258dup p.(Asn87GlnfsX9)	Exon 2	c.258dup p.(Asn87GlnfsX9)	Exon 2	A (very severe)	672	0,12
4	c.896 T>C p.(Leu299Arg)	Exon 5	c.896 T>C p.(Leu299Arg)	Exon 5	B (Potentially less severe)	456	0,26
5	c.896 T>C p.(Leu299Arg)	Exon 5	c.896 T>C p.(Leu299Arg)	Exon 5	B (Potentially less severe)	389	0,21
6	c.896 T>C p.(Leu299Arg)	Exon 5	c.896 T>C p.(Leu299Arg)	Exon 5	B (Potentially less severe)	474	0,1
7	c.2019C>A p.(Asn673Lys)	Exon 14	c.2019C>A p.(Asn673Lys)	Exon 14	Unknown	567	0.1
8	c.1237 G>T p.(Asp413Tyr)	Exon 8	c.-32-13T>G	Intron 1	Unknown/ D (potentially mild)	651	0,42
9	c.418 A>T	Exon 2	c.-32-13T>G	Intron 1	Unknown/ D (potentially mild)	497	0,36
10	c.-32-13T>G	Intron 1	c.-32-13T>G	Intron 1	D (potentially mild)	532	0,28

heterozygous variant in 2 patients.

Of the 20 alleles studied, 12 were identified as missense (12/20, 60%), 4 as splice-sites (4/20; 20%), and 4 as frameshift (4/20, 20%). The most common variant was c.896 T> C (8/14, 57.1%) and the second most common mutation was c.258dup (4/20, 20%). Of the 6 variants we identified, 3 had already been described in the literature; while c.1237G> T (p. Asp413Tyr), c.2019 C> A(P.asn673lys) , c.418A> T (p.Asn140Tyr) variants were detected for the first time. Variants C.1237 G>T and c.418 A>T were classified as variant of uncertain significance (VOUS) according to the ACMG classification; and c.2019 C>A variant was classified as 'likely pathogenic', but all 3 variants were considered as pathogenic because of their location in a highly conserved region among species and interpretation by in-silico prediction programs as damaging.

Enzyme Replacement Therapy

Three of our IOPD patients received ERT at a dose of 20 mg/kg/2 weeks and 4 patients at a dose of 20 mg/kg/week. One patient died without receiving ERT. CRIM status could not be evaluated in our patients. Desensitization was performed in one patient due to anaphylaxis developed during ERT.

DISCUSSION

The phenotype and genotype relationship of Pompe disease in different ethnic groups has been discussed.(16-19) There are no studies investigating phenotype-genotype characteristics of IOPD patients in our country.

- When the initial symptoms were evaluated in two different groups, hypotonicity was the most and respiratory distress was the second most frequently seen disorders in IOPD patients. The first symptom was most frequently muscle weakness in LOPD patients. When the initial symptoms are compared, hypotonicity is seen in IOPD and muscle weakness in LOPD. While noninvasive mechanical ventilator support was required in 3 IOPD patients (3/7; 45%), respiratory support was not required in LOPD patients during follow-up. Most (90%) of our IOPD patients whereas 33% (1/3) of LOPD patients had HCM at the time of diagnosis,. Arrhythmia, which is an important part of cardiac involvement in Pompe disease, was seen in 57% (4/7) of IOPD and in 33% (1/3) of LOPD patients. Our initial symptoms were evaluated to be consistent with the literature. However, wheelchair use was not seen in our LOPD group. The lack of need for wheelchair and respiratory support in our patients can be explained by the early initiation of ERT. In the literature, in the natural course studies performed before ERT, wheelchairs was used in 38% and respiratory support in 31% of the patients with LOPD. All of our LOPD patients had muscle weakness at the time of diagnosis. All 3 patients received initial diagnosis of LGMD and long-term follow-up. Pompe disease should be considered in patients followed up with a preliminary diagnosis of LGMD who have not been definitely diagnosed by molecular genetic methods.

When the diagnostic process of the patients was evaluated, two patients (patient 4 and patient 6) were diagnosed based on sibling history, and one

patient (patient 4) was diagnosed after incidental detection of HCM during the investigation of the etiology of hemolytic anemia. All three of these patients were diagnosed early in life and enzyme replacement therapy was started in the early period. During the follow-up with ERT of all three patients, HCM regressed completely. When the literature is examined, it is observed that HCM can completely return to normal in 46% of patients started on ERT during the early stage of the disease [20].

To date, around 600 pathogenic variants have been detected in the GAA gene (http://www.hgmd.cf.ac. uk/ac/gene.php?gene=ga to). GAA pathogenic variants, namely, exon 2 with start codon, exon 10 and 11 with enzyme catalytic domain and exon 14 with a highly conserved region among species are seen in three critical regions.(21) Six different variants detected in our patients were distributed in intron 1, exon 2, exon 5, exon 8 and exon 14. c.1237G>T (p. Asp413Tyr), c.2019 C>A (p.Asn673Lys), c.418A>T (p. Asn140Tyr), variants were detected for the first time in our study. The variant c.2019 C>A (p.Asn673Lys) was detected only in exon 14 in the region highly conserved among species. All of these variants are missense variants (Tables 1, 2).

When the variant types of patients were evaluated out of 20 alleles, 12 missense (12/20, 60%), 4 splice-site (4/20; 20%), and 4 frameshift (4/20, 20%) variants were detected While missense variants are commonly thought to have a better course than nonsense and frameshift variants that lead to premature stop codon; it is difficult to make clear comments on other than c.-32-13T>G variant. In their study towards resolving the confusion in this regard, Kroos et al. divided the detected variants in 6 groups.(17,22-24) The most severe variants are CRIM negative (class A, very severe), followed by classes ending in class F according to severity. c.258dup variant class A, c.896T>C variant class B (potentially less severe), c. da-32-13T>Gclass D (potentially mild) were detected in our patients. The classification of the newly identified 3 variants is not yet known. CRIM status is not known in our patients due to the fact that CRIM status is needed to be determined before ERT for technical reasons, because of the necessity of waiting for sample transport material to become available and necessity of urgent ERT initiation to the patients. For

this reason, classification could not be made especially in newly identified variants, since CRIM status, which is the first condition in the classification of Kroos et al., could not have been checked. Sibling patients 2 and 3, who carried c.258dup variant, a class A variant, homozygously, showed very different clinical courses. When the patient 2 was brought to the hospital at the age of 12 months due to hypotonicity that started at 4 months of age, HCM was detected and the diagnosis of Pompe disease was made very quickly. However, due to immigrant status of the patient, ERT could not be provided with health insurance and the patient died very quickly before ERT could be started. Patient 3 was diagnosed with Pompe disease in the first month of its life and ERT could be started immediately. At present 4-year-old patient's HCM findings completely regressed and neuromotor development is close to normal. It is clear that the clinical difference between the two siblings is due to the early start of ERT.

The phenotype-genotype correlation of Pompe disease varies considerably. Clinics of siblings are very important in determining phenotype- genotype correlation. While sibling concordance in late-onset Pompe disease has been investigated, sibling concordance in early-onset Pompe disease has not been addressed much. In our patient group, 4 patients (2 families) were siblings. In the concordance study conducted by Smith et al., it was demonstrated that clinics of the siblings were very similar [25]. When the prognosis and clinical features of our patients were compared among siblings, it was found that the sibling after the proband had better clinical progression due to index case being diagnosed late and treatment being started in the newborn period with siblings detected in the family screening. When patients 1, 4, 5 and 6, who had class B c.896 C> A variant which was the most common in our series, were evaluated among themselves, there was no significant difference in the initial symptoms of the disease, age at onset, enzyme activity and ERT start time; though differences were observed in clinical findings and prognosis. This suggests that there may be other factors or other modifying genes in the same gene, other than the GAA gene variant in Pompe disease. Filippi et al. suggested that polymorphisms in the ACE gene affect the prognosis of the disease [22].

CONCLUSION

Pompe disease is the first metabolic myopathy in which corrective treatment is started. Since the start of the active use of ERT, there has been an improvement in the course of the disease and a significant increase in the number of surviving patients. Therefore, it is one of the diseases where early diagnosis is vital. While the phenotype-genotype is not known to be well correlated, it is of great importance in predicting prognosis and response to treatment as in all congenital metabolic diseases. Although the molecular genetic features of LOPD patients have been presented in the literature, there are limited studies about the molecular genetic features of IOPD patients Our study is one of the first studies in our country to discuss the molecular and clinical features of both LOPD and IOPD patients.

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Is There a Way to Predict Granulosa Cell Tumor of the Ovary? The Role of Peripheral Blood Test Parameters

Overde Granüloza Hücreli Tümörü Tahmin Etmenin Bir Yolu Var mı? Periferik Kan Testi Parametrelerinin Rolü

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ABSTRACT

Objective: As the clinical characteristics and clinical presentation of granulosa cell tumour of the ovary (GCTO) are not specific, predictive markers are required. The aim of this study was to evaluate the use of peripheral blood parameters in the preoperative prediction of GCTO.
Method: This retrospective case-control study included 34 patients with GCTO (Group 1) and 158 females with benign ovarian mass (Group 2). Data were recorded and the groups were compared in respect of age, gravida, parity, neutrophil- to- lymphocyte ratio (NLR) and platelet- to- lymphocyte ratio (PLR) and red cell distribution width (RDW).
Results: With the exception of age, no difference was determined between the groups in respect of the other demographic parameters. In the study group, the RDW values were lower and NLR and PLR were higher than in the control group. The differences between the groups were statistically significant (p=0.003, p=0.013, p=0.038, respectively). The cutoff values obtained from the ROC curve for RDW, NLR and PLR were 14.3, 2.03 and 129.3, respectively. RDW was the only marker with sensitivity (67.6%) and specificity (65.8%) over 60%. In the study group a positive correlation was determined between tumour diameter and NLR (r=0.46, p=0.006).
Conclusion: Although increased RDW is a strong determinant of mortality, including cancer-related deaths, the results of this study showed decreased RDW in GCTO. Low RDW could possibly be used as a screening tool in GCTO.

Keywords: granulosa cell tumor, red cell distribution width, ovary

ÖZ

Amaç: Granüloza hücreli over tümörünün (GHOT) klinik özellikleri ve sunumu spesifik olmadığından, prediktif belirteçler gereklidir. Bu çalışmanın amacı, preoperatif GHOT'nü öngörmede periferik kan parametrelerinin kullanımını değerlendirmektir.
Yöntem: Bu retrospektif vaka kontrol çalışması, GHOT'ü olan 34 hasta (Grup 1) ve benign ovaryen kitlesi olan 158 kadın (Grup 2) üzerinde yapıldı. Hastaların yaş, gravida, parite, nötrofil-lenfosit oranı (NLO), trombosit-lenfosit oranı (PLO) ve kırmızı hücre dağılım genişliği (RDW) dahil olmak üzere preoperatif verileri kaydedildi ve gruplar arasında karşılaştırıldı.
Bulgular: Demografik parametreler, yaş hariç, gruplar arasında farklılık göstermedi. Çalışma grubunda kontrol grubuna göre RDW düşük, NLO ve PLO daha yüksekti. Gruplar arasındaki farklar istatistiksel olarak anlamlıydı (sırasıyla 0.003, 0.013 ve 0.038). RDW, NLO ve PLO için ROC eğrisinden elde edilen kesim noktaları sırasıyla 14.3, 2.03, 129.3'tü. RDW duyarlılık ve özgüllüğü % 60'ın üzerinde olan tek belirteçti (sırasıyla % 67.6 ve % 65.8). Olgu grubunda tümör çapı ile NLO arasında pozitif korelasyon vardı (rs=0.46, p=0.006).
Sonuç: Artmış RDW, kansere bağlı ölümler de dahil olmak üzere güçlü bir mortalite belirleyicisi olmasına rağmen, bu çalışmanın sonuçları GHOT'nde RDW'nin azaldığını göstermiştir. Düşük RDW muhtemelen GHOT'nde bir tarama aracı olarak kullanılabilir.

Anahtar kelimeler: granüloza hücreli tümör, kırmızı küre dağılım genişliği, over

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INTRODUCTION

Granulosa cell tumour of the ovary (GCTO) is formed of somatic cells of the sex cord [1]. GCTO is an uncommon form of cancer, constituting 5% of all ovarian malignancies [2]. There is a relationship between GCTO and hyperoestrogenisation-related symptoms such as postmenopausal bleeding, which renders early diagnosis possible [3]. The clinical characteristics and presentation of GCTO are not specific, and diagnosis is based on the histopathological evaluation of tissue obtained during surgery.

According to the clinical presentation and histological pathology, there are two types of GCTO; the pediatric form and the adult form. The adult type is seen at the rate of 95% and generally in females aged 50-54 years [4,5]. Unlike epithelial ovarian cancers, GCTO is characterised by a good prognosis [1].

Peripheral blood examination is cheap, repeatable and is sufficient for diagnosis in some patients. When screening methods are limited in patients, such as for cancer, the full blood count is promising for assisting in clinical decision-making. The accumulated evidence has shown that the inflammatory micro-environment related to the tumour facilitates tumour growth and metastasis [6]. White blood cells contained in the mature leukocyte spectrum include lymphocytes, neutrophils and monocytes. There is lymphocytic suppression in the peripheral blood of more than half of malignant cases. The lymphocyte reaction plays a critical role in the immune response and is also an influential factor in the suppression of cancer progression. The neutrophil mechanisms in proliferation and metastasis include the expression of reactive oxygen species or nitric oxide and the remodelling of the extracellular matrix [7].

Platelets contribute to the inflammatory reaction by increasing angiogenesis or releasing growth factors. To predict prognosis and the potential for malignancy of adnexial masses during preoperative period, inflammatory markers such as the neutrophil- to-lymphocyte ratio (NLR) and platelet- to- lymphocyte ratio (PLR) have been examined [8-10]. A previous study reported that NLR was a predictor for GCTO [11]. RDW is a part of the routine full blood count and

reflects the heterogenity of the red blood cell dimensions. Previous studies have shown that RDW is a strong indicator of all mortality causes, including cancer-related deaths [12,13].

The aim of this study was to investigate preoperative predictive parameters of adult-type GCTO, using the full blood count values of NLR, PLR, RDW, and mean platelet volume (MPV).

MATERIAL and METHODS

Design
Approval for the study was granted by the local ethics committee of a tertiary health care center in Istanbul. Hospital records were retrospectively reviewed for the period between January 2006, and June 2015.

Exclusion criteria were defined as a history of local or systemic infection, chronic diseases such as diabetes, chronic heart disease or chronic liver disease, anti-coagulant or anti-platelet treatment , or blood transfusion within the last 3 months. Patients diagnosed with an ovarian mass or adnexial mass, who were then diagnosed postoperatively with paratubal cyst, para-ovarian cyst, myoma or tubo-ovarian abscess, were also excluded from the study. The patients were separated into 2 groups as Group 1 comprising patients with a diagnosis of GCTO (study group) and Group 2 consisting of patients with a benign ovarian mass (control group).

Measures
The data of all patients including age, tumor diameter, preoperative laboratory values, postoperative pathology results, history of drug use and chronic diseases were retrieved from the electronic medical records and patient files. Complete blood count (CBC) was analysed with a Cell-Dyn 3700 Hematology Analyzer (Abbott, USA). The platelet and neutrophil counts were divided with lymphocyte count to calculate PLR and NLR, respectively. MPV is a machine-calculated measurement of the average size of platelets found in the blood and is typically included in blood tests as part of the CBC. RDW is a measure of the range of variation of red blood cell volume that is reported as part of a standard CBC.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences software, version 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Armonk, NY, USA). Before the intergroup comparisons, conformity of the data to normal distribution was evaluated with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were presented as mean±SD values and compared with the Student's T-test or Mann-Whitney test. Categorical variables were expressed as percentages (%) and compared with the chi-square test.

Associations were assessed by correlation analysis and multivariate regression analysis. Predictive values of variables and cut-off values with optimal sensitivity and specificity were established by ROC curves. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

The study included 34 patients with GCTO (study group) and 158 patients with a benign ovarian mass (control group) who were diagnosed between 2006 and 2015. The masses in the control group were determined as serous cysts in 81 (51%), mucinous cysts in 49 (31%), mature cystic teratomas in 22 (14%) and fibroma in 6 (4%) cases. All the GCTO were adult type. The full blood count test results were analysed using the normality test, and only body mass indices (BMI) showed normal distribution. Therefore, for all comparisons other than BMI, non-parametric tests were used. Statistically signficant differences were determined between the groups in respect of NLR, RDW and PLR (p:0.013, p:0.003, p:0.038, respectively) (Table 1).

When the two groups were evaluated together, no correlation was observed using Spearman Correlation analysis between age, BMI, tumour diameter and NLR, PLR and RDW. In the evaluation of the groups separately, a significant positive correlation was determined in the study group between tumour diameter and NLR (rs=0.46, p=0.006).

ROC curves for NLR and PLR are shown in Figure 1. The AUC values obtained for each parameter are

Table 1. Demographic and hematologic parameters.

Parameters	Group 1 (n=34) Mean± SD	Group 2 (n=158) Mean±SD	P
Age (year)	51.5±13.5	36±12.3	<0.001[b]
BMI (kg/m²)	27.1±4.7	26.3±4.8	0.328[a]
Tumor Diameter (cm)	8.1±5.5	6.9±3.5	0.674[b]
RDW	14.4±2.4	15.3±2.1	0.003[b]
NLR	2.9±1.8	2.3 ±1.1	0.013[b]
PLR	150.9±51.9	131±47.2	0.038[b]

BMI: body mass index, RDW: red cell distribution width,
NLR: neutrophil -to- lymphocyte ratio,
PLR: platelet- to- lymphocyte ratio. Group values is given as mean (± SD).
[a] Student T-Test
[b] Mann- Whitney U Test.

Table 2. Area under curve values derived from ROC curves for some parametres.

Variables	AUC	Standard Error	P	95% Confidence Interval
RDW	0.665	0.052	0.003	0.564-0.766
NLR	0.637	0.052	0.013	0.534-0.739
PLR	0.614	0.053	0.038	0.510-0.717

RDW: red cell distribution width, NLR: neutrophil –to- lymphocyte ratio, PLR: platelet –to- lymphocyte ratio.

Table 3. Sensitivity, specificity, PPV and NPV of cutoff points for variables from ROC curve.

Variables	Cut-off points	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
RDW	14.3	67.6	65.8	29.9	90.4
NLR	2.03	61.8	56.3	23.3	87.3
PLR	129.3	58.8	57	22.7	86.5

RDW: red cell distribution width, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PPV: positive predictive value, NPV: negative predictive value.

shown in Table 2. The highest value was found to be 0.665 for RDW.

Using the ROC curve analysis cut-off values, the sensitivity, specificity, positive (PPV), and negative predictive values (NPV) were calculated (Table 3). The cut-off values were determined as 14.3 for RDW, 2.03 for NLR and 129.3 for PLR. Only the cut-off value for RDW was determined with sensitivity and specificity of more than 60%.
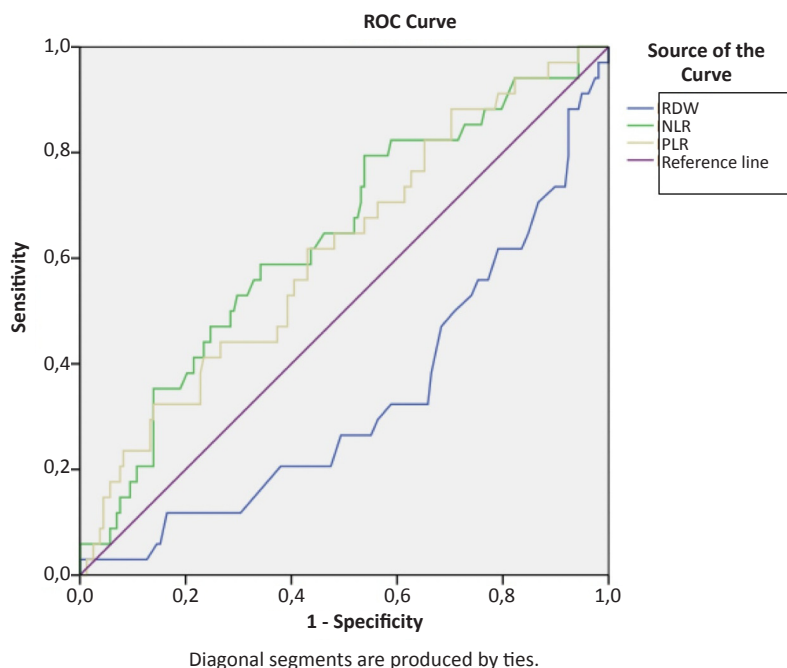
Figure 1. ROC curve for red cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte (PLR).

DISCUSSION

Mortality rates for ovarian cancer are high as there is no effective screening method and at the time of diagnosis 75% of patients are at an advanced stage. The risk of ovarian cancer shows an increase for each additional year of approximately 2% in females aged <50 years and 11% in those aged ≥ 50 years [14]. There are several markers such as Ca-125 and vascular endothelial growth factor (VEGF), that have been studied in the preoperative period for the early diagnosis of ovarian cancer [15]. Yeşilyurt et al. evaluated Ca-125 as a marker for GCTO and showed increased mean values in GCTO (64.5±130.3 IU/mL) [11].

Recent studies have shown that AMH is beneficial as a tumour marker, especially for GCTO, with sensitivity of 92% and specificity of 81% for primary GCTO [16]. However, the combined use of Ca-125 and imaging methods, which is still widespread, has come into question. Ca-125 has low sensitivity in early diagnosis and because of the costs of imaging methods, this is not sufficiently robust marker for early diagnosis. Therefore, there is a need for new diagnostic methods that are simple, cheap and reliable to increase the rates of early diagnosis, and the

complete blood count (CBC) seems to be suitable for this. It has been reported that some parameters such as platelet counts, NLR, PLR, RDW and the monocyte- to- lymphocyte ratio (MLR) estimated from preoperative CBC values could predict both diagnosis and prognosis in cancer patients [17,18].

As a marker of systemic inflammation, NLR is related to disease severity and prognosis in several different malignancies such as colon, endometrium and ovarian cancer [19-21]. In a recent study, NLR was found to be statistically significantly different in GCTO and benign ovarian masses. ROC curve analysis has shown that NLR could be a differentiating factor in the preoperative prediction of GCTO [11]. In a more recent meta-analysis, a significant relationship was determined between high NLR and poor general survival (HR: 1.88, 95% CI 1.30-.73) and shorter progression-free survival (HR 1.65, 95% CI 1.18-2.29). In addition, increased NLR was found to be significantly correlated (-3.04) with tumour size (OR 2.05, 95% CI 1.14-3.65), advanced FIGO stage (OR 2.12, 95% CI 1.28-3.49) and lymph node involvement (OR 2.24, 95% CI 1.65) [22].

However, the underlying mechanisms of the relati-

onship between high NLR and poor outcomes in cancer patients are still not sufficiently understood. Several cancer studies have used NLR in the prediction of survival, but the wide range of cut-off values reported as 1.9-5.020 restrict its use in this area [23]. In the current study, the NLR cut-off value was determined as 2.03.

In previous studies in the literature, a relationship has been found between high RDW levels and atherosclerosis, inflammatory intestinal diseases, prostate cancer, oesophageal carcinoma, upper urinary system urothelial carcinoma and endometrial cancer [24-28]. In addition, oxidative stress and inflammation have been shown to affect RDW but this relationship has not been well defined [13,29].

A meta-analysis reported that RDW was a strong determinant of mortality in elderly adults with and without age-related diseases such as cardiovascular diseases and cancers [12,13]. Although the underlying biological mechanism of this relationship is not clear, it is probably related to the role of cytokines in circulation, such as systemic expressions of IL-6, TNF-α, and hepcidin [30,31]. Finally, increased RDW has been shown in conditions of increasing mortality in literature. In the current study, RDW could have been low as there was no life-threatening condition. On the ROC curve, the RDW curve was observed to be on the right of the reference curve, as small values for RDW were selected for GCTO (Figure 1). Furthermore, oestrogen, anti-oxidant, pro-inflammatory and anti-inflammatory effects could have been responsible for the decrease in RDW and increase in NLR.

As it has a low prevalence in general population, any screening test for ovarian malignant tumors, such as ovarian cancer to achieve a positive predictive value of 10%, should have at least 75% sensitivity and 99.6% specificity. This means that maximum 10 surgical procedures should be performed to find one cancer case. RDW is not suitable as a screening test because the ROC curve analysis showed that the best cut-off value had test sensitivity in the range of 60%-65%. This is far too low in clinical practice when compared to the predictive values of many existing ultrasound-based models such as the IOTA group's LR1, LR2, the Simple Rules or ADNEX, mixed models, such as various RMIs and serum tumor marker-

based models such as ROMA or OVA1.

In conclusion, herein we found an increase in NLR and PLR and a decrease in RDW in GCTO. To the best of our knowledge, this is the first study which evaluated RDW in the diagnosis of GCTO. Of these 3 parameters, although RDW should not be used in differential diagnosis for GCTO because of the low sensitivity and specificity values, it could be a simple, low-cost preoperative test for screening. In addition, as the GCTO diameter increased, a statistically significant increase was observed in NLR. Nevertheless, there is a need for further randomised controlled studies on this subject.

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Psychiatric Disorders, Delirium and Mortality in Patients Referred for Consultation in a Burn Center: A Four-Year Retrospective Study

Yanık Merkezinde Konsültasyon İstenen Hastalardaki Psikiyatrik Bozukluklar, Deliryum ve Mortalite: Dört Yıllık Bir Retrospektif Çalışma

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ABSTRACT

Objective: *The aim of this study was to examine psychiatric disorders after burn trauma and burn-related features in adults.*
Method: *The records of the cases who were hospitalized in the burn center between January 2015 and January 2019 and for whom psychiatric consultation was requested were retrospectively reviewed. Sociodemographic characteristics, burn-related features, psychiatric diagnoses, and treatments of the patients were examined.*
Results: *The mean rate of psychiatric consultations requested in a burn center within a four-year period was 34.05% and 49 (28.5%) of these consulted cases had a work-related accident. Mean hospitalization time was 37.2±24 days and the most common burn type was a fire/flame injury. In the majority of the study sample (63.4%) the total body surface area burnt was more than 20%. Nineteen (11%) cases had a history of psychiatric disorder. The most common psychiatric diagnosis before burn injury was alcohol-drug addiction (n=14, 73.7%). The most common diagnosis after psychiatric consultation was adjustment disorder (31.9%). Among psychotropic drugs the initial treatment was started most frequently treatment with benzodiazepines (30.8%) and antipsychotics (58.1%). In 33 deceased cases, the most common psychiatric diagnosis was delirium with a rate of 42.4%.*
Conclusion: *The incidence of psychiatric disorders before and after burn injury was found to be high in the individuals. Conditions with a high risk of morbidity and mortality, such as delirium, should be diagnosed and treated priorly. Due to the early and long-term effects of burn trauma, a multidisciplinary approach should be developed and psychiatrists should be included in the management of treatment.*

Keywords: *burn, psychiatric disorder, delirium, mortality*

ÖZ

Amaç: *Erişkinlerde yanık travması sonrasında ortaya çıkan psikiyatrik bozuklukların ve yanıkla ilişkili özelliklerin incelenmesi amaçlanmıştır.*
Yöntem: *Ocak 2015-Ocak 2019 yılları arasında yanık merkezinde yatarak tedavi gören ve psikiyatri konsültasyonu istenen olguların kayıtları geriye dönük olarak taranmıştır. Olguların sosyodemografik özellikleri, yanıkla ilişkili özellikleri, psikiyatrik tanıları ve tedavileri incelenmiştir.*
Bulgular: *Yanık merkezinde 4 yıllık süre içinde psikiyatri konsültasyonu istenme oranı %34.05'ti, danışılan olguların 49'u (%28.5) iş kazası geçirmişti. Ortalama yatış süreleri 37.2±24 gün olup, en sık yanık şekli yangın/alev yaralanmasıydı. Örneklemin büyük çoğunluğunda (%63.4) toplam vücut yüzey alanı %20'den fazlaydı. 19 (%11) olgunun geçmişte psikiyatrik hastalığı mevcuttu. Yanık öncesi en sık görülen psikiyatrik tanı alkol-madde bağımlılığıydı.(n=14, %73.7). Psikiyatrik konsültasyon sonucu en yüksek konulan tanı ise uyum bozukluğuydu (%31.9). Psikotrop ilaçlar içinde benzodiyazepin (%30.8) ve antipsikotik (%58.1) başlanma oranı yüksekti. Vefat eden 33 olguda en sık görülen psikiyatrik tanı %42.4 oranıyla deliryumdu.*
Sonuç: *Yanık geçiren bireylerde yanık öncesinde ve sonrasında psikiyatrik hastalıkların görülme oranı yüksektir. Özellikle deliryum gibi morbidite ve mortalite riski olan durumlar öncelikle tedavi edilmelidir. Yanık travmasının erken ve uzun dönemdeki ruhsal etkileri nedeniyle multidisipliner yaklaşım sağlanarak tedavi yönetimine psikiyatristlerin dahil edilmesi önemlidir.*

Anahtar kelimeler: *yanık, psikiyatrik bozukluk, deliryum, mortalite*

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INTRODUCTION

Severe physical injuries and burns constitute approximately 12% of the diseases in the world [1]. Whatever the reasons are, injuries are a major burden on the healthcare system which is responsible for the care and support of victims. Researchers believe that 98% of these cases are preventable. Although the age-adjusted injury mortality rate has been reduced by 21% between 1980 and 1997, the intentional and unintentional injuries are still the leading cause of death for children, adolescents and young adults [1]. Physical and psychological rehabilitation of these patients have become more important as a result of the increase in survival rates due to the developments in medicine [2].

From an etiological point of view, psychiatric disorders and burns are interrelated. After a severe trauma, such as burn injury, especially burns which cause distinct physical distortion of the face, can lead to psychiatric diseases, and mental illnesses eventually to a predisposition to burn injuries [1,3]. From a psychiatric point of view, people with substance use disorders are at higher risk of injury, including burns [4]. Similarly, suicidal patients with a mental disorder may also deliberately burn themselves [5,6]. The prevalence of depression is higher among individuals who are traumatically injured and have a medical illness compared to the general population [7,8]. The presence of a pre-existing psychiatric disorder in burn patients is associated with worse outcomes in the treatment of burns and is an important predictor of morbidity. In addition, the development of psychiatric disorder after burn injury is reported to be a factor negatively affecting the quality of life [9-11].In the burn injury process and during the treatment, mental illnesses can be seen in patients due to severe pain, prolongation of treatment process, being confined to bed, and changes in body image [12]. In this respect, it is important that patients are also evaluated from a psychiatric point of view after the initial emergency intervention in the burn unit, and psychiatrists should be included in the burn treatment team [13].

Delirium is one of the most common diagnoses in patients referred to psychiatric services from different wards [14]. Prevalence of delirium among inpati-

ents is found to range from 10 to 30% [15]. Delirium is characterized by an acute decline in the level of consciousness and cognition with particular impairment in attention. Other associated features include abnormal psychomotor activity, sleep cycle impairment and psychiatric symptoms such as abnormalities of mood, perception and behaviour. It develops over a short period of time and fluctuates during the course of the day [16]. Studies on this field frequently state that delirium has significant effects on medical morbidity, hospitalization time, and postdischarge course [17,18]. Delirium is therefore a clinical diagnosis that requires emergent medical care and treatment in burn patients and it may be fatal if not treated [19].

Studies conducted in Turkey examining burns and mental disorders were reviewed, and a study analyzing family characteristics of children and adolescents with corrosive burns and another study evaluating burn related psychiatric disorders in children were identified [20,21]. There was only one study examining psychiatric disorders in the early period in an adult population [22]. Therefore, our study will contribute to the literature in this field. The aim of this study is to examine the distribution of psychiatric diagnoses, clinical characteristics and treatments in psychiatric consultations requested by the burn center.

MATERIAL and METHODS

The burn center in our hospital consists of 12 beds -eight for service and four for intensive care-, an operating room, two dressing rooms, hydrotherapy halls, one hyperbaric oxygen therapy device and one polyclinic. It is a tertiary treatment center providing healthcare to an important population in the Aegean region, which accepts moderate and severe burn patients and patients with additional trauma or comorbidities over 18 years of age. This center provides healthcare services to 250 inpatients per year on average. A total of 172 cases that were hospitalized in the burn center between January 2015 and January 2019 and for whom psychiatric consultation was requested were retrospectively evaluated. According to the good clinical practice guidelines written approval was obtained from the hospital comittee in order to examine the medical records of

the cases retrospectively. Data such as age, gender, education, marital status, occupation, cause , and location of the burnt area on body, whether it is an work-related accident, percentage of total body surface area (TBSA%) burnt, psychiatric history and diagnosis, alcohol-substance abuse, number of consultations requested from psychiatry, the time between hospitalization and request for psychiatric consultation length of hospital stay , and the psychotropic drugs used were examined.

Statistical Analysis: SPSS 22 statistical package program was used in all analyses. In addition to descriptive statistics (median and percentage distributions), Mann Whitney-U test was used and categorical variables were compared using chi-square test. P <0.05 was considered statistically significant.

RESULTS

In 505 cases hospitalized in the burn center during the four-year period, psychiatric consultations were requested for 172 (34.05%) cases. Of these cases, 39 (22.7%) were female and 133 (77.3%) were male. The median age of the patients was 37 (25-52) years and the majority were married (n=94, 54.7%). The median duration of education was 5 (5-11) years, and 91 patients (52.9%) were unemployed. Forty-nine (28.5%) patients had an occupational accident, and the majority of these cases were male workers (p=0.014). Overall and gender-based sociodemographic characteristics of the cases are given in Table 1.

The median length of hospitalization in the intensive care unit was 6.5 (4-11) days and total length of hospitalization was 15.5 (3-40) days. The most common burn pattern was fire-flame injury (n=120, 69.8%). The most common areas of burn injury were the areas apart from the head and neck, hands and the genital region (n=87, 50.6%). Nineteen (11%) patients had a history of psychiatric disorder, including alcohol-drug addicts (n= 14: 73.7%), those with bipolar mood disorder (n= 2: 10.5%), psychotic disorder (n= 1), delirium (n=1), and adjustment disorder (n=1: 5.3%). In the whole sample, 10 (5.8%) cases were hospitalized due to self inflicted burns. Of the 10 patients who burned themselves, 2 had dependence, 1 had bipolar mood disorder, and 1 had psychotic disorder before burn trauma. Psychiatric consultation was requested for 94 patients (54.6%), during the first week of hospitalization and the most common psychiatric diagnosis after evaluation of all cases was adjustment disorder (n=54, 31.4%). As a result of the consultation, antidepressants were used in 78 (45.3%), benzodiazepines in 53 (30.81%), antipsychotics in 100 (58.1%), and multiple psychotropic agents in 49 (28.5%) cases. The details of the psychiatric consultation requested for burn patients are given in Table 2 and the distribution of psychiatric diagnoses received by the patients is given in Table 3.

Thirty-three (19.2%) patients died due to cardiac arrest, sepsis, multiple organ failure and adult respiratory distress syndrome during burn treatment. The most common psychiatric diagnosis among these

Table 1. Sociodemographic characteristics of cases who were evaluated by the psychiatrist.

Clinical variables	Men (n=133)	Women (n=39)	Total (n=172)	Z / X^2	P
Age (median)	36	41	37	-1.681	0.93
(25-75%)	(25-48)	(30-66)	(25.25-52.75)	-1.075	0.283
Education (median)	5	5	5	17.376	0.000*
(25-75%)	(5-11)	(0-11)	(5-11)		
Marital status (n, %)				9.316	0.002*
Single	58 (43.6%)	11 (28.2%)	69 (40.1%)		
Married	73 (54.9%)	21 (53.8%)	94 (54.7%)		
Widowed/Separate	2 (1.5%)	7 (17.9%)	9 (5.2%)		
Job (n, %)				6.07	0.014*
Unemployed	62 (46.6%)	29 (74.4%)	91 (52.9%)		
Employed	71 (53.4%)	10 (25.6%)	81 (47.1%)		
Work-related accident	44 (33.1%)	5 (12.8%)	49 (28.5%)		

*p<0.05 was considered as statistically significant

Table 2. Clinical chracteristics of the patients who were evaluated by the psychiatrist.

Clinical variables	Men (n=133)	Women (n=39)	Total (n=172)	Z / X²	P
Duration of intensive care stay (median)	6	7	6.5	-0.227	0.634
(25-75%)	(4-11)	(2-11)	(4-11)	-0.634	0.526
Duration of total hospitalization (median)	17	14	15.5	15.31	0.000*
(25-75%)	(3-41)	(1-39)	(3-40)		
Type of burn (n, %)					
Fire/flame	90 (67.7%)	30 (76.9%)	120 (69.8%)	4.257	0.235
Scald	8 (6%)	8 (20.5%)	16 (9.3%)		
Other (chemical-electrical)	33 (24.8%)	1 (2.6%)	36 (20.9%)		
Site of injury (n,%)					
Head	32 (30.9%)	8 (20.5%)	40 (23.3%)	2.646	0.084
Hand	21 (15.8%)	4 (10.3%)	25 (14.5%)		
Genital area	12 (9%)	8 (20.5%)	20 (11.6%)		
Other	68 (51.1%)	19 (48.7%)	87 (50.6%)		
Mortality (n, %)	22 (16.5%)	11 (28.2%)	33 (19.2%)		
TBSA (n, %)					
0-10	12 (9%)	1 (2.6%)	13 (7.6%)	2.5	0.287
10-20	36 (38.7%)	14 (35.9%)	50 (29.1%)		
>20	85 (63.9%)	24 (61.5%)	109 (63.4%)		

*TBSA: Total body surface area, *p<0.05 was considered as statistically significant*

Table 3. Distribution of psychiatric diagnoses in patients who were evaluated by the psychiatrist.

Psychiatric diagnosis (n,%)	Men (n=133)	Women (n=39)	Total (n=172)	X²	P
Adjustment disorder	44 (33.1%)	10 (25.6%)	54 (31.4%)		
Anxiety disorders	25 (18.8%)	8 (20.5%)	33 (19.2%)		
Depression	18 (13.5%)	11 (28.2%)	29 (%16.9)	7.105	0.130
Delirium	20 (15%)	7 (17.9%)	27 (15.7%)		
Other Diagnosis	26 (19.6%)	3 (7.7%)	29 (16.9%)		
Substance use disorder	16 (12%)	-	16 (9.3%)		
Acute stress disorder	8 (6%)	2 (5.1%)	10 (5.8%)		
Bipolar disorder	1 (0.8%)	1 (2.6%)	2 (1.2%)		
Psychotic disorder	1 (0.8%)	-	1 (0.6%)		

p<0.05 was considered as statistically significant

Table 4. Distribution of psychiatric diagnoses in patients who died in burn center.

Psychiatric diagnosis (n,%)	Men (n=22)	Women (n=11)	Total (n=33)
Adjustment disorder	5 (22.7%)	3 (27.3%)	8 (24.2%)
Anxiety disorders	3 (13.6%)	-	3 (9.1%)
Depression	-	2 (18.2%)	2 (6.1%)
Delirium	10 (45.5%)	4 (36.4%)	14 (42.4%)
Other Diagnosis	4 (18.2%)	2 (18.2%)	6 (%18.2)
Substance use disorder	4 (8.21%)	-	4 (12.1%)
Acute stress disorders	-	1 (9.1%)	1 (3%)
Bipolar disorders	-	1 (9.1%)	1 (3%)
Psychotic disorders	-	-	-

p<0.05 was considered as statistically significant

cases was delirium (n=14, 42.4%). Distribution of psychiatric diagnoses in these 33 cases according to gender is given in Table 4.

DISCUSSION

Burn trauma results in outcomes with negative psychological, social and physical effects in the exposed individuals in the short-, and long- term. In the present study, retrospective evaluation of the four-year period revealed that psychiatric consultation was requested in 34% of the patients who were hospitalized at the burn center. When a study was

evaluated in the literature, it was observed that the rate of psychiatric consultation after burn injury was reported as 19.6% [23]. Gender and age are important risk factors for severe burn injuries associated with adverse developmental and behavioral patterns [24]. In our study, the mean age of burn patients was 40.51 years and majority of the patients were male (F/M ratio=1/3). These results are consistent with the results of other studies in the literature [25-27]. Similarly, employment status and rate of work-related accidents were found to be significantly higher in men, consistent with other studies [25-28]. This result may be attributed to a higher proportion of males working in high risk sectors in Turkey, as is the case in rapidly industrializing countries.

In the present study, the majority of cases requiring psychiatric consultation were hospitalized in the intensive care unit. Mean length of hospitalization in the burn center was 37.2±24.3 days. When the literature is reviewed, it can be seen that the mean length of hospitalization varies between centers. Ter Smitten et al. (2011) reported mean length of hospitalization as 27±30 days [27], whereas Logsetty et al. (2016) as 15.1±21.8 days [9]. The length of hospitalization in burn centers can be affected by various parameters such as severity of burn, presence of intensive care unit, additional medical diseases, complications, and premorbid psychiatric diagnosis [29]. In the present study, the most common cause of burn was fire/flame with a ratio of 76.9%. Second most common cause was scalding in women and other (electric/chemical) burns in men, and there was a statistically significant difference between the genders. Similar to our study, there was a difference between the genders in the literature [26,28,30]. When three studies conducted in Turkey were examined, it was seen that scalding burns (60.7%, 69%, 47.7%) were reported as the most common causes of burns [31-33]. However, there is no gender comparison in these studies, and we believe that the absence of a burn intensive care unit in those centers and the referral of severe/complicated cases to other hospitals may have affected the causes of burns. In another retrospective study, Yücel and Kılavuz reported that among moderately severe burns the scalding burns (52.6%) and among severe burns flame burns (54.4%) were the most common causes of burn injuries [30].

When location of burn was examined in our study, it was observed that the body regions other than the head, hands and the genital region were affected the most. The severity of the burn is an important risk factor in the development of psychiatric disorder. In one study, at least one mental disorder was found to develop in one third of minor burns (TBSA<5%), two thirds of moderate burns (TBSAP = 5-20%), and almost all of severe burns (TBSA>20%) [23]. In our study, the majority of the cases requiring psychiatric consultation (n=109, 63.4%) had a TBSA of over 20%. This finding is consistent with the results of another study examining 10 years of data in Turkey [28]. In the literature, Özçetin et al. (2012) reported that TBSA was 6-10% in the majority of cases [32], and Sıkar et al. (2018) reported that TBSA was 6-15% [31] In the presence of severe burns, as encountered in the intensive care units, psychiatric support is especially important for patients who develop complications [26]. The higher rate of hospitalization in the intensive care unit in our study supports the need for psychiatric evaluation. Another important issue is that the mean length of hospitalization and the duration of transition to independent life are higher in patients with pre-burn psychiatric disorders compared to others [34]. In individuals, the presence of mental illness before burn may sometimes be the cause of the burn itself (self-harm), and reasons such as the low treatment motivation caused by depression, the lack of proper wound care due to the difficulty in assessing reality can make the treatment and healing process difficult [35,36]. In some studies, it has been reported that a significant number of patients admitted to burn centers have pre-burn Axis I and Axis II psychiatric disorders, and some personality traits such as impulsivity predisposes to burn injury [26,37]. It was also found that this patient group stayed longer in the hospital and required greater number of surgical procedures, thus creating difficulties for various disciplines in the treatment and rehabilitation process [35]. In our study, 19 patients (11%) had a psychiatric diagnosis before burn incident. When the distribution of the diagnoses in this group was examined, it was found that 74% of them had alcohol-drug dependence and 11% of them bipolar mood disorder. Palmu et al. (2010) evaluated 107 acute burn patients and reported the rate of previous psychiatric treatment as 29% [26]. Logsetty et al. (2016) found that the rate of any psychiatric disorder in burn vic-

tims in the last 2 years before burn injury was 25.5% [9]. In our study, it was determined that 10 (5.8%) cases experienced burn trauma due to self-harm/suicide. In this group, two cases had alcohol and drug dependence, one case had bipolar mood disorder, and the other one had psychotic disorder. In our study, it is noteworthy that most of the individuals who suffered burns due to self-harm did not receive psychiatric support before the burn. Therefore, it can be thought that this group demonstrates impulsive decision and behavioral characteristics.

Burn team requested psychiatric consultations within the first week in 54.6% of the patients and the most frequent diagnosis based on psychiatric evaluation was adjustment disorder (31.4%). In a similar study, the rate of adjustment disorder was found to be 61.5% [38]. Adjustment disorder is among the most common psychiatric diagnoses in patients hospitalized for medical and surgical reasons, and its prevalence in patients receiving palliative care in hematology and oncology clinics was reported to be 15.4% and 19.4% respectively [39,40]. In the case of emotional and behavioral symptoms that do not meet the criteria of acute stress disorder after acute trauma, psychiatrists may turn to the diagnosis of adjustment disorder [41,42]. This may have also increased the rate of this diagnosis in our sample. When the distribution of other psychiatric diagnoses was examined in our study, anxiety disorder was found in 19.2%, major depression in 16.9% and delirium in 15.7% of the cases. In a study investigating the distribution of psychiatric diagnoses in inpatients in the overall hospital sample in Turkey, the prevalence of depressive disorders, delirium, schizophrenia-psychosis, anxiety disorder, trauma and related disorders, and alcohol-substance use disorder were reported to be 19.5%, 18.2%, 7.4%, 6.1%, 5.6%, and 4.3%, respectively [43]. The prevalence of mental disorders in the overall hospital sample is affected by variables such as the duration of the additional medical disease(s), the nature of the trauma, characteristics of previous psychiatric disorder, the knowledge of the treatment team about the psychiatric disorder, the presence of psychosocial support systems and the loss of functioning in the individual [24,42,44]. Palmu et al. (2010) reported substance-related disorders (46.7%) as the most common lifetime disorder among burn patients [26]. This ratio is quite high compared to our

results. This may be due to the fact that the prevalence of substance abuse in Turkey is lower compared to other developed countries [45]. In the same study, the diagnosis of lifetime psychotic disorder was 10.3% which was above the community average. One in four people had mood disorder throughout their life, and 5.6% of them had depression during the month before the burn. Similar to our results, anxiety disorder was defined in 14% and acute stress disorder in 5.8% of their patients [26]. Yabanoğlu et al. (2012) reviewed the files of 1369 cases, and reported that the rate of psychiatric diagnosis within 15 days after the burn incident was 3.2%, and the diagnoses were PTSD in 26.6%, delirium in 24.4%, anxiety disorder in 17.7%, depression in 15.5% of the patients, respectively [22]. In our study, we observed that 33 patients (19%) died during the four-year period and the majority of this group was diagnosed as delirium (n=14, 42.4%). In another study with large sample of cases in which burn patients were examined in general, the mortality rate was found to be 7.4% [30]. Delirium can be seen in one fifth of burn patients [36]. Previous studies have reported that delirium is a predictor of mortality in risky groups [46,47]. Delirium may lead to increased mortality and morbidity as new risk factors are added to the underlying etiology due to inadequate diagnosis of the delirium and the application of inappropriate treatments [48]. Therefore, early diagnosis and management of the treatment of delirium are important issues.

In a study examining psychiatric consultations requested at a university hospital, it was found that 35.2% of the patients were treated with antidepressants followed by antipsychotics (22.6%), benzodiazepines (9%) and 32% of them were followed-up without drug treatment [49]. On the other hand, Göktaş et al. (2006) recommended antidepressants to 65.4% of the patients consulted, antipsychotic to 9.8%, and benzodiazepine to 3.7%; and 19.4% of the patients were recommended with unmedicated follow-up [50]. Similarly, Köroğlu et al. (2011) initiated antidepressants in 65.4%, antipsychotics in 10.8%, and benzodiazepines in 6.7% of their patients [51]. When the distribution of psychotropic drugs initiated in our study as a result of psychiatry consultation was examined, it was found that antidepressants were used in 45.3%, benzodiazepines in 30.8%, and antipsychotics in 58.1% of the patients. The rate of

multiple psychotropic drug use was 28.5%. In our study, the use of benzodiazepines and antipsychotics was higher compared to studies investigating clinics other than burn centers, which can be attributed to reasons such as severe anxiety, fear of death, disturbance in the sleep-wake cycle, and delirium risk in burn patients as reported in the literature [52].

Studies have reported that individuals suffering from burn injuries use more health care in general before and after the incident, which increases the burden of care in health services [9]. Burn victims constitute a sensitive group for healthcare personnel due to increased risk of psychopathology and ongoing care needs. Therefore, it is important to examine the parameters for maintaining mental health in this population and to plan multidisciplinary approaches in the early and late stages of treatment.

The present study has some limitations. These include the nonuse of structured psychiatric interview scales and the retrospective methodology. When current literature is reviewed, this study is important because of the limited number of studies investigating burn data with respect to psychiatric consultations in Turkey. As a result of this study, another prospective study was planned in which the individuals hospitalized in the burn center of our hospital will be examined.

CONCLUSION

Mental disorders are more common in burn victims before and after the incident compared to the general population. Screening the symptoms of mental disorders and psychotherapeutic and pharmacological interventions in syndromic cases after acute care in hospital conditions will lead to better management of burn treatment and rehabilitation as well as psychiatric disorders. Especially syndromes with a high risk of mortality, such as delirium, should be treated promptly because of the adverse effects on the course of treatment and clinical picture and since most of these syndromes are most likely reversible. Therefore, delirium should be recognized in hospitalized burn patients, and co-operation should be made with the burn treatment team on prevention and treatment modalities. In addition, there is a need for prospective studies evaluating long-term

psychiatric disorders in individuals suffering from burn trauma.

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Investigation of Drug Dose Calculation Skills and Self-Ratings Among Nursing Students

İlaç Doz Hesaplama Becerilerinin ve Öz Değerlendirmelerinin Hemşire Grubunda Araştırılması

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ABSTRACT

Objective: Medication errors are important concerns in terms of patient safety. Dose calculation skills contribute to medication errors. The aim of this study is to evaluate the calculation skills and self-ratings of nursing students.

Method: Four multiple-choice questions with five alternative responses were asked and an electronic questionnaire form was used for the assessment of their perceptions of their self-competencies.

Results: The rates of correct answers to the questions varied between 20% and 63%. In their self-assessments, 26.4% of them stated that they had sufficient dose calculation skills.

Conclusion: The results of the study showed that skills should be improved. Drug dose calculation skills should be improved, and further education should be provided on this issue.

Keywords: pharmacology, education, medication errors

ÖZ

Amaç: İlaç hataları, hasta güvenliliği için önemlidir. Doz hesaplama becerileri ilaç hatalarına neden olabilir. Bu çalışma hemşirelik öğrencilerinin ilaç doz hesaplama becerilerini değerlendirmeyi ve yeterliliklerinin öz değerlendirmelerinin araştırılmasını amaçlamaktadır.

Yöntem: Dört adet beş seçenekli çoktan seçmeli soru soruldu ve kendi yeterliliklerini algılamalarını değerlendirmek için elektronik form kullanıldı.

Bulgular: Doz hesaplama sorulara doğru cevap % 20 ile% 63 arasında değişmekteydi. Öz değerlendirmelerinde, % 26.4'ü doz hesaplama becerileri için yeterli olduğunu belirtti.

Sonuç: Çalışmanın sonuçları becerilerin geliştirilmesi gerektiğini göstermiştir. İlaç dozu hesaplama becerilerinin arttırılması ve daha fazla eğitime ihtiyaç vardır.

Anahtar kelimeler: farmakoloji, eğitim, ilaç hatası

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INTRODUCTION

Patient safety is an important concern that dates back to the first declaration of "primum non nocere". Medication errors are reported to cause more deaths from motor vehicle accidents, breast cancer, or workplace injuries [1]. To increase patient safety and decrease medication errors; all integrated medication delivery process from prescribing, transcribing, dispensing to administering medications is under the microscope [2]. There are many factors that may lead to medication errors. Lack of knowledge of prescribing skills, lack of pharmacological knowledge of physicians and nurses, poor compliance with drug prescribing and administration guidelines, lack of reporting of medication errors, heavy workload and being new staff, factors related to communication between health care professionals can result in a medication error [3]. In England and Wales, medication incident reports represented 9.68% of all patient safety incidents and 15% of medication incidents were about the incorrect dosages [4]. In Middle East countries incorrect dosage is also found to be within the most common types of errors [3]. Medication errors may stem from primarily physicians and nurses. Wrong dosages are reported to be in the context of nurse- related medication errors.

In Maltepe University School of Nursing curriculum, nursing-specific pharmacology lectures take two hours a week as a one-semester course in the second year, totaling 28 hours. Students have the opportunity to take this course in different years. The content of drug dose calculation is included in the pregraduate pharmacology course.

In this study, it was aimed to evaluate the dose calculation of the nursing students and also to investigate their self-ratings of their competence.

MATERIALS and METHODS

The was a retrospective descriptive study in Nursing Pharmacology Course in Maltepe University. To determine the dose calculation skills, students in the first, second and fourth-years at the School of Nursing who took the Nursing Pharmacology Course were evaluated.

Nursing students were asked four multiple choice questions with five alternative responses about evaluating their dose calculation skills in their final exam. The questions were prepared in accordance with a previous study in this field [5]. The answers were provided with optical forms. Marking the right choice among the five-choices was considered as "correct", marking other than the correct choice as "incorrect". Questions left blank were considered unanswered. Correct response rates were calculated, and results were evaluated retrospectively. Students' answers to multiple-choice questions were evaluated anonymously. The correct and incorrect answers of the students were calculated by using descriptive statistical methods and their frequencies were calculated using SPSS 25. The participation rate was calculated by dividing the number of surveys by the total number of students.

An electronic questionnaire form consisting of eighteen questions was constructed to maintain the feedback about the course. The self-rating of competence in dose calculation was included in the questionnaire. A Likert scale was used to rate responses obtained. The link of the electronic questionnaire was announced to the class by the student representative. In the self-assessment of their competence, no information was received about the respondent. Participation in the electronic questionnaire was based on volunteriness. The study was performed in compliance with the guidelines of the Helsinki Declaration.

RESULTS

A total of 120 nursing students attended the final examination. The examination consisted of forty questions. Four multiple-choice questions on dose calculation skills were responded correctly by 60%, 20%, 59%, and 63% of the respondents according to the question order. The highest accuracy rate was related to the calculation of the dose of oral antibiotics used in childhood. Total dose of insulin dose was correctly indicated in %60 of the responses. Morphine related question was responded incorrectly at a rate of %80 and 9 students even did not answer this question.

Self-rating of electronic questionnaire response rate

Table 1. Rates of correct, and incorrect answers to four questions about calculation of drug doses.

Questions	True n (%)	False n (%)
1. In stock, you have insulin 100 U/ml. You need to inject 28 U. How many ml do you have to inject?	72 (60%)	47 (39.17%)
2. In stock, you have morphine 3% (1%=1 g/100 ml). How many mg morphine does one ampoule of 2ml contain?	24 (20%)	96 (80%)
3. You need to administer 25 mg furosemide per hour via an infusion pump. One 10 ml ampoule contains 100 mg of furosemide. When you have to set up the infusion pump, how many ml/hour do you program?	71 (59.16%)	28 (23.33%)
4. A child of 30 kg needs antibiotics at a dosage of 4 mg/kg/day. In stock, you can find ampoules of 100 mg/ 5 ml. How many ml do you administer per day?	76 (63.33%)	44 (36.67%)

*TBSA: Total body surface area, *p<0.05 was considered as statistically significant*

was 65% (n=74). Self-rated competency in dose calculation skills was 31.9% (n=23) Eighteen (25%) participants indicated that they felt themselves completely incompetent. While 12 (9.7%) respondents had no idea about the subject ("undecided group"), and 12 participants indicated that they felt themselves completely competent

DISCUSSION

Nursing education at a university level has been started in 1955 in Turkey [6]. Turkey was reported to be one of only five European countries providing a basic university-level nursing education with Belgium, England, Greece, and Iceland [7]. In Turkey nursing education is regulated with national and international guiding principles; and curriculum of nursing education involves 4,600 hours of theoretical and practical training [6,8]. A total of 26 hours in pharmacology courses may not be sufficient to teach adequately all aspects of the medications. Since it is very important for nursing practice, it is suitable to be included not only in pharmacology course content but also in other courses. Drug dose calculation should be included in different course titles. There should be a better correlation between nursing education outputs and needs in nursing practices.

The rates of correct answers to the second question asked in the exam were at the lowest level with 20%, and to the fourth question were at the highest level with 63.33 %. Although rates of correct answers vary according to the question, question related to dose calculation was responded by higher number of participants when compared with those concerning self-perceived competencies The students also stated that they had difficulty in calculating oral doses.

The questions about drug dose calculations are prepared in reference to the study by Dills et al. [5] Although these doses and drugs may not represent the medications in our country, the participants were asked to evaluate their calculation skills so as to be able to compare the correct response rates.

In our study, correct answers were obtained at a rate of 60% for the question about insulin dose calculation (question 1, Table 1), while the relevant rate in the reference study was 61.8% for the same question in the other sample group. The correct dose of high-risk drugs such as insulin is important. Indeed, inappropriate doses, can lead to life-threatening clinical conditions such as hypoglycemia and hyperglycemia. Knowledge of high-risk drugs by nurses and proper labeling of high-risk drugs by the pharmacy can contribute to increased awareness of nurses. Insulins also differ according to their duration of action. It is important to plan nurses' post-administration follow-up according to the duration of insulin administered.

Second question was correctly answered by 20% of the participants, whereas accuracy rate for this question was 28.9% in Belgium [5]. For the safety of controlled and high-risk drugs, such as morphine, it is particularly important to calculate the dose ccrrectly. In our study, the last question was answered correctly by 59.16% of the participants while this rate

was 67.5% in the reference study [5]. Dose calculation is important for drugs; given in perfusion solutions. These drugs may represent separate challenges for nurses due to the choice of appropriate device, changing models, and the need for automatic dose calculation to be controlled by nurses. In terms of electrolyte and fluid imbalance, the dose and duration of administration of furosemide and similar drugs are important. Fluid monitoring and nursing follow-up are vital.

The fourth question was about antibiotic dose in the pediatric age group. The rate of correct answers was 63.33% in our study and 65.6% in the study in Belgium. Lack of mathematical knowledge on the calculations skills in other studies performed at two different nursing schools in Turkey negatively effected the rates of correct answers, and, students in these studies reported that they had poor mathematical skills [9]. In our study students' mathematical skills have not been evaluated. Therefore, it is not known whether the incorrect answers given to the dose calculation questions stem from the students' inability to perform mathematical operations. Mathematical skill is reported as it is not the factor for insufficiency in dose calculating [10].

In a study conducted in the UK, it was concluded that students' drug dose calculation skills were not very different from working nurses [11]. In another study conducted in Finland, it was shown that nurses working in the study area had better mathematical skills than nursing students [12]. In-service training or experience may serve to improve the capacity.

There is a perception of insufficiency in their own dose calculation skills in nursing students. It may point out a need for further education in undergraduate education and/or in-service training courses. Physicians should be aware of the weakness and strengths of the health care team they work with. Medication errors also may be due to prescription errors by physicians. Further studies are needed to evaluate the dose calculation skills of medical students.

One of the limitations of the study was evaluation of only one nursing school. In addition, students' response rates to the electronic questionnaire form was

at a low level. Therefore, it should be taken into consideration that the answers do not reflect the opinions of the whole class and the interest and success of the course may affect the response rates. The assessment method, namely the multiple-choice question format was different from the reference study. The data were collected retrospectively, which may be an advantage when compared with a prospectively designed study. If the assessment of dose calculation skills was made in a prospectively designed study there might be a bias of participation of the students who felt more competent.

CONCLUSION

Correct response rates of nursing students to the questions about dose calculation ranged from 20% to 63.3%. Increasing the accuracy of dose calculation is important to avoid medication errors. There is a need to improve training outcomes to increase rates of accuracy.

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Predictive Value of Neutrophil/Lymphocyte Ratios in the Diagnosis of Acute Appendicitis

Akut Apandisit Tanısında Nötrofil/Lenfosit Oranlarının Prediktif Değeri

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ABSTRACT

Objective: The debate on the value of laboratory tests in the diagnosis of acute appendicitis (AA) continues. In this study, we aimed to evaluate the blood count parameters and the diagnostic value of neutrophil/lymphocyte ratio in the diagnosis of acute appendicitis.
Method: 851 patients who underwent appendectomy under emergency conditions were included in the study. Patients were divided into 2 groups; Group 1 was negative appendectomy and Group 2 was acute appendicitis. In addition, they were divided into subgroups as 18-39 years, 40-59 years, and 60 years and older. Neutrophil, platelet, lymphocyte count and Neutrophil/lymphocyte ratio were compared in groups and subgroups.
Results: There were 146 patients (17.1%) in Group 1 (negative appendectomy group) and 705 patients (82.9%) in Group 2 (acute appendicitis group). Male sex was dominant in Group 2 (p=0.049). Neutrophil count and neutrophil / lymphocyte ratio (NLR) were higher in Group 2 (p<0.001, p<0.001, respectively), whereas in Group 1, lymphocyte count and platelet count were higher (p=0.008, p=0.002, respectively). The cutoff value for NLR was found to be 5.29 in the ROC curve analysis. In this value, NLR sensitivity was found as 57.3%, specificity as 69.9%, positive predictive value as 57.1%, negative predictive value as 69.2%. Multivariate analysis showed that the risk of acute appendicitis was 6.71 times higher in patients with NLR I5.29 (OR: 6.71+0.28; 95% CI: 6,150-7,276; p=0.024). In subgroups, the cut-off point for NLR was 5.10 for 18-39 years; 6.63 for 40-59 years; and 5.80 for 60 years and older. The highest sensitivity for these cut-off points was in the age group of 60 and over with 69%, while the highest specificity was in the 40-59 years age group with 58.2%.
Conclusion: Although the sensitivity and specificity of neutrophil /lymphocyte ratio (NLR) varies according to age groups, it is a useful and helpful parameter for physical examination and other diagnostic methods in the diagnosis of acute appendicitis.

Keywords: neutrophil-to-lymphocyte ratio, acute appendicitis, diagnosis

ÖZ

Amaç: Bu çalışmada akut apandisit tanısı koymada kan sayımı parametreleri ve nötrofil/lenfosit oranının tanısal değerini değerlendirmeyi amaçladık.
Yöntem: Acil şartlarda appendektomi yapılan 851 hasta çalışmaya dahil edildi. Postoperatif patoloji bulhusuna göre hastalar Grup 1 negatif appendektomi; Grup 2 akut apandisit olmak üzere iki gruba ayrıldı. Ayrıca 18-39, 40-59, 60 yaş ve üstü olmak üzere subgruplara ayrıldı. Nötrofil, platelet, lenfosit sayısı ve Nötrofil/lenfosit oranı gruplarda ve subgruplarda karşılaştırıldı. p<0,05 değeri istatistiksel olarak anlamlı kabul edildi.
Bulgular: Grup 1 negatif appendektomi grubunda de 146 hasta %17,1 Grup 2 akut apandisit grubunda 705 hasta %82,9 yer alıyordu. Grup 2 de erkek cinsiyet baskındı p=0,049. Grup 2'de nötrofil sayısı p<0,001 ve nötrofil/ lenfosit oranı (NLO) p<0,001 daha yüksek iken Grup 1'de lenfosit sayısı p=0,008 ve platelet sayısı p=0,002 daha yükek bulundu. NLOiçin (ROC) eğrisi analizinde kesme noktası 5,29 bulundu. Bu değer-de NLO sensitivesi %57.3, spesifitesi %69,9 pozitif prediktif değerini %57,1 negatif prediktif değeri %69,2 bulundu. Multivariant analizde NLO ≥5,29 olan olgularda akut apandisit riskinin 6,71 kat daha yüksek olduğu saptandı (OR: 6,71+0,28; 95% CI: 6, 150-7, 276; p=0,024). Sub grup-larda NLO için kesme noktası 18-39 için 5, 10; 40-59 için 6,63 ve 60 yaş ve üzeri için 5,80 bulundu. Bu kesme noktaları için en yüksek sensivite %69 ile 60 yaş ve üzeri grupta iken en yüksek spesivite %58,2 ile 40-59 yaş grubunda bulundu.
Sonuç: Nötrofil/lenfosit oranının (NLO) sensitivesi ve spesivitesi yaş gruplarına bağlı olarak değişmekle birlikte; akut apandisit tanısı koymada fizik muayene ve diğer tanısal yöntemlere yardımcı ve kullanışlı bir parametredir.

Anahtar kelimeler: nötrofil/Lenfosit oranı, akut apandisit, teşhis

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INTRODUCTION

The most common cause of acute abdomen requiring surgical intervention is acute appendicitis (AA) globally [1]. Approximately 8% of the general population in Western countries undergo appendectomy during their lifetime [2]. The overall incidence of perforated appendicitis in cases with acute appendicitis is 4-39%, and the rate of negative appendectomy in patients operated for acute appendicitis is reported to be 9-15% in the literature [3-6].

The diagnosis of acute appendicitis is still difficult when it's only based on clinical and laboratory data. Pathologies of gastrointestinal, urological or gynecological origin mimicking acute appendicitis make diagnosis even more difficult in adult patients. There is no laboratory marker which can distinguish AA by itself, from various other etiologies of abdominal pain [7].

Delay in diagnosis leads to perforation and thus increased morbidity rates, while negative appendectomy rates increase with premature decisions to perform surgery [8]. To increase early detection of acute appendicitis and reduce misdiagnosis rates, researchers have used many parameters . Erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, C-reactive protein (CRP) and bilirubin levels, immature granulocyte ratio and neutrophil / lymphocyte ratio (NLR) are some of them [2,9,10].

The physiological response of leukocytes to inflammation increases neutrophil and decreases lymphocyte counts Therefore, the ratios of these leukocyte subsets (neutrophil / lymphocyte ratio) can be used as an important marker of inflammation [7,11].

Goodman et al. demonstrated neutrophil-lymphocyte ratio (NLR) as a diagnostic tool for the first time, and when this ratio was greater than 3.5, they found that it was significant in diagnosing acute appendicitis [12]. In the following years, many authors have reported that the neutrophil / lymphocyte ratio (NLR) is a marker of inflammation and found it to have a preoperative diagnostic parameter in AA [13-15].

Kahramanca et al. associated a 4.68 NLR value with acute appendicitis (p<0.001). The sensitivity, specificity, negative (NPV), and positive predictive values (PPV) of this cut-off value were 65.3%-54.7%, 23.0%, and 88.4% respectively [13].

With this study, we aimed to determine the diagnostic value of NLR in the diagnosis of acute appendicitis.

MATERIAL and METHOD

The study included 851 patients who were surgically treated for acute appendicitis between January 2013 and January 2019 at Erciyes University Faculty of Medicine General Surgery Clinic. 12.06.2019 dated and numbered Approval was received from the local Ethics Committee. (date: 06. 12. 2019 decision no. 2019/431) Patient files and records of the hospital information system were reviewed and a database was created. Using this database, cases were analyzed retrospectively. The diagnosis of acute appendicitis was made based on physical examination, medical history, and supporting laboratory values and radiological findings. Patients who underwent appendectomy with the diagnosis of acute appendicitis and their pathology reports were included in the study. Patients under 18 years of age, pregnants, patients with a chronic inflammatory disease (tuberculosis, sarcoidosis), an autoimmune disease, hematologic disease, patients using steroids, pathological tumors and those whose records couldn't be reached were excluded from the study.

Based on histopathological evaluation, the patients were divided into 2 groups as Group 1 (negative appendectomy patients), and Group 2 (acute appendicitis patients). The basic demographic data (age, sex) and preoperative laboratory findings (lymphocyte count/mm^3, neutrophil count/mm^3, platelet count/mm^3, and neutrophil/lymphocyte ratio (NLR)) were compared between Groups 1 and 2. Additionally, Groups 1 and 2 were divided into 3 subgroups by age; as subgroups of patients aged 18-39, 40-59, and ≥ 60 years. The same parameters were compared between the age subgroups.

The total blood count was measured using an automated hematology analyzer (Roche Hitachi Cobas® 8000 Roche Diagnostics, Indianapolis, IN, USA). The NLR was calculated for each patient by dividing neutrophil counts by lymphocyte counts

Statistical Analysis

The data were analyzed using the IBM SPSS Statistics for Windows, version 24 package program (IBM Corp., Armonk, N.Y., USA). Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) as well as the Student's t test were used to compare quantitative data, and the Mann Whitney U test was used for the evaluation of the non-normally distributed neutrophil / lymphocyte ratios. For the comparison of qualitative data, Pearson's chi-square test and Fisher's exact test were used. Multivariate logistic regression tanalysis was also employed. The diagnostic accuracy was evaluated and examined using receiver operating characteristic (ROC) curve analysis. The appropriate cut-off values were identified, and the specificity, sensitivity, positive, and negative predictive values, positive, and negative likelihood ratios were calculated for the parameters with an area under the curve (AUC) value of above 0.600. p<0.05 value was considered statistically significant.

RESULTS

A total of 851 patients were included in the study. The negative appendectomy group (Group 1) consisted of 146 and the acute appendicitis group (Group 2) consisted of 705 patients. The mean age of the patients was 33.6±13.7 years in Group 1; and 35.4±15.1 in Group 2 (p=0.184). Sex distribution was equal in Group 1, while male patients constituted 57.9% of the patient population in Group 2. In univariate analyses, neutrophil, lymphocyte, platelet counts and NLR values were found to be significantly different between the two groups. These parameters were determined to be independent variables in the diagnosis of acute appendicitis in multivariate logistic regression analysis. The comparison between Groups 1 and 2 is detailed in Table 1. In the ROC curve analyses of these independent variables, AUC was above 0.600 for the neutrophil count and NLR (Figure 1). The proposed cut-off values and the performance characteristics of these variables are detailed in Table 2. When the patients were subgrouped by
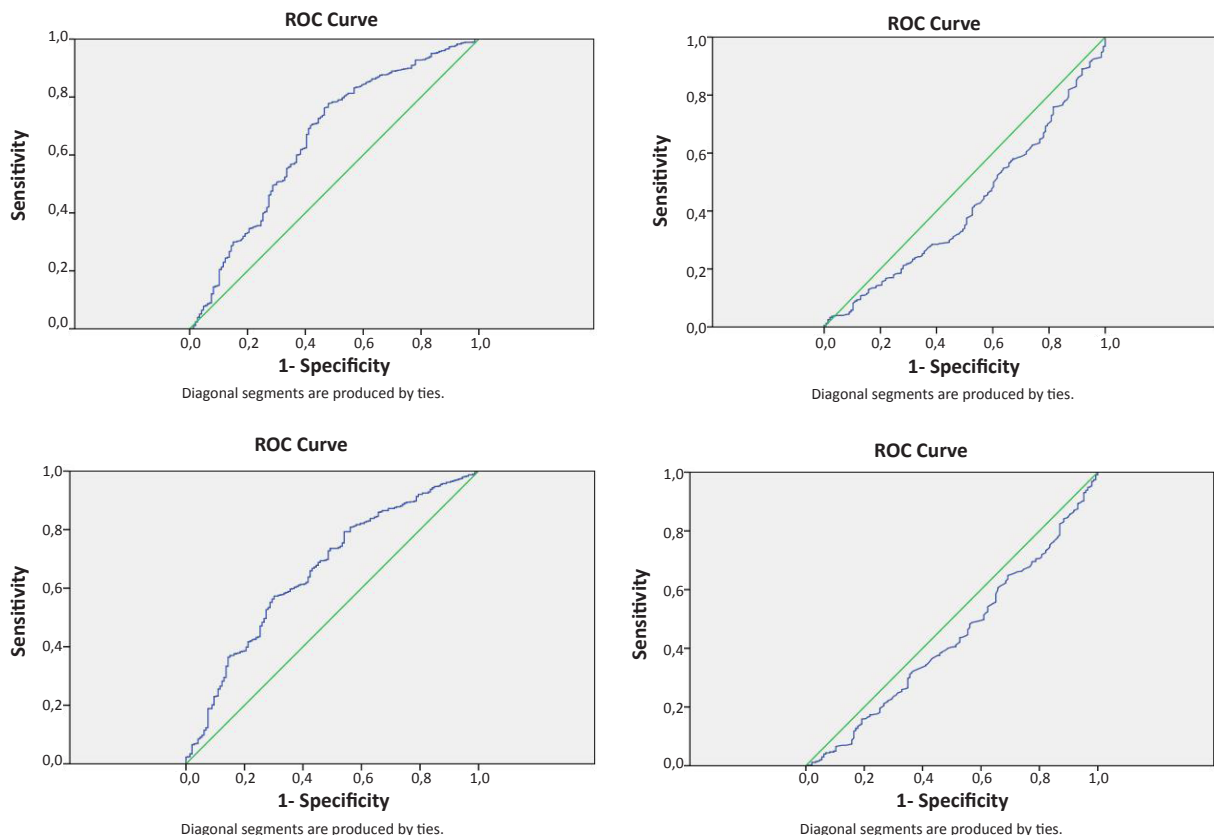
Figure 1. Receiver operating characteristic (ROC) curve analyses of significant parameters for the diagnosis of acute appendicitis: (a) Neutrophil count (b) Lymphocyte count (c) Neutrophil/lymphocyte ratio (NLR), (d) Platelet count.
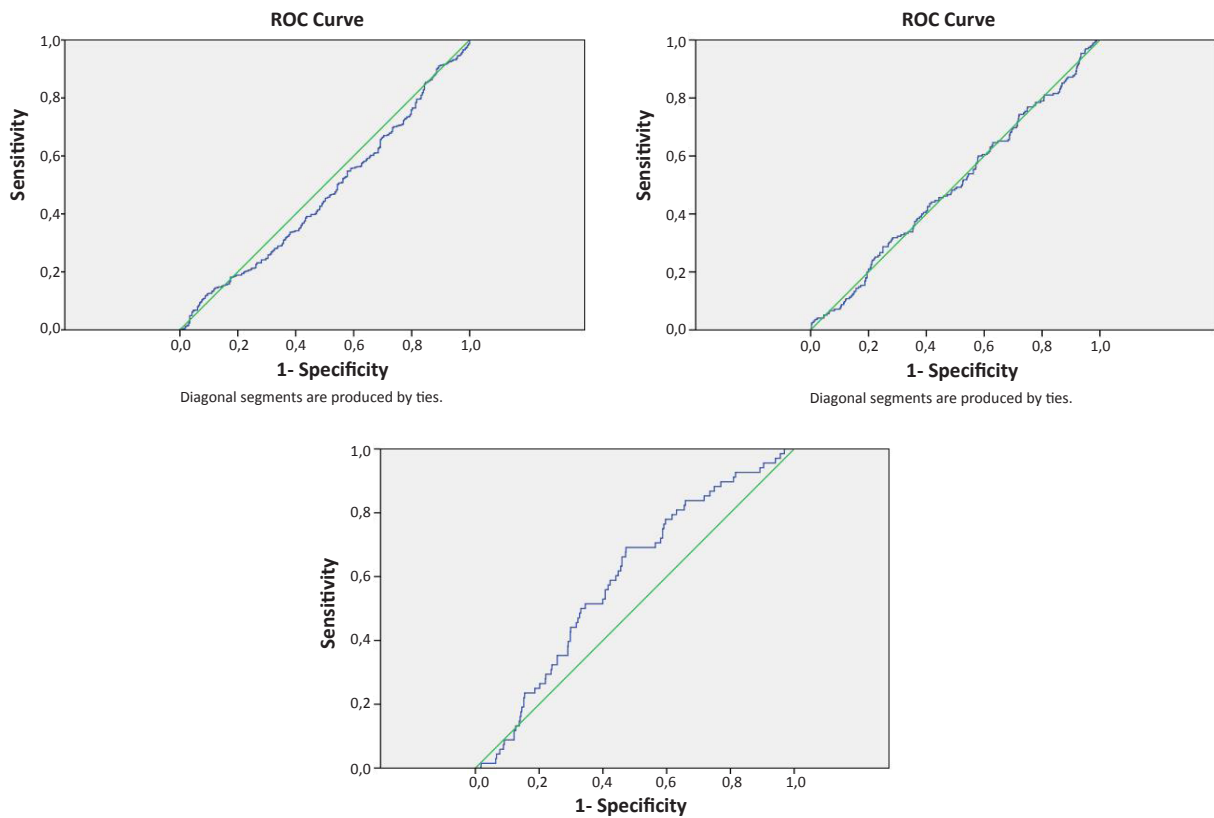
Figure 2. Receiver operating characteristic (ROC) curve analyses of NLR for the diagnosis of acute appendicitis in the age subgroups.

Table 1. Comparison of the two groups.

Parameters	Univariate analysis			Multivariate analysis			Roc curve analysis		
	Negative appendectomy	Acute appendicitis	p	OR	95% Cl (min-max)	p	AUC	95%Cl (min-max)	p
Patient number	146	705							
Age	33,6+13,7 (18-85)	35,4+15,1 (18-87)	0,184						
Sex Male Female	73 (50,0) 73 (50,0)	408 (57,9) 297 (42,1)	0,049						
Neutrophil (x10³/mm³)	8,2+4,5 (1,31-29,16)	10,1+3,9 (1,75-23,83)	0,000	9,21+0,18	8,850-9,570	0,033	0,654	0,602-0,706	0,000
Lymphocyte (x10³/mm³)	1,95+0,8 (0,51-4,81)	1,74+0,8 (0,26-7,29)	0,008	1,84+0,04	1,771-1,927	0,008	0,419	0,36-0,469	0,002
NLR	5,39+4,7 (0,52-26,08)	8,03+6,5 (0,72-48,46)	0,000	6,71+0,28	6,150-7,276	0,024	0,660	0,611-0,709	0,000
PLT (x10³/mm³)	267,2+94,7 (92-810)	245,5+73,4 (64-758)	0,002	256,38+3,52	249,46-263,29	0,011	0,436	0,386-0,487	0,016

Neutrophil-to lymphocyte ratio (NLR), PLT: Platelet count, AUC: Area under the curve, OR: Odds ratio

Table 2. Proposed cut-off values for significant parameters in the diagnosis of acute appendicitis.

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV	NPV	OR	pLLR	nLRR	AUC
Neutrophil (x10³/mm³)	8,04	70,1	58,2	69,1	58,1	6,14	1,24	0,38	0,654
Lymphocyte (x10³/mm³)	1,57	52,3	38,4	51,2	38,3	1,25	0,93	1,37	0,419
NLR	5,29	57,3	69,9	57,1	69,2	4,55	1,20	0,39	0,660
PLT (x10³/mm³)	238,5	48,2	43,8	47,3	55,4	1,21	0,94	1,29	0,436

Neutrophil-to-lymphocyte ratio (NLR), PLT: Platelet count, AUC: Area under the curve,PPV: Positive predictive value; NPV: Negative predictive value; OR: Odds ratio; pLLR: Positive likelihood ratio; nLLR: Negative likelihood ratio

Table 3. Comparison of the subgroups.

	Univariate analysis				Multivariate analysis			Roc curve analysis		
Parameters	18-39	40-59	60 and older	p	OR	95% Cl (min-max)	p	AUC	95%Cl (min-max)	p
Patient number	588	195	**68**							
Age										
Sex										
Male	332 (56,5)	113 (57,9)	36 (52,9)	0,772						
Female	256 (43,5)	82 (42,1)	32 (47,1)							
Neutrophil (x10³/mm³)	10,1+4,1 (1,31-29,16)	9,2+3,9 (1,59-23,07)	9,2+3,6 (2,38-16,29)	0,024	9,5+0,2	9,173-9,958	0,009	0,559 0,445 0,460	0,519-0,600 0,400-0,490 0,391-0,529	0,006 0,019 0,273
Lymphocyte (x10³/mm³)	1,85+0,8 (0,34-7,29)	1,69+0,8 (0,26-6,59)	1,38+0,6 (0,35-3,56)	0,000	1,64+0,04	1,562-1,729	0,023	0,581 0,464 0,351	0,540-0,622 0,418-0,510 0,288-0,415	0,000 0,125 0,000
NLR	7,4+6,2 (0,52-48,46)	7,7+7,1 (1,13-47,64)	8,2+4,7 (1,34-26,78)	0,568	7,8+3,1	7,203-8,429	0,001	0,469 0,498 0,594	0,428-0,511 0,452-0,544 0,530-0,658	0,152 0,934 0,010
PLT (x10³/mm³)	248,0+70,8 (64-810)	254,8+90,6 (98-758)	243,5+95 (75,2-629)	0,464	248,8+3,8	241,33-256,29	0,002	0,509 0,509 0,45	0,466-0,553 0,462-0,556 0,371-0,532	0,665 0,702 0,183

Neutrophil-to-lymphocyte ratio (NLR), PLT: Platelet count,AUC: Area under the curve,OR: Odds ratio

Table 4. Proposed cut-off values for NLR in diagnosis of acute appendicitis to age groups.

Age Groups	Cut-off value	Sensitivity (%)	Specificity (%)	PPV	NPV	OR	pLLR	nLRR	AUC
18-39	5,10	54,8	42,2	54,1	41,1	6,44	0,95	1,10	0,469
40-59	6,63	44,1	58,2	44,3	57,1	5,99	0,89	0,81	0,498
60 and older	5,80	69,1	52,7	70,2	52,3	13,49	2,40	0,92	0,594

Neutrophil-to-lymphocyte ratio (NLR), AUC: Area under the curve,PPV: Positive predictive value; NPV: Negative predictive value; OR: Odds ratio; pLLR: Positive likelihood ratio; nLLR: Negative likelihood ratio

age, there were 588 patients aged 18-39, 195 patients aged 40-59, and 68 patients aged 60 years and older. Male sex dominance was present in all age subgroups. In univariate analyzes for age subgroups, lymphocyte and neutrophil counts were significantly different between groups. In multivariate logistic regression analysis, neutrophil, lymphocyte, platelet counts and NLR were independent variables in the diagnosis of acute appendicitis. The comparison between the subgroups by age is given in Table 4. In the ROC curve analyses of these independent variables in age subgroups, an AUC above 0.600 was not determined. The results of ROC curve analysis for NLR in age subgroups iare given in Figure 2. The proposed cut-off values and performance characteristics for NLR in age subgroups are shown in Table 4.

DISCUSSION

Early diagnosis of acute appendicitis may not always be possible. Making the decision to observe a patient until a clear diagnosis can be made or to operate prematurely to prevent undesirable complications such as perforation and peritonitis represents a very serious dilemma for surgeons [13,16].

In general, finding suitable, easily accessible and cost-effective diagnostic markers for early detection of diseases has always been the focus of interest of researchers. Many markers that can be used for early diagnosis were investigated because of morbidity and mortality caused by delayed diagnosis in patients followed up for acute abdominal pain in the emergency departments [9,10,13,17].

The diagnosis of acute appendicitis, even in this modern era, is still a problem. A combination of physical examination, certain laboratory tests and a number of imaging studies are used for definitive diagnosis. There are several diagnostic tests which are used for appendicitis, including leukocyte count, percentage of neutrophils, C-reactive protein (CRP), procalcitonin and D-Dimer [18-20].

Complete blood count is an easily accessible and rapidly evaluated test in the emergency department. Neutrophil, leukocyte, lymphocyte, and platelet counts, and neutrophil-lymphocyte ratio in complete blood counts have been investigated in various stu-

dies as markers of inflammation [7,9,10,13,14].

However, there is no single laboratory test or imaging method with 100% diagnostic sensitivity for acute appendicitis.

The mean age of the patients included in our study did not differ statistically between the groups. In accordance with the studies in the literature, male sex was dominant in the acute appendicitis group and male/female ratio was similar in the negative appendectomy group [9,13,17]. The negative appendectomy rate was 19.7% in female patients. We think that this rate is higher than male patients because of the gynecological causes of pelvic pain mimicking acute appendicitis symptoms.

In studies investigating the diagnostic value of NLR, for negative appendectomy was reported to be between 12.9-18.5% [8,9,13,17,21]. In our series, this rate was found to be 17.1%.

Complete blood count is an important component of diagnosis in patients with suspected acute appendicitis. Although leukocyte count generally increases in patients with acute appendicitis, it is not a specific marker for acute appendicitis and may increase in many diseases associated with other inflammatory conditions considered during differential diagnosis. In acute appendicitis, neutrophilia and a left shift in hemogram are often associated with lymphopenia [21,22]. In a meta-analysis (neutrophil count> 6500 / mm^3), Anderson reported a sensitivity of 71-89% and specificity of 48-80% [21]. In our study, the neutrophil count was found to be higher in the acute appendicitis group (p=0,000). The cut-off value determined according to the ROC curve analysis was found to have 70% specificity and 58% specificity (AUC: 0.654 (95% CI: 0.602-0.706) p=0.000)).

N. Boshnak et al. found low lymphocyte count as a risk factor in both univariate and multivariate analyses. When they determined the lymphocyte count (OR: 0.0125; 95% CI: 0.0015-0.1031; p<.001) cut-off value as 2.3×10^9/L, they found the sensitivity (82.76%), specificity (63.64%), positive (85.7%), negative (58.3%) predictive values as indicated. In the same study, the mean platelet counts in the groups with acute appendicitis, and negative appendec-

tomy were found to be 109 / L 237.45±54.08 and 257.00±48.55, respectively (p=0.02). When the cut-off value for the platelet count was taken as 188x109 × / L, they found the sensitivity (31.03%), specificity (100%), positive (100%), and negative (35.5%) predictive values as indicated [23]. In our study, the lymphocyte count was lower in the acute appendicitis group when compared to the negative appendectomy group (p=0.008). Multivariate analysis (OR: 1.84+0; 95% CI: 1.771-1.927; p=.008)x10³/mm³ showed a sensitivity of 52.3%, a specificity of 38%, a positive predictive value of 51,2% and a negative predictive value of 38,3% when the cut-off value was taken as 1,57 x10³/mm³. Platelet counts were higher in the negative appendectomy group (p=0.002). Multivariate analysis (OR: 256.38+3.52; 95% CI: 249.46-263.29; p=0.011) showed a sensitivity of 48.2%, a specificity of 43.8%, a positive predictive value of 47.3% and a negative predictive value of 55.4% when the cut-off value was taken as 1.57 x10³/mm³. Although there are contradictory views regarding platelet counts in acute appendicitis and complicated appendicitis, our series were similar to that of N. Boshnak et al [24-26].

The physiological response of leukocytes to stress is manifested as increased neutrophil, but decreased lymphocyte counts. Therefore, the ratio of these two parameters to each other is used as a marker of inflammation. During the inflammatory response, the ratio of leukocytes in the circulatory system changes. The increase in neutrophils is accompanied by relative lymphopenia. NLR can be claimed as a simple indicator of inflammatory response [27]. The evaluation of NLR can give us information regarding two different immune pathways simultaneously and it is also indicative of the body's overall inflammatory state. First, neutrophils responsible for inflammation and second, lymphocytes has a regulatory function [28]. Previous studies have shown that NLR may be significant in a variety of clinical situations and is a robust diagnostic marker of acute appendicitis [12,13,27,29].

Goodman et al. first suggested NLR as a potential diagnostic tool and they found it to be significant for diagnosing acute appendicitis when this value was greater than 3.5 [15]. Many studies in the literature have reported preoperative NLR to be a useful parameter that helps diagnose acute appendicitis and differentiates between uncomplicated and complicated appendicitis [9,12,13,21]. In contrast, Aktimur et al. found that NLR did not differ significantly between patients with positive and negative appendectomy [26].

Shimizu et al. recommends 5.0 as an cut-off value for NLR, with 44% sensitivity and 22% specificity for acute appendicitis.(30) Sevinç et al. reported an NLR cut-off value of 3.0 with a sensitivity of 81%, and specificity of 53% for the diagnosis of acute appendicitis and a cut-off value of 5.5 with a sensitivity of 78.4%, and a specificity of 4.1 % for the diagnosis of perforated appendicitis [9]. Kahramanca et al. reported in their series of 1067 cases that the preoperatively measured NLR cut-off value was 4.68 and it was statistically related with the detection of acute appendicitis. They found the sensitivity of NLR as 65.3%, specificity as 54.7%, a positive predictive value of 88.4%, and a negative predictive value of 23% [13]. In our study, NLR was found to be statistically significant for diagnosing acute appendicitis in the univariate (p=0.000) and multivariate analyses (p=0.024). The sensitivity and specificity of NLR were calculated as 57.3% and 69.9%, respectively, and the positive predictive value was 57.1% while the negative predictive value was 69.2%. In our study, the risk of acute appendicitis was 6.71 times higher in cases with NLRs ≥5.29 (OR: 6.71+0.28; 95% CI: 6.150-7.276;p=0.024).

We explain these sensitivity and specificity values which are rather low, by the inclusion of only patients who were operated on, in this study, as previously mentioned in the literature. We believe that the data on other suspected cases that were not operated on, or medically treated were not known, which could be the source of this finding [13].

It has been reported that as the severity of appendiceal inflammation increases, lymphocyte counts decrease greatly in addition to neutrophilia. Consequently, NLR increases as appendicitis progresses to appendiceal gangrene and subsequent perforation [21,31]. Sevinç et al. found the cut-off value as 3 for NLR. The rate of complicated appendicitis was 6.5% in their series [9]. In our series, we concluded that the cut-off value was higher than the series

cited in the literature, which was related to the fact that the rate of complicated appendicitis in our acute appendicitis patients was higher than the literature. Indeed, in 10% of the patients had complicated appendicitis. Despite conflicting recommendations in the literature regarding cut-off values, we believe that NLR is an important diagnostic parameter.

There are limited number of studies in the literature regarding the diagnostic value of NLR in different age subgroups. Yavuz et al. found in their study that for the ROC curve for NLR; the sensitivity was 92.5% while the specificity was 59.3% when the cut-off value was taken as 3.93; the sensitivity was 87.5% and the specificity was 63% when the cut-off value was taken as 4.51; and the sensitivity was 85% while the specificity was found to be 64.2% when the cut-off value was taken as 4.64. They found that diagnostic values for diagnosing acute appendicitis were increased when the cut-off value decreased [32]. Cigsar et al. found the cut-off value of NLR as 4.9 by the evaluation of ROC curve analysis in their series, the sensitivity and specificity were found to be 73% [33]. In our study, when the cut-off value was taken as 5.80 in the group of patients who were aged 60 years and older, the sensitivity was found to be 69.1%, specificity was 52.7%, the positive predictive value was 70.2% and the negative predictive value was calculated as 52.3%. The highest sensitivity for these cut-off values was detected in the age subgroup of 60 and over (69%), while the highest specificity was found in the 40-59 years age subgroup (58.2%).

The most important limitation of our study was that it was designed retrospectively. In addition, only appendectomy patients were included in the study; the patients who were suspected of acute appendicitis and followed up with medical treatment were excluded. However, our patient population was wider than the series in the literature. We believe that our study provides comprehensive data on the diagnostic accuracy of simple laboratory parameters in the suspicion of acute appendicitis, and this study contributes to the literature with useful and valuable reference data.

In conclusion, an NLR value of 5.29 seems to be a reliable parameter to help us diagnose acute appendicitis. Although sensitivity and specificity of NLR varies according to age subgroups, we have found the highest sensitivity in patients aged 60 years and older and the highest specificity in patients aged 40-59 years. However estimation of NLR value alone is not sufficient for the diagnosis of acute appendicitis, and normal NLR values alone cannot exclude acute appendicitis. The clinical evaluation of the surgeon should continue to be a priority in diagnosing acute appendicitis. In order to determine the diagnostic accuracy of NLR, further prospective randomized trials are needed.

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Angle Measurement in Critical Forearm Radiography in Pediatric Patients with Forearm Fractures Undergoing Conservative Treatment: Interobserver and Intraobserver Correlation Study

Konservatif Tedavi Uygulanan Önkol Kırıklı Pediyatrik Hastalarda Kritik Önkol Radyografisinde Açı Ölçümü: Gözlemciler Arası ve Gözlemciler İçi Korelasyon Çalışması

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ABSTRACT

Objective: Forearm fractures account for approximately 40% of child fractures. The elbow is treated conservatively with a 90° flexion cast. The aim of this study was to determine whether patients with forearm fractures who underwent open or closed reduction and fixation after loss of reduction in plaster follow-up is to make interobserver, and intraobserver comparisons of the radiological measurements of fracture angulations and to investigate the effect of these measurements on surgical decision.

Method: In the medical records of our clinic between 2013 and 2014, 36 forearm fractures were detected in 35 patients aged 10-15 years who had undergone open reduction, and fixation because of loss of reduction. Patients who had a 1/3 mid-diaphyseal fracture of the radia and ulna and whose radiological controls on days 5, 10, 15 and 31 revealed displacement fractures were retrospectively included in the study.

Results: Twenty –two patients who underwent open reduction and fixation were evaluated in terms of concordance between preoperative radiological measurements. ICC (Intraclass correlation coefficient) coefficients were 0.84 (0.69-0.92) for AP radius, 0.95 (0.91-0.97) for AP ulna, and 0.89 (0.80-0.95) for lateral radius, and 0.79 (0.60-0.90) for lateral ulna. According to this, there was a high level of concordance between these four parameters.

Conclusion: The decision for surgical treatment of the patients made by different surgeons who are responsible for the treatment is based on the evaluation of the patients as a whole, but not based on measurement of radiological parameters. Although it is considered that the measurement technique may change by experience, there is no statistical difference between the measurements performed by the same person at different times.

Keywords: forearm fractures, child, radiological, interobserver

ÖZ

Amaç: Önkol kırıkları çocuk kırıklarının yaklaşık %40'nı oluşturmaktadır. Genel olarak dirsek 90° fleksiyonda alçılama yapılarak konservatif tedavi edilir. Bu çalışmanın amacı, alçı ile takiplerinde redüksiyon kaybı sonrası açık veya kapalı redüksiyon ve tespit uygulanan önkol kırıklı çocuk hastaların, radyolojik kırık açılanması ölçümlerini gözlemciler arası ve gözlemciler içi olarak karşılaştırmak ve bunun cerrahi karara etkisini araştırmaktı.

Yöntem: Kliniğimizin 2013-2014 yılları arasındaki tıbbi kayıtlarında önkol kırıklarına redüksiyon kaybı nedeni ile açık redüksiyon ve tespit yapılan 10-15 yaş arası 35 hastanın 36 ön kol kırığı saptandı. Radius ve ulnanın 1/3 orta diafiz kırığı olan ve 5, 10, 15 ve 31'inci günlerdeki radyolojik kontrolleri sırasında kayma saptanarak operasyon kararı alınan hastalar retrospektif olarak çalışmaya dahil edildi.

Bulgular: Açık redüksiyon ve tespit yapılan 22 hasta ameliyat öncesi grafilerdeki radyolojik ölçüm sonuçları arasındaki uyumları değerlendirildiğinde; ICC (Intraclass correlation coefficient) katsayıları: AP radius için 0.84 (0.69-0.92), AP ulna için 0.95 (0.91-0.97) lateral radius için 0.89 (0.80-0.95), lateral ulna için 0.79 (0.60-0.90) hesaplandı. Buna göre değerlendirmeciler arasında 4 parametre için de yüksek uyum olduğu görüldü.

Sonuç: Tedavinin sorumluğunu yüklenen farklı cerrahlar tarafından hastaların cerrahi tedavisine karar verilmesi, hastaların sadece grafi üzerinden değerlendirilmeyip bütün olarak değerlendirilmesinden kaynaklanmaktadır. Ölçüm tekniğinin tecrübeyle değişebileceği düşünülmekle birlikte, aynı kişi tarafından farklı zamanlardaki ölçümler istatiksel olarak fark yoktur.

Anahtar kelimeler: çocuk, önkol kırığı, radyoloji, gözlemciler içi

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INTRODUCTION

Forearm fractures constitute approximately 40% of child fractures. Generally, elbow is fixated conservatively by plastering at 90° flexion [1,2]. The successful treatment is possible by maintaining the reduction in the correct position and ending the plastering at the appropriate time [3,4]. Failure, the risk of opening, depends on the movement in the plaster [5]. There was no relationship between the type, and location of the fracture and treatment failure. The general approach of pediatric orthopedics to pediatric forearm fractures is the application of surgical treatment in patients with a fracture displacement angle of 10° -15° or more than 50% [6].

The aim of this study was to compare the measurements of anterior or closed reduction and fixation of the forearm fractures in children based on interobserver measurements of traumatology residents and radiology specialists with different experiences between the observers and the effects of these measurements on the surgical decision.

MATERIAL and METHOD

Ethics committee decision was taken. Our study was planned retrospectively. In the medical records of our clinic between 2013 and 2014, 36 forearm fractures of 35 patients aged 10-15 years, who had undergone reduction and fixation due to fracture displacement were detected (Table 1). Patients who had 1/3 mid-diaphyseal fracture of the radius and ulna with a shift detected during their radiological controls on days 5, 10, and 31 were included in the study retrospectively. For 5 patients whose reduction was not considered adequate, immediately decision of surgical treatment was made Two patients with open fractures, 1 patient with fractures in both arms, 3 patients who could not be followed up properly, 1 patient with multiple organ injuries and 1 patient with metabolic bone disease were excluded from the study.

Table 1. Age, gender and location of fractures of the patients.

Variables	Mean±SD / Range
Age (years)	12.3±1.7 (10-15)
Gender	1female (4.5%) / 21 males (95.5%)
Location of the fracture	Middle right 16 (72.7%)
	Middle left 6 (27.3%)

Fractures were analyzed, and evaluated in AP and lateral radiograms. Angulations between 60 and 90 degrees in cortex are considered as transverse fractures, and less than 60 degrees were considered an oblique fracture. There were transverse fractures in 18 and oblique fractures in 4 patients. Spiral oblique and fragmented complex fractures were absent in our study.

At their first admissions, closed reduction and circular cast were applied to all patients and reduction was evaluated with control radiographs. Long-arm circular cast was applied in all patients with elbow at 90° flexion, forearm at neutral position and wrist at 10° extension in closed reduction. No patient's full cast was replaced with splint to relieve swelling.

Follow-ups were made on the 5th, 10th, and 15th days after reduction. On the 30th day, a short arm circular cast was applied. After reduction, AP and lateral radiograms showed that the reduction was sufficient if the angles were less than 10° and the translation was less than 50% in both radius and ulna.

During the follow-up of the cast, in two patients the cast became loosei So it was reconstructed on the 5th day, and a plaster replacement was performed without loss of reduction These two patients had union in the control radiograms obtained 20 days later.

When the reduction loss was observed in the patients, surgical treatment was applied within 15 (5-31) days. Surgical treatment was performed in three patients due to a shift of 12° (10°-14°) on day 5, 15° (11°-20°) on day 10, and 17° (16°-18°) on day 15 of 2 patients. On the 10th day, two patients who had translation were found to have an angle of 15°.

Evaluations were made by a specialist in orthopedics and traumatology with 10 year experience, and a resident in the clinic of orthopedics and traumatology by examining the latest digital radiograms before surgery. On the PACS (Picture archiving and communication system), the proximal of the radius is the middle of the bicipital tuberosity, the distal of the radius; was defined as the middle of the distal radius fiz line. The distance of these two points was divided into 3 identical parts and evaluated as middle third
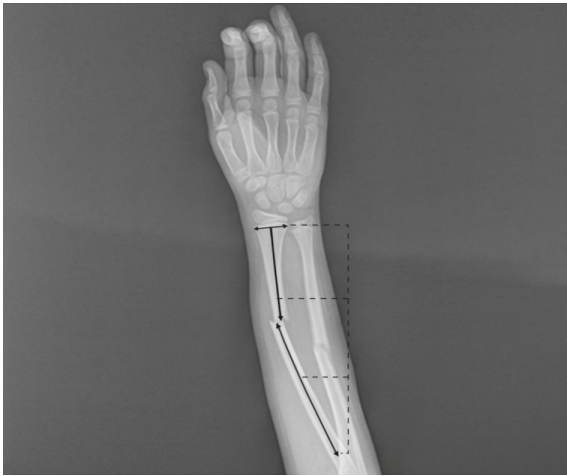
Graph 1. Evaluation of fracture site on AP forearm x-ray.
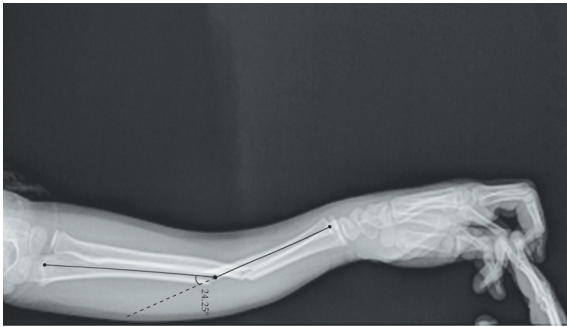
Graph 2. Measurement of fracture angulation on lateral forearm x-ray.

shaft fractures and included in our study. Ulna fractures were also identified by associating them with the radius (Graph 1).

The opening of both bones (radius and ulna) was defined as the angle between the lines drawn from the above-mentioned starting points to the midpoint of the fracture line in the radioulnar and dorsoventral plan (Graph 2). Inter-, and intra-observer measurements were made on the PACS system.

Angles were measured separately by the radiology, orthopedics and traumatology specialists in the same patients on the last digital radiograms before the operation and on the PACS system 6 weeks later.

For data analysis, 16.0 computerized version of the statistical program "SPSS (Statistical Package for Social Science) for Windows" was used. Descriptive methods were used to analyze the demographic and clinical features of the subjects at the beginning of the study. The agreement between the observers' evaluations was evaluated with "Intraclass Correlation Coefficient (ICC)"within the 95% confidence interval.

RESULTS

The BMIs of 3 female and 19 male patients were between 15-20 kg/m^2 (Table 1). There was no patient with excess swelling accompanying fractures. The reasons for the fracture in terms of fracture mechanism and energy included falling from a bicycle, or a ladder and falling while running.

When the compliance between the results of radiological measurements based on preoperative radiograms performed by radiologists, 10-year orthopedist, first year orthopedist and orthopedic surgery resident was evaluated. ICC (Intraclass correlation coefficient) coefficients: 0.84 (0.69-0.92) for AP radius, 0.95 (0.91-0.97) for AP ulna, 0.89 (0.80-0.95) for lateral radius, 0.79 (0.60-0.90) for lateral ulna were estimated. Accordingly, it was observed that there was a high agreement among the evaluators for all 4 parameters (Table 2).

In the evaluation of preoperative radiograms of the patients according to the radiologist, there were 16 patients with at least one angle above 10° and 11 patients with angle above 15°. According to the evaluation of the radiologist 6 weeks later, there were

Table 2. Conformity between observers in angle measurements.

	Experienced orthopedist Mean±SD (min-max)	Experienced radiologist Mean±SD (min-max)	One-year orthopedist Mean±SD (min-max)	First-year resident in orthopedics Mean±SD (min-max)	ICC** coefficients (within 95 confidence interval)
AP* radius°	10.1±8.2 (0-25)	7.5± 7.9 (0-30)	5±7.8 (0-30)	9.5±8.2 (0-30)	0.84 (0.69-0.92)
AP* ulna°	6.7±7.6 (0-27)	6.5±6.9 (0-23)	6.1±7.3 (0-25)	6.6±7.7 (0-27)	0.95 (0.91-0.97)
Lateral radius°	14.1±11 (0-35)	13.8±9.6 (0-33)	13.8±9.7 (0-37)	13.9±10.1 (0-35)	0.89 (0.80-0.95)
Lateral ulna°	6±8.3 (0-35)	6.4±7.5 (0-26)	3.6±4.7 (0-15)	6.1±7.3 (0-25)	0.79 (0.60-0.90)

Table 3. Measurements of the observer (orthopedist) and the intra-observer consistency in the decision for surgery.

	1. Measurement	2. Measurement	ICC** coefficient (95% confidence interval)
AP* radius°	10.1±8.2 (0-25)	8.4±7.6 (0-25)	0.89 (0.73-0.95)
AP* ulna°	6.7±7.6 (0-27)	7.3±7.7 (0-25)	0.97 (0.93-0.98)
Lateral radius°	14.1±11 (0-35)	13.9±12.4 (0-36)	0.95 (0.89-0.98)
Lateral ulna°	6±8.3 (0-35)	6.4 8.2 (0-36)	0.97 (0.92-0.98)

*AP: anterio-posterior, **ICC: Intraclass correlation coefficient*

17 patients with an angle of 10° and 11 patients with an angle of 15°.

According to the evaluation of preoperative AP and lateral radiograms of 16 patients after 6 weeks by the senior orthopedic specialist, operation decision was taken for 16 patients. According to the evaluation of the orthopedist; operation decision was taken for 16 patients (Table 3).

DISCUSSION

In this study, it was investigated whether the measurement of fracture angles on plain AP and lateral X-ray in forearm fractures, which were previously scheduled for surgery, was performed properly. This measurement is important because the fracture is operated in consideration of the measured angles.

The characteristics of displacement effects the surgical decision Angle of displacement is just one of the factors that is effective in decision-making process. Besides the angle, factors such as translation, rotation, shortening and elongation, number of parts and shape of the fracture line should be also evaluated.

There is no inter-observer and intra-observer study in the literature on this subject. In a study of 38 diseases related to medial epicondyle fractures in children with comparable demographic characteristics, though at a low level, inter-, and intra-observer differences were noted [7].

In a similar study, in the evaluation of cast index (CI), which is suggested as a factor in reduction loss, inter-observer and intra-observer differences were observed. Ten radiograms were randomly selected by two authors to measure CI, and for each intra-observer variability, each author re-evaluated the same radiograms for CI after a 6-week interval. When they used Pearson correlation, they found that CI showed good correlation between 0.61 and 0.80 and excellent correlation after 0.81 [8].

Many treatment algorithms have been proposed for forearm fractures. While many authors accept the opening up to 10° for forearm fractures as a limit for conservative treatment [9,10], some accept the opening up to 20° as the surgical limit [11,12]. There is consensus that rotation incompatibility should not be accepted for surgical treatment [9]. In patients with narrowed interosseous distance, significant rotational loss [13] or angular deformities [9,14] can be seen in the forearm. In a cadaver study, it was revealed that the 20° opening in the forearm fractures of the forearm caused a significant loss in the pronation-supination of the forearm [9]. The authors suggested that the decision of surgical treatment in 22 patients was based on 10° fracture opening by different surgeons who were responsible for the treatment.

When the reduction loss is seen, surgical decision is made within 15 (5-31) days in accordance with the literature [15].

The limitations of the study were its retrospective design, evaluation of angular deformity in only 2 plans, and the failure to measure the natural inclination of the radial bone on the intact side. The maximum angle shown in the accepted radioulnar and dorsoventral plan was excluded. However, real size can be approximated with the geometry used [10]. Translation was considered acceptable based on previous studies, and rotation was not evaluated [16,17].

In conclusion, it was determined that measurement of the fracture angles observed on plain AP and lateral radiograms was performed in pediatric forearm fractures. Although the compatibility between the mean of the interpersonal fracture angles is good,

the experienced orthopedic surgeon made the surgical decision in 16 patients.

It was thought that the decision to operate was made according to the 10° tilt rather than 15° tilt which is accepted as the general principle. Again, during the follow-ups, it was observed that a surgical approach was made due to the high possibility of shifting to the acceptable reduction limits. Another reason for this may be the increase of self-confidence of surgeons with the advancement of surgical techniques. The specialist in orthopedics and traumatology may have been affected by the anxiety of the parents and decided on surgery.

The decision of surgical treatment of patients by different surgeons who are responsible for the treatment is due to the fact that the patients are not only radiologically evaluated but rather as a whole. Although the measurement technique is thought to change and improve with experience, measurements at different times by the same person are not statistically significantly different.

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Idiopathic Sudden Hearing Loss: Relationship with Stress Perception, Coping Styles, Temperament and Personality Traits

İdiopatik Ani İşitme Kaybı: Stres Algısı, Baş Etme Stilleri ve Mizaç ve Kişilik Özellikleri ile İlişkisi

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ABSTRACT

Objective: *Literature knowledge about the etiology of idiopathic sudden sensorineural hearing loss (ISSHL) is limited. In many cases any cause cannot be demonstrated and the disease is termed as idiopathic. We aimed to compare the sudden hearing loss patients with healthy controls, in terms of their stress perception, coping styles and temperament and character traits. We hypothesized that ISSHL patients have higher stress levels and they are more sensitive to stressfull conditions.*

Method: *The study was conducted with a total of 94 participants, consisting of 44 patients with a diagnosis of sudden sensorineural hearing loss and 50 healthy controls'. Any participant with a psychiatric disease, history of medical treatment for psychiatric or organic brain disorder were excluded from the study. All participants were evaluated by self reports of The Perceived Stress Scale, Coping Inventory, for Stressful Situations Temperament and Character Inventory (TC) applied to the patients on the day of their hospitalization.*

Results: *Compaired to healty controls, patients with ISSHL had higher perceived stress scores, lower harm avoidance scores and higher reward dependence scores when compaired to controls. The ways of coping with stres were not different in-between the patients with sudden hearing loss and healthy controls. Moreover there was no correlation between the perceived stress levels and temperament and personality traits in groups.*

Conclusion: *In the present study, ISSHL patients had higher stress levels, lower harm avoidance, and higher reward dependence scores compaired to controls. These findings point out the importance of psychosocial factors in the etiology of ISSHL. ISSHL patients should be evaluated together with consultation-liaison psychiatry outpatient clinic, character, temperament characteristics and stress perception should be taken into conside.*

Keywords: *Idiopathic sudden sensorineural hearing loss, stress perception, coping styles, temperament and character*

ÖZ

Amaç: *İdiyopatik ani sensorinöral işitme kaybının (ISSHL) etiyolojisi hakkında literatür bilgisi sınırlıdır. Birçok durumda herhangi bir neden gösterilemez ve hastalık idiopatik olarak adlandırılır. Bu çalışmada ISSHL hastalarının, stres algıları, başa çıkma stilleri, mizaç ve kişilik özellikleri sağlıklı kontrollerle karşılaştırıldı. ISSHL hastalarının stres düzeylerinin daha yüksek olduğu ve stres koşullarına daha duyarlı oldukları varsayıldı.*

Yöntem: *Çalışma, 44'ü ISSHL tanısı alan ve 50'si sağlıklı kontrol olmak üzere toplam 94 katılımcı ile gerçekleştirildi. Psikiyatrik bir hastalığı olan, psikiyatrik veya organik beyin hastalığına yönelik tıbbi tedavi öyküsü olan hastalar çalışma dışı bırakıldı. Tüm katılımcılar, hastaneye yatış günün de Algılanan Stres Ölçeği, Başa Çıkma Envanteri, Mizaç ve Karakter Envanteri ile değerlendirildi.*

Bulgular: *Kontrol gurubu ile karşılaştırıldığında, ISSHL olan hastalarda, algılanan stres puanları ve zarardan kaçınma puanları düşük ve ödül bağımlılık puanları ise daha yüksek bulundu. Stresle başa çıkma yolları açısından ISSHL hastaları ve sağlıklı kontroller arasında anlamlı farklılık bulunmadı. Ayrıca algılanan stres düzeyleri ile mizaç ve kişilik özellikleri açısından gruplar arasında bir ilişki bulunamamıştır.*

Sonuç: *Bu çalışmada, ISSHL hastalarının, stres düzeyleri daha yüksek, zarardan kaçınma skorları daha düşük ve kontrollerle karşılaştırıldığında ödül bağımlılık skorları daha yüksek olarak bulundu. Bu bulgular ISSHL etiyolojisinde psikososyal faktörlerin önemine işaret etmektedir. ISSHL hastaları konsültasyon-liyezon psikiyatrisi polikliniği ile birlikte değerlendirilmeli, karakter, mizaç özellikleri ve stres algısı dikkate alınmalıdır.*

Anahtar kelimeler: *İdiopatik ani sensörinöral işitme kaybı, stres algısı, başa çıkma stilleri, mizaç ve karakter*

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INTRODUCTION

Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) is characterized by the development of at least 30 dB hearing loss in 3 consecutive audiometric frequencies measured within less than three days [1]. Vestibular symptoms, tinnitus, and fullness in the effected ear can accompany the hearing loss [2]. ISSHL can affect patients with any age however the incidence peaks between 43-53 years of age [3]. The disease is slightly more common in males [4].

Etiological factors can be determined in only 7% to 45% of ISSHL patients and the disease is termed as idiopathic in vast majority of cases [2]. Its pathophysiological mechanisms may include not only viral infections, tumor and immune system dysfunction but also pyschological stress and vascular events can be the etiological factors [3]. Cochlea has an increased risk for damage due to hypoxia or ischemia because of it is an end organ in terms of vascularisation. Kropp & Rad suggested that acute or chronic psychological stress may cause increased intravascular hemoconcentration in the cochlear artery and cause hypoxia or ischemia.

Stress is the effort that an individual exerts beyond his/her physical and psychological boundaries due to disturbing conditions in surrounding physical and social environment [5]. Stress stimulates the sympathic nervous system and hypothalamo-pituitary-adrenal axis. Allostatic load effects many types of tissues and organs and leads to neuronal atrophy, immune deficiency and atherosclerosis. Thus high level of stress causes negative consequences such as worsening of well-being, reducing and compelling the capacity of the person [6]. The stress level of an individual relates to the characteristics of stressful condition and also specific features of the individual. The specific features are stress perception, coping styles and personality traits. Each individual may perceive different levels of stress and use different ways of coping in a particular stressful situation. Coping with stress is defined as behavioral and mental effort that focus on controlling external or internal reactions or conflicts in between them with the purpose of decreasing the perceived threat and the resulting damage [5,7].

Personality is another feature which determines the person's response to stress. Personality directly effects stress perception level of the individual. Different kind of personality classifications have been performed. Cloninger et al, distinguish between seven personality traits within the domains of temperament (Novelty Seeking, Harm Avoidance, Reward Dependence, Persistence), and character (Self-Directedness, Cooperativeness, Self-Transcendence) [8,9]. Importance of knowing personality, temperament and character specialities in the pathophysiology and prognosis of the diseases has been reported.

Schüssler et al. showed that disease prognosis was positively influenced by tendency towards negative dependency and balanced emotional personality traits in patients with ISSHL [10]. In another study, it was observed that ISSHL patients had emotional instability and aggressive personality traits [11]. In addition, ISSHL has been shown to be associated with sensuality, guilt, and repressed seizures [12].

However, according to the English-language literature there is lack of knowledge about the etiology of ISSHL. In the present study we aimed to investigate the relationship between stress perception, coping skills and personality traits with ISSHL.

MATERIALS and METHODS

Participant and Treatment Protocol

The charts of 94 patients were evaluated retrospectively. Perceived Stress Scale, Ways of Coping Inventory, Temperament and Character Inventory tests were applied to a total of 44 patients who were admitted to the Ear Nose Throat Clinic in Bakırköy Dr Sadi Konuk Training and Research Hospital with sudden hearing loss and diagnosed as ISSHL. Patients with a psychiatric disease, history of medical treatment for psychiatric or organic brain disorder were excluded from the study. The control group consisted of 50 healthy participants who were subjected to Perceived Stress Scale, Ways of Coping Inventory, Temperament and Character Inventory tests

Statistical Analysis

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program was used for statistical

Table 1. Distribution of descriptive features.

	Total (n=94)	Patient Group (n=44)	Control Group (n=50)	P
Age; mean±SD	38,19±9,51	38,77±9,74	37,68±9,47	ª0,699
Gender: n (%)				
Male	38 (40,4)	18 (40,9)	20 (40)	ᵇ0,949
Female	56 (59,6)	26 (59,1)	30 (60)	

ª *Independent Samples test (Student t test)*
ᵇ *Ki-Square test*

analysis. Independent Samples t-test (Student t test) was used as descriptive statistical methods (mean, standard deviation, median, frequency and ratio), and for the correlation analysis of normally distributed variables in groups. Pearson's chi-Square test was used to compare qualitative data. Significance was evaluated at p<0.05.

RESULTS

Patient and control groups consisted of 94 participants. The mean age of participants was 39.19 ± 9.51 (22-25) years. Thirty -eight (40.4%) cases were male; and fifty-six (59.6%) were women. Distribution of descriptive features is presented in Table 1. The groups were similar in terms of age and sex of the participants (p>0.05).

There were not any statistically significant differen-

Table 4. Distribution of Perceived Stress Scale scores in groups.

	Perceived Stress Score		
	Mean	SD	P
Patient Group	30,95	8,62	0,001**
Control Group	23,08	3,10	
Total	26,77	7,39	

Independent Samples test (Student t test)
**p<0,01

ces between groups according to scores of novelty seeking (NS), persistence, self-directedness (SD), cooperativeness and self-transcendence (ST) in temperament and personality inventory (p>0.05). The patient group had statistically significantly lower Harm Avoidance (HA) and statistically significantly higher Reward Dependence (RD) scores than the control group (p<0.01). Distribution of the scores of subdimensions of temperament and character inventory are shown in Table 2.

There were no statistically significantly differences between the patient and control groups according to the scores of problem solving, social support and avoidance subscale scores of WCI (p>0.05) (Table 3).

Perceived stress scores were found to be statistically significantly higher in the patient group than the control group (p<0.01) (Table 4).

Table 2. Distribution of the scores of sub-dimensions of temperament and character inventory.

Temperament and Character Invantory	Total Mean±SD	Patient Group Mean±SD	Control Group Mean±SD	P
Novelty Seeking	15,87±3,88	15,41±4,08	16,28±3,74	0,449
Harm Avoidance	20,51±5,19	17,77±6,09	22,92±2,50	0,001**
Reward Dependence	15,66±3,20	17,32±3,64	14,20±1,80	0,001**
Persistence	4,77±1,61	4,55±1,54	4,96±1,67	0,383
Self directedness	24,38±7,03	25,68±6,07	23,24±7,72	0,239
Cooperativeness	26,70±5,23	25,82±7,14	27,48±2,54	0,310
Self-Transcendence	19,57±4,84	19,32±5,87	19,80±3,84	0,738

Independent Samples test (Student t test), **p<0,01

Table 2. Distribution of the scores of sub-dimensions of temperament and character inventory.

Stress-Coping Style Inventory Subscales	Total Mean±SD	Patient Group Mean±SD	Control Group Mean±SD	P
Problem Solving	19,96±4,12	20±3,95	19,92±4,35	0,948
Social Support	18,51±4,27	18,32±4,01	18,68±4,57	0,776
Avoidance	20,57±4,30	20,55±4,83	20,60±3,88	0,966

Independent Samples test (Student t test), **p<0,01

DISCUSSION

In the present study, we aimed to compare ISSHL patients with healthy controls according to their stress perception, ways of coping mechanisms, temperament and character traits. We found that ISSHL patients had higher perceived stress scores, lower harm avoidance scores and higher reward dependence scores than the control group.The ways of coping with stress were not different between the ISSLH patients and healthy controls. Furthermore there was no correlation between the perceived stress levels and temperament and personality traits in two groups.

Miguel et al. (2009) suggested that stress causes vasoconstriction, hyperviscosity and platelet aggregation in the labyrinthine artery, inner ear hypoxia or ischemia [13]. In ISSHL, patients reported higher stress levels and more stressful life-events before the sudden hearing loss occurred when compared with healthy controls. While certain single-case studies have reported the association between stress and ISSHL which used qualitative interviews as assessment instruments [14-16]. However, any standardized assesment methods were not found, and quantitative statistical analysis of the collected data was not performed Two other studies, which limited by method and design, had similar results [14,16]. Consistent with these previous researches in our study, the results showed that patients with ISSHL have significantly higher levels of perceived stress scores compaired with the control group.

However the disease is termed as idiopathic. Many factors have been stated in the etiology of ISSHL. Yamasoba et al. (1993) reported that insufficiency of the vertebrobasilar system can cause sudden hearing loss [17]. Suckfüll et al. found higher plasma fibrinogen ratio in ISSHL patients which indicates the increased coagulability [18]. In 3% of ISSHL patients vascular or hematologic pathologies were causative factors [19]. Psychological stress is an important factor in vascular pathologies. It stimulates the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis and causes vasoconstriction in visceral organs and reduces tissue perfusion [20]. Psychological stressors, depression and anxiety have been shown to cause severe hypercoagulability in patients with atherosclerosis [21].

Coping mechanisms are important in determining how the individual experiences the stress in a specific stressful situation. In other words the ways of coping with stress are important for psychiatric and physiological outcomes of stress on our body. The negative effects of stress are directly related to the coping behavior. It was reported that the ability of using effective coping strategies has protective effects on the individual health [7].

There are similarities in the pathophysiology of acute myocardial infarction and ISSHL. In our study, reward dependence (RD) scores were found to be higher in the patient group than in the control group. Similar to our study, In a study RD scores were found to be higher in patient with acute MI than in control group [22]. The patients with higher RD scores are defined as having tendency to be affectionate, warm, sensitive, dependent and social. They seek a social relationship and are open to communicate with others. Although capable of warm social relationships is one of the most important advantage of people with high RD, these people has an important disadvantage; their opinions and emotions can be easily influenced by others. Efforts to please the other people is a major burden on these people who have higher reward dependence levels [22,23].

Harm avoidance scores were found to be higher in patients who had psychosomatic disease, chronic pain, irritable bowel syndrome or tinnitus. Increased harm avoidance scores are related to careful planning and high cautiousness in the event of danger [23,24]. In our study, the harm avoidance scores were found to be lower in ISSHL patients than the control group. The people with lower harm avoidance scores are confident, relaxed, courageous, energetic, sympathetic, optimistic even in situations that concern most people. It was thought that lower harm avoidance scores could be related to the possibility of danger or stress situation that cannot be predicted and higher perception of stress in stressful life events [23,25]. Studies have shown that patients with ISSHL have a higher level of emotional instability, aggressive personality traits, and repressed guilt associated with very severe attacks of anger [11,12].

Schüssler et al. suggested that; while psychosocial factors may have an affect on the onset of ISSHL,

there is a positive effect of balanced emotional personality, good friendship and reduction of stress factors on the prognosis of the disease and the prognosis is worser in patients with a tendency to addiction [10]. Personality traits may exert an important role on the occurrence and prognosis of the disease [26]. ISSHL patients should be evaluated together with consultation-laison psychiatry outpatient clinic and the patients must be evaluated in terms of character, temperament characteristics and stress perception.

In conclusion we found that ISSHL patients had higher stress levels, lower harm avoidance and higher reward dependence scores compaired to the control group. These findings point out the importance of psychosocial factors in ISSHL etiology. Consideration of psychosocial factors in a case -spesific approach may contribute to the understanding of the pathophysiology, prognosis and also treatment of the disease. We suggest that the treatment of ISSHL patients should be done in a multidiciplinary approach.

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T.C. SAĞLIK BAKANLIĞI İL SAĞLIK MÜDÜRLÜĞÜ SAĞLIK BİLİMLERİ ÜNİVERSİTESİ BAKIRKÖY DR. SADİ KONUK EĞİTİM VE ARAŞTIRMA HASTANESİ