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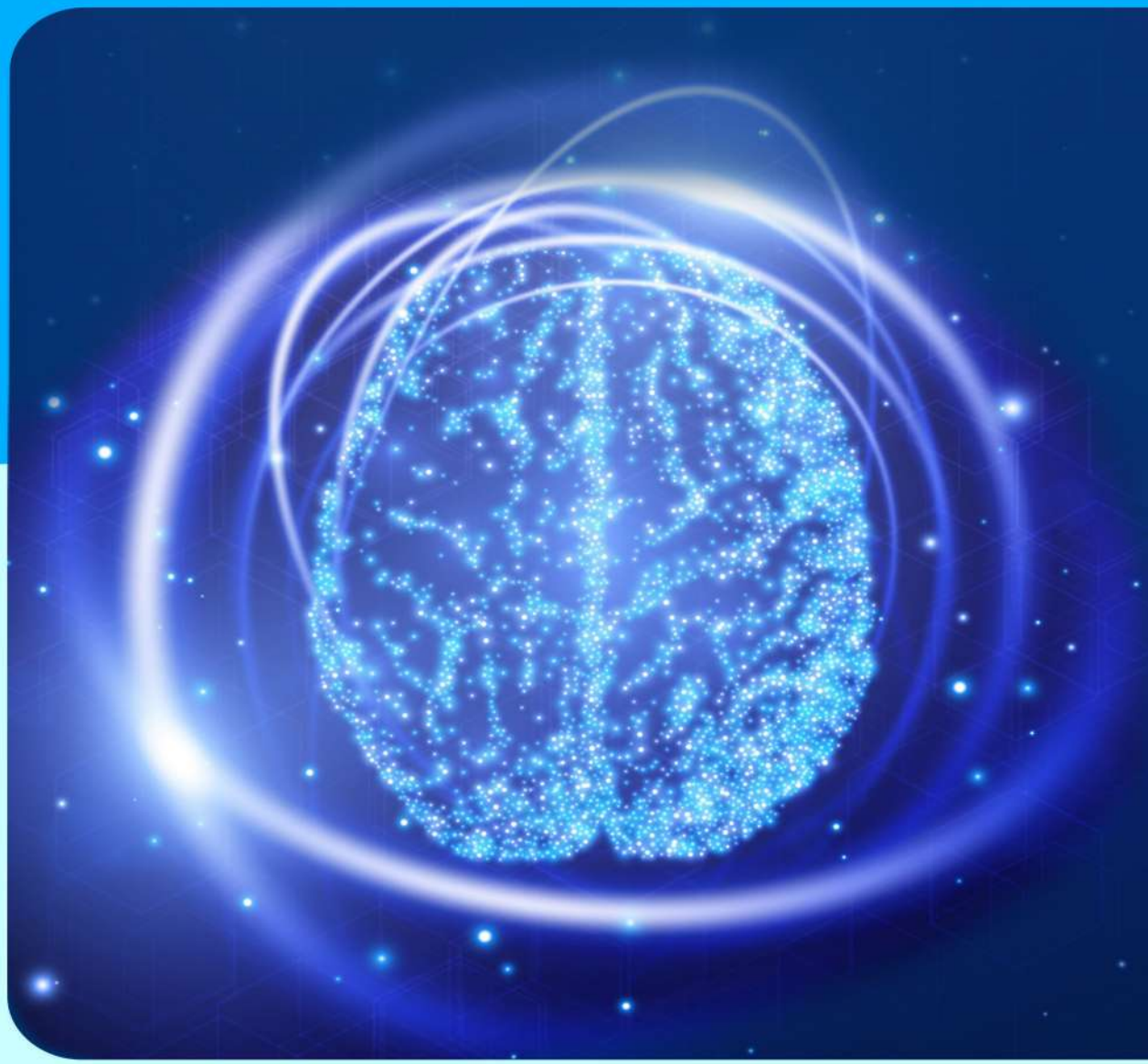

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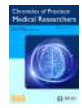

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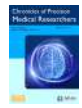

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If the "Animal" item was used in the study, the authors stated that in the Material and Method section of the article, they protect the animal rights in their studies in accordance with the principles of Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) and that they have received approval from the ethics committees of their institutions. must specify.

In case reports, Informed Consent a should be obtained from patients regardless of the identity of the patient.

If the article includes the institution (directly or indirectly) providing financial support for the commercial connection or work, the authors; the commercial product used, the drug, the company has no commercial relationship with, or if there is any relationship (consultant, other agreements, etc.), the editor must inform the presentation page.

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Case Reports should not exceed 1000 words and 10 references, and should be arranged as follows: Abstract, Introduction, Case Report, Discussion and References. It may be accompanied by only one figure or table.

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b) All pages should be numbered consecutively in the top right-hand corner, beginning with the title page.

c) The title page should not include the names and institutions of the authors.

d) The manuscript should be presented in the following order: Title page, Abstract (English, Turkish), Keywords (English, Turkish), Introduction, Materials and Methods, Results, Discussion, Conclusion, Acknowledgements (if present), References, Figure Legends, Tables (each table, complete with title and foot-notes, on a separate page) and Appendices (if present) presented each on a separate page.

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The title should be short, easy to understand and must define the contents of the article.

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Abstract should be in both English and Turkish and should consist "Aim, Materials and Methods, Results and Conclusion". The purpose of the study, the setting for the study, the subjects, the treatment or intervention, principal outcomes measured, the type of statistical analysis and the outcome of the study should be stated in this section (up to 300 words). Abstract should not include reference. No abstract is required for the letters to the Editor.

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Authors should use subheadings to divide sections regarding the type of the manuscript as described above. Statistical methods used should be specified in the Materials and Methods section.

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In the text, references should be cited using Arabic numerals in parenthesis in the order in which they appear. If cited only in tables or figure legends, they should be numbered according to the first identification of the table or figure in the text. Names of the journals should be abbreviated in the style used in Index Medicus. The names of all authors should be cited when there are six or fewer; when seven or more, the first three should be followed by et al. The issue and volume numbers of the referenced journal should be added.

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Supplement

Solca M. Acute pain management: Unmet needs and new advances in pain management. Eur J Anaesthesiol 2002; 19(Suppl 25): 3-10.

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Online article not yet published in an issue

Butterly SJ, Pillans P, Horn B, Miles R, Sturtevant J. Off-label use of rituximab in a tertiary Queensland hospital. Intern Med J doi: 10.1111/j.1445-5994.2009.01988.x

Book

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Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. I n: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93113.

Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website

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

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The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

Acknowledgements

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

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All illustrations (including line drawings and photographs) are classified as figures. Figures must be added to the system as separate .jpg or .gif files (approximately 500x400 pixels, 8 cm in width and at least 300 dpi resolution). Figures should be numbered consecutively in Arabic numbers and should be cited in parenthesis in consecutive order in the text.

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All measurements must be given in metric system (Système International d'Unités, SI). Example: mg/kg, µg/kg, mL, mL/kg, mL/kg/h, mL/kg/min, L/min, mmHg, etc. Statistics and measurements should always be given in numerals, except where the number begins a sentence. When a number does not refer to a unit of measurement, it is spelt out, except where the number is greater than nine.

Abbreviations that are used should be defined in parenthesis where the full word is first mentioned. Some common abbreviations can be used, such as iv, im, po, and sc.

Drugs should be referred to by their generic names, rather than brand names.

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YAZARLARA BİLGİ

AMAÇ ve KAPSAM

Chronicles of Precision Medical Researchers Dergisi, dört ayda bir yayımlanır ve üç sayı ile bir cilt tamamlanır. Dergi; pediatri ile ilgili tüm nitelikli klinik ve deneysel araştırmaları, olgu sunumlarını ve editöre mektupları yayımlar.

Chronicles of Precision Medical Researchers Dergisi, bilimsel yayınlara açık erişim sağlar. Dergi basımından hemen sonra, makalelerin tam metinlerine ücretsiz ulaşılabilir.

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Yazının Başlığı

Kısa, kolay anlaşılır ve yazının içeriğini tanımlar özellikte olmalıdır.

Özetler

Türkçe (Öz) ve İngilizce (Abstract) olarak yazılmalı, Amaç, Gereç ve Yöntem, Bulgular ve Sonuç (Aim, Materials and Methods, Results, Conclusion) olmak üzere dört bölümden oluşmalı, en fazla 300 sözcük içermelidir. Araştırmanın amacı, yapılan işlemler, gözlemsel ve analitik yöntemler, temel bulgular ve ana sonuçlar belirtilmelidir. Özette kaynak kullanılmamalıdır. Editöre mektup için özet gerekmemektedir.

Anahtar Sözcükler

Türkçe Öz ve İngilizce Abstract bölümünün sonunda, Anahtar Sözcükler ve Keywords başlığı altında, bilimsel yazının ana başlıklarını yakalayan, Index Medicus Medical Subject Headings (MeSH)'e uygun olarak yazılmış en fazla beş anahtar sözcük olmalıdır. Anahtar sözcüklerin, Türkiye Bilim Terimleri'nden (www.bilimterimleri.com) seçilmesine özen gösterilmelidir.

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Kaynaklar

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Chronicles of Precision
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Chronicles of Precision Medical Researchers

VOLUME 4 ISSUE 1 YEAR 2023

CONTENTS

ORIGINAL ARTICLES

Evaluation of Cervical Vestibular Evoked Myogenic Potentials in Conductive or Mixed Hearing Losses
İletim Tipi veya Mikst Tip İşitme Kayıplarında Servikal Vestibüler Uyarılmış Miyojenik Potansiyellerin Değerlendirilmesi
1 ..... *Tanyeri Toker G, Ceylan S, Gümüşgün A.*

An Etiological Evaluation of Children with Acute Recurrent Pancreatitis: Based on Genetic Analysis and Pancreaticobiliary Maljunction without Biliary Dilatation
Akut Rekürren Pankreatitli Çocukların Etiyolojik Değerlendirmesi: Genetik Analiz ve Biliyer Dilatasyonsuz Pankreatikobiliyer Bileşke Anomalisi Temelinde
7 ..... *Yucel A, Mutlu B, Kerimoglu U, Asil M, Ozbek O, Ozcan E, Gumus M, Unal G, Pekcan S, Yuksekkaya HA.*

Juvenile Localized Scleroderma from a Pediatric Rheumatology Perspective: A Single-Center Experience
Çocuk Romatoloji Perspektifinden Juvenil Lokalize Skleroderma; Tek Merkez Deneyimi
15 ..... *Güngörer V, Çelikel E, Ekici Tekin Z, Tekgöz N, Sezer M, Karagöl C, Coşkun S, Kaplan MM, Öner N, Polat MC, Çelikel Acar B.*

Evaluation of Children (<2 Years Old) with Respiratory Syncytial Virus Bronchiolitis in Terms of Disease Course and the Requirements of Additional Treatment
Respiratuar Sinsisyal Virüs Bronşiyoliti Olan Çocukların (<2 Yaş) Hastalığın Seyri ve İlave Tedavi Gereksinimleri Açısından Değerlendirilmesi
22 ..... *Söğütlü Y, Namdar M, Şah O, Çağ Y, Kepenekli E, Kurt G, Altunok EÇ.*

Investigating the Presence of Inflammation in Lateral Epicondylitis with Platelet/Lymphocyte Ratio, Neutrophil/Lymphocyte Ratio, and Systemic Immune-Inflammation Index
Lateral Epikondilitte Enflamasyon Varlığının Trombosit/Lenfosit Oranı, Nötrofil/Lenfosit Oranı ve Sistemik İmmün-İnflamasyon İndeksi ile Araştırılması
29 ..... *Uysal A.*

Lepidik Patern Akciğer Adenokarsinomlarında İmmünohistokimyasal Anti-Rage Antikorunun Rolü
The Role of Immunohistochemical Anti-Rage Antibody in Lepidic Pattern Lung Adenocarcinomas
34 ..... *Çelik M, Ateş MC, Gencel E, Harmankaya İ, Çelik ZE, Sanal Yılmaz B, Yıldıran H.*

Morphological Analysis of Foramen Ovale and Foramen Lacerum in terms of Percutaneous and Endoscopic Endonasal Approaches
Foramen Ovale ve Foramen Lacerum'un Perkutanöz ve Endoskopik Endonasal Yaklaşımlar açısından Morfolojik Analizi
39 ..... *Tuğtağ Demir B.*

Does Maternal Vitamin D Deficiency Affect Perinatal Outcomes?
Maternal Vitamin D Eksikliği Perinatal Sonuçları Etkiler Mi?
45 ..... *Cevher Akdulum MF, Biberoğlu KÖ.*

Preterm ve Term Bebeklerde Serum γ-Glutamil Transferaz Düzeylerinin Referans Değerlerinin Belirlenmesi
Determination of Reference Values of Serum γ-Glutamil Transferase Levels in Preterm and Term Babies
50 ..... *Menekşe E, Baş M.*

ISSN: 2757-6124

Chronicles of Precision Medical Researchers

VOLUME 4 ISSUE 1 YEAR 2023

CONTENTS

ORIGINAL ARTICLES

HAV, HBV, HCV and HIV Seroprevalence in Patients Who Requested ELISA Examination in the Emergency Department, a Retrospective Study
Acil Serviste ELISA Tetkiki İstenen Hastalarda HAV, HBV, HCV ve HIV Seroprevalansı, Retrospektif Bir Çalışma
54 ..... *Arıkan C, Bora ES.*

Çocuklarda Ewing Sarkom Ailesi Tümörler: Tek Merkez Sonuçları
Ewing's Sarcoma Family of Tumors in Children: The Results from A Single Center
59 ..... *Saran R, Aydın BK, Kara B, Düzova M, Çelik ZE, Köksal Y.*

Can Inflammatory Markers Measured before Total Knee Replacement be an Early Indicator of Revision?
Total Diz Protezi Öncesi Ölçülen İnflamatuar Belirteçler Revizyonun Erken Belirteci Olabilir Mi?
64 ..... *Bozduman Ö, Çıtır ÖC.*

Ailevi Akdeniz Ateşi ile İlişkili Renal Amiloidozu Değerlendirmede Renal Dupleks Doppler Ultrasonografinin Tanısal Değeri
Diagnostic Value of Renal Duplex Doppler Ultrasonography in the Evaluation of Renal Amiloidosis Associated with Familial Mediterranean Fever
68 ..... *Bekar Ü, Acu B.*

Evaluation of the Factors Affecting the Clinical Course and Prognosis in a Group of Patients with Transverse Myelitis
Transvers Miyeliti Olan Bir Grup Hastada Klinik Seyir ve Prognozu Etkileyen Faktörlerin Değerlendirilmesi
73 ..... *Kurt Gök D, Baydemir R.*

Does Carpal Tunnel Syndrome Affect Disease Activity in Patients with Fibromyalgia?
Karpal Tünel Sendromu Fibromiyaljili Hastalarda Hastalık Aktivitesini ve Yaşam Kalitesini Etkiler mi?
79 ..... *Karakuyu AC, Cankurtaran D, Güzel Ş, Umay E.*

Long-Term Prognostic Evaluation of Patients Presenting to the Emergency Department with a Pre-Diagnosis of Sepsis
Acil Servise Sepsis Ön Tanısı İle Başvuran Hastaların Uzun Dönem Prognostik Değerlendirilmesi
86 ..... *Çınaroğlu OS, Efgan MG.*

Efficacy of Acetic Acid and Lugol's Iodine Assisted Colposcopic Imaging in Cases with Anormal Pap Smear Test Results
Anormal Pap Smear Testi Sonucu Olan Olgularda Asetik Asit ve Lugol İyot ile Kolposkopik Görüntülemenin Etkinliği
91 ..... *Gursoy A, Atasayan K, Balcicek HB, Celik A.*

Survival and Failure Outcomes of Neoadjuvant/Definitive Radiotherapy in Locally Advanced Esophageal and Gastro-Oesophageal Junction Cancer: A Single Institute Experience
Lokal İleri Evre Özofagus ve Gastroözofageal Bileşke Tümörlerinde Neoadjuvan/Definitif Radyoterapinin Sağkalım ve Başarısızlık Sonuçları: Tek Merkez Deneyimi
96 ..... *Guler Avci G, Demir F.*

Sağlık Hizmetleri Meslek Yüksekokulu Öğrencilerinin Delici Kesici Alet Yaralanmaları Hakkında Bilgi Düzeylerinin Belirlenmesi
Determination of the Knowledge Levels of The Health Services Vocational School Students about Sharps Injuries
101 ..... *Şahinoğlu MS, Dindar Demiray EK, Alkan S, Öntürk Akyüz H.*

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Chronicles of Precision Medical Researchers

VOLUME 4 ISSUE 1 YEAR 2023

CONTENTS

CASE REPORTS

Hereditary Spastic Paraparesis Accompanied by Sensorimotor Axonal Polyneuropathy-A Case Report
Sensorimotor Aksonal Polinöropatiye Eşlik Eden Herediter Spastik Paraparezi-Olgu Sunumu
107 ..... *Kırac Unal Z, Gündüz YÖ, Cankurtaran D, Ünlü Akyüz E.*

Muhtemel COVID-19 Tarafından Tetiklenen Poliarteritis Nodosa Olgusu
A Case of Polyarteritis Nodosa Triggered by Possible COVID-19
110 ..... *Günay S, Gündoğdu A, Çapar E.*

A Case of Deep Thrombocytopenia which had Successfully Received Prolonged Trimethoprim Sulfametaxazole Treatment for Nocardiosis
Derin Trombositopeniye Rağmen Uzun Süreli Trimetoprim Sülfametaksazol Tedavisini Başarıyla Tamamlayan Bir Nokardiyoz Olgusu
114 ..... *Altay FA, Aslan V, Şentürk GÇ, Albayrak M, Okutan H, Şencan İ.*

The Efficacy of Pazopanib in Ewing Sarcoma
Ewing Sarkomunda Pazopanib'in Etkinliği
117 ..... *Kayikcioglu E, Onder AH, Cetin FB, İnal G.*

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Evaluation of Cervical Vestibular Evoked Myogenic Potentials in Conductive or Mixed Hearing Losses

İletim Tipi veya Mikst Tip İşitme Kayıplarında Servikal Vestibüler Uyarılmış Miyojenik Potansiyellerin Değerlendirilmesi

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ABSTRACT

Aim: To evaluate the role of Cervical Vestibular Evoked Myogenic Potentials (cVEMP) in the differential diagnosis of middle and inner ear pathologies by analyzing the test results in conductive or mixed hearing loss in patients with intact tympanic membrane.

Material and Method: The study included 50 patients (67 ears) with intact tympanic membranes and had air-bone gap in pure tone audiometry test, who applied to otorhinolaryngology department between January 2019 and September 2022. The cVEMP test results of these patients were evaluated and analyzed.

Results: The age range of the patients was 18-75, the mean age was 47.55±13.59, half of them were male and half were female. The most common middle ear pathology was otosclerosis (62%), while the most common inner ear pathology was superior semicircular canal dehiscence (10%). In the other patients (28%), pathologies such as tympanosclerosis, chronic mastoiditis, serous otitis media, ossicular chain pathology, otic capsule dehiscence, and middle ear mass were found. While no cVEMP response was obtained in 41 (82%) of the patients, cVEMP response was obtained in 9 (18%) patients.

Conclusion: Preoperative cVEMP response, threshold and amplitude values may help in the differential diagnosis of conductive or mixed hearing loss in patients with intact tympanic membrane. Thus, it can be used to determine the patients to be operated on and the surgical approach.

Keywords: Cervical vestibular evoked myogenic potentials, conductive hearing loss, mixed hearing loss, air-bone gap, otosclerosis, semicircular canal dehiscence

ÖZ

Amaç: Timpanik membranın intakt olduğu iletim tipi veya mikst tip işitme kayıplarında Servikal Vestibüler Uyarılmış Miyojenik Potansiyeller (cVEMP) testi sonuçları analiz edilerek orta ve iç kulak patolojilerinde cVEMP testinin ayırıcı tanıdaki rolünün değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya Ocak 2019-Eylül 2022 tarihleri arasında Kulak Burun Boğaz Hastalıkları polikliniğine başvuran ve timpanik membranları intakt olup saf ses odyometri testinde hava-kemik aralığı mevcut olan 50 hasta (67 kulak) dahil edilmiştir. Bu hastaların cVEMP testi sonuçları değerlendirilerek analiz edilmiştir.

Bulgular: Hastaların yaş aralığının 18-75, yaş ortalamasının 47,55±13,59, yarısının erkek ve yarısının kadın olduğu saptanmıştır. Hastalarda en sık orta kulak patolojisi otoskleroz olup (%62), en sık iç kulak patolojisi ise süperior semisirküler kanal dehissansı (%10) olarak saptanmıştır. Diğer patolojiler (%28) ise timpanoskleroz, kronik mastoidit, seröz otitis media, kemikçik zincir patolojisi, otik kapsül dehissansı, orta kulakta kitledir. Hastaların 41'inde (%82) cVEMP yanıtı alınamamışken 9'unda (%18) cVEMP yanıtı alınmıştır.

Sonuç: Ameliyat öncesi cVEMP yanıtı, eşik ve amplitüd değerleri, sağlam kulak zarı olan hastalarda iletim tipi veya mikst işitme kaybının ayırıcı tanısında yardımcı olabilir. Böylelikle ameliyat edilecek hastaların ve kullanılacak cerrahi yaklaşımın belirlenmesinde kullanılabilir.

Anahtar Kelimeler: Servikal vestibüler uyarılmış miyojenik potansiyeller, iletim tipi işitme kaybı, mikst tip işitme kaybı, hava kemik aralığı, otoskleroz, semisirküler kanal dehisansı

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INTRODUCTION

In the presence of air-bone gap in pure tone audiometry test, if the bone conduction thresholds are <20 dB at 250-4000 Hz, it is considered as conductive hearing loss (CHL), and if it is >20 dB at one or more frequencies, it is considered as mixed hearing loss (MHL) (1). Conductive hearing loss is mostly caused by the outer and/or middle ear, but it can also be caused by the inner ear (third window syndrome). Sensorineural hearing loss is usually seen in inner ear pathologies. In the third window syndrome, the hearing threshold increases due to the loss of sound energy transmitted to the inner ear by the air conduction. As a result of the decrease in the impedance of the inner ear fluids, the hearing threshold decreases due to the increase in the sound energy transmitted to the inner ear by the bone conduction and air-bone gap occurs (2).

Vestibular evoked myogenic potentials (VEMP) is a neurophysiological evaluation technique used to evaluate the vestibular functions of the patients (3). VEMPs can be classified as ocular VEMP (oVEMP) and cervical VEMP (cVEMP) according to where the electrodes are recorded. Cervical VEMP is a short-latency inhibitory response that can evaluate the function of the sacculocolic pathway measured over the ipsilateral sternocleidomastoid muscle (4). In recent years, the use of cVEMP test in audio-vestibular clinical applications has become increasingly common.

Halmagyi et al. (5) showed that cVEMP responses were not obtained when the air-bone gap was greater than 20 dB in pure tone audiometry, Bath et al. (6) reported that 97% of patients with CHL did not have a cVEMP response. Even if the vestibulospinal reflex arc is intact in CHLs due to outer and middle ear pathologies, cVEMP response may not be obtained due to decreased air conduction (7). For these reasons, it is not suitable to be used in the differential diagnosis of outer and middle ear pathologies. In inner ear pathologies such as superior semicircular canal dehiscence (SSCD), the dehiscence plays the role of the third window, making the inner ear membranes more sensitive to sound and pressure (8). For this reason, cVEMP responses can be obtained even at low sound intensities in CHLs due to inner ear pathologies. This enables the cVEMP test to be used in the differential diagnosis of inner ear and middle ear pathologies.

There are limited studies in the literature evaluating the role of cVEMP test in differential diagnosis. However, the fact that the tympanic membrane is intact in most CHLs originating from the inner ear and the tympanic membrane is perforated or adhesive due to chronic otitis media in middle ear pathologies makes the use of cVEMP unnecessary in the differential diagnosis. In addition, cVEMP may have a role in differentiating middle ear pathologies with intact tympanic membrane, such as otosclerosis, from inner ear pathologies. Therefore, it would be more accurate to compare cVEMP findings in patients with intact tympanic membrane. Furthermore, immitancemetry, another test used in differential diagnosis, can also be used in patients with intact tympanic membranes, and when evaluated together with cVEMP, it can make the diagnosis easier. However, there is no such study in the literature. Current studies either included patients with perforated/adhesive tympanic membranes, or acoustic immitancemetry was not evaluated.

In our study, it was aimed to evaluate the findings of cVEMP test in conductive or mixed hearing loss with intact tympanic membrane and to determine the importance of this test in the differential diagnosis of inner and middle ear pathologies.

MATERIAL AND METHOD

Study design and ethical approval

The study is in the nature of a retrospective patient cards review and ethical approval of the study was obtained from the Non-Invasive Clinical Research Ethics Committee (Date - No: 21.10.2021-0426). Informed consent form did not obtained from the participants due to the nature of the study.

Study group

Fifty patients (67 ears) who applied to the otorhinolaryngology department between January 2019-September 2022 and were evaluated in the audiology unit were included. The tympanic membranes of all patients were intact and those with air-bone gap in the pure tone audiometry test were analyzed by evaluating together the acoustic immitancemetry, cVEMP test and computed tomography results, if any.

Inclusion criteria

1. Absence of external ear canal (EEC) pathology
2. Intact tympanic membrane
3. Presence of pure tone audiometry, acoustic immitancemetry, and cVEMP tests
4. Air-bone gap in pure tone audiometry greater than 10 dB at more than 3 frequencies between 250 and 4,000 Hz or more than 15 dB at 2 or more frequencies

Exclusion criteria

1. EEC pathology
2. Perforated/adhesive or severe retracted tympanic membrane
3. Absence of at least one of the pure tone audiometry, acoustic immitancemetry, and cVEMP tests
4. Pure sensorineural hearing losses

Obtaining and evaluating data

Pure tone audiometry: Tests were performed using the Interacoustics model AC40 S3.6, 1996 (Interacoustics AS, Assens, Denmark). 500 Hz, 1 kHz, 2 kHz and 4 kHz air and bone conduction hearing thresholds were averaged. Those with air-bone gap were included in the study.

Acoustic immitancemetry: It was carried out with Neurosoft Audio-Smart Immitancemeter (Ivonovo, Russia) using 226 Hz probe tone. Along with tympanometry, ipsilateral and contralateral acoustic reflex measurements were made at frequencies of 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz.

Cervical vestibular evoked myogenic potentials: Tests were performed using the Interacoustics Eclipse Ep 15 ABR system (Middelfart, Denmark). The active electrodes were placed on the middle 1/3 of the sternocleideomastoid (SCM) muscle, the ground electrode was placed on the mid-forehead, and the reference electrode was placed on the sternoclavicular joint where the SCM muscle was attached to the sternum. Attention was paid to ensure that the impedances of the surface electrodes were below 5 kΩ. In the sitting position, the participants rotated their heads to the opposite side of the tested ear. In this way, tonic activation of the ipsilateral SCM muscle is provided. Records were taken by setting the "EMG controlled recording" option, which can collect data only when the desired muscle tone can be achieved in the test system. A 500 Hz tone burst stimulus was delivered using insert headphones (E-A-R Tone 3A ABR, 3M, St. Paul, MN, USA). Stimulus Polarity: Rarefaction, Rate: set to 5.1. In filtering; High Pass Filter: 10 Hz and Low Pass Filter: 3000 Hz. The average number is taken as 200. First, the electromyographic activity of the SCM muscle was measured by sending a stimulus at the level of 100 dB nHL to the right ears. Afterwards, cVEMP threshold values were determined by decreasing the stimulus level in 5 dB steps. After testing the right ear, the left ear was tested with the same test pattern. The latency of the first positive component (p13) and first negative component (n23) of each cVEMP response was measured in milliseconds (ms). The amplitude of p13n23 was measured in microvolts (μV) from the positive peak (p13) to the next trough (n23).

Computed tomography (CT): It was preferred for imaging middle ear and inner ear pathologies. Patients with suspected SSCD were evaluated with high resolution CT (HRCT).

Statistical Analysis

Study data were analyzed with software SPSS 24.0 (SPSS Inc., Chicago, IL, USA). A descriptive statistical evaluation was made in terms of the groupings of the data and their relations with each other. In the descriptive findings, categorical variables were presented as percentage distributions and continuous variables as mean ± standard deviation.

RESULTS

Descriptive data

The gender distribution and mean age of the patients are presented in **Figure 1**.

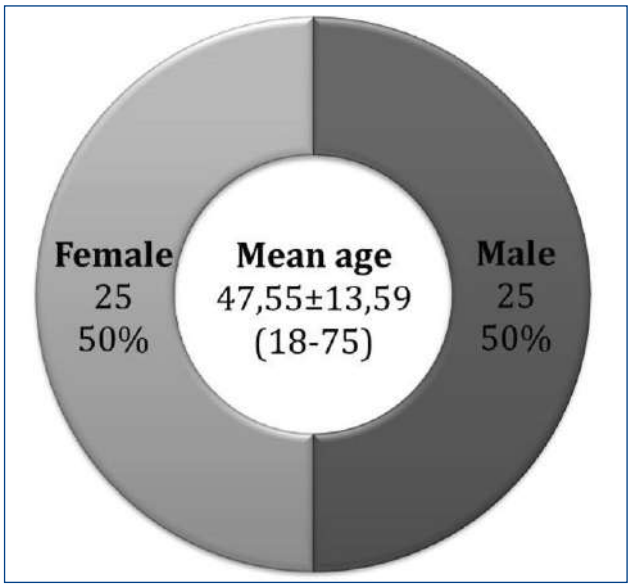

Figure 1. Gender distribution and mean age of the patients

Preliminary diagnoses of patients

The definitive diagnosis of the patients behind an intact tympanic membrane is very unlikely without explorative tympanotomy. Therefore, the diagnosis of patients should be considered as a preliminary diagnosis. Otosclerosis (n=31) was found to be the most common middle ear pathology in the patients, and SSCD was found to be the most common inner ear pathology in 5 of them. In the other 14 patients, tympanosclerosis (n=4), chronic mastoiditis (n=4), serous otitis media (n=3), ossicular chain pathology (n=1), otic capsule dehiscence (n=1), middle ear mass (n=1) pathologies were found. The most common diagnoses and distributions of the patients are given in **Figure 2**.

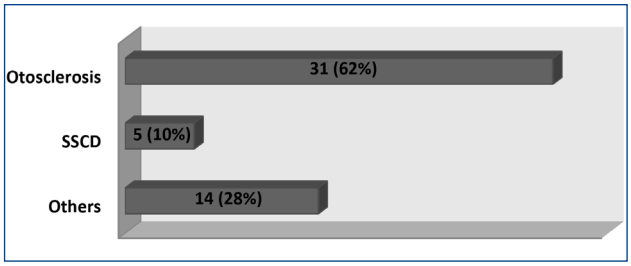

Figure 2. The most common diagnoses and distribution of patients (SSCD: Superior Semicircular Canal Dehiscence)

Cervical VEMP findings

While no cVEMP response was obtained in 41 (82%) of the patients, cVEMP response was obtained in 9 (18%) patients. An example for each patient with or without a response to the cVEMP test is given in **Figure 3**. Of the patients without cVEMP response, 28 were otosclerosis and 13 had other middle ear pathologies. Of the patients with cVEMP response, 5 had SSCD, 1 had otic capsule dehiscence, and 3 had otosclerosis. Retrofenestral type was found in temporal CT in two of those with otosclerosis, and antefenestral type in one. Air-bone gap mean, acoustic immitancemetry and cVEMP findings of middle ear and inner ear pathologies are summarized in **Table 1** comparatively.

DISCUSSION

In our study, cVEMP results of 50 patients (67 ears) with intact tympanic membrane and hearing loss with air-bone gap were evaluated together with pure tone audiometry, acoustic immitancemetry and temporal CT (if necessary). In this context, it is the first study in the literature to the best of our knowledge. There are studies evaluating the results of cVEMP in hearing loss with air-bone gap in the literature, but these are studies that either include tympanic membrane pathologies or other tests evaluated in this study in the differential diagnosis were not evaluated (9,10). In addition, while cVEMP cannot be obtained in conductive hearing losses originating from the middle ear, cVEMP thresholds can be obtained at lower levels in conductive hearing losses originating from the inner ear. In order to examine this difference, cVEMP thresholds were also examined in our study.

cVEMP response was obtained in 9 of the patients with conductive and mixed hearing loss in our study, and 6 of them were inner ear pathology, while 3 of them were otosclerosis. Konukseven et al.(10) reported that 4 of 176 patients with CHL had cVEMP response, and 3 of them had SSCD and one had enlarged vestibular aqueduct syndrome. Zhou et al.(9) evaluated 120 patients and found that no cVEMP response was obtained in patients with middle ear pathology (n=50), and cVEMP response was obtained in all 59 patients with inner ear pathology. In addition, they reported that cVEMP response was also obtained in 11 patients with Meniere's disease and high jugular bulb. Yang et al. (11) found that cVEMP response

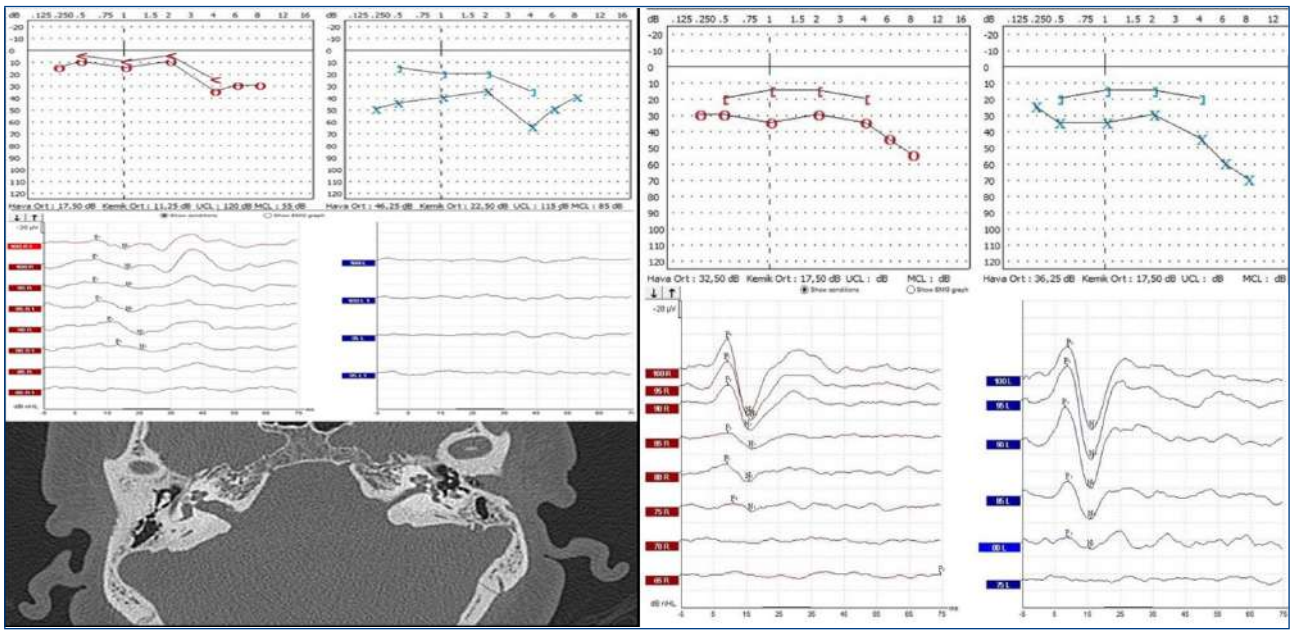

Figure 3. Pure tone audiometry, cVEMP and CT image of the patient with prediagnosis of otosclerosis on the left and pure tone audiometry, cVEMP results of the patient with bilateral SSCD on the right. The patient on the left had CHL in the left ear, and cVEMP response could not be obtained in the same ear. On temporal CT, antefenestral type otosclerosis was reported on the left. The patient on the right had bilateral CHL and cVEMP response was obtained in both ears. In the temporal CT report, it was stated that he had bilateral SSCD.

Table 1. Findings of middle ear and inner ear pathologies

	Air-bone gap mean	Tympanometry		Acustic reflex		cVEMP	
		Type A	Other types	(+)	(-)	response (+)	response (-)
Middle ear pathologies	Right:24,0 dB (n=23 ears) Left: 24,97 dB (n=37 ears)	13	47	17	43	3	57
Inner ear pathologies	Right: 14,33 dB (n=3 ears) Left: 22, 25 dB (n=4 ears)	7	-	7	-	7	-
Total	67 ears	20	47	24	43	10	57

cVEMP: Cervical vestibular evoked myogenic potentials

was obtained in the early period in patients with otosclerosis, but cVEMP response could not be obtained with the progression of the disease. In our study, when temporal bone CT of 3 patients with cVEMP response was examined, retrofenesteral type otosclerosis was reported in 2 and antefenesteral type otosclerosis was reported in 1 patient. The reason for the response positivity in these patients was thought to be related to the localization of the disease in the retrofenesteral type, and the possibility of being in the early stage of the disease in the antefenesteral type. Because antefenestral type otosclerosis was detected in the other 28 otosclerosis patients without cVEMP response, and this finding was confirmed in 8 patients who were operated on.

Pathologies that cause conductive hearing loss originating from the inner ear; semicircular canal and otic capsule dehiscences, large vestibular aqueduct syndrome, Paget's disease and congenital inner ear malformations are some of them (10). While it is possible to distinguish most of these pathologies with temporal bone CT, dehiscences cannot be differentiated despite thin section high resolution computed tomography (HRCT). It has been reported that this condition can mostly be confused with otosclerosis, but if there is a cVEMP response, SSCD should be considered in the differential diagnosis (12-14). In our study, SSCD was detected in 5 patients and otic capsule dehiscence was found in 1 of the patients with suspected otosclerosis, and cVEMP responses were obtained in all of these 6 patients. It was observed that these patients had low cVEMP thresholds such as 65 dB nHL, 75 dB nHL. This result shows that cVEMP thresholds can also be used as a diagnostic tool in clarifying the diagnosis of conductive hearing loss originating from the inner ear. Although our findings support the literature, they also contribute by evaluating cVEMP thresholds. Therefore, despite the air-bone gap determined in the audiogram, SSCD should be considered first in cases with normal acoustic reflexes and who cVEMP thresholds are obtained, especially at low sound intensity. We believe that it may be more appropriate to evaluate cVEMP response and thresholds before HRCT in these patients. However, there are studies in the literature showing that conductive hearing loss originating from the middle ear and inner ear can coexist, although it is rare. Since there are no other clinical, audiological, or electro-physiological criteria to rule out the presence of SSCD associated with otosclerosis, HRCT is recommended before each stapes surgery in case of coexistence of ipsilateral otosclerosis and SSCD (14).

In addition to obtaining cVEMP response at low thresholds in patients with SSCD, larger cVEMP wave amplitudes can be obtained. Roditi et al. (15) reported that cVEMP wave amplitudes were larger (173.8 microvolts) in patients with SSCD and lower thresholds were found in these patients. For this reason, further studies that can examine cVEMP wave amplitudes as well as cVEMP thresholds in conductive hearing loss originating from the inner ear may be beneficial. In addition, Zuniga et al. (16) investigated which of the cVEMP thresholds and oVEMP wave amplitudes is more specific and sensitive in the diagnosis of SSCD. They determined that oVEMP amplitudes were more effective than cVEMP thresholds in the diagnosis of SSCD. Hunter et al. (17), on the other hand, reported that both cVEMP thresholds and oVEMP amplitudes depend on a number of factors, and both are good diagnostic test tools for defining SSCD. In the light of this information, studies that will investigate the effectiveness of the oVEMP test in the diagnosis of conductive hearing loss originating from the inner ear will contribute to the literature.

Limitations of the study

Since our study is of a retrospective nature, its implications may be limited. In order to accurately define the true sensitivity and specificity of the cVEMP test in the differential diagnosis of air-bone gap in pure tone audiometry in middle and inner ear pathologies, prospective studies that evaluate more patients are needed.

CONCLUSION

When the data of our study and the literature data are combined, evaluating the response and threshold values in the cVEMP test may help in the differential diagnosis of hearing loss with an air-bone gap for which no obvious cause can be detected by otoscopy or otomicroscopy, and can be used as a screening test, especially in patients who are considered for surgery. It can reduce radiation exposure and cost by reducing the need for temporal high-resolution computed tomography, especially in patients who are not considering surgery.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Izmir Katip Celebi University Atatürk Training and Research Hospital Non-Invasive Clinical Research Ethics Committee (Date: 21.10.2021 Decision No: 0426).

Informed Consent: Informed consent form did not obtained from the participants due to the nature of the study.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

An Etiological Evaluation of Children with Acute Recurrent Pancreatitis: Based on Genetic Analysis and Pancreaticobiliary Maljunction without Biliary Dilatation

Akut Rekürren Pankreatitli Çocukların Etiyolojik Değerlendirmesi: Genetik Analiz ve Biliyer Dilatasyonsuz Pankreatikobiliyer Bileşke Anomalisi Temelinde

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ABSTRACT

Aim: The most common risk factors in acute recurrent pancreatitis (ARP) are genetic and anatomical/obstructive causes. Some cases of ARP have been considered as 'idiopathic' without detailed genetic analysis. The aim of this study is to evaluate the genetic risk factors and the presence of long common channel in cases evaluated as idiopathic ARP.

Material and Method: In this study, 19 patients who were evaluated as idiopathic ARP after primary care evaluation, between January 2017 and January 2022, were included. The CFTR, PRSS1, SPINK1 and CTRC genes were analyzed in these patients. The length of the pancreaticobiliary common channel was measured and compared with normal values for age by the evaluation of MRCP imaging.

Results: The mean age was 11.21 ±3.70 years and 57.9% (n=11) of the patients were female. In 52.6% (n=10) of the cases, the pancreaticobiliary channel length was above the normal values determined for age. Mutations in the CFTR (7/19), PRSS1 (2/19) and CTRC (1/19) genes were detected in 52.6% (n=10) of the patients.

Conclusions: The results of our study showed the presence of genetic risk factors (CFTR, PRSS1 and CTRC) and PBM without biliary dilatation in approximately half of the cases named as idiopathic ARP. In the presence of long common channel without biliary dilatation, diagnostic delay due to the subtle radiological findings may cause gallbladder cancer in adulthood. Therefore, children with ARP should also be evaluated for PBM without biliary dilatation before being labeled as 'idiopathic'.

Keywords: Acute recurrent pancreatitis, CFTR, PRSS1, CTRC, pancreaticobiliary maljunction, long common channel

ÖZ

Amaç: Akut rekürren pankreatitte (ARP) en sık görülen risk faktörleri genetik ve anatomik/obstrüktif nedenlerdir. Bazı ARP vakaları, ayrıntılı genetik analiz yapılmadan 'idiyopatik' olarak kabul edilmektedir. Bu çalışmanın amacı idiyopatik ARP olarak değerlendirilen olgularda genetik risk faktörlerini ve uzun pankreatikobiliyer ortak kanal varlığını değerlendirmektir.

Gereç ve Yöntem: Bu çalışmaya, Ocak 2017-Ocak 2022 tarihleri arasında birinci basamak değerlendirme sonucu idiyopatik ARP olarak değerlendirilen 19 hasta dahil edildi. Bu hastalarda CFTR, PRSS1, SPINK1 ve CTRC genleri analiz edildi. MRCP ile pankreatikobiliyer ortak kanal uzunluğu ölçülerek yaşa göre normal değerlerle karşılaştırıldı.

Bulgular: Hastaların yaş ortalaması 11.21 ±3.70 yıldı ve %57.9 (n=11)'u kızdı. Olguların %52.6 (n=10)'sında pankreatikobiliyer ortak kanal uzunluğu, yaşa göre belirlenmiş normallerin üzerindeydi. Hastaların %52.6 (n=10)'sında CFTR (7/19), PRSS1 (2/19) ve CTRC (1/19) genlerinde mutasyonlar tespit edildi.

Sonuç: Çalışmamız idiyopatik ARP olarak adlandırılmış olguların yaklaşık yarısında genetik risk faktörlerinin (CFTR, PRSS1 ve CTRC) ve biliyer dilatasyonsuz pankreatikobiliyer bileşke anomalisinin varlığını göstermiştir. Biliyer dilatasyonsuz bileşke anomalisi varlığında, radyolojik bulguların belirgin olmamasına bağlı tanısal gecikme, erişkin yaşta safra kesesi kanserine neden olabilir. Bu nedenle ARP'li çocuklar 'idiyopatik' olarak etiketlenmeden önce biliyer dilatasyonsuz bileşke anomalisi açısından da değerlendirilmelidir.

Anahtar Kelimeler: Akut rekürren pankreatit, CFTR, PRSS1, CTRC, pankreatikobiliyer bileşke anomalisi, uzun ortak kanal

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INTRODUCTION

Acute recurrent pancreatitis (ARP), defined as 2 or more distinct episodes of pancreatitis, is a relatively rare condition. Most of the data on ARP are obtained from the adult literature (1). Thanks to increasing definition of ARP, the International Study Group for Pediatric Pancreatitis: In Search has focused on the identification, diagnosis and management of risk factors for these cases (2). Risk factors in children are different from adults. Currently, the most common risk factors defined in children include genetic and anatomical factors (3). However, when the INSPPIRE database was evaluated, it was found that many cases were defined as idiopathic ARP, without genetic testing (2).

A normal pancreaticobiliary junction is formed by the joining of the main pancreatic duct and the common bile duct and opening into the duodenum by forming a common channel. The localization of this junction is the submucosal layer of the duodenum. This intramural localization of the common channel provides it to be controlled by the intramurally located sphincter of Oddi. In the case of pancreaticobiliary maljunction (PBM), the bile and pancreatic ducts join outside the duodenal wall, forming a long common channel that is not under the control of the Oddi sphincter (4). In adults, a common channel length greater than 15 mm is defined as PBM (5). However, in children, the maximal length of the common channel varies according to the age. The maximal length of common channel is 3 mm in infants under 1 year of age and increases up to 5 mm until 15 years of age (6).

Pancreaticobiliary maljunction may be with or without biliary dilatation, depending on the diameter of the common bile duct (7). Pancreaticobiliary maljunction without biliary dilatation is seen less frequently than PBM with dilatation. In PBM without biliary dilatation, acute pancreatitis is seen more frequently in pediatric patients compared to adults (8). In PBM with biliary dilatation imaging findings are more definite compared to PBM without biliary dilatation. In cases with PBM without biliary dilatation, diagnosis may be delayed due to indefinite radiological findings. In some cases, the diagnosis can be possible with the detection of biliary cancer in adulthood (9).

The presence of indefinite radiological findings and the frequency of acute pancreatitis in cases with PBM without biliary dilatation suggest that some of the cases defined as idiopathic acute recurrent pancreatitis may be PBM without biliary dilatation. The aim of this study is to investigate genetic risk factors and the presence of PBM without biliary dilatation in children, who had been diagnosed with idiopathic ARP, in the primary care evaluation.

MATERIAL AND METHOD

Study Population

This cross-sectional study was carried out at Necmettin Erbakan University Meram Medical Faculty, Pediatric Gastroenterology clinic between January 2017 and January 2022, prospectively. Patients aged 0-18 years who were diagnosed with ARP and no proven cause (toxic, autoimmune, metabolic, and obstructive) could be found in the primary care evaluation were included in the study.

The diagnosis of acute recurrent pancreatitis was made according to the recommendations of the INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) consortium (10). According to INSPPIRE recommendations, the main criterion was 2 or more episodes of acute pancreatitis. The other criteria include the absence of pain for at least 1 month after the first attack or both the absence of pain regardless of the duration and the return of pancreatic enzyme levels to normalcy (10). The number of patients diagnosed with ARP according to these criteria was 33. The study was conducted on 19 patients who were defined as idiopathic ARP, after excluding 14 patients whose etiology was determined in the first step evaluation (5 patients with gallstones, 4 patients with PBM with biliary dilatation, 2 patients with autoimmune pancreatitis, 1 patient with pancreatic divisum, 1 patient with valproic acid use, 1 patient with 3-Hydroxy-3-Methylglutaryl-CoA Lyase deficiency). In the first step evaluation; Anamnesis (drug use, signs of infection, family history of pancreatic disease, consanguineous history), laboratory evaluation (transaminase, gamma glutamyl transferase (GGT), total/direct bilirubin, calcium, fasting lipids) and imaging methods were performed. Ultrasonography was the primary imaging method and when no anatomical/obstructive cause was detected in ultrasonography, cases with increased GGT were evaluated with Magnetic Resonance Cholangiopancreatography (MRCP).

Two of the patients had been diagnosed with cystic fibrosis (CF) before the ARP clinic developed and CFTR gene analysis had already been performed. The remaining 17 patients underwent gene analysis for Serine Protease 1 (PRSS1), CF Transmembrane Conductance Regulator (CFTR), Serine Peptidase Inhibitor Kazal type 1 (SPINK1), and Chymotrypsin C (CTRC). Common bile duct diameter and pancreaticobiliary common channel length were measured by MRCP in all cases.

Genetic Analysis

The next-generation sequencing analysis of the SPINK1, PRSS1, CTRC, and CFTR genes were performed using the MiSeq NGS platform (Illumina, San Diego, CA, USA). The extraction of genomic DNA was performed following the manufacturer's standard procedure and using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The exome sequencing necessary for the synthesis of the primers to be used in the study was taken from the www.ensembl.

org genetic data banks. To design the primers from those sequences, the www.ncbi.nlm.nih.gov/tools/primer-blast/ database was used. Gene pools were prepared for all patients and each pool was measured at Qubit according to the standard Qubit protocol. The library was prepared in accordance with the Nextera XT DNA Library Prep Kit (Illumina Inc.) procedure and by following the manufacturer's instructions. The library preparation phase included the genomic DNA fragmentation, labeled DNA amplification, DNA purification, and denaturation that were performed respectively. The "Integrative Genomics Viewer (IGV)" program was used to evaluated the variants of interested genes in this study. Sanger Sequencing was conducted along with 3500DX Genetic Analyzer (Applied Biosystems, United States) as a verification method.

In this study, we analyzed the coding regions and splice sites of four genes in a group of ARP patients. Since we aimed to be conservative in our estimate of the major genetic cause of ARP, we excluded synonymous, intronic, and 5'- or 3'-untranslated region variants in the four genes from consideration except where there was persuasive evidence of a functional consequence. The pathogenicity classification of variants was evaluated in accordance with ACMG criteria (11).

Evaluation of Biliary Dilatation and Common Channel Length

MRCP imaging was performed with 1.5 Tesla Siemens (Allegra, Germany) by using body coil. First three planes True FISP imaging was taken for localizing the abdominal structures. Axial images must include the liver from the anterior wall to the posterior wall of the abdomen. T2 HASTE images with fat saturation were performed first in axial plane. Then coronal oblique imaging was performed for whole liver from diaphragm to the third and fourth segment of the duodenum to include all biliary system. For oblique coronal imaging the block was positioned across the common bile duct. These images were taken while the patients hold their breath. The diameter of common bile duct was measured for assessment of congenital biliary dilatation. Biliary dilatation was defined using reference values for age in the diagnostic criteria for congenital biliary dilatation defined by the Japanese Study Group on Pancreaticobiliary Maljunction (JSGPM) in 2015 (12).The length of the common channel was measured from the coronal oblique T2 HASTE images. Measurements were analyzed using reference values for age that previously reported by Guelrud et al and subsequently used in several studies (6, 13, 14).

Statistical analysis

Statistical analyzes of the study were performed by using SPSS 20.0 (IBM Inc, Chicago, IL, USA). The conformity of the variables to the normal distribution was evaluated by the Shapiro Wilk test. Descriptive statistics were presented as mean ±SD and median (Q1-Q3) for numerical variables and frequency (percentage ratio) for categorical variables. Comparisons of attack number and attack age according to Common Channel scores were performed by Mann-Whitney U test. A value of $p<0.05$ was considered statistically significant for the type-I error rate of 5% in the analyses.

RESULTS

A total of 19 pancreatitis patients were included in the study. The mean age was 11.21 ±3.70 years and 57.9% (n=11) of the patients were female and 42.1% were males (n=8). The mean weight z score was -0.17 ±1.36 and the mean height z score was -0.43 ±1.06. The median BMI z score was -0.40 (-0.88-1.33). The mean follow-up period was 29.79 ±15.10 months, the age at first attack was 8.37 ±3.77 years, and the number of attacks was 5.16 ±3.07 (**Table 1**). In 31.6% (n=6) of the patients a family history of pancreatitis was present and in 31.6% (n=6) of the patients a family history of cystic fibrosis was present.

Table 1. The demographic characteristics, clinical and radiological findings of patients with acute recurrent pancreatitis

	N (%) / Mean ±SD / Median (Q1-Q3)
Gender	
Female	11 (57.9)
Male	8 (42.1)
Age (year)	11.21 ±3.70
Weight z score	-0.17 ±1.36
Height z score	-0.43 ±1.06
BMI z score	-0.40 (-0.88-1.33)
Follow-up time (month)	29.79 ±15.10
Age at first pancreatitis attack (year)	8.37 ±3.77
Number of pancreatitis attacks	5.16 ±3.07
Common bile duct diameter (mm)	2.47 ±0.64
Length of the common channel (mm)	4.94±0.63
Long common channel	
Yes	10 (52.6)
No	9 (47.4)

Radiologic Measurements

The mean common bile duct diameter measured on MRCP was found to be 2.47 ±0.64 mm and it was within the normal range for age in all cases. Common channel length was found to be 4.94 ±0.63mm. Pancreaticobiliary channel length was above the normal values determined for age in 52.6% (n=10) of the cases (**Table 2**). The mean age at first attack (6.70 ±3.88 years) in patients with long common channel was smaller than those with normal common channel length (10.22 ±2.77 years); however, the difference was not statistically significant (p=0.053). The mean number of attacks was 5.40 ±3.98 in cases with long common channel and 4.89 ±1.83 in those with normal common channel length (p=0.72).

Table 2. The radiologic findings and detected mutations in patients with acute recurrent pancreatitis

Case	CFTR	PRSS1	CTRC	Sweat test (mEq/L)	Diameter of CBD (mm)	Maximal diameter of CBD for age (mm)	Length of PBC (mm)	Maximal length of PBC for age (mm)
1	-/-	K170E*/S181N†	-/-	27	3.5	4.5	5.3	4.4
2	-/-	S181N†/-	-/-	22	2	5.0	5.0	5.0
3	G85E/ L568F	-/-	-/-	42.8	2.8	4.5	5.7	4.4
4	G85E/ L568F	-/-	-/-	47	2.5	4.8	5.0	5.0
5	F508del/-	-/-	-/-	61	3.6	5.0	5.7	5.0
6	-/-	K170E*/S181N†	-/-	28	2.1	4.8	4.8	5.0
7	-/-	-/-	-/-	24	2	3.7	4.6	3.6
8	L233V‡/-	-/-	-/-	25.7	1.9	3.7	4.1	3.6
9	-/-	R122C/-	-/-	26.5	2	5.3	5.0	5.0
10	-/-	-/-	-/-	26.7	2.4	4.3	3,5	4.1
11	-/-	-/-	-/-	21	2.1	4.9	4.2	5.0
12	D1152H/ D1152H I1051V/I1051V	-/-	-/-	89	2.6	4.3	5.5	4.1
13	F508del / R334W	-/-	-/-	92.1	2.1	5.2	5.0	5.0
14	-/-	Q98PfsTer10/-	-/-	37.6	1.8	3.9	5.4	4.1
15	-/-	-/-	-/-	32	2.8	4.0	4.5	4.1
16	F334W/ N1303K	-/-	-/-	135	1.5	5.1	4.3	5.0
17	G1069R/-	-/-	-/-	48.6	3.2	5.0	6,0	5.0
18	-/-	-/-	-/-	29.4	3.7	4.9	5.0	5.0
19	E217G†/-	-/-	R254W/-	22.2	2.3	4.7	5.4	5.0

*Likely benign †Benign ‡Variant of uncertain significance

Mutation Data Analysis and Classification

The mutations in CFTR, PRSS1 and CTRC genes were detected in 52.63% (n=10) of patients with ARP. Heterozygous variants contributed to the development of ARP were detected in the PRSS1 gene in 10.52% (n=2) of patients, and in the CTRC gene in 5.26% (n=1) of patients. CFTR genotypes contributed to the development of ARP in 36.84 % of cases, heterozygous, compound heterozygous and homozygous variants in the CFTR gene were identified in 7 of the 19 ARP patients.

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Detected CFTR Variants

CFTR genotypes contributed to the development of ARP in 36.84% of cases. The heterozygous, compound heterozygous and homozygous variants in the CFTR gene were identified in 7 of the 19 ARP patients.

In two patients who were siblings (Case 3 and 4), p.G85E/p.L568F variants were detected in the compound heterozygous state. These patients had normal pulmonary functions and equivocal sweat tests (42.8 and 50 mEq/L). p.Gly85Glu variant (NM_000492.4; c.254G>A; chr7:117149177) causes the substitution of a Glycine into an Glutamine residue at position 85 in exon 3. This variant position has a submission in ClinVar (ID: 7143), previously been reported in publications associated with CFTR gene (15). The detected variant is classified as "Pathogenic" (PP5, PM1, PM5, PP3, PM2). p.Leu568Phe variant (NM_000492.4; c.1704G>T; chr7:117230431) causes the substitution of a Leucine into an Phenylalanine residue at position 568 in exon 13. This variant has been reported in publications associated with CFTR gene (16). The detected variant is classified as "Likely Pathogenic" (PM1, PP3, PM2).

In the Case 5, a previously described in frame p.Phe508del variant was detected (NM_000492.4; c.1521_1523del; chr7:117199645) in the heterozygous state. This patient had normal pulmonary functions and abnormal sweat tests (61 mEq/L). The detected variant causes the substitution of a Phenylalanine into a del residue at position 508 in exon 11. This variant has submissions in ClinVar (ID: 634837), previously been reported in publications (17, 18). The detected variant is classified as "Pathogenic" (PS3, PM1, PP5, PM4, PM2).

In the case 12, p.Asp1152His/p.Asp1152His and p.Ile1051Val/p.Ile1051Val variants in the homozygous state had detected already. This patient had been previously diagnosed with cystic fibrosis and the sweat test were 89mEq/L. p.Asp1152His is a missense

variant (NM_000492.4; c.3454G>C; p.Asp1152His; chr7:117254753) causes the substitution of a Aspartic acid into an Histidine residue at position 152 in exon 21. This variant has a submission in ClinVar (ID: 35867), previously been reported in publications (19) and classified as "Pathogenic" (PM2, PP3, PP2, PP5). p.Ile1051Val is a missense variant (NM_000492.4; c.3151A>G; p.Ile1051Val; chr7:117251646) causes the substitution of a Isoleucine into an Valine residue at position 1051 in exon 20. This variant has been reported in publication (20) and classified as "Likely Pathogenic" (PM2, PM1, PP2, PP3).

In the Case 13, p.Phe508del/p.Arg334Trp variants in the compound heterozygous state had detected already. This patient had been previously diagnosed with cystic fibrosis and the sweat test were 92.1 mEq/L. The p.Arg334Trp variant (NM_000492.4; c.1000C>T; p.Arg334Trp; chr7:117180284) causes the substitution of a Arginine into an Tryptophan residue at position 334 in exon 8. This variant has a submission in ClinVar (ID: 7139), previously been reported in publication (21) and classified as "Pathogenic" (PM1, PP2, PM2, PM4).

In the Case 16, p.Asn1303Lys/p.Arg334Trp variants were detected in the compound heterozygous state. The sweat test 135 mEq/L was detected in this patient and bronchiectasis developed in the follow-up of the patient. The p.Arg334Trp variant is classified as "Pathogenic" (PM1, PP2, PM2, PM4). p.Asn1303Lys variant (NM_000492.4; c.3909C>G; chr7:117292931) causes the substitution of a Asparagine into an Lysine residue at position 1303 in exon 24. This variant has a submission in ClinVar (ID: 7136), previously been reported in publication (22). The detected variant is classified as "Pathogenic" (PS1, PM5, PM1, PP2, PM2).

In case 17, p.Gly1069Arg variant was detected in the heterozygous state. This patient had normal pulmonary functions and equivocal sweat test (48.6 mEq/L). p.Gly1069Arg is a missense variant (NM_000492.4; c.3205G>A; p.Gly1069Arg; chr7:117251700) causes the substitution of a Glycine into an Arginine residue at position 1069 in exon 75. This variant has been reported in publication (23). The detected variant is classified as "Likely Pathogenic" (PVS1, PP5, PM2).

Detected PRSS1 Variants

The heterozygous variants in the PRSS1 gene were identified in 2 of the 20 ICP patients.

In the Case 9, p.Arg122Cys variant was detected in the heterozygous state. The p.Arg122Cys variant (NM_002769.5; c.364C>T; chr7-142459788) causes the substitution of a Arginine into an Cysteine residue at position 122 in exon 3. This variant has a submission in ClinVar (ID: 11883), previously been reported in publication (24). The detected variant is classified as "Pathogenic" (PS3, PM1, PM5, PP3, PP5).

In the Case 14, p.Gln98ProfsTer10 variant was detected in the heterozygous state. p.Gln98ProfsTer10 variant (NM_002769.5; c.292dup; chr7:142459712) causes the substitution of a Glutamine into an Proline residue at position 98 in exon 3. It is a frameshift variant and gives rise to termination after 10 codons. There is no recorded publication in the literature. To our knowledge, it was detected for the first time in this study. The detected variant is classified as "Likely Pathogenic" (PVS1, PM2).

Detected CTRC Variants

CTRC genotype contributed to the development of ICP in 5% of cases. Heterozygous variant in the CTRC gene was identified in 1 of the 20 ICP patients.

In the Case 19, p.Arg254Trp variant was detected in the heterozygous state. p.Arg254Trp variant (NM_007272.3; c.760C>T; p.Arg254Trp; chr1:15772212) causes the substitution of a Arginine into an Tryptophan residue at position 254 in exon 7. This variant position has been reported in publications (25). The detected variant is classified as "Likely Pathogenic" (PM2, PP3, PP5).

DISCUSSION

Pancreaticobiliary maljunction is the joining of the pancreas and bile duct outside the duodenal wall and in PBM the common channel is longer than normal. Since the control of the sphincter of Oddi over the common channel is lost, the junction cannot be occluded by sphincter contraction. This situation may cause mutual reflux of biliary and pancreatic fluid, and may cause pancreatitis, cholangitis, and biliary tract cancers. PBM may be with (congenital choledochal cyst) or without biliary dilatation (26).

Acute pancreatitis is more common in children with PBM than in adults. Pancreatitis may recur and cause chronic pancreatitis (8). Miyake et al. in their study, in which they evaluated long common channel cases without biliary dilatation retrospectively, reported that abdominal pain and hyperamylasemia were more common in cases with long common channel without biliary dilatation compared to cases with biliary dilatation (27). In our study, we showed that PBM without biliary dilatation with MRCP was present in 52.6% of the cases with ARP.

The gold standard method in the diagnosis of PBM is ERCP. However, since it is an invasive method, MRCP should be preferred when there is a therapeutic necessity or a strong suspicion of ductal anomaly (1, 28). In the literature, the diagnostic roles of MRCP and ERCP in the diagnosis of PBM have been compared and the diagnostic rates of MRCP were reported to be 75-82% (29, 30). However, common channel length is not routinely evaluated in radiological imaging (31). In the radiologic evaluation, the presence of bile duct dilatation is an indicator for the diagnosis of PBM

with biliary dilatation and the presence of gallbladder wall thickening is an indicator for PBM without biliary dilatation. However, cases without biliary dilatation are often diagnosed with gallbladder cancer in adulthood since gallbladder wall thickening is a condition that develops in advancing age due to diffuse epithelial hyperplasia and dysplasia of the gallbladder and in the absence of biliary dilatation, the radiological findings are indefinite (9). In this study, we found that the common channel length was longer than the upper limit determined for age in 52.6% of the cases who had been considered normal, in the primary level radiological evaluations. Although not statistically significant, it is observed that recurrent pancreatitis attacks started at earlier ages in the presence of long common channel. We suggest that this difference may be more significant if the number of patients was higher.

Kumar et al. evaluated risk factors for ARP and chronic pancreatitis (CP) in the INSPPIRE cohort, and found that 48% of children with ARP had mutations in at least 1 gene. They reported that the identified mutations were in the PRSS1 gene (46%) in chronic pancreatitis and in the CFTR gene (34%) in ARP (3). Similar to the INSPPIRE cohort, in our cohort, we identified mutations in at least one gene in 52.63% of patients with ARP. In addition, we found that 36.84% of the cases had CFTR gene mutations.

All of the mutations we identified in the CFTR gene were previously identified and reported to be associated with cystic fibrosis. We found that 4 patients were compound heterozygous (G85E/ L568F, R334W/F508del, F334W/N1303K), one patient with 2 homozygous mutations in the CFTR gene (D1152H/D1152H, I1051V/I1051V), and 2 patients with mutations heterozygous for CFTR (F508del/- and G1069R/-). The importance of a single heterozygous mutation in the CFTR gene in the pathogenesis of ARP is controversial (32). However, in cases without respiratory findings, CFTR mutations have been associated with conditions such as congenital bilateral absence of the vas deferens and pancreatitis. Cohn et al. showed that the risk of pancreatitis increased fourfold in cystic fibrosis patients with a normal CFTR allele (33). Sobczyn´ska-Tomaszewska et al. showed the F508del/- variant in 3 patients with ARP and chronic pancreatitis. They reported that there may be additional genetic or environmental risk factors in cases with ARP with a single heterozygous CFTR variant (33). In our study, long common channel was present in 2 patients with a single heterozygous mutation. We suggest that, this can be considered as an additional risk factor for the development of long common channel ARP in these 2 patients.

In our study, we detected R122C and Q98PfsTer10 mutations in the analysis of the PRSS1 gene. Le Maréchal et al. reported that the R122C mutation causes hereditary pancreatitis, for the first time in 2001 and this was later supported by other studies (24,35,36). Q98PfsTer10 mutation, defined as “Likely Pathogenic” (PVS1, PP5, PM2), has not been reported in the literature before. To the best of our knowledge, this is the first study to report the Q98PfsTer10 mutation.

In the INSPPIRE cohort, including 301 children with ARP and chronic pancreatitis, CTRC mutation rates of 10% and 5% (respectively) were reported (3). Palermo et al., in their study analyzed genetic variants in children with ARP and CP, found R254W mutation in the CTRC gene in 7% of the cohort (37). In our study, we detected the R254W mutation in 5.26% of our cohort.

One of the limitations of our study is that, although we have shown that ARP attacks begin at an earlier age in long common channel cases, we could not show a statistically significant difference due to the small number of patients. However, one of the aims of our study was to evaluate the rate of the long common channel without biliary dilatation cases without anatomic/obstructive pathology in the primary care evaluation. Therefore, cases with an obstructive/anatomical diagnosis were not included in the study. Although our focus on this specific group resulted in the small number of patients, it was a good single-center number for this highly specific group. In this context, we think that our study will guide multicenter studies with larger number of patients. Another limitation of our study was that channel lengths measured by MRCP were not confirmed by ERCP. However, according to the EPC/HPSG (The European Pancreatic Club/The Hungarian Pancreatic Study Group) guideline recommendations, MRCP should be the first-choice imaging method in children unless there is a therapeutic necessity (38). In previous studies, it has been shown that MRCP is 75-82% diagnostic in the diagnosis of PBM (29, 30). In this context, we planned to follow up long common channel cases without biliary dilatation in terms of gallbladder cancer that may occur in adulthood. Pre-surgical ERCP can be considered when there is a need for surgery based on the clinical course. Additionally, the study population could be evaluated using endoscopic ultrasound (EUS). However, we do not have the opportunity to perform endoscopic ultrasound in this age group in our clinic. EUS is used safely in adults to detect the presence of chronic pancreatitis and the etiology of acute recurrent pancreatitis. However, data on the use of EUS in children with acute recurrent pancreatitis are limited. In the study of Singh et al. in which they evaluated children with ARP using endoscopic ultrasound, it was reported that EUS can be used safely in the detection of changes due to chronic pancreatitis in children. However, the evaluation of common channel length in children using EUS remains uncertain (39).

CONCLUSION

In this study, we showed the presence of genetic risk factors (CFTR, PRSS1 and CTRC) and PBM without biliary dilatation in a significant proportion of cases labeled as idiopathic ARP. In the pediatric age group, data of long common channel cases without biliary dilatation is insufficient. Considering the possibility of diagnostic delay due to the lack of definite radiological findings in the presence of long common channel without biliary dilatation, we suggest that our study will provide a guide for clinicians and radiologists.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of the Ethics Committee of Necmettin Erbakan University Medical Faculty (protocol code:2017/885 and date of approval: 14.04.2017).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Juvenile Localized Scleroderma from a Pediatric Rheumatology Perspective: A Single-Center Experience

Çocuk Romatoloji Perspektifinden Juvenil Lokalize Skleroderma; Tek Merkez Deneyimi

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ABSTRACT

Aim: To evaluate juvenile localized scleroderma, which is a disease with high rates of cosmetic and functional sequelae in children, from a pediatric rheumatology perspective.

Material and Method: We retrospectively investigated the data of patients who were diagnosed with juvenile localized scleroderma (JLS) in our pediatric rheumatology clinic between 2015 and 2022, were aged <18 years, and attended their follow-ups regularly. Demographic, clinical, treatment-related, and prognostic data of the patients were included.

Results: Among the 19 patients diagnosed with JLS, 12 (63.2%) were female, and 7 (36.8%) were male. The female-to-male ratio in the sample was 1.7. Eight (42.1%) patients had circumscribed JLS, 8 (42.1%) had linear JLS, 2 (10.6%) had mixed JLS, and 1 (5.3%) had generalized JLS. The patients' mean age of onset of symptoms was 8.2±5.5 years, while their mean age of diagnosis was 9.4±4.9 years. The most frequently involved anatomical regions were the extremities, whose involvement was found in 15 (78.9%) patients. The prevalence of lesions crossing joints was 57.9%, and joint damage was seen in 21.1% of the patients. The rate of cosmetic sequelae was 73.7%. There was antinuclear antibody positivity in 52.6% of the patients. Systemic involvement did not occur in any patients during their follow-ups. The most frequently used treatment agent was methotrexate. Complete remission was achieved in 2 (10.6%) patients.

Conclusion: As it can lead to high degrees of cosmetic and functional sequelae, it is necessary to diagnose juvenile localized scleroderma early and start an aggressive treatment in the early period. To avoid wasting time, it is essential, especially for pediatricians, to immediately order biopsies from suspected lesions or refer these patients to pediatric rheumatology clinics.

Keywords: Juvenile localized scleroderma, morphea, treatment

ÖZ

Amaç: Çocuklarda kozmetik ve fonksiyonel sekel oranı yüksek bir hastalık olan juvenil lokalize sklerodermayı çocuk romatoloji perspektifinden değerlendirmek.

Gereç ve Yöntem: Çocuk romatoloji kliniğimizde 2015-2022 yılları arasında juvenile lokalize skleroderma tanısı almış <18 yaş altı, takiplerine düzenli gelen hastalar retrospektif olarak incelendi. Hastalara ait demografik, klinik, tedaviye ilişkin ve prognostik veriler kaydedildi.

Bulgular: Juvenil lokalize skleroderma tanısı olan 19 hastanın 12'si (63.2%) kız, 7'si (36.8%) erkek cinsiyetteydi. Kız/erkek oranı 1,7'ydi. JLS tanısı olan hastalardan 8'i (42.1%) plak, 8'i (42.1%) lineer, 2'si (10.6%) miks ve 1'i generalize tipte idi. Şikayetlerin ortalama başlangıç yaşı 8.2±5.5 yaş, tanı yaşı ise ortalama 9.4±4.9 yaştı. En sık tutulan anatomik bölge 15 hasta (78.9%) ile ekstremitelerdi. Eklem ile ilişkili cilt lezyonu oranı 57.9% iken eklem hasarı 21.1% hastada görüldü. Kozmetik sekel oranı 73.7%'ydi. Hastaların 52.6%'sında antinükleer antikor pozitifliği vardı. Takip süresince hiçbir hastada sistemik tutulum gelişmedi. En sık kullanılan tedavi metotreksat idi. 2 hastada (10.6%) tam remisyon sağlanabildi.

Sonuç: Yüksek oranda kozmetik ve fonksiyonel sekellere yol açabileceğinden juvenil lokalize sklerodermanın erken tanınması ve erken agresif tedavisi gerekmektedir. Özellikle çocuk hekimlerinin şüphelendikleri lezyonlardan bekletmeden biyopsi yaptırması veya bu hastaları çocuk romatoloji kliniklerine yönlendirmesi zaman kaybetmemek adına önemlidir.

Anahtar Kelimeler: Juvenil lokalize skleroderma, morfea, tedavi

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INTRODUCTION

Juvenile scleroderma is a rarely encountered chronic autoimmune disease characterized by excessive collagen accumulation in connective tissue and fibrosis (1,2). It has two subtypes: juvenile localized scleroderma (JLS) and juvenile systemic scleroderma (3-5). JLS, also known as morphea, is the most frequently seen form of scleroderma in childhood that predominantly affects the skin and subcutaneous tissue and can reach the fascia and muscles below the skin (1,2). Extracutaneous symptoms, including neurological, musculoskeletal, and eye complications, can be seen in 22% of patients (6). The term localized scleroderma is a general term, and it includes various subtypes with different clinical presentations and disease severities. The latest classification, which was made by the Pediatric Rheumatology European Society (PReS), divides the disease into five subtypes. These subtypes are as follows: (1) circumscribed morphea, (2) linear scleroderma, (3) generalized morphea, (4) pansclerotic morphea, and (5) mixed morphea (7).

While the etiopathogenetic mechanisms that cause localized scleroderma are not entirely known, it is thought that several factors, such as infections, drugs, hormones, and autoimmune mechanisms, are influential in the onset of the disease (8,9).

The treatment of the disease varies depending on the subtype of the disease, the size of the lesion, the number of lesions, and the existing damage. Initially, treatments such as phototherapy, imiquimod and topical steroids are used in localized morphea. Systemic steroids, immunosuppressive drugs such as methotrexate and mycophenolate mofetil are preferred when morphea progresses despite topical treatments and in linear, generalized, mixed and pansclerotic scleroderma subtypes (10,11). Mortality in JLS cases is rare, but patients suffer high rates of cosmetic problems, disfigurement, dysfunctions, and neurological issues.

There are a limited number of studies conducted in Turkey on this disease, which is seen in children ten times as prevalently as systemic sclerosis and can create severe cosmetic and functional problems. Existing studies are usually those conducted by dermatologists (12-14). This study aims to investigate the demographic, clinical, and laboratory characteristics and treatment methods of JLS patients from a pediatric rheumatology perspective.

MATERIAL AND METHOD

This retrospective observational study included patients diagnosed with JLS in our pediatric rheumatology clinic between 2015 and 2022, were aged <18 years and attended their follow-ups regularly. Patients with JLS who had not been followed up for at least six months and patients with a diagnosis of juvenile systemic sclerosis were excluded.

For the patients, data on the age of diagnosis, the age of onset of complaints, sex, JLS subtype, disease duration, anatomical region of involvement, accompanying systemic symptoms, the presence of triggering factors, family history of rheumatic disease, laboratory data [hemogram, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), infection screenings, antinuclear antibody (ANA), rheumatoid factor (RF), anti-extractable nuclear antibody (ENA)], the presence of comorbidities, treatments used, treatment response status, and follow-up duration were retrospectively collected from their electronic records. The sequelae of the patients causing morbidity were recorded by dividing them into cosmetic, functional (e.g., contracture, joint deformity, extremity shortening), and neurological categories.

Disease subtypes were classified as circumscribed, generalized, linear, pansclerotic, or mixed. One or more oval or round plaques localized in at most two anatomical regions (head and neck, each extremity, posterior and anterior trunk) were classified as limited morphea; four or more infiltrating plaques, each larger than 3 cm, involving at least two anatomical regions were categorized as generalized morphea. Sclerotic lesions showing linear bands [en coup de sabre (ECDS) affecting the extremities and head, Parry-Romberg variants] were classified as linear morphea; those with a combination of 2 or more types were classified as mixed; and those involving deep layers of skin and connective tissue (e.g., adipose tissue, fascia, muscle tissue, bone tissue) were classified as pansklerotic morphea (7).

Treatment response was categorized as complete remission, partial remission, or treatment resistance. Complete remission was accepted as the absence of new lesions for at least a year despite the termination of drug treatment and the inactivation of existing lesions. Partial remission was obtained to alleviate initial symptoms (fading of color, reduced hardness, shrinking size) for at least three months. Treatment resistance was defined as the persistence of active disease despite full-dose treatment. Finally, relapse was considered the activation of the disease during the tapering of the treatment or after the completion of the treatment (15, 16).

The local ethics committee approved the study (approval no: E2-23-3179).

Statistical Analysis

The statistical analyses were conducted using the SPSS Version 20 (SPSS Inc., Chicago IL, USA) software. The qualitative variables are expressed as percentages, and the quantitative variables are presented with a mean (± standard deviation) values if they were normally distributed and median (minimum-maximum) values

if they were non-normally distributed. The categorical data were compared using $\chi 2$ tests, and the numeric data were compared using Student's t-test.

RESULTS

In the study period, the number of patients diagnosed with rheumatic diseases in our pediatric rheumatology clinic and regularly followed up was 3870. Nineteen (0.5%) of these patients were diagnosed with JLS. Among the JLS patients, 12 (63.2%) were female, and 7 (36.8%) were male. The female-to-male patient ratio was 1.7. Eight (42.1%) patients had circumscribed JLS, 8 (42.1%) had linear JLS, 2 (10.6%) had mixed JLS, and 1 (5.3%) had generalized JLS. There was no statistically significant difference between the sexes regarding their localized scleroderma subtypes (p=0.782). Among the patients with linear localized scleroderma, 2 (10.5%) patients had ECDS. The patients' mean age of onset of symptoms was 8.2±5.5 years, while their mean age of diagnosis was 9.4±4.9 years. While the mean age of onset of symptoms in the female patients was 7.3±5.7 years, the mean age of onset of symptoms in the male patients was 9.9±4.7 years, and there was no significant difference between the female and male patients (p=0.332). The mean ages of onset of symptoms among the patients also did not vary significantly based on their disease subtypes (p=0.303). The median delay in diagnosis was five months (minimum: 1 month - maximum: 5.1 years). Five (26.2%) patients had comorbidities. Among these five patients, 1 had asthma, 1 had hydronephrosis, 1 had immune thrombocytopenic purpura, 1 had idiopathic facial paralysis, and 1 had pangastritis. Three (15.8%) patients had a family history of rheumatoid arthritis, an autoimmune disease, in their first-degree relatives. Two (10.6%) patients had a family history of Behçet's disease.

Factors that could potentially trigger localized scleroderma were present in 4 (21.1%) patients (**Table 1**). The initial symptoms of the disease were skin hardening in 5 (26.3%) patients, skin redness-bruising in 5 (26.3%), brown spots on the skin in 4 (21.1%), white patches on the skin in 2 (10.6%), skin swelling in 1 (5.3%), skin thinning in 1 (5.3%), and hair loss in 1 (5.3%). The most frequently involved anatomical regions are the extremities, whose involvement was encountered in 15 (78.9%) patients, followed by trunk involvement in 5 (26.3%) patients, and head-neck region involvement in 4 (21%) patients (**Table 1**). The lesions of 11 (57.9%) patients crossed joints, whereas those of 8 (42.1%) patients were unrelated to joints. The lesions crossed ankle joints in 5 (26.3%) patients, knee joints in 3 (15.8%), hip joints in 2 (10.5%), and elbow joints in 1 (5.3%). Four (21.1%) patients had joint involvement. Two (10.6%) patients had Raynaud syndrome.

ANA positivity was found in 10 (52.6%) patients. This positivity was at 1/100 titers in 6 (31.5%) patients, 1/320 titers in 3 (15.7%), and 1/1000 titers in 1 (5.2%). ENA positivity was detected in 2 (10.5%) patients, one of these cases showed DFS-70 positivity, and the other showed SS-A positivity. ANA positivity was not significantly related to systemic treatment requirement, prognosis, or sequelae (p=0.162, p=0.468, p=0.620). RF positivity was found in only 1 (5.3%) patient. All patients had negative viral panel results. Borrelia IgG was examined in 8 patients, whose results were all negative. CRP positivity was seen in only 1 (5.3%) patient, and ESR positivity was present in 4 (21.2%) patients. The median CRP value was 0.5 mg/L (0-10 mg/L), while the median ESR value was 6 mm/h (2-15 mm/h). While 6 (31.5%) patients had vitamin D deficiency, one had iron deficiency, and no patients had vitamin B12 deficiency. Biopsies were performed on all patients except for two patients with ECDS and 1 with a facial lesion. Fourteen patients who underwent biopsies had typical localized scleroderma symptoms (epidermis thinning, dermis collagen fiber increase, atrophy in subcutaneous adipose tissue, and fibrosis), and two patients showed nonspecific symptoms.

Topical treatments were given to 9 (47.3%) patients (**Table 1**). While 2 (10.6%) patients received only topical treatments, 17 (89.4%) received systemic therapies. There was no significant difference among the subtypes of localized scleroderma in terms of systemic treatment requirement (p=0.451). The most frequently used systemic treatment was methotrexate, which 15 (78.9%) patients used. This was followed by systemic corticosteroids in 11 (57.9%) patients, colchicine in 1 (5.3%), hydroxychloroquine in 1 (5.3%), and mycophenolate mofetil in 1 (5.3%). The combination of systemic corticosteroids and methotrexate was the most frequently observed treatment modality, which 9 (47.3%) patients used. The median follow-up duration of the patients was 2.5 years (minimum: 6 months - maximum: 9 years). The treatment responses of the patients are shown in **Table 1**. There was no significant difference among the subtypes of localized scleroderma in terms of prognosis (p=0.893). Cosmetic sequelae were found in 14 (73.7%) patients, cosmetic and functional sequelae were found in 4 (21.1%) patients, and 1 (5.3%) patient did not have any sequelae. The functional sequelae were in the form of joint movement restriction in 3 (15.8%) patients, whereas 1 (5.3%) patient had contracture. The demographic, clinical, and treatment-related characteristics of the patients are presented in **Table 1.**

Table 1: Demographic, clinical and treatment-related data of patients with juvenile localized scleroderma

Patient No	Gender	Age at diagnosis*	Time to diagnosis*	Disease duration*	JLS subtype	Anatomical localization	Trigger Factor	Treatment	Prognosis	Sequelae
1	M	14	2	3,9	Linear scleroderma	Head	-	CS+MTX	Partial remission	Cosmetic
2	F	5	4,5	3	Linear scleroderma	Lower extremity	-	MTX+ topical tacrolimus	No response	Cosmetic
3	M	2,7	0,5	8	Linear scleroderma	Upper&lower extremity	Pneumonia	CS+MTX	Partial remission	Cosmetic, fonctionel
4	F	13,1	0,5	6	Generalize scleroderma	Head, trunk &lower extremity	-	HQ	No response	Cosmetic
5	F	7,6	5,1	1,7	Linear scleroderma	Head	COVID-19	MTX+ Colchicine	Partial remission	Cosmetic
6	F	17,3	0,3	0,8	Circumscribed scleroderma	Upper extremity	-	Topical steroid	Partial remission	Cosmetic
7	F	4	1	2	Linear scleroderma	Upper extremity	-	CS+MTX	Partial remission	Cosmetic, Fonctionel
8	M	15	0,4	1,5	Circumscribed scleroderma	Trunk	-	Topical calcipotriol & betamethasone	Partial remission	Cosmetic
9	F	17,8	2	0,8	Circumscribed scleroderma	Lower extremity	Upper respiratory tract infection	CS+MMF	No response	Cosmetic, Fonctionel
10	F	11,3	0,2	1,2	Circumscribed scleroderma	Lower extremity	-	CS+MTX+ Centaury oil	Complete remission	Cosmetic
11	M	7,7	0,2	6	Mix scleroderma	Trunk& Lower extremity	-	CS+MTX	Partial remission	Cosmetic
12	F	9	0,7	6	Circumscribed scleroderma	Lower extremity	-	CS+Topical tacrolimus	Partial remission	No sequel
13	F	2,5	1,9	4	Circumscribed scleroderma	Trunk& Lower extremity	-	MTX+ Topical steroid	No response	Cosmetic
14	M	13,6	0,6	3	Linear scleroderma	Upper extremity	-	CS+ MTX	Partial remission	Cosmetic, Fonctionel
15	M	6,1	0,1	9	Circumscribed scleroderma	Lower extremity	-	MTX+ Topical tacrolimus	Complete remission	Cosmetic
16	F	4	1,8	1,6	Mix scleroderma	Lower extremity	-	CS+ MTX+ Topical calcipotriol& betamethasone	Partial remission	Cosmetic
17	F	7,6	0,4	1,1	Linear scleroderma	Upper& Lower extremity	-	CS+ MTX	No response	Cosmetic
18	M	14,5	0,3	0,3	Circumscribed scleroderma	Head	COVID-19	CS+ MTX	Partial remission	Cosmetic
19	F	6	0,6	2,5	Linear scleroderma	Lower extremity	-	MTX+Topical steroid+ Centaury oil	Partial remission	Cosmetic

JLS: Juvenile localized scleroderma, F: Female, M: Male, CS: Cortikosteroid, MTX: Methotrexate, HQ: Hydroxychloroquine, MMF: Mycophenolate mofetil, *year

DISCUSSION

Juvenile localized scleroderma is a rarely encountered chronic pediatric disease characterized by skin and subcutaneous tissue fibrosis. Among these patients, who are usually followed up in dermatology clinics, only those requiring systemic treatment are followed up in pediatric rheumatology outpatient clinics. The rate of these patients among all patients with rheumatic diseases who are regularly followed up in our clinic is approximately 0.5%. Our study found the ratio of female JLS patients to male JLS patients as 1.7. In our study, the ratio of female JLS patients to male JLS patients was found as 1.7. Circumscribed scleroderma and linear scleroderma were the most frequently diagnosed types of JLS. Although there was no statistically significant difference between the female and male patients, it was seen that the complaints of the female patients started at earlier ages. It was observed that in this rare disease, despite systemic and aggressive treatment, the rate of complete remission was very low.

The incidence of JLS varies in the range of 0.4-1 in 100,000, and various studies have reported female/male patient ratios differing from 1.2/1 to 2.4/1 (17,18,19). In the multi-center study that was conducted with 489 patients diagnosed with JLS by the Juvenile Scleroderma Working Group of the Pediatric Rheumatology European Society (PReS), it was reported that the mean age of disease onset was 7.3 years, and this did not significantly change based on the subtypes of the disease (20,21,22). In a study in Taiwan, the mean age of disease onset in JLS was reported as 6.7 years (23). The mean age of disease onset was determined to be 8.2 years in our study, and like in other studies, there was no significant difference in this value based on sex or disease subtypes. To understand whether there are regional differences in the age of disease onset in JLS, nationwide multi-center studies are needed.

While the most frequently diagnosed form of localized scleroderma in adulthood is circumscribed morphea, linear scleroderma is the most prevalent JLS subtype in childhood, usually seen in the first two decades of life (24). In our study, the circumscribed and linear localized scleroderma rates were equal, and both were 42.1%. The rate of extracutaneous involvement in linear scleroderma is high, and it can lead to various sequelae, especially in the extremities of patients (12,25,26). Moreover, in ECDS, another form of linear scleroderma, the forehead and scalp are involved, cutaneous, subcutaneous, bone, and even brain tissue can be affected, and the disease can lead to various neurological symptoms (27,28). ECDS was detected in 10.5% of the patients in our study. In the study by the Juvenile Scleroderma Working Group, has the broadest series of patients so far, 22.4% of the 489 pediatric patients had non-skin involvement. Among these non-skin involvement cases, 47.2% were articular, 17.1% were neurological, 9.3% were vascular, 8.3% were ocular, 6.2% were gastrointestinal, 2.6% were respiratory, 1% were cardiac, and 1% were renal involvement cases (7). Among our patients, other than joint involvement, only 2 (10.6%) patients had Raynaud syndrome. While most of our patients had lesions crossing their joints, joint involvement was present in 21.1%. Three of these patients had restricted joint motion, and one had developed contracture. The rate of restricted joint movement and contracture has been reported in the range of 18-21% in the literature (7,27,29,30). The rate of arthritis has been reported as 5-20%, whereas none of our patients had arthritis. The rate of restricted joint movement and contracture in our study was similar to those reported in other studies in the literature.

It has been stated that autoantibody positivity accompanies JLS, and the prevalence of ANA positivity varies in the range of 32-76% (21, 22, 24, 31). Regarding other autoantibodies, various studies have demonstrated that the prevalence of anti-Scl-70 positivity is 2-3%, and the prevalence of anti-cardiolipin positivity is 0-12% (7,24,32). Our study found ANA positivity in 52.6% of the patients. One patient had SS-A positivity, and another had DFS-70 positivity, but the positivity of these autoantibodies was not associated with the clinical statuses of these patients. It has been stated in the literature that in case autoantibodies are detected in localized scleroderma, it is necessary to carefully monitor these patients in terms of systemic symptoms that can develop later, and these patients can have systemic involvement later in life (32-34). However, the Juvenile Scleroderma Working group did not find a significant difference between patients with and those without ANA positivity in terms of prognosis, treatment, or sequelae. On the other hand, in the same study, a significant correlation was identified between RF positivity and arthritis (7). Our study did not find any relationship between ANA positivity and systemic treatment requirement, sequelae, or prognosis. During their follow-ups, no patients included in our study developed systemic symptoms. While one patient in our study showed RF positivity, no patient had arthritis.

In circumscribed morphea cases, various topical treatments are usually recommended for patients (35-37). These patients usually undergo these topical treatments as a result of their examination by dermatology clinics before rheumatology clinics. Patients who do not respond to topical treatment and require systemic treatment are referred to rheumatology clinics for the examination of systemic symptoms and recommendations for treatment modalities. While 84.2% of the JLS patients being followed up in our clinic received systemic treatments, 47.3% received topical treatments. The most frequently used systemic therapy was methotrexate, which was used in 78.9% of the patients. Studies conducted with large samples of JLS patients have also reported methotrexate as the most prevalently used systemic treatment (7,15). According to the EULAR treatment guidelines, mycophenolate mofetil treatment is recommended for patients who are intolerant to methotrexate or do not respond to treatment with methotrexate (16). Studies performed by dermatology clinics in Turkey have reported the usage of colchicine treatment and its effective outcomes (38). The treatment decision for JLS patients should be made based on joint monitoring by dermatology and pediatric rheumatology clinics.

In JLS cases, especially in circumscribed morphea, complete remission was reported to occur at the end of the first five years. While it was observed that juvenile linear localized scleroderma could have a much more aggressive course, and remission was not seen in 10-year follow-up (15). Long-term morbidity is highly prevalent in JLS cases, and the most frequently encountered sequelae cosmetic and musculoskeletal damage (39). The rate of complete remission in our study was very low. Complete remission could be achieved by aggressive treatment in only 2 (10.6%) patients, who had circumscribed morphea. During their follow-ups, cosmetic sequelae were seen in 73.1% of our patients, whereas 21.1% had joint damage. In a study carried out with 133 patients in Italy, subcutaneous adipose tissue loss and cosmetic sequelae in the early period were reported in 2/3 of the patients (15). The reason for the low remission rate in our study, even with the inclusion of the circumscribed morphea cases, maybe that most patients who do not respond to various topical treatments and have a more aggressive course of the disease are followed up in pediatric rheumatology clinics, and the follow-up durations of our patients were short.

This study had some limitations. The most important limit was the low number of patients. Because it was

a retrospective study, accessing detailed clinical data and investigating long-term outcomes was impossible. Nonetheless, our study is valuable in the scientific sense because the number of studies in Turkey investigating JLS cases from a pediatric rheumatology perspective is insufficient.

CONCLUSION

Consequently, although JLS is a pediatric disease that is rarely encountered, it constitutes a significant group of conditions because it has high rates of cosmetic and functional sequelae. In this sense, it will be an appropriate approach for clinicians to not refrain from ordering biopsies for lesions that they consider suspicious and refer such patients to pediatric rheumatology clinics in the early period. Considering the high sequela rates of the disease, it is clear that there is a need for multi-center studies in Turkey that will allow us to understand JLS better.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 18.01.2023, Decision No: E2-2023-3179).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Evaluation of Children (<2 Years Old) with Respiratory Syncytial Virus Bronchiolitis in Terms of Disease Course and the Requirements of Additional Treatment

Respiratuar Sinsisyal Virüs Bronşiyoliti Olan Çocukların (<2 Yaş) Hastalığın Seyri ve İlave Tedavi Gereksinimleri Açısından Değerlendirilmesi

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ABSTRACT

Aim: To evaluate the demographic and clinical characteristics of children and the types and frequencies of treatments given in the setting of respiratory syncytial virus (RSV) bronchiolitis.

Material and Method: Sixty-three children (39 females, 24 males; mean age 8.7 months; range 2 to 24 months) were diagnosed with acute bronchiolitis due to RSV between November 2017 to February 2018. The microbiological diagnosis was made with the detection of RSV antigens by the immunochromatographic assay. Retrospective data included risk factors, symptoms and signs at presentation, laboratory and radiographic findings, and treatment methods.

Results: Fifty-three patients (84.1%) were younger than 12 months. The birth weights were between 1,600 and 4,250 g and the gestational ages were between 31 and 41 weeks. Prematurity was found in 11 patients (17.5%), and comorbid conditions 17 patients (27%). Hospitalization was required in 34 patients (54%), of whom three patients (4.8%) were further admitted to the intensive care unit. The following treatment modalities were more frequently used: multiple bronchodilators for comorbidities (35.3%), tachypnea (29.7%); inhaled steroid therapy for hypoxemia (90.9%), tachypnea (89.2%); systemic steroid treatment for tachypnea (40.5%); intravenous fluid therapy for tachypnea (78.4%); antibiotherapyfor comorbidities (76.5%). Hospitalization was more frequently required in patients with tachypnea (83.8%) and, hypercarbia (83.3%). Treatment methods significantly differed between patients with and without comorbidity, age <12 months, tachypnea. (p<0.05).

Conclusions: The presence of comorbid conditions and tachypnea seems to play a critical role in determining the need for treatment. Tachypnea as a symptom can help predict the need for hospitalization, as well as multiple bronchodilator therapy, steroid therapy, and antibiotic use for the treatment. The presence of tachypnea, hypoxemia, comorbidity, and radiographic infiltration seems to be associated with the need for antibiotics. In addition, the presence of infiltration on chest X-ray, acidosis, hypoxemia, and hypercarbia are also indicators of hospitalization.

Keywords: Bronchiolitis, infant, respiratory syncytial virus, tachypnea, treatment

ÖZ

Amaç: Respiratuar sinsisyal virüs (RSV) bronşiyoliti tedavi sürecinde çocukların demografik ve klinik özelliklerini ve verilen tedavilerin türlerini ve sıklıklarını değerlendirmek.

Gereç ve Yöntem: Kasım 2017-Şubat 2018 tarihleri arasında 63 çocuğa (39 kız, 24 erkek; ort. yaş 8,7 ay; dağılım 2-24 ay) RSV'ye bağlı akut bronşiyolit tanısı kondu. Mikrobiyolojik tanı, İmmünokromatografik yöntemle ile RSV antijenleri tespit edilerek yapıldı. Risk faktörleri, başvuru anındaki semptom ve bulgular, laboratuvar ve radyografik bulgular ve tedavi yöntemleri gibi bilgiler retrospektif olarak tarandı.

Bulgular: Elli üç hasta (%84,1) 12 aydan küçüktü. Doğum ağırlıkları 1600 ile 4250 gr arasında ve gebelik yaşları 31 ile 41 hafta arasındaydı. 11 hastada (%17,5) prematüre, 17 hastada (%27) ek hastalık saptandı. 34 (%54) hastada yatış gerekti ve bunların üçü (%4,8) yoğun bakıma alındı. Aşağıdaki tedavi modaliteleri belirtilen durumlarda daha sık kullanılmıştır: çoklu bronkodilatörler, komorbid durumlar (%35,3) ve takipne (%29,7) varlığında; inhale steroid tedavisi, hipoksemi (%90,9) ve takipne (%89,2) varlığında; sistemik steroid tedavisi, takipne (%40,5) varlığında; intravenöz sıvı tedavisi, takipne (%78,4) varlığında; antibiyoterapi, komorbid durum (%76,5) varlığında daha sık kullanılmıştır. Takipne (%83,8) ve hiperkarbi (%83,3) olan hastalarda hastaneye yatış daha sık gerekmiştir. Tedavi yöntemleri, komorbidite, yaş <12 ay ve takipnesi olan ve olmayan hastalar arasında anlamlı farklılık gösterdi (p<0,05).

Sonuç: Komorbid durumların varlığı ve takipne, tedavi ihtiyacının belirlenmesinde kritik bir rol oynuyor gibi görünmektedir. Takipne bir semptom olarak hastaneye yatış ihtiyacını öngörmenin yanısıra, çoklu bronkodilatatör tedavisi, steroid tedavisi ve antibiyotik tedavisini öngörme konusunda da yardımcı olabilir. Takipne, hipoksemi, komorbidite ve radyografik infiltrasyonun varlığı, antibiyotik ihtiyacı ile ilişkili görünmektedir. Ayrıca akciğer grafisinde infiltrasyon varlığı, asidoz, hipoksemi ve hiperkarbi de hastaneye yatış göstergesidir.

Anahtar Kelimeler: Bronşiyolit, infant, respiratuar sinsisyal virüs, takipne, tedavi

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INTRODUCTION

Acute bronchiolitis is a viral lower respiratory tract disease characterized by obstruction of the small airways. The mortality ratio associated with bronchiolitis is estimated to be 2 per 100.000 live births (1). Among the causes of bronchiolitis, respiratory syncytial virus (RSV) is the most frequent cause, with a wide range of presentations from slight viral upper respiratory tract symptoms to respiratory failure (2). Patients may develop infectious complications, dehydration, respiratory distress, and/or insufficiency, which may require oxygenation, bronchodilator medications, intravenous fluid therapy, antibiotics, and other noninvasive or invasive ventilation treatments. The decision for the type of treatment is usually made based on the findings or complications identified during the course of the disease. It has been shown that RSV affects at least 50% of children during the first year of life and almost all children till the age of 2 years (3), and that 1-3% of all children require RSV-associated hospitalizations during the first year of life, with 0.1-2% requiring mechanical ventilation due to severe lower respiratory tract infections (4,5). Of children admitted with RSV, 8% require intensive care (6) and up to 3% are at risk for mortality (7). In particular, high-risk children are at an increased risk for morbidity and mortality. Risk factors include the first 6 weeks after birth, prematurity, chronic lung diseases such as bronchopulmonary dysplasia, congenital heart diseases resulting in impaired hemodynamic status and, in particular, pulmonary hypertension, congenital or acquired immunodeficiency, neuromuscular diseases, and low socioeconomic status (8-10). Mortality associated with RSV infections may be as high as 35% in children with risk factors (8). This study aimed to evaluate the demographic and clinical characteristics of children and the types and frequencies of treatments given in the setting of RSV-associated bronchiolitis.

MATERIAL AND METHOD

Study population and definition

The study included 63 infants and children, ages up to 2 years, who were diagnosed with acute bronchiolitis due to RSV (ICD-10-CM Diagnosis Code J21.0) during a three-month interval from November 2017 to February 2018. The patients were divided into two age groups <12 months and ≥12 months. All data were obtained retrospectively from the hospital and patient records.

At our center, microbiological diagnosis of RSV is made with the detection of RSV antigens by the immunochromatographic assay as the routine part of patient care for bronchiolitis. In all patients, RSV antigens were demonstrated in the nasopharyngeal aspiration samples by the chromatographic immunoassay method using a commercial kit (CerTestBiotec®, Zaragoza, Spain).

A detailed inquiry was made into risk factors that could worsen the course of the disease, including comorbidities (congenital heart diseases, bronchopulmonary dysplasia, and other chronic lung diseases, metabolic disease, malignancy/immunosuppression, central nervous system diseases, gastrointestinal diseases), and history of prematurity (<38. gestational weeks) and low-birth weight (<10th percentile for gestational age). Symptoms and findings of physical examination were recorded, in particular, fever, cough, rhinorrhea, dyspnea, tachypnea, decreased oral intake, and dehydration. Laboratory [CBC, C-reactive protein (CRP), blood gas analysis] and imaging findings were examined to determine leukocytosis, leukopenia, elevated CRP, hypoxemia, hypercarbia, acidosis, and infiltration or atelectasis on a chest X-ray. The sections where treatments were applied (emergency green zone, emergency yellow zone, pediatric wards, pediatric intensive care unit) and the treatment methods (intravenous fluid therapy, antibiotics, systemic or inhaled steroid treatment) were recorded as well as data on presentation, admission, discharge or referral. In addition, the use of multiple bronchodilators and/or antibiotic treatments was inquired about in the same patient during the same time interval. The symptoms and clinical and laboratory findings of the patients were classified according to the zones of monitoring and care and treatment methods.

Statistical Analysis

We investigated whether there were any statistical differences in treatment and hospitalization between patients with comorbidity, prematurity, acidosis, hypoxemia, hypercarbia, leukocytosis, leukopenia, positive radiologic findings, tachypnea, antibiotic use, multiple antibiotic use, systemic steroid use, and inhaled steroid use. Data were analyzed using the SPSS version 23 statistical software package. The P values of the Chi-square test and Fisher's exact test were taken into account for data having frequencies of greater than and less than 5, respectively. A P value of less than 0.05 was accepted as statistically significant.

Ethics Statement

The present study protocol was reviewed and approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval No. 09.2017.389). Informed consent was submitted by all subjects when they were enrolled. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

RESULTS

Demographic Characteristics

Thedemographic, clinical, and laboratory findings of the patients are summarized in Table 1. Of 63 patients treated with the diagnosis of RSV bronchiolitis, 39 were

females and 24 were males, with a mean age of 8.7 months (range, 2 to 24 months). The majority of the patients (n=53, 84.1%) were 0-12 months old. The birth weights of the patients were between 1,600 and 4,250 grams and the gestational ages were between 31 and 41 weeks. Prematurity was found in 17.5% of the patients, and comorbid conditions in 27% (**Table 1**).

Table 1. Demographic findings of the patients

	n (%)
Gender	
Male	24 (38.1)
Female	39 (61.9)
Age (Mean:8.7 months)	
< 12 months	53 (84.1)
≥ 12 months	10 (15.9)
Prematurity	11 (17.5)
Comorbid conditions	17 (27.0)
Central nervous system disease	5 (29.4)
Chronic pulmonary disease	4 (23.5)
Congenital heart disease	4 (23.5)
Malignancy/immunosuppression	3 (17.6)
Gastrointestinal system disease	1 (5.9)

Symptoms and Signs

The presenting symptoms and signs in a descending frequency were cough (81%), rhinorrhea (71.4%), dyspnea (61%), tachypnea (58.7%), hypoxemia (34.9%), fever (27%), and dehydration (25.4%) (Table 2). A chest X-ray was obtained in 92.1% of the patients, blood gas analysis in 79.4%, hemogram in 77.8%, and C-reactive protein (CRP) in 77.8%, with corresponding results of decompensated respiratory acidosis in 7.9%, compensated respiratory acidosis in 6.3%, pulmonary infiltration in 63.5%, elevated CRP (>3.3 mg/L) in 28.5%, leukocytosis in 12.7%, and leukopenia in 3.2% (**Table 2**).

Table 2. Clinical and laboratory findings of the patients

Symptoms, signs, and laboratory findings	n (%)
Cough	53 (81.0)
Rhinorrhea	45 (71.4)
Dyspnea	41 (61.0)
Tachypnea	37 (58.7)
Hypoxemia	22 (34.9)
Fever	17 (27.0)
Dehydration	16 (25.4)
Respiratory acidosis	9 (14.2)
Decompensated	5 (7.9)
Compensated	4 (6.3%)
Elevated CRP(>3.3 mg/L)	18 (28.5)
Leukocytosis	8 (12.7)
Leukopenia	2 (3.2)
Pulmonary infiltration	40 (63.5)
Paracardiac infiltration	37 (59.5)
Lobar infiltration	3 (%4.8)
Atelectasis	1 (%1.6)

Monitoring and Treatment

Hospitalization was required in 54%, including 22 patients (34.9%) hospitalized in the pediatric ward, and 12 patients (19%) in the pediatric emergency unit. Of all the patients hospitalized, three patients (4.7%) were further admitted tointensive care. 29 patients (46%) resulting in discharge from the pediatric emergency unit.

At the emergency unit, the patients received salbutamol (77.8%), oxygen therapy (68.3%), inhaled steroids (63.5%), intravenous fluid therapy (50.8%), antibiotics (55.6%), systemic steroids (27%), ipratropium bromide (19%), multiple bronchodilators (salbutamol + ipratropium bromide 19%), multiple antibiotics (17.5%), 3% NaCl (12.7%), and intravenous magnesium sulfate (1.6%).

Table 3 summarizes the distribution of treatment methods and the need for hospitalization to the clinical and laboratory findings of the patients. The use of multiple bronchodilators was greater in patients with comorbidities, tachypnea, and pulmonary infiltration on chest X-rays ($p<0.05$). Inhaled steroidswere more frequently administered in patients and those having comorbidities, tachypnea, hypoxemia ($p<0.05$) and systemic steroid treatments. The frequency of antibiotic administration increased in the presence of comorbid conditions, hypoxemia, tachypnea, and radiological infiltration. Patients with acidosis, hypoxemia, hypercarbia, tachypnea, comorbid conditions, prematurity, and radiographic infiltration had higher hospitalization rates ($p<0.05$).

Patients with comorbidities had higher rates of multiple bronchodilator treatment and hospitalization than those without comorbid conditions ($p<0.05$). The presence of tachypnea was associated with increased use of multiple bronchodilators, inhaled steroids, systemic steroids, intravenous fluid therapy, and antibioticsas well as a greater need for hospitalization ($p<0.05$). Similarly, the presence of infiltration on chest X-rays resulted in increased use of multiple bronchodilators, intravenous fluid therapy, and antibiotics and a greater need for hospitalization ($p<0.05$). The majority of hypoxemic patients (90.9%) received inhaled steroid treatment ($p<0.05$)(**Table 3**).

DISCUSSION

Treatment and hospitalization needs and durations of patients with bronchiolitis may vary depending on the severity and complications of the condition. The severity of the disease is linked to the causative agent, age, prematurity, and comorbid conditions as well as to clinical and laboratory findings. These factors can also be used for prophylaxis and to predict follow-up and treatment methods. Passive immunization against RSV

Table 3.Treatment methods and hospitalization needs of the patients about demographic, clinical, and laboratory findings

Demographic, clinical, and laboratory findings	Multiple inhaled bronchodilators (n=12, 19%)	Inhaled steroids (n=40, 63.5%)	Systemic steroids (n=17, 27%)	Intravenous fluid therapy (n=32, 50.8%)	Antibiotherapy (n=35, 55.6%)	Hospitalization (n=34, 54%)
Prematurity‡ (n=11, 17.5%)	3 (27.3%)	7 (63.6%)	3 (27.3%)	8 (72.7%)*	7 (63.6%)	9 (81.8%)*
Comorbidity § (n=17, 27%)	6 (35.3%) *	13 (76.5%)*	6 (35.3%)	13 (76.5%)*	13 (76.5%)*	14 (82.4%)†
Age <12 months (n=53, 84.1%)	10 (18.9%)	33 (62.3%) *	16 (30.2%)†	26 (49.1%)	27 (51%)	31 (58.5%)
Tachypnea (n=37, 58.7%)	11 (29.7%)†	33 (89.2%) †	15 (40.5%)*	29 (78.4%)*	26 (70.3%) *	31 (83.8%)†
Acidosis ◊ (n=6, 9.5%)	1 (16.7%)	3 (50%)	2 (33.3%)	4 (66.7%)	4 (66.7%)	6 (100%)*
Hypoxemia ¶ (n=22, 34.9%)	5 (22.7%)	20 (90.9%)†	7 (31.8%)	14 (63.6%)	16 (72.7%)*	16 (72.7%)*
Hypercarbia ◊ (n=6, 9.5%)	1 (16.7%)	3 (50%)	2 (33.3%)	3 (50%)	3 (50%)	5 (83.3%)*
Radiographic infiltration ** (n=40, 63.5%)	11 (27.5%)†	29 (72.5%)	13 (32.5%)	26 (65%) *	28 (70%) *	29 (72.5%) *

*: P<0.05 (Chi-square test), †: P<0.05 (Fisher's exact test), ‡: Births before the 38. gestational week. §: Congenital heart diseases, bronchopulmonary dysplasia, and other chronic lung diseases, malignancy/immunosuppression, central nervous system diseases, gastrointestinal diseases; ¶: SpO_2 <%95; ◊: Blood gases were measured in 50 patients (79.4%); **: Pulmonary infiltration on chest X-ray, (which was obtained in 58 (92.1%) patients.

is only considered for some risk groups due to its high cost (11). It is estimated that there are about 34 million episodes of RSV bronchiolitis annually, of which 3.4 million require hospitalization (12). In the United States, the incidence of RSV-related admissions between 1996 and 2006 was 26.0/1,000 for cases ≤ 12 months of age (48.9/1,000 for ≤ 3 months and 28.4/1,000 for 3-5 months of age) and 1.8/1,000 for cases>12 months of age (13). A total of 66,000 deaths occur annually secondary to RSV infections, with a significant proportion of mortalities occurring in infants younger than 2 years living in developing or underdeveloped countries (12). For 2004 and 2012, the annual mortality rates due to RSV bronchiolitis in Spain were reported as 120 and 69 in 100,000 cases, respectively (14). In cases of severe infections, the leading risk factors are congenital heart diseases, congenital pulmonary malformations, chronic pulmonary disease, and neuromuscular diseases. Additional risk factors for hospitalization are age less than 6 months, male gender, accompanying sibling at home, receiving care at day-time nurseries, and exposure to cigarette smoke (9,10,12). Prematurity (<35 gestational weeks), chronic pulmonary disease, and congenital heart disease causing hemodynamic instability have been implicated as the leading causes of morbidity and mortality from RSV infections (15,16). Neurologic deficits have also been shown among comorbid conditions that may be associated with mortality (17). In our series, there were 17 patients with comorbid conditions, with central nervous system disease being the most frequent (n=5), followed by chronic pulmonary disease (n=4) and congenital heart disease (n=4). There were no cases of peripheral nerve disorder (e.g. muscular disease).

The hospitalization rate was 54%, with three patients (4.7%) requiring intensive-care admission. The rates of cases requiring intensive care have been reported between 2-8% in the literature (5,6,18). The key element in the management of acute RSV bronchiolitis is supportive therapy. Hospitalized patients often require oxygen therapy in the acute setting of hypoxemia and intravenous fluid and electrolyte therapy to prevent or treat dehydration (19). Routine use of bronchodilators and systemic steroids are not recommended as they are often not effective (20-22).

Presentation of our cases with RSV infections falls between December and February. Clinical studies conducted in countries in the northern hemisphere, which also includes our country, have reported the seasonal emergence of RSV infections in the fall-winter and spring months, usually between October and May (23,24). Although the cause of this rise in the incidence of the disease during this period remains uncertain, it may be partly explained by the keeping of children indoors, particularly at school, increased hospital presentations, and increased air pollution (24,25).

Despite unproven efficacy, bronchodilator drugs are commonly used in the treatment of bronchiolitis, generally through inhalation, which includes salbutamol (albuterol), a beta-2 agonist; ipratropium bromide, an anticholinergic agent; and adrenaline, an alpha-adrenergic agonist (11,19-22,26). Although these bronchodilators provide early clinical improvement through dilation of the bronchial mucosa, their efficacy is of short duration and has been shown not to reduce hospital presentations, hospital stay, or disease duration (11,27). Taking into account their unproven efficacy

in bronchiolitis, the current recommendation for the use of these drugs is that they may be continued on an individual basis provided that positive effects are observed such as increased oxygen saturation and decreased respiratory problems (3,11,19,28).In our cases, salbutamol was used in 77.8% of the patients, and ipratropium bromide was used in 19%, always in combination with salbutamol.

Despite their transient efficacy and lack of conclusive data about their effectiveness, combined use of multiple bronchodilators may be necessary in cases with moderate-to-severe clinical conditions. This was the case in 19% of our cases, particularly in patients with tachypnea and/or infiltration on chest X-rays, suggesting the role of these conditions in decreased responsiveness to treatment, aggravation of the clinical course, and increased need for hospitalization.

Inhaled or parenteral steroids are commonly used in patients with bronchoconstriction (11,19,22,26). Although sufficient evidence is lacking in terms of their effectiveness on the rate and duration of hospitalization (22,29,30), they are mainly used for anti-inflammatory efficacy, especially in cases with underlying asthma/allergic conditions (22). In RSV bronchiolitis, the rate of systemic steroid use was reported as 19% (11). Inhaled (budesonide) and systemic (methylprednisolone) steroids were administered in 63.5% and 27% of cases, respectively. Of those younger than 12 months, 62.3% received inhaled, and 30.2% received systemic steroid treatment, suggesting that steroids were mainly added because of suspicion of asthma.

Inhalation of normal saline (0.9% NaCl) can be used in patients with bronchiolitis to increase mucus clearance (26), but this treatment option is not mentioned in some current guidelines and literature reviews (3,28). On the other hand, despite the lack of recommendations for routine use, hypertonic saline (3% NaCl) seems to be widely used in the treatment of bronchiolitis (26). Hypertonic saline may increase mucus clearance through the passage of excess water to the mucus layer (31), but it should be combined with a bronchodilator agent as it may cause bronchoconstriction (26,32,33). The guideline on the diagnosis, management, and prevention of bronchiolitis by the American Academy of Pediatrics recommends hypertonic saline only for hospitalized patients, but not for patients receiving care in the emergency department, as it is effective at improving symptoms after 24 hours of use (34,35). Thus, data on the use of hypertonic saline in outpatient and emergency settings are insufficient and inconclusive (32,36). Hypertonic saline was used in 12.7% of our cases.

Patients with bronchiolitis often develop fluid loss due to tachypnea, and accompanying fever also increases fluid requirement (26,37). In the presence of inadequate or impaired oral intake, fluid therapy is recommended through a nasogastric/orogastric tube. However, parenteral fluid therapy may be more convenient in moderate-to-severe cases of bronchiolitis due to marked dyspnea and tachypnea (>60-70/min) to avoid or prevent aspiration (3,26,38). Intravenous fluid-electrolyte therapy was administered in 50.8% of our cases, being more frequent in the presence of tachypnea, comorbidity, prematurity, and infiltration on chest X-rays.

The frequency of secondary bacterial infections was found to be 1.2% in a large series of infants with severe RSV bronchiolitis (39). In contrast, about 25% of infants admitted with bronchiolitis were reported to have infiltration or atelectasis, which was initially considered to be a bacterial infection (40). There are few studies supporting the use of antibiotics in patients with bronchiolitis and its routine use is not recommended (26,41). Antibiotics may be required in the presence of suspected bacterial pneumonia, particularly in cases with infiltration, or for prophylaxis to prevent secondary bacterial infections (11). More than half of our cases (55.6%) received antibiotics possibly due to the severity of the clinical course and prolonged hospitalization due to comorbidities, hypoxemia, tachypnea, and infiltration on chest X-rays. Literature reports from several countries vary considerably concerning antibiotic rates in hospitalized patients without mechanical ventilation, 34% in New Zealand (42), 45% in the UK (43), and 45% in the US. A prospective multicenter study from France even reported an antibiotherapy rate of 53% for cases receiving ambulatory management (45).

Routine antibiotic use has been recognized in guidelines as having little benefit. But in one review, roughly half of the children, both inpatients, and outpatients, are reported to be commonly prescribed antibiotics (46).

Intravenous magnesium sulfate is used at our center for bronchiolitis in cases with bronchoconstriction resistant to other treatments, which was the case in 1.6% of the patients in the present study. Delivered intramuscularly or by inhalation, magnesium sulfate acts as a muscle relaxant through calcium blockage on respiratory muscles, resulting in bronchodilation. However, it should be delivered slowly during a 20-minute infusion as it may be associated with hypotension (47). A randomized study of 162 previously healthy infants with bronchiolitis whose ages ranged between 22 days and 17.6 months (median, 3.7 months) found no superiority of magnesium sulfate (n=78) over placebo (n=82) in terms of the severity score of bronchiolitis and hospital stay (48). Of note, current guidelines for the treatment of bronchiolitis include no recommendation for the use of magnesium sulfate (3,34).

Limitations of the Study

Due to the retrospective design of the present study from a single center, small sample size, inability to access information about whether patients are vaccinated with palivizumab for immunoprophylaxis, the lack of clinical staging of disease severity, and the small size of patients requiring ventilation treatment, it was not possible to obtain reliable data for correlations between the treatment modalities and the severity of bronchiolitis (mild, moderate, or severe). Instead of the immunochromatographic assay, which is the preferred technique at our pediatric emergency department due to the advantages of lower cost and rapid results, more sensitive molecular techniques could have been used, which would have avoided false negatives and allowed virological diagnoses to be made. Unfortunately, these methods are not expected to be routinely used in emergency departments until they are less costly and provide rapid results.

CONCLUSION

As a symptom, the respiratory rate may help predict the need for multiple bronchodilators, steroid treatment, and antibiotic use for the treatment of bronchiolitis, as well as the need for longer observation/treatment or hospitalization. The presence of comorbid conditions and tachypnea seems to play a critical role in determining treatment needs. In addition, the presence of infiltration on chest X-rays is also indicative of treatment needs and hospitalization.

ETHICAL DECLARATIONS

Ethics Committee Approval: The present study protocol was reviewed and approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval No. 09.2017.389).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Investigating the Presence of Inflammation in Lateral Epicondylitis with Platelet/Lymphocyte Ratio, Neutrophil/Lymphocyte Ratio, and Systemic Immune-Inflammation Index

Lateral Epikondilitte Enflamasyon Varlığının Trombosit/Lenfosit Oranı, Nötrofil/Lenfosit Oranı ve Sistemik İmmün-İnflamasyon İndeksi ile Araştırılması

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ABSTRACT

Aim: This study aims to assess the existence of inflammation in the physiopathology of lateral epicondylitis (LE) and to evaluate the levels of blood inflammation parameters.

Material and Method: 72 patients with LE and 50 healthy individuals were included in this retrospective study. Age, gender, erythrocyte sedimentation rate (ESR), neutrophil, white blood cell (WBC), C-reactive protein (CRP), lymphocyte, platelet counts, platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) levels were scanned retrospectively from the hospital information system.

Results: While the patient and control groups were similar in terms of gender, age, CRP, ESR, lymphocyte, NLR and PLR values (p=0.902, p=0.108, p=0.193, p=0.902, p=0.523, p=0.140 and p=0.253, respectively), the median value of neutrophils, mean platelet, mean WBC and median SII score parameters were higher in the patient group (P=0.022, p=0.037, p=0.037, p=0.038, respectively). A strong correlation was detected between SII and NLR and PLR (both p<0.001, r:0.833 and r:0.778, respectively). The area under the curve (AUC) was calculated as 0.61 for SII via the receiver operating characteristics (ROC) curve analysis, (p=0,038).

Conclusion: The SII value, which is an indicator of inflammation, was more elevated in the LE group than in the healthy group. More study is needed on this subject.

Keywords: Lateral epicondylitis, systemic immune-inflammation index, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, inflammation

ÖZ

Amaç: Bu çalışma lateral epikondilitin (LE) fizyopatolojisinde inflamasyonun varlığını ve kan inflamasyon parametrelerinin düzeylerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: LE tanılı 72 hasta ve 50 tane sağlıklı birey bu retrospektif çalışmaya dahil edildi. Hasta ve kontrol gruplarında yaş, cinsiyet, eritrosit sedimentasyon hızı (ESH), nötrofil, beyaz kan hücresi (WBC), C-reaktif protein (CRP), lenfosit, trombosit sayıları, trombosit-lenfosit oranı (PLO), nötrofil-lenfosit oranı (NLO) ve sistemik immün-inflamasyon indeksi (Sİİ) düzeyleri hastane bilgi sisteminden retrospektif olarak tarandı.

Bulgular: Hasta ve kontrol grubu cinsiyet, yaş, CRP, ESH, lenfosit, NLO ve PLO değerleri açısından benzer iken (sırasıyla p=0,902, p=0,108, p=0,193, p=0,902, p=0,523, p=0,140 ve p=0,253), nötrofil, ortalama trombosit, ortalama WBC ve ortanca SII skor parametrelerinin medyan değeri hasta grubunda daha yüksekti (sırasıyla P=0,022, p=0,037, p=0,037 ve p=0,038). Sİİ ile NLO ve PLO arasında güçlü bir korelasyon saptandı (her iki p<0.001, sırasıyla r:0.833 ve r:0.778). İşlem karakteristik (ROC) eğrisi analizi ile Sİİ için eğri altındaki alan (AUC) 0,61 olarak hesaplandı (p=0,038).

Sonuç: Enflamasyonun göstergesi olan Sİİ değeri LE grubunda sağlıklı gruba göre daha yüksekti. Bu konuda daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Lateral epikondilit, sistemik immün-enflamasyon indeksi, nötrofil-lenfosit oranı, trombosit-lenfosit oranı, inflamasyon

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INTRODUCTION

Lateral epicondylitis (LE) is an overuse tendinopathy of the wrist extensor muscles and tendons and pain is often seen in the lateral epicondyle of the humerus, which is the attachment site. This pain can radiate to the forearm (1). In addition, patients often have difficulty grasping and lifting objects. On physical examination, punctate tenderness is typically detected around the lateral epicondyle. In addition, there is an increase in pain with excessive wrist flexion and resistant elbow extension (2).

Histopathological studies have shown the absence of inflammatory cells in chronic LE biopsies. It was named angiofibroblastic hyperplasia because of the abundant fibroblasts, vascular hyperplasia and collagen in the biopsy (3). However, Al-Dhafer et al. compared patients' extensor carpi radialis brevis tendons with those of the healthy controls in their study published in 2021. They showed that expression levels of glutamate receptors, neuropeptides and inflammatory mediators were significantly increased, as well as macrophage in the LE group. These findings imply that inflammation has a function in the physiopathology of chronic LE (4).

Since two conflicting studies have been conducted to research the existence of inflammation in the pathogenesis of epicondylitis or tendinopathy (5, 6), conducting studies on this situation can contribute to the literature. Therefore, this study aims to reveal whether low-level systemic inflammation is effective in the etiopathogenesis of LE and the relationship between hematological parameters such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII), which are markers in inflammatory conditions.

MATERIAL AND METHOD

Patients between the ages of 18-65 who were diagnosed with LE and admitted to the outpatient clinic between 2018 and 2022 were accepted to the current study. The data of LE patients were scanned retrospectively from the hospital automation system. Exclusion criteria of the study were the presence of malignancy, infection, pregnancy, metabolic disease, inflammatory rheumatic disease, fracture in the upper extremity, neuropathy, radiculopathy, arthropathy and injection or physical therapy for lateral epicondylitis. The control group consisted of people who applied to the outpatient clinic between 2018 and 2022, whose hemogram, ESR and CRP tests were requested due to iron deficiency and vitamin deficiencies or acute muscle pain and whose results were within normal limits. The control group was formed to be similar in age and gender to the patient group. Blood parameters were collected retrospectively from the hospital automation system (FONET) by scanning patient files. The NLR value was calculated by the ratio of the neutrophil count to the lymphocyte count, while the PLR value was calculated by the ratio of the platelet count to the lymphocyte count. SII was calculated by multiplying the platelet count by the neutrophil count and dividing by the lymphocyte count (7).

Age, gender, white blood cell (WBC), neutrophil, lymphocyte, platelet counts, NLR, PLR, SII, ESR and CRP values were compared between these two groups.

Statistical analysis

Conformity of continuous data to normality assumption was assessed according to the Kolmogrov Smirnov Test and coefficient of variation. Normally distributed continuous data and non-normally distributed continuous data were defined as mean±standard deviation and median (minimum-maximum), respectively. Categorical data were given as frequency and percentage. If the assumption of normality was satisfied, the Independent Sample t-test was used to assess the statistical difference between groups for continuous variables; If not, the Mann Whitney-U Test was preferred. Statistical difference between groups for categorical variables was determined by Pearson Chi-Square Test. The relationship between numerical variables was evaluated with Spearman correlation analysis. ROC analysis was performed to assess the sensitivity and specificity of SII. All statistical analyzes were performed with SPSS 22 program. A p-value below 0.05 was approved as significant.

RESULTS

The patient and control groups were statistically similar in terms of gender, age, ESR, CRP, lymphocyte, NLR and PLR values (p=0.902, p=0.108, p=0.902, p=0.193, p=0.523, p= 0.140 and p=0.253, respectively).

The median value of neutrophils, mean platelet, mean WBC and median SII score in the LE group were more elevated than the control group (p=0.022, p=0.037, p=0.037 and p=0.038, respectively).

A very weak positive correlation was determined between ESR and CRP (r:0.208, p=0.022). A moderate positive correlation was determined between NLR and PLR (r:0.546, p<0.001). A high level of positive correlation was found between SII score and NLR and PLR (both p<0.001, r:0.833, r:0.778, respectively).

The ideal SII cut-off value was determined as 458.50 by ROC analysis. The area under the ROC curve was 0.611. Confidence intervals for this area were determined as 0.508 and 0.713. Taking this point as the optimal cut-off point, the sensitivity was 0.556 and the specificity was 0.440. The obtained area was considered statistically significant (p=0.038) (**Figure 1**) (**Table 3**).

Table 1. Comparison of demographic and laboratory parameters of the patient and control groups

Variables	Patient Group (n=72)	Control Group (n=50)	P
Gender			0,902*
Male (n/%)	44 (61,1)	30 (60,0)	
Female (n/%)	28 (38,9)	20 (40,0)	
Age (Mean±SD)	47,88±9,12	50,66±9,54	0,108**
ESR (Median (min-max))	9,0 (3,0-30,0)	10,0 (2,0-30,0)	0,902***
CRP (Median (min-max))	2,42 (0,29-10,0)	1,86 (0,15-6,11)	0,193***
Nötrofil (Median (min-max))	4,40 (2,30-7,00)	3,63 (1,92-7,22)	0,022***
Lenfosit (Mean±SD)	2,32±0,66	2,25±0,58	0,523**
Platelet (Mean±SD)	275,79±67,50	251,44±54,87	0,037**
WBC (Mean±SD)	7,41±1,53	6,81±1,57	0,037**
NLR (Median (min-max))	1,91 (0,74-5,16)	1,67 (0,86-3,48)	0,140***
PLR (Median (min-max))	126,08 (41,25-266,43)	117,16 (62,75-364,71)	0,253***
SII (Median (min-max))	473,53 (144,38-1628,33)	422,90 (212,61-1086,28)	0,038***

n: Number, CRP: C-reactive protein, WBC: White blood cell, NLR: Neutrophil-lymphocyte ratio, SII:Systemic immune inflammation index, PLR: Platelet-lymphocyte ratio, ESR: Erythrocyte sedimentation rate, *Pearson Chi-Square Test, **Independent Sample T-Test, ***Mann Whitney -U Test

Table 2. Correlation analysis of laboratory parameters

		ESR	CRP	NLR	PLR	SII
ESR	r	1,000	0,208	0,023	0,075	0,097
	p*	.	0,022**	0,797	0,412	0,288
CRP	r	0,208	1,000	-0,017	-0,014	0,146
	p*	0,022**	.	0,850	0,882	0,109
NLR	r	0,023	-0,017	1,000	0,546	0,833
	p*	0,797	0,850	.	<0,001**	<0,001**
PLR	r	0,075	-0,014	0,546	1,000	0,778
	p*	0,412	0,882	<0,001**	.	<0,001**
SII	r	0,097	0,146	0,833	0,778	1,000
	p*	0,288	0,109	<0,001**	<0,001**	.

r: Spearman correlation coefficient, *Spearman correlation analysis (<0.25 very weak relation; 0.26-0.49 weak relation; 0.50-0.69 medium relation; 0.70-0.89 high relation; 0 .90-1.0 very high correlation) **p<0.05

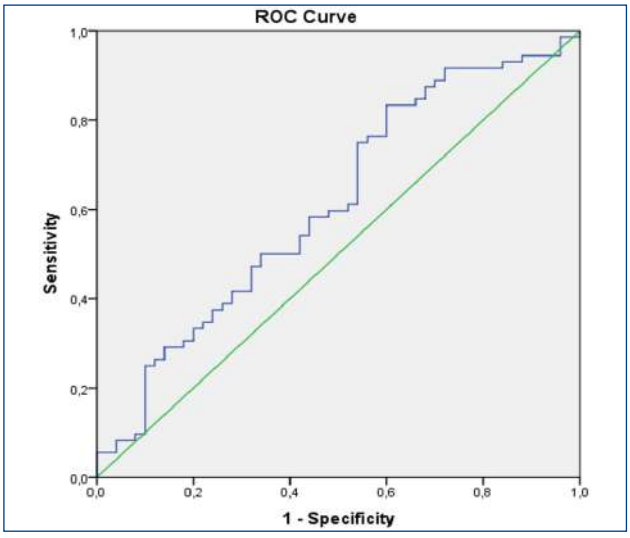

Figure 1. ROC analysis of SII score in patients with lateral epicondylitis

Table 3. ROC analysis of SII score in patients with lateral epicondylitis

	SII
AUC	0,611
95 % CI	0,508-0,713
Sencitivity %	%55,6
Specificity %	%44,0
P	0,038
Cut-off	458,50

AUC: Area Under The Curve

DISCUSSION

In this study, ESR, CRP, lymphocyte, NLR and PLR values were similar between the LE group and the healthy control group. When the groups were compared in terms of median neutrophil value, mean platelet, mean WBC and median SII score, higher values were found in the patient group. A high level of positive correlation was observed between SII score and PLR and NLR. According to the results of our study, it may be thought that inflammation plays a role in the pathogenesis of LE.

ESR and CRP are the most frequently used laboratory parameters in clinical practice as indicators of inflammation. In addition, PLR and NLR have been used as a marker of inflammation in diverse diseases in recent years (5). Another new marker of inflammation is the SII (7). SII has been shown in many studies to be a good indicator of inflammation and disease activity (8-11).

In a meta-analysis published in 2018, PLR and NLR values were shown to be more elevated in individuals with rheumatoid arthritis (RA) compared to healthy people (12). Wu et al. found that the SII level was higher in ankylosing spondylitis (AS) patients than in healthy individuals in their study published in 2021. They found that the active AS group had higher SII levels than the remission AS group (9). Li et al showed that PLR, NLR and lymphocyte to monocyte ratio (LMR) are good indicators of RA disease activity in their study published in 2021 (13).

In addition to rheumatic diseases, PLR and NLR values have been studied as inflammation markers in diseases such as cardiovascular disease, malignancy, cerebrovascular diseases, kidney diseases, diabetes mellitus, hypertension and ulcerative colitis. High PLR and NLR values have been related to poor prognosis in various studies (5).

The relationship between blood inflammation parameters and musculoskeletal system diseases has been evaluated in various studies (6, 14, 15). Cai et al. found that NLR values were more elevated in patients with OA than in healthy individuals. They suggested that NLR level is associated with disease progression and is an independent risk factor (14). Tasoglu et al. evaluated the blood parameters of patients with knee

OA and they showed that the severe OA group had higher mean NLR levels than the mild-to-moderate OA group (16). Büyükavcı et al. found that blood NLR levels were associated with radiographic staging (Kellgren-Lawrence) of knee OA in their study published in 2018. They detected higher NLR levels in patients with advanced knee OA compared to individuals with mild to moderate knee OA (17). Low-grade systemic inflammation is one of the theories proposed in the etiopathogenesis of OA (18) and the above studies support this idea.

In a study published in 2021, it was shown that mean ESR levels were more elevated in patients with fibromyalgia syndrome (FMS) compared to healthy people and PLR and NLR values were alike between both groups (19). Aktürk et al. found that NLR levels were more elevated in FMS patients than in healthy individuals and suggested that NLR could be used as an inflammatory marker in the diagnosis of FMS (15). İlgün et al. found that NLR values were similar between FMS and healthy control groups, while PLR values were more elevated in FMS patients (20). Al-Nimer et al. found PLR and NLR levels to be more elevated in patients with FMS than in healthy people and they found a relationship between these rates and the severity of FMS disease (21). Studies on the use of inflammation-related blood parameters in the diagnosis of FMS contradict each other.

A study published in 2022 found evidence that the NLR value is an important indicator of tendinopathy (elbow, rotator cuff, hamstring, patellar and achilles) (6). However, Karakoyun et al. did not find a significant difference between epicondylitis patients and healthy people in terms of PLR, NLR and other blood parameters in their study published in 2020. They stated that using these parameters to demonstrate the existence of inflammation in the physiopathology of epicondylitis is not significant and there is no relationship between epicondylitis severity and these rates (5). Neither of these studies included the level of SII in the assessment. In the present study, PLR and NLR values were statistically similar between the LE group and the healthy control group whereas SII value was higher in the LE group. This could mean that inflammation contributes to the pathogenesis of the disease.

In previous studies, recurrent microtraumas and related degenerative changes (angiofibroblastic hyperplasia) rather than inflammation were accepted in the pathophysiology of lateral epicondylitis (4).

Since no neutrophils were detected as a result of histopathological evaluation in previous studies, it was thought that inflammation was not effective in the etiopathogenesis of tendinopathy and the term tendinosis was preferred instead of tendinitis (22). However, neutrophils are detected in the first two days of inflammation. Then the process continues with macrophages, platelets, cytokines and growth factors (6, 23).

Al-Dhafer et al. evaluated the extensor carpi radialis brevis muscle tendon of the patients with chronic LE histopathologically and found an increase in inflammatory cytokine levels and macrophage count compared to the healthy group. Macrophages may have modulating effects on pain, tissue remodeling and healing in chronic tendinopathies (4).

The present study is the first in the literature to evaluate the level of SII in patients with LE. Üstündağ et al. suggested that a significant increase in SII and PLR levels may be related to subclinical low-grade inflammation (24). In the current study, the SII value was more elevated in the LE group compared to the control group. In addition, as a result of the ROC analysis, it was found that SII could be a significant indicator in predicting lateral epicondylitis. The low sensitivity and specificity rates of the present study may be due to the small number of patients. The findings of the present study will contribute to the literature, but more comprehensive studies with a large patient cohort are needed to confirm these results.

The retrospective character of the study and the small study groups are the limitations of the present study.

CONCLUSION

SII value which is an indicator of inflammation was more elevated in the LE group than in the control group. Although this could mean that inflammation contributes to the pathogenesis of the disease, studies with more participants and including histopathological evaluation are needed to understand the presence of inflammation in the pathophysiology of LE.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Hatay Mustafa Kemal University Ethics Committee (Date: ..... , Decision No: .....)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Lepidik Patern Akciğer Adenokarsinomlarında İmmünohistokimyasal Anti-Rage Antikorunun Rolü

The Role of Immunohistochemical Anti-Rage Antibody in Lepidic Pattern Lung Adenocarcinomas

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ÖZ

Giriş: Akciğer kanseri, tüm dünyada kansere bağlı ölümlerin önde gelen nedeni olmaya devam etmektedir. Adenokarsinom, küçük hücreli dışı akciğer kanserinin en yaygın alt tipidir. Lepidik patern, alveoler yüzey boyunca büyüme gösteren akciğer adenokarsinom subtipidir. Receptor for Advanced Glycation End-products (RAGE), immünoglobulin gen süper ailesine ait transmembran bir resöptördür ve pulmoner AT-I epitel hücrelerinden eksprese edilir. Yüksek düzeyde RAGE ekspresyonu, birincil olarak pro-oksidatif ve pro-inflamatuar mekanizmalar yoluyla birçok pulmoner hastalığın patogenezinde yer alır. Bu çalışmada başta lepidik patern adenokarsinomlar olmak üzere akciğer adenokarsinomlarında Anti-Rage immünohistokimyasal belirtecinin boyanma paterninin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya, Selçuk Üniversitesi Tıbbi Patoloji Anabilim Dalı arşivinden, 2009-2022 yılları arasında akciğerde lepidik patern dominant adenokarsinomu tanısı alan toplam 32 hasta dahil edilmiştir. İmmünohistokimyasal Anti-rage boyama ile Adenokarsinom alanı ile komşu normal akciğer dokusunun boyanma paterni karşılaştırılmıştır.

Bulgular: Tüm hastalarda immünohistokimyasal Anti-Rage antikoru ile tümör çevresi normal alveol yapılarında kuvvetli membranöz boyanmalar izlenir iken, adenokarsinom alanlarında lepidik patern ve eşlik eden diğer tüm paternlerde belirgin boyanma kaybı ya da zayıf fokal boyanma izlenmiştir. Bunun ile birlikte akciğer kanseri evresi ve prognozunu etkileyen tümör boyutu, plevra invazyonu ve tümörün hava boşlukları içerisinde yayılımının değerlendirmesinde Anti-rage immünhistokimyasal belirtecinin kullanılabilirliği ortaya konmuştur.

Sonuç: Anti-Rage antikoru, akciğer adenokarsinom tanısında ve prognostik faktörlerin tanımlanmasında yardımcı yöntem olarak kullanılabilir. Bunun ile birlikte fibrozis veya inflamasyon sonrası oluşan reaktif değişikliklerde Anti-Rage immünohistokimyasal boyamanın rolünün geniş olgu çalışmaları ile gösterilmesi faydalı olabilir.

Anahtar Kelimeler: Akciğer, Adenokarsinom, İmmünohistokimya, RAGE

ABSTRACT

Introduction: Lung cancer remains the leading cause of cancer-related death worldwide. Adenocarcinoma is the most common subtype of non-small cell lung cancer. The lepidic pattern is the subtype of lung adenocarcinoma growing along the alveolar surface. The receptor for advanced glycation end products (RAGE) is a transmembrane receptor in the immunoglobulin gene superfamily and is expressed in pulmonary AT-I epithelial cells. High-level expression of RAGE is involved in the pathogenesis of many pulmonary diseases, primarily through pro-oxidative and pro-inflammatory mechanisms. In this study, it was aimed to investigate the staining pattern of Anti-Rage immunohistochemical marker in lung adenocarcinomas, especially in lepidic pattern adenocarcinomas.

Material and Method: A total of 32 patients diagnosed with lepidic pattern dominant adenocarcinoma of the lung between 2009 and 2022 from the archives of the Selçuk University Department of Medical Pathology were included in the study. The staining pattern of the adenocarcinoma area and adjacent normal lung tissue was compared with immunohistochemical Anti-rage staining.

Results: While strong membranous staining was observed in normal alveolar structures around the tumor with immunohistochemical Anti-Rage antibody in all patients, significant loss of staining was observed in all patterns in adenocarcinoma areas. In addition, the effectiveness of the Anti-Rage immunohistochemical marker has been demonstrated in the evaluation of tumor size, pleural invasion, and spread of the tumor within the air spaces, which affect the stage and prognosis of lung cancer.

Conclusion: Anti-Rage antibodies can be used as an auxiliary method in the diagnosis of lung adenocarcinoma and the identification of prognostic factors. However, it may be useful to demonstrate the role of Anti-Rage immunohistochemical staining in reactive changes after fibrosis or inflammation with large case studies.

Keywords: Lung, Adenocarcinoma, Immunohistochemistry, RAGE

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GİRİŞ

Akciğer kanseri, dünya çapında kansere bağlı ölümlerin en yaygın nedenidir. Hemen tüm akciğer kanserleri karsinom olup baskın histolojik tipler adenokarsinom, skuamöz hücreli karsinom, küçük hücreli akciğer karsinom ve büyük hücreli karsinomdur. Akciğer adenokarsinomunda histomorfolojik olarak lepidik, asiner, papiller, mikropapiller ve solid subtip olmak üzere beş patern tanımlanmıştır. Bu subtipler tümör içerisinde pür halde bulunabildikleri gibi çoğunlukla birden fazla subtip aynı anda tümör içerisinde kompleks halde görülebilmektedir. Tümör dokusu içerisinde en az %5 alanda görülen subtiplerin, semikantitatif olarak tanıya yazılması önerilmiştir. En yaygın görülen subtip ise "predominant" subtip olarak tanıda belirtilir. Lepidik patern alveoler yüzey boyunca büyüme gösteren subtiptir. Yapılan çalışmalarda, lepidik baskın adenokarsinom, adenokarsinom in situ ve minimal invaziv adenokarsinom için olumlu prognostik ilişkiden, bunun yanı sıra baskın mikropapiller ve solid alt tipler için kötü prognostik ilişkiden bahsedilmektedir (1).

Receptor for Advanced Glycation End-products (RAGE), immünoglobulin gen süper ailesine ait transmembran bir resöptördür (2). RAGE, pulmoner AT-I epitel hücrelerinin bazolateral membranında eksprese edilir ve tüm pulmoner alveoler epitel hücrelerinin yaklaşık%95'ini oluşturur (3). Yüksek düzeyde RAGE ekspresyonu, birincil olarak pro-oksidatif ve pro-inflamatuar mekanizmalar yoluyla birçok pulmoner hastalığın patogenezinde yer alır ve akciğer hasarının potansiyel bir biyobelirteci olarak kabul edilir (4,5). RAGE' nin karsinogenezdeki rolü belirsizliğini korumaktadır. Bunun ile birlikte RAGE'nin P53 bağımlı P21 gen ekspresyonunu arttırdığı yönünde yapılmış çalışmalar mevcuttur (6).

Bu çalışmada başta lepidik patern adenokarsinomlar olmak üzere akciğer adenokarsinomlarında Anti-Rage immünohistokimyasal belirtecinin boyanma paterninin araştırılması amaçlanmıştır.

GEREÇ VE YÖNTEM

Hasta Seçimi

Selçuk Üniversitesi Tıp Fakültesi Hastanesi Tıbbi Patoloji laboratuvarına 2009-2022 yılları arasında gelen akciğer kama rezeksiyon ve lobektomi materyallerine ait biyopsi örneklerinden lepidik patern baskın adenokarsinom tanısı alan 32 hasta çalışmaya dahil edilmiştir. Bunun ile birlikte tümörler içerisinde lepidik dışı patern mevcut ise ayrıca değerlendirilmiştir. Çalışmaya alınan 32 olguya ait H&E ile boyalı kesitler Tıbbi Patoloji Anabilim Dalı arşivinden çıkartılmış ve tekrar incelenmiştir. Normal doku ile kanser dokusu karşılaştırmasının yapılabilmesi için tümör etrafı normal akciğer dokusu içeren lamlar seçilmiştir. Lepidik patern içermeyen adenokarsinom olguları ile iğne veya tru-cut biyopsi gibi tümörün bir kısmını içeren biyopsiye ait materyaller çalışmaya dahil edilmemiştir. Bu çalışma, 31.01.2023 tarihinde 2023/67 sayılı Karar ile Selçuk Üniversitesi Tıp Fakültesi Etik Kurul tarafından onaylanmıştır.

İmmünohistokimya

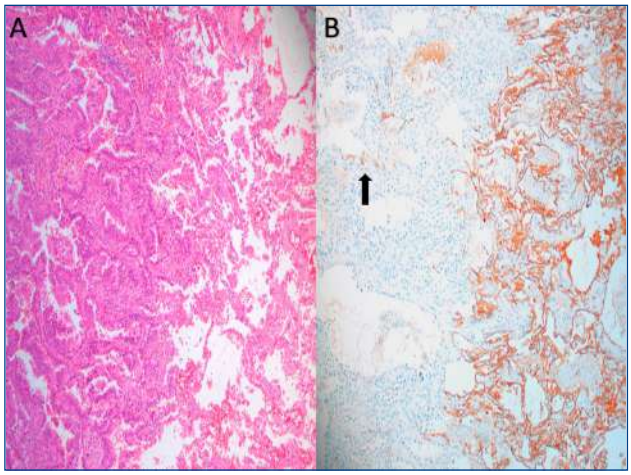
İmmunohistokimyasal boyama için formalin fiksasyonu sonrası parafine gömülü bloklardan, lizinli lamlara 4 mikron kalınlığında kesitler alınmıştır. Hazırlanan kesitlere Anti-Rage (Dako, Ihc-human, 100ug) antikorları kullanarak Dako otomatik boyama cihazında standart boyama prosedürü uygulanmıştır. Hücrelerde izlenen kahverengi kuvvetli, sitoplazmik ve komplet membranöz boyanma pozitif olarak kabul edilmiştir. Kahverengi boyanmayan veya soluk ve inkomplet boyanmalar negatif boyanma olarak kabul edilmiştir.

BULGULAR

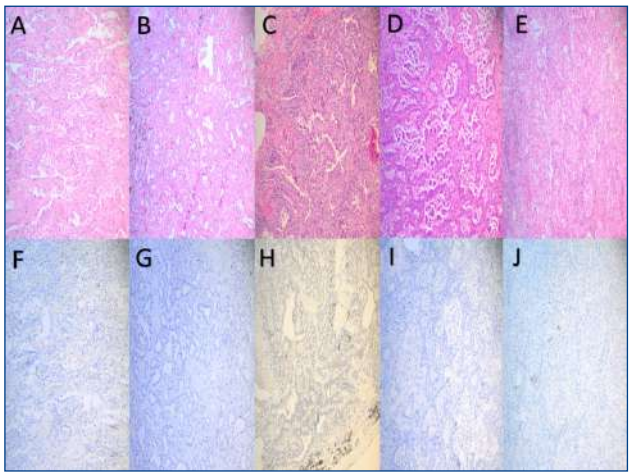
Çalışmaya 32 hasta dahil edilmiştir. Hastaların %50'si kadın, %50'si erkektir. Hastaların ortalama yaşı 65'tir. Hastaların 16'sında (%50) plevra invazyonu mevcut olup, 16'sında (%50) plevra invazyonu görülmemiştir. Adenokarsinom olgularının tamamında lepidik patern mevcuttur. Lepidik patern dışında ayrıca hastaların 21'inde (%66) asiner patern, 5'inde (%16) papiller patern, 5'inde (%16) mikropapiller patern ve 5 'inde (%16) solid patern izlenmiştir. Tüm hastalarda immünohistokimyasal Anti-Rage belirteci ile tümör çevresi normal alveol yapılarında kuvvetli membranöz boyanmalar izlenirken, adenokarsinom alanlarında tüm paternlerde belirgin boyanma kaybı izlenmiştir (**Resim 1,2**). Boyanma kaybı tüm paternlerde yüzde 90'nın üzerindedir. Bunun ile birlikte lepidik paternde 25 (%78) olguda (**Resim 1B**), asiner paternde 3 (%14) olguda, mikropapiller paternde 3 (%60) olguda ve papiller paternde 2 (%40) olguda genellikle tümör periferinde olmak üzere tümör içerisinde seyrek, soluk ve inkomplet boyanmalar izlenmiştir. Solid patern adenokarsinom alanlarında Anti-Rage ile tamamen boyanma kaybı izlenmiştir (**Tablo 1**).

Tablo 1. Akciğer adenokarsinomu histolojik paternlerinde Anti-Rage antikoru ile boyanma farklılıkları

	Lepidik patern (n, %)	Asiner patern (n, %)	Papiller patern (n, %)	Mikropapiller patern (n, %)	Solid patern (n, %)	Normal akciğer parankimi (n, %)
Anti-Rage ile diffüz kuvvetli boyanma	0, %0	0, %0	0, %0	0, %0	0, %0	32, %100
Anti-Rage antikoru ile tam boyanma kaybı	7, %22	18, %86	3, %60	2, %40	5, %100	0, %0
Anti-Rage ile fokal zayıf boyanma	25, %78	3, %14	2, %40	3, %60	0, %0	0, %0
Hasta sayısı	32	21	5	5	5	32



Resim 1. A. Resmin sol tarafında lepidik patern adenokarsinom alanı, sağ tarafında normal alveoler yapılar görülmektedir (H&E, 100x). **B.** İmmünohistokimyasal Anti-Rage ile resmin sol tarafında belirgin kayıp izlenirken, resmin sağ tarafında normal alveoler yaoılarda kuvvetli ve diffüz boyanma görülmektedir. Tümör içerisinde özellikle normal akciğer dokusuna yakın alanlarda fokal ve kesintili boyanmalar görülmektedir (ok)(IHK, 100x).



Resim 2. A. Lepidik patern adenokarsinom (H&E, 100x). **B.** Asiner patern adenokarsinom (H&E, 100x). **C.** Papiller patern adenokarsinom (H&E, 100x). **D.** Mikropapiller patern adenokarsinom (H&E, 100x). **E.** Solid patern adenokarsinom (H&E, 100x). **F.** Lepidik patern adenokarsinomda Anti-Rage ile boyanma kaybı (IHK,100x). **G.** Asiner patern adenokarsinomda Anti-Rage ile boyanma kaybı. **H.** Papiller patern adenokarsinomda Anti-Rage ile boyanma kaybı (IHK,100x). **I.** Mikropapiller patern adenokarsinomda Anti-Rage ile boyanma kaybı (IHK,100x). **J.** Solid patern adenokarsinomda Anti-Rage ile boyanma kaybı (IHK,100x).

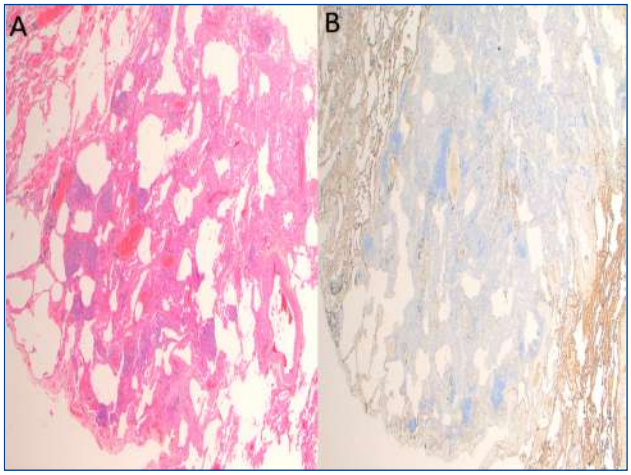
TARTIŞMA

RAGE, ilk olarak 1993 yılında Schmidt ve ark. tarafından keşfedilmiş ve RAGE' nin, AT-1 epitel hücreleri dışında endotel hücrelerinde, düz kas hücrelerinde, kardiyomyositlerde ve makrofajlarda eksprese olduğu gösterilmiştir (7).

Bir dizi araştırma, küçük hücreli dışı akciğer karsinomu dokusunda RAGE ekspresyonunun değiştiğini bildirmiştir (8,9,10). Birkaç çalışma, RAGE'nin akciğer dokularını tümör duyarlılığından koruduğunu ileri sürerek, RAGE supresyonunun küçük hücreli dışı akciğer karsinomu gelişimini kolaylaştırdığı hipotezini ortaya koymaktadır (11,12). Bazı çalışmalarda ise, RAGE'nin sadece akciğer kanserlerinin değil, aynı zamanda meme, prostat, melanom ve pankreas dahil olmak üzere diğer birçok kanserin patofizyolojisine katkıda bulunduğunu bildirilmektedir (13).

Akciğer karsinomlarının Hematoksilen-Eozin (H&E) rutin boyamalar ile tanınması birçok patolog için zor değildir. Ancak lepidik patern akciğer adenokarsinomu alveoler yüzey boyunca büyüme gösterdiği için özellikle küçük boyutlardaki tümörlerde tanı zorluğuna neden olabilir (14). Bu nedenle çalışmamızda da özellikle lepidik patern içeren olgular ön plana çıkmaktadır. Anti-Rage ile yaptığımız immünohistokimyasal boyama sonrası adenokarsinom olgularında lepidik patern dahil olmak üzere tüm paternlerde boyanma kaybı izlenirken, çevre normal akciğer alveoler yapılarında diffüz kuvvetli boyanmalar görülmüştür. Anti-Rage immünohistokimyasal belirtecinin adenokarsinom ve nonneoplastik epitel ayrımında önemli rol aldığı çalışmamızla ortaya çıkmaktadır.

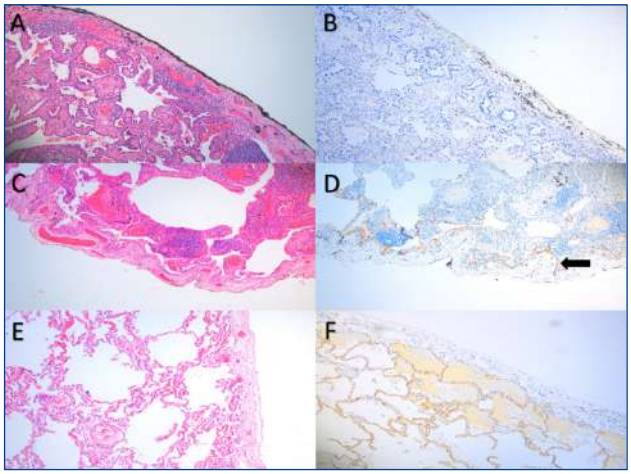
Akciğer kanserlerinin evrelendirilmesinde tümör boyutu önemli bir faktörü teşkil etmektedir (15). Tümörün evresini değiştirebileceğinden tümör boyutunun en doğru şekilde verilmesi gerekmektedir. Tümör etrafı fibrotik ve atalektazik değişiklikler makroskopik olarak tümör boyutu değerlendirmede yanıltıcı olabilmekte, bu nedenle tümör boyutu belirlenmesinde mikroskobik ölçüm ile korelasyon gerekmektedir. Mikroskobik olarak H&E boyalarda özellikle lepidik patern adenokarsinomlarda tümör boyutunun hesaplanması zor olabilir. Bu gibi olgularda immünohistokimyasal Anti-Rage antikorunun kullanımı oldukça fayda sağlamaktadır. **Resim 3**'de görüldüğü gibi tümör ve normal akciğer parankim sınırının histomorfolojik olarak değerlendirme zorluğu olan olgularda immünohistokimyasal Anti-Rage kullanımı değerlendirme kolaylığı sağlayabilir. Bunun yanında, H&E ile gözden kaçabilen küçük tümör odaklarının tespitinde Anti-Rage antikoru yardımcı yöntem olarak kullanılabilir.



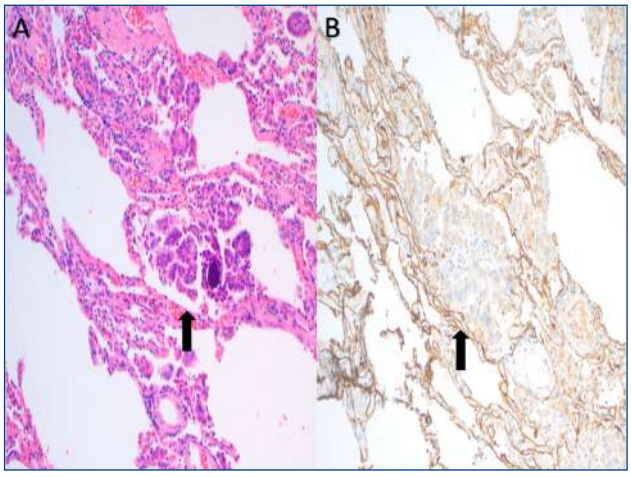
Resim 3. A. İnflamasyonun eşlik ettiği ve tümör sınırlarının net olarak seçilemediği lepidik patern adenokarsinom alanı (H&E, 50x). **B.** Anti-Rage antikoru ile tümör sınırları net olarak seçilebilmektedir (IHK,50x).

Akciğer kanserlerinin evrelendirilmesinde bir diğer önemli parametre plevral invazyondur. Visseral plevral invazyon (VPI), genellikle küçük hücreli dışı akciğer kanserinde (KHDAK) kötü bir prognostik faktör olarak kabul edilir. VPI, kanser hücrelerinin visseral plevranın elastik tabakasının ötesine penetrasyonu olarak tanımlanır (16). Bu nedenle visseral plevral invazyonun sadece visseral plevral yüzeye uzanan tümörlerde değil, aynı zamanda visseral plevranın elastik tabakasının ötesine geçen tümörlerde de mevcut olduğu düşünülmelidir. Plevral invazyon Hammar kalsifikasyonuna (17) göre şu şekilde sınıflandırılır: PL0, elastik tabakasının ötesinde plevral tutulumu olmayan tümör; PL1, visseral plevranın elastik tabakasının ötesine yayılan ancak plevral yüzeyde açığa çıkmayan tümör; PL2, plevral yüzeyi istila eden tümör ve PL3, pariyetal plevrayı invaze eden tümör. PL0, VPI olarak sınıflandırılmazken, PL3, pariyetal plevra invazyonu ile ilişkili olarak göğüs duvarı invazyonu olarak sınıflandırılır. Ayrı ayrı sınıflandırılmasına rağmen, PL1 ve PL2'nin her ikisi de TNM evreleme sisteminde VPI olarak yorumlanır (15,16,18). PL0 ve PL1 aşamasında H&E boyalı camlarda elastik tabakayı değerlendirmek kolay olmayabilmektedir. Bu durumda otörler elastin tabakayı göstermek için histokimyasal elastin boyaları kullanmayı tavsiye etmişlerdir (18). Ancak, histokimyasal elastin boyaları da elastin tabakayı değerlendirme de her zaman yardımcı olamayabilmektedir. Histokimyasal elastin boyanın kalitesi, uygulanma şekli veya doku içerisindeki elastik tabakanın kalınlığı değerlendirmeyi etkileyecek faktörler arasında sayılabilir. Bu gibi durumlarda Anti-Rage antikorunun uygulanması özellikle invazyonun olmadığını kanıtlamak için yardımcı olabilir. Plevraya yakın yerleşimli tümörlerde, plevra ile tümör arasında kalan alveoler yapılar H&E boyaları ile görülemeyebilmektedir. Anti-Rage antikoru ile tümör üzerinde alveol yapının gösterilmesi tümörün plevral elastik tabakadan uzak olduğunun kanıtı olarak kullanılabilir. Anti-Rage ile alveolar yapıların görülmemesi sonrası VPI'yı değerlendirmek için ek tetkikler yapılabilir. Anti-Rage ile alveol yapının görülmemesi invazyon olup olmadığını göstermez ancak anti-Rage ile tümör üzeri alveol yapının gösterilmesi VPI olmadığını kanıtlar (**Resim 4**).

İnvazyon kriterleri içerisinde yer alan, tümörün hava boşlukları içinde yayılımı (STAS), ana tümörün sınırının ötesindeki normal akciğer parankiminde hava boşlukları içindeki tümör hücreleri olarak tanımlanır. Bir dizi bağımsız çalışma, STAS'ın rezeke edilmiş akciğer adenokarsinomunda ve araştırılan tüm majör histolojik akciğer kanseri türlerinde daha kötü klinik sonucun bir göstergesi olduğunu göstermiştir. Ek olarak, STAS'lı hastalarda, sınırlı rezeksiyon lobektomiden daha yüksek nüks riskine muhtemel katkıda bulunduğu düşünülmektedir. STAS'ın evrelemede yeri yoktur ancak prognoz ve nüks açısından önemli bir yerde bulunmaktadır (1). H&E ile boyanan camlarda özellikle küçük boyutlardaki hava boşlukları içerisindeki tümör odakları gözden kaçabilmektedir. Ana tümör dışı alanlarda Anti-rage ile boyanan normal akciğer parankimi içerisinde Anti-rage ile boyanmayan tümör odaklarının tespiti STAS'ın tanınmasında yardımcı olabilir (**Resim 5**).



Resim 4. A. Visseral plevral duvara yakın yerleşimli lepidik patern adenokarsinom (H&E, 100x). B. Resim A'ya ait alana uygulanan Anti-Rage antikoru ile tamamen boyanma kaybı görülmektedir. Bu hali ile hastada visseral plevral invazyon şüphesi mevcuttur (IHK,100x). C. Visseral plevral duvara yakın yerleşimli lepidik patern adenokarsinom (H&E, 100x). D. Resim C' ye ait alana uygulanan Anti-Rage antikoru ile üstte tümör alanında boyanma kaybı izlenirken, plevranın hemen altında kuvvetli kesintisiz alveoler boyanma görülmektedir (ok) (IHK,100x). Bu hali ile hastada plevral invazyon şüphesi mevcut değildir. E. Visseral plevra ve normal akciğer alveoler yapılar (H&E, 100x). F. Anti-Rage antikoru ile alveoler yapılarda kuvvetli diffüz boyanma görülmektedir (IHK,100x).



Resim 5. A. Alveoler hava boşlukları içerisinde yayılım gösteren tümör dokusu (ok) (H&E, 200x). B. Anti-Rage antikoru ile kuvvetli boyanan alveoler yapılar içerisinde Anti-Rage ile boyanmayan tümör dokusu (ok) (IHK, 200x).

Çalışmamız rezeksiyon materyallerinden yapılmıştır. Tümör alanlarında Anti-Rage belirteci ile belirgin boyanma kayıpları izlenmiştir. Ancak özellikle tümör-normal parankim geçiş alanlarında ve nadiren tümör merkezlerinde fokal, zayıf ve kesintili boyanmalar görülmüştür. Özellikle fiksasyonun iyi olmadığı olgularda boyanma değişiklikleri tanı zorluğuna neden olabilir. Bu gibi olgularda mutlaka internal kontroller ile değerlendirme ya-

pılmalıdır. Anti-rage ile normal alveoler yapılarda boyanmalar izlenmesine rağmen bronş epitelinde boyanma görülmemektedir. Bu gibi olgularda Anti-Rage antikorunu H&E boyalı lamlar ile korele değerlendirilmesi gerekmektedir. Çalışmada bazı olgularda akciğer dokusunda atelektazik değişiklikler izlenmiş olup bu alanlarda Anti-rage ile kuvvetli boyanma izlenmiştir. Bununla birlikte geniş olgu çalışmaları ile atelektazik, fibrotik veya inflamatuar değişiklikler gibi alanlarda veya küçük biyopsi örneklerinde Anti-Rage immünohistokimyasal boyanma paternin tümör ile normal doku ayrımında etkili olup olmadığının araştırılması faydalı olacaktır.

SONUÇ

Çalışmamızda immünohistokimyasal olarak Anti-Rage antikoru ile akciğer normal parankiminde kuvvetli boyanmalar izlenirken, adenokarsinom alanlarında anlamlı kayıplar izlenmiştir. Bu boyanma farklılığı ile adenokarsinom ve normal akciğer parankim ayrımı kolaylıkla yapılabilmektedir. Ayrıca, akciğer kanseri evresi ve prognozunu etkileyen tümör boyutu, plevra invazyonu ve tümörün hava boşlukları içerisinde yayılımının değerlendirmesinde Anti-rage immünhistokimyasal belirteci yardımcı teknik olarak kullanılabilir.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Morphological Analysis of Foramen Ovale and Foramen Lacerum in terms of Percutaneous and Endoscopic Endonasal Approaches

Foramen Ovale ve Foramen Lacerum'un Perkutanöz ve Endoskopik Endonasal Yaklaşımlar açısından Morfolojik Analizi

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ABSTRACT

Aim: It is clinically extremely important to determine the surrounding structures and variations of the foramen ovale, the region where mandibular nerve blockade is performed during percutaneous and endoscopic endonasal procedures. Therefore, this study was conducted to guide clinicians in determining and choosing the surgical method to be applied, especially percutaneous and endoscopic endonasal approaches, by investigating the relationship between foramen ovale, foramen lacerum and pterygoid processes on morphological basis.

Material and Method: The study was conducted with 56 skulls (right and left, 112 in total). In the lower view of the skull base, the horizontal relationship between the foramen ovale/foramen lacerum and the posterior border of the base of the lateral pterygoid processes was taken into account. Skulls with injuries to the lateral plate of the pterygoid process or foramen ovale and foramen lacerum on both sides were excluded.

Results: When the position of the foramen ovale relative to the processus pterygoideus lateralis was evaluated; the most common type II (medial type) was on the right with a rate of 30.3%, and type III (direct type) was on the left with a rate of 23.3%. The lowest rate was type IV. The foramen lacerum was in direct relationship with the medial pterygoid process posteromedially at a rate of 50%.

Conclusion: The fact that the foramen ovale is far from the foramen lacerum and pterygoid processes may make surgical procedures risky, as it will make it difficult to detect the origin of the mandibular nerve.

Keywords: Foramen ovale, Percutaneous approach, Foramen lacerum

ÖZ

Amaç: Perkutanöz ve endoskopik endonasal prosedürler sırasında mandibular sinir blokajının yapıldığı bölge olan foramen ovale'nin, çevre yapıları ve varyasyonlarını belirlemek klinik olarak son derece önemlidir. Dolayısı ile bu çalışma, foramen ovale, foramen lacerum ve processus pterygoideus'lar arasındaki ilişkiyi morofolojik temeller üzerinde araştırarak, perkutanöz ve endoskopik endonasal yaklaşımlar başta olmak üzere uygulanacak cerrahi yöntemin belirlenmesi ve tercih edilmesinde klinisyenlere yardımcı olmak amacı ile yapılmıştır.

Gereç ve Yöntem: Araştırma, 56 kafatası (sağ sol toplam 112) ile yapılmıştır. Kafa tabanının alttan görünümünde foramen ovale ve formaen lacerum ile processus pterygoideus lateralisin tabanının arka sınırı arasındaki yatay ilişki dikkate alındı. Her iki taraftaki pterygoid işlemin yanal plakasında veya foramen ovale ve foramen lacerum'da yaralanma gösteren kafatasları hariç tutuldu.

Bulgular: Foramen ovale'nin processus pterygoideus lateralis'e göre konumu değerlendirildiğinde, sağ tarafta en fazla tip II (medial tip) %30.3 oranında, sol tarafta ise en fazla tip III (direkt tip) %23.3 oranında bulunmaktaydı. Her iki tarafta en az ise tip IV bulunmaktaydı. Foramen lacerum ise %50 oranında posteromedial olarak direkt medial pterygoid çıkıntı ile ilişki göstermekteydi.

Sonuç: Foramen ovalenin foramen lacerum ve pterygoid çıkıntılardan uzak olması nervus mandibularisin çıkış yerini tespit etmeyi zorlaştıracağı için cerrahi prosedürleri riskli hale getirebilir.

Anahtar Kelimeler: Foramen ovale, Perkutanöz yaklaşım, Foramen lacerum

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INTRODUCTION

The foramen ovale (FO), one of the holes in the ala major of the os sphenoidale, is usually located near the upper end of the posterior border of the lateral pterygoid processes (LLP). It is located posterolateral to the foramen rotundum, anteromedial to the foramen spinosum, and lateral to the foramen lacerum (FL). It connects the fossa cranii media to the fossa infratemporalis. Nervus mandibularis, ramus meningeus accesorius of arteria maxillaris, and sometimes nervus petrosus minor pass through it (1).

FL does not represent a true foramen, meaning the bony canal containing neurovascular structures. The foramen lacerum is a cavity located at the junction of 3 basic structures that make up the skull base (corpus and ala major of os sphenoidale, pars petrosa of os temporale, clival part of os occipitale). Although no major anatomical formation passes through the FL, it is adjacent to important anatomical structures. Arteria carotis interna crosses this hole from above. Nervus canalis pterygoidei (vidian nerve) is formed above the hole and enters the canalis pterygoideus anterior to the FL. In addition, the clinically important ganglion trigeminale (glasser ganglion, semilunar ganglion) sits on the posterior-outer side of the foramen lacerum (2).

Today, endoscopic approaches are accepted as the standard procedure in anterior skull base surgeries. However, pathologies located around the fossa infratemporalis and FO are among the more difficult pathologies in endoscopic approaches. Therefore, approaches such as endoscopic endonasal, transmaxillary, and transpterygoid guide the surgeon (3). From the endoscopic endonasal perspective; The FL is a key structure due to its location at the junction between the sagittal and coronal planes. It is an important point for the endonasal approach, as it is located at the junction of most surgical routes in the coronal plane (4). FO which is located just lateral to the FL, is also an important component of cranial anatomy in neurosurgery. It facilitates anesthesia by providing access to the trigeminus nerve, especially in trigeminal nerve neuralgia (5). In percutaneous procedures aLLPied to the FO, the processus pterygoideus of the os sphenoidale is the guide point used to reach the foramen (6). Since the needle insertion site is adjacent to the trigeminal nerve, complications of this approach have been reported as masseter weakness, decreased corneal reflex, oculomotor nerve palsies, and carotid cavernous fistula (7,8). In addition, the atypical location of FO may cause neuralgias by affecting the adjacent bone structures and the anatomical organization of the nerves passing through it (9-11).

Trigeminal neuralgia is a serious condition that results in penetrating, episodic facial pain, and medical treatments usually give short-term results (12). Today, surgical procedures such as microvascular decompression, glycerol rhizolysis (13), trigeminal ganglion balloon compression and percutaneous stereotactic radiofrequency rhizotomy, which is one of the most risk-free methods of recent years, are aLLPied in the treatment of trigeminal neuralgia (14). However, for the efficient, effective and safe use of these techniques, a complete understanding of the surgical anatomy of the foramen ovale and surrounding structures is required (15). This study was conducted to describe the anatomical variations of the foramen ovale (FO) and to evaluate its relationship with the FL and pterygoid processes.

In summary, skull foramen are of great clinical importance due to variations in their size, location, shape and neurovascular structures passing through them. Knowing these variations helps clinicians in radiology and surgery. This study aims to guide clinicians in percutaneous and endoscopic endonasal approaches, with detailed morphological examination of FO and FL and determination of its clinical relationship with processus pterygoideus.

MATERIAL AND METHOD

This descriptive study was conducted with the skulls found *in Erciyes University and Ankara Medipol University Faculty of Medicine Anatomy* laboratories. The study was carried out with 56 skulls (right and left; 112 in total).

Inclusion criteria: Bones with preserved integrity and no structural defects were included in the study.

Exclusion criteria: Bones with fractures in the basis cranii externa that may affect the foramen ovale and foramen lacerum were excluded from the study.

Research design: The position of the FO relative to the LLP was evaluated with reference to the study of Iwanaga et al. (2018) (6) (**Figure 1**). Also, FO shape was evaluated with reference to the study of Iwanaga et al. (2018) and Elnashar et al. (2019).

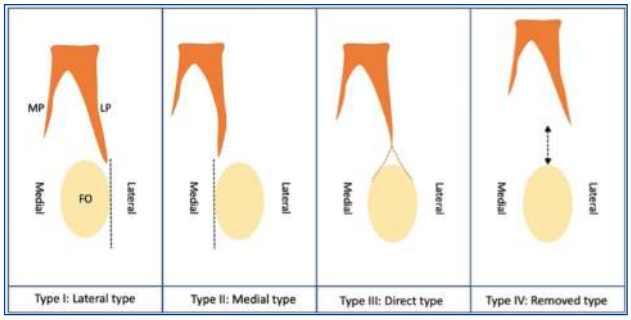

Figure 1. Position of foramen ovale relative to lateral pterygoid processes (6)

On the basis of the relationship between the FO and the posterior border of the base of the lateral plate of the pterygoid process, these were classified into four types (**Figure 2**):

- Type I: the posterior border of the base of the lateral plate ends at or close to the lateral border of the FO
- Type II: the posterior border of the base of the lateral plate of the pterygoid process ends at or close to the medial border of the FO
- Type III: the posterior border of the base of the lateral plate of the pterygoid process ends at or close to the center of the FO
- Type IV: the posterior border of the base of the lateral plate of the pterygoid process ends distant from the FO

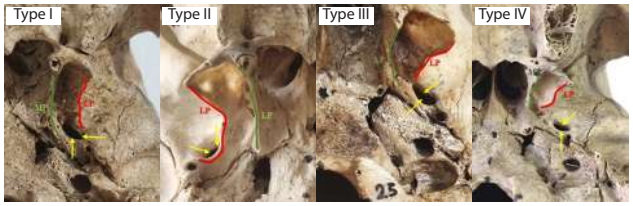

Figure 2. Position of FO relative to LPP.
Type I: Lateral type, Type II: Medial type, Type III: Direct type, Type IV: Far type

The position of the FL relative to the processus pterygoideus medialis (MPP) was classified into 3 groups as a result of the evaluations made by the researcher (**Figure 2**).

- Type I, in which the FL is located posteromedially to the MPP and in front of the inner mouth of the canalis caroticus,
- Type II, which is seen as a thin canal completely closed by the canalis caroticus and located on the posteriomedial of the MPP,
- Type III (**Figure 3**), in which the FL spreads to both sides of the MPP, covering a large area and expanding towards the FO

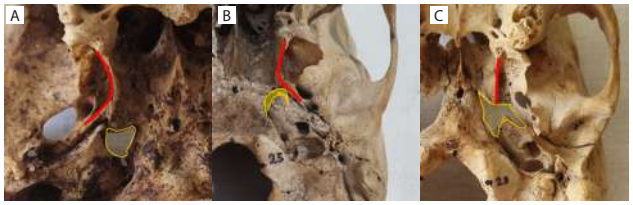

Figure 3. Position of FL relative to MMP
A: Posteromedial-direct, B: Posteromedial- embedded like canal, C: Both side-spread

Statistical Analysis

Basic descriptive statistics were employed to analyze the data were done by the computer software SPSS. The mean, standard deviation and range for each of the measurements were measured. Comparison of the values of all measurements was made between sides of each subject. All measurements and frequencies of the data were tabulated and separated according to the sides. p values less than the 0.05 level of significance was considered to be statistically significant.

RESULTS

In the study, it was determined that FO was seen in oval, almond, triangular and cordate shapes (**Figure 4**).

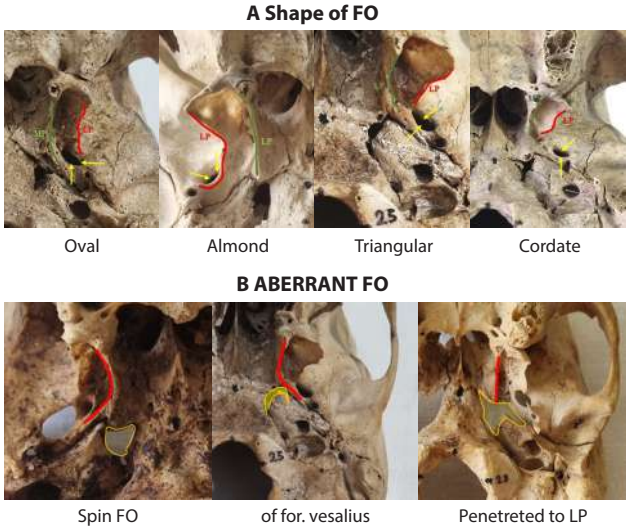

Figure 4. Shape (A) an d Aberrant (B) FO (LP: Lateral processes, MP: Medial processes)

While the oval type, which is the classical FO shape, is most common on the right and left; it was determined that triangular (8.9%) type was observed on the right side and the cordate type (3.5%) was observed on the left side at the lowest rate (**Table 1**).

Table 1. Shapes of FO

Shape of FO	Right	Left	Total	p
Oval	32 (28.5)	34 (30.4)	66 (58.9)	p>0.05
Almound	12 (10.7)	13 (11.6)	25 (22.3)	p>0.05
Triangular	5 (4.4)	7 (6.3)	12 (10.7)	p>0.05
Cordate	7 (6.2)	2 (1.7)	9 (8.1)	P<0.05
Total	56 (50)	56 (50)	112 (100)	

Test: ındependent t testi, p<0.05

Considiring atypical forms of FO (Elongation of the bony prominence into the FO), it was determined that spin-like protrusions tended towards the FO. Also, foramen vesalis were located immediately adjacent to the FO, or a portion of the FO penetrated well into the LP and some of it was located in the LP (**Figure 5**). Regardless of the side (n=112), it was determined that the rate of spin FO was 23.4%, FO accompanied by foramen vesalis was 44.6%, and FO penetrating into the LP was 32%.

When the position of the FO relative to LLP is evaluated, type II (medial type), which is the most common type, is observed with a rate of 30.3% on the right side and 23.2% on the left side; Type III (direct type) was observed in 23.3% on the left side and 13.2% on the right side. It was determined that Type II was observed at a higher rate on the right side ($p<0.05$). It was determined that Type III was observed at a higher rate on the left side ($p<0.05$) (**Table 2**).

Table 2. Position of FO relative to PPL				
Position of FO relative to PPL	**Right (%)**	**Left (%)**	**Total (%)**	**p**
Type I (Lateral type)	4 (4.4)	4 (4.4)	8 (7.1)	p>0.05
Type II (Medial (type)	34 (30.3)	26 (23.2)	60 (53.5)	p<0.05
Type III (Direct type)	15 (13.4)	26 (23.2)	41 (36.6)	P<0.05
Type IV (Far type)	3 (3.3)	2 (1.6)	5 (4.4)	p>0.05
Total	56 (50)	56 (50)	112 (100)	
Test: ındependent t testi, p<0.05				

It was determined that, on the right side FL was located posteromedial to the MMP at the highest rate (55.3%), and on the left side, it was located in the form of a thin canal under the canalis caroticus at the highest rate (44.6%). FL was expanding towards the FO, including the MMP at a rate of 17.8% on the right and 21.4% on the left (**Table 3**).

Table 3. Position of FL relative to PPM				
Position of the foramen lacerum relative to the medial pterygoid process	**Right (%)**	**Left (%)**	**Total (%)**	**p**
Type I-Posteromedial-direct	31 (55.3)	19 (33.9)	50 (50)	p<0.05
Type II- embedded thin channel	15 (26.7)	25 (44.6)	40 (35.7)	p<0.05
Type III- spread on both sides	10 (17.8)	12 (21.4)	22 (19.6)	p>0.05
Total	56 (50)	56 (50)	112 (100)	
Test: independent t testi, p<0.05				

In the FO-FL relationship, without discriminating between parties; In 46.8% of the samples, fissura petrooccipitalis was found together with a thick bone layer between the FO-FL, and in 53.2% of the samples, there was a canal-shaped fissura petrooccipitalis between the FO-FL (**Figure 5**).

Figure 5. FO-FL relationship (Purple line: Lateral processes, Red line: Medial processes)

In our study, it was determined that 65.9% of the FO was in the form of a canal and 34.1% of it was in the form of a hole. In addition, oval (38.5%) and cordate (19.8%) types of FO were mostly observed in the form of canals, while almound (12.8%) and triangular (5.4%) shapes were mostly observed in the form of foramen (**Figure 6**).

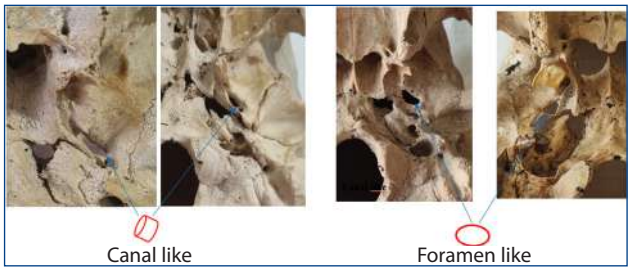

Figure 6. Presence of FO as foramen or canal for the surgical approach

DISCUSSION

Different definitions have been used to determine the position of FO in surgical approaches. Zdilla et al. used the maxillary molar plane and the interemens plane (the line between the bilateral mandibular eminence) and found that these planes passed the FO in more than 80% of cases (16). Peris-Celda et al. reported that the FO is located slightly lateral (2.3 mm) to the posterior base of the pterygoid process and can be accessed with a needle insertion strictly parallel to the sagittal plane as close as possible to the maxilla (17). Iwanaga et al. (2022) reported that in the percutaneous procedure, the location of the FO can be determined more easily by evaluating its position relative to the PL. They classified FO into 4 different types according to its relationship with PL, and reported that in types I and III, it guided the needle to the FO by following the base of the LLP from behind, providing relatively easy access to the FO. They emphasized that while type IV is found in 21% of all parties, it may be difficult to locate the FO of this type due to its disconnection from the base of the lateral plate of the pterygoid process (6). In the classification we made according to the study of Iwnaga et al. (2022), we determined that type II (medial type) was found mostly on the right side (30.3%), and type III (direct type) was found on the left side (23.3%). Type IV was found at the lowest rate, while types II and III were observed at a higher rate on the right side.

There are many studies reporting that the deep location of the FO in the form of a hole or canal in the surgical approach is important for the course of the surgery (18-23). FO morphology has been investigated in many studies. Prakash et al. (10) divided FO into four groups as oval, almond, round and irregular in their study, while Elnashar et al. (7) classified FO into six types as oval, crescent, cordate, almond, longitudinal and round. In our study, FO was divided into four groups as oval, almond, triangular and cordate. Oval type, which is the most classical FO shape, was observed on the right and left, while triangular type (8.9%) was observed on the right side and cordate type (3.5%) was observed on the left side at the lowest rate. In this context, our study is similar to the studies in the literature (1,5,10). We think that it is important to know the morphological shape of the foramen ovale better, especially in terms of avoiding incorrect injections.

It is thought that the spin-like extensions penetrating into the FO are associated with the pterygoid fascia or ligament, and tissue extensions that may be found in this region may cause mandibular nerve compression because they close the hole (18). In addition, it has been reported that the presence of the foramen vesalius may cause confusion for surgeons in operative approaches to FO (19). This foramen variant, particularly when large, may be misidentified as FO on imaging, leading to failure of transfacial approaches to FO. Reymond et al. (2005) reported the rate of foramen vesalius to be 22% (20) while Berlis (1992) stated that it can vary between 12.5-35%. In our study, it was determined that the spin-like protrusions tended towards the FO, or several foramen vesalis were located immediately adjacent to the FO, or a part of the FO penetrated well into the LP and remained under the protrusions of the LP. Regardless of the side (n=112), the rate of spin FO was 23.4%, FO accompanied by foramen vesalius was 44.6%, and FO penetrating into the LP was 32%. Elnaslar et al. (2019) stated that morphometrically, in 7.8% of the samples in FO measurements, obstruction caused by a calcified pterygoid ligament occurred and this ligament penetrated into the FO in the form of a spin-like protrusion (7). They reported that this situation made it difficult to cannulate 8% of the FO, so there was a 12% risk of accidental cannulation of the FL or foramen vesalisus.

Knowledge of endoscopic endonasal distances and landmarks such as foramen ovale, foramen rotundum, and foramen spinosum helps to predict and understand the depth of dissection, especially when extensive pathological processes obscure critical structures and their interrelationships. The distance from the foramen ovale to the pterygoid process helps to estimate the puncture size of the pterygoid process, which can be achieved by avoiding transection of the lateral pterygoid muscle; therefore, it provides less postoperative pain and trismus (11). Our study, when the position of the FO with respect to LLP is evaluated, ıt was observed that type II (medial type), which is the most common form, is seen with a rate of 30.3% on the right side and 23.2% on the left side, and types II have a higher incidence on the right side ($p<0.05$ This study, it was determined that the FL was located directly on the posterior medial of the MMP with a maximum of 55.3% on the right side, and was seen as a thin channel under the canalis caroticus at a maximum rate of 44.6% on the left side. Since the FO is in the form of a canal or hole determines the angle of entry of the cannula in percutaneous surgeries, it is important to know the shape of the FO (21-23). In our study, it was determined that 65.9% of the FO was in the form of a channel and 34.1% was in the form of a hole. In addition, it was determined that oval (38.5%) and cordate (19.8%) types of FO were mostly observed in the form of canals, while almound (12.8%) and triangular shapes were mostly observed in the form of foramen.

CONCLUSION

In most skulls in this study (53.5%), the FO was medial to the PL, while the FL opened directly to the posteromedial of the MPP, and it was easier to reach both the FO and the FL in these examples. However, in 4.4% of cases, the FO was located far from the LP and was difficult to reach. Knowing the shape of FO and its relationship with PL and FO is extremely important for possible safe and effective surgery. Preoperative imaging with 3D head CT can be helpful in estimating the ease of cannulation and surgical procedure and in guiding the determination of surgical procedures to be performed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ankara Medipol University Non-Invasive Clinical Research Ethics Committee (Date: 02.02.2023, Decision No:E-81477236-604.01.01-445)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Does Maternal Vitamin D Deficiency Affect Perinatal Outcomes?

Maternal Vitamin D Eksikliği Perinatal Sonuçları Etkiler Mi?

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ABSTRACT

Aim: Vitamin D affects placental joining, immune functions, inflammatory response and glucose homeostasis. Vitamin D deficiency can harm both the mother and the fetus' health by boosting the generation of inflammatory cytokines and activating the activation of T- regulatory cells. We aimed to evaluate the perinatal outcomes of vitamin D deficiency.

Material and Method: We evaluated 290 pregnant women who were seen at the Gazi University Medical Faculty Obstetrics and Gynecology Department. The perinatal effects of maternal vitamin D deficiency are studied to learn whether it increases complications during pregnancy such as gestational diabetes mellitus (GDM), preeclampsia, small-for-gestational age (SGA).

Results: Vitamin D insufficiency and vitamin D deficiency in the pregnant women were established as 91% and 66%, respectively. GDM, preeclampsia, type of delivery, preterm delivery, SGA, median baby birth weight, and median baby birth height also did not differ significantly among the groups (p>0.05).

Conclusions: Maternal complications that may result from vitamin D deficiency are currently being examined. In our study, we could not demonstrate a correlation between vitamin D and GDM, SGA or preeclampsia.

Keywords: Pregnancy, vitamin D insufficiency

ÖZ

Amaç: D vitamini plasental tutunmayı, immün fonksiyonları, inflamatuar yanıtı ve glukoz homeostazını etkiler. D vitamini eksikliği, inflamatuar sitokinlerin üretimini artırarak ve T-regulatuar hücrelerin aktivitesini uyararak hem annenin hem de fetüsün sağlığını etkileyebilir. D vitamini eksikliğinin perinatal sonuçlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Gazi Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı'nda görülen 290 gebe değerlendirildi. Maternal D vitamini eksikliğinin perinatal etkileri, gebelik sırasındaki komplikasyonları (Gestasyonel diabetes mellitus (GDM), preeklampsi, gestasyonel yaşa göre küçük bebek (SGA)) artırıp artırmadığını öğrenmek için araştırma yapıldı.

Bulgular: Gebelerde D vitamini yetersizliği ve D vitamini eksikliği sırasıyla %91 ve %66 olarak saptandı. GDM, preeklampsi, doğum şekli, erken doğum, SGA, medyan bebek doğum ağırlığı ve medyan bebek doğum boyu da gruplar arasında anlamlı farklılık göstermedi (p>0,05).

Sonuç: D vitamini eksikliğinden kaynaklanabilecek maternal komplikasyonlar halen araştırılmaktadır. Çalışmamızda D vitamini ile GDM, SGA veya preeklampsi arasında bir ilişki görülmedi.

Anahtar Kelimeler: Gebelik, D vitamini, vitamin D eksikliği

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INTRODUCTION

Vitamin D deficiency during pregnancy is a worldwide epidemic (1). According to studies, the prevalence ranged from 18% to 84% depending on the country that subjects were from and the type of clothing they wore (2-5).

Calcium homeostasis in the mother and fetus is impacted by vitamin D levels during pregnancy. A mother provides a fetus with the vitamin D it needs through the placenta (6).Vitamin D deficiency can harm both the mother and the fetus' health by boosting the generation of inflammatory cytokines and activating the activation of T- regulatory cells (7). Additionally, vitamin D influences the placental joining, immune system, inflammatory response, and glucose homeostasis (8-10). Low vitamin D levels have been linked in several studies to a number of pregnancy-related problems, such as preeclampsia (11–13), gestational diabetes mellitus (14), delivery of small-for-gestational-age (SGA) newborns (15, 16), an increase in the cesarean delivery rate (17), and preterm delivery (12, 18).

Research on vitamin D is currently being conducted worldwide and in Turkey. In the current study, the perinatal effects of maternal vitamin D deficiency are examined to determine whether it led to more pregnancy complications (GDM, preeclampsia, SGA).

MATERIALS AND METHODS

Case Selection

In this cohort study, 290 pregnant women in the third trimester who had visited the Obstetrics and Gynecology Department of Gazi University Medical Faculty were included. The Ethics Committee of the Gazi University Faculty of Medicine approved this single-center study.

Written consent was obtained from all patients. Patients' medical history was recorded. The study excluded pregnant women with liver diseases, kidney diseases, inflammatory bowel disease, diseases that may cause enteropathy, and diabetes mellitus.

Pregnant women were divided into four groups based on the categories of sufficient, insufficient, deficient, and severely deficient vitamin D levels, which were defined as levels above 30 ng/ml, between 29.9 ng/ml and 20 ng/ml, between 19.9 ng/ml and 10 ng/ml, and below 9.9 ng/ml, respectively.

The pregnant women's follow-up files were examined to see if they had GDM or preeclampsia. Between the 24th and 28th pregnancy weeks, patients underwent a 50 gram oral glucose tolerance test. The 100 gr oral glucose tolerance test was administered to cases whose first-hour (1 h) glucose levels were greater than 140 mg/dl. During the 3-hour OGTT carried out using 100 gr glucose; fasting, and 1 h, 2 h, and 3 h glucose levels were measured. The following normal values were noted: fasting 95 mg/dl, 1 h 180 mg/dl, 2 h 155 mg/dl, and 3 h 140 mg/dl. GDM was identified in cases with at least two high glucose test results (18).

Preeclampsia was diagnosed when the blood pressure reached 140/90 mmHg or higher after the 20th week of pregnancy, and it was associated with one or more of the following symptoms and laboratory findings: Proteinuria (300 mg protein in 24-hour urine or urine protein to creatinine ratio ≥0.3 or +1 protein determination by dipstick in spot urine specimen); or thrombocytopenia (platelet <100.000/microL); renal failure (creatinine >1.1 mg/dl or two-fold increase when compared to baseline); liver involvement (two-fold increase in serum transaminase levels); cerebral symptoms (headache, visual symptoms, convulsions); pulmonary edema symptoms [18].

The delivery types were documented, and the delivery times were classified as preterm or term. The newborns' height, weight, and gender were all recorded. SGA was diagnosed based on the Turkish Neonatology Association's 2011 growth curves.

Analysis

The pregnant women's calcium and phosphorus levels were analyzed by using the spectrometric method (Beckman Coulter AU auto analyzer). The electrochemiluminescence method was used to determine the levels of parathyroid hormone (Roche cobas E601 auto analyzer). Maternal vitamin D levels were measured using the LC-MSMS method (ULTIMATE 3000 device). Vitamin D levels of all samples were measured using the LC-MSMS method (ULTIMATE 3000 device).

Statistical Methods

Statistical analysis of the data was performed by using SPSS Statistics Program 22. The Kolmogorov–Smirnov test was used to determine if continuous and discrete numerical variables showed normal distribution and Levene's test was used to determine the homogeneity of variances. Descriptive statistics for continuous and discrete variables were expressed as a mean±standard deviation or median (minimum-maximum) while categorical variables were expressed in number of cases and percentage (%).

One-way variance analysis (one-way ANOVA) was used to determine the significance of differences between the groups. To determine the significance of differences between the median values, the

Mann–Whitney-U test was used in evaluating the significance between two independent groups and the Kruskal–Wallis test was used in evaluating the significance in more than two groups. The categorical variables were evaluated using Pearson's chi-square test, Fisher's exact test or a probability ratio test. P value <0.05 was accepted to be significant.

RESULTS

The following number of pregnant women were included in the study groups: 25 pregnant women with sufficient vitamin D levels, 73 with insufficient vitamin D levels, 113 with deficient vitamin D levels and 79 with severely deficient vitamin D levels. The prevalence of vitamin D deficiency and insufficiency in pregnant women was 91% and 66%, respectively.

There were no statistically significant differences in mean age, educational level, mean pregnancy week, median parity, multiparity ratio, mean BMI before pregnancy, BMI classification before pregnancy, smoking habit, and physical activity among these four groups (p>0.05). GDM, preeclampsia, type of delivery, preterm delivery, SGA, median baby birth weight, and median baby birth height were not significantly different between groups (p>0.05) (**Table 1**).

Furthermore, pregnant women with pathological conditions (GDM, SGA, or preeclampsia) (n=45) were compared to healthy pregnant women (n=245). The levels of vitamin D in these two groups did not differ significantly (p=0.927).

The area below the ROC curve for vitamin D levels was found to be statistically insignificant in separating pathological (pregnancies with GDM, SGA, and preeclampsia) and normal pregnancies (AUC=0.504, 95% CI=0.410-0.599, P=0.927).

DISCUSSION

Vitamin D deficiency and insufficiency were found to be 91% and 66%, respectively, in this study. Although Turkey does not have a lack of sunlight, there is a high rate of vitamin D insufficiency and deficiency. GDM and vitamin D deficiency were found to have no significant relationship (p=0.230).

The second trimester 25(OH)D levels and GDM were not related in a study by Farrant et al. which involved 559 pregnant Indian women (20). Vitamin D deficiency and GDM were not found to be significantly related. Another study by Clifton-Bligh et al. measured maternal serum 25(OH)D levels as part of a GDM screening and discovered a significant negative correlation between fasting glucose and vitamin D levels, but no significant correlation between vitamin D levels and GDM (21). Makgoba et al. evaluated 158 control subjects and 90 patients with GDM, and they found no significant correlation between first trimester 25(OH)D levels and GDM (22). However, there was a negative correlation between the 25(OH)D levels and second hour fasting glucose levels. No significant correlation was found between the third trimester 25(OH) D levels and GDM in a study by Park et al. (23). In this study, the relationship between the first trimester vitamin D level and insulin resistance and beta-cell function was also examined. In another study evaluating 723 women, there was no difference in pregnancy 25(OH) D concentration between GDM and non-GDM mothers (82 vs 82 nmol/L, P=0.99 results of this study support those of ours (24). According to a recent study, individuals with vitamin D deficiency had a 26% higher risk of developing gestational diabetes than those with normal serum vitamin D concentrations (25). Wang et al meta-analysis revealed that pregnant women with GDM had significantly lower vitamin D levels than pregnant women without the condition. GDM risk has been linked to vitamin D deficiency (OR = 1.15, %95 GA: 1.07-1.23) (26).

Table 1: Relationship Between Vitamin D levels and pregnancy complications

	Sufficient	Insufficient	Deficient	Severely Deficient	p-value
Number of cases	25	73	113	79	
GDM	5 (%20.0)	5 (%6.8)	10 (%8.8)	6 (%7.6)	0.230*
Preeclampsia	1 (%4.0)	1 (%1.4)	4 (%3.5)	3 (%3.8)	0.761‡
Delivery types					0.308*
NSVD	6 (%24.0)	13 (%17.8)	16 (%14.2)	8 (%10.1)	
C/S	19 (%76.0)	60 (%82.2)	97 (%85.8)	71 (%89.9)	
Preterm	1 (%4.0)	5 (%6.8)	6 (%5.3)	3 (%3.8)	0.850‡
SGA	-	3 (%4.1)	7 (%6.2)	3 (%3.8)	0.376‡
Birth weight					0.072¶
Median	3400	3250	3170	3330	
Minimum-Maximum	2710-4380	790-4590	1580-5240	2050-4170	
Birth height					0.126¶
Median	50	49	49	50	
Minimum-Maximum	45-52	34-53	41-55	45-54	

* Pearson's chi-square test, ‡ Probability Ratio test, ¶ Kruskal Wallis test. GDM: Gestational Diabetes Mellitus, NSVD: Normal Spontan Vaginal Delivery, CS: Cesarean Section, SGA: Small for Gestational Age

There are studies on the correlation of preeclampsia with vitamin D deficiency. It is believed that vitamin D deficiency is related to the vascular endothelial dysfunction due to inflammation and therefore may be related to preeclampsia. Some studies, however, disagree with this association. The relation between preeclampsia and vitamin D is still being debated. In our study, we found no evidence of a link between vitamin D deficiency and preeclampsia (p=0.761). The risk of preeclampsia was found to be increased in a study by Wei et al. when there was a vitamin D deficiency; supporting this finding, the placental growth factor was found to decrease significantly (27). In another study, Dorota et al. found no significant correlation between 25(OH)D levels and preeclampsia markers (28). Bodnar et al. revealed that maternal vitamin D deficiency is associated with severe preeclampsia but not with mild preeclampsia (29). Because our study included cases of mild preeclampsia, this finding backs up ours. Diaz et al. observed that as vitamin D levels decreased, so did the risk of preeclampsia. The meta-analysis, however, contains heterogeneity among studies, and randomized controlled trials were excluded (30).

In our study, there was no significant connection between SGA and vitamin D deficiency (p=0.376). Wei et al. found a significant correlation between vitamin D deficiency and SGA in a review and meta-analysis of six studies on the relationship of vitamin D to SGA, but no significant correlation between SGA and vitamin D insufficiency (27). In a study by Aydoğmuş et al., SGA.. rate was found to be 16.7% in the babies born to mothers with a vitamin D deficiency; this value was 4.9% in the babies born to mothers with normal vitamin D levels and this difference was statistically significant (31). The number of babies with SGA in our study was not as high. Clifton-Bligh et al. noticed that mid-trimester 25(OH)D levels were not related to the infant's birth weight, height, or head circumference (20). We also found no link between vitamin D levels and birth weight and height.

Limitations

A small number of patients were included in the study, whose vitamin D levels were examined. This is the biggest limitation of our study. Additionally, because the study's patients were chosen from the local population, our community is not accurately represented.

CONCLUSION

We were investigate elaborately the maternal problems caused by vitamin D deficiency. In our study, we found no link between vitamin D and GDM, SGA, or preeclampsia. There is a need for more research into the relationship between vitamin D levels and fetal weight or height.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Gazi University, Faculty of Medicine Ethics Committee (Date: 04/2013, Decision No: 122).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Preterm ve Term Bebeklerde Serum γ-Glutamil Transferaz Düzeylerinin Referans Değerlerinin Belirlenmesi

Determination of Reference Values of Serum γ-Glutamil Transferase Levels in Preterm and Term Babies

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ÖZ

Amaç: Γ-Glutamil transferaz (GGT) enziminin normal düzeyleri her yaş grubunda değişkendir; bu yüzden artmış GGT seviyeleri yaş için uygun değerlere göre yorumlanır. Özellikle yenidoğan yoğun bakım ünitelerinde (YYBÜ), GGT seviyeleri obstruktif karaciğer hastalıkları veya oksidatif karaciğer hasarı ekarte edilmek istendiğinde sık kullanılan bir değerdir, ancak yenidoğan için normal GGT değerleri belirlenmediği için yorum yapmak zor olabilmektedir. Çalışmamızda amaç; serum GGT değerleri ile gebelik yaşı arasında ilişkiyi araştırmak, ve gebelik yaşının, cinsiyetin, doğum şeklinin serum GGT değerlerini etkleyip etkilemediğini incelemekti.

Gereç ve Yöntem: Amasya Sabuncuoğlu Şerefeddin Eğitim ve Araştırma Hastanesinde Ocak 2021 – Aralık 2022 tarihleri arasında yenidoğan yoğun bakım ünitesine 26-42 gebelik hafta arası yatan 200 hastanın karaciğer fonksiyon testlerinden GGT düzeyi, gebelik haftaları, doğum ağırlıkları, cinsiyetleri, doğum şekli (sezeyan veya normal doğum) retrospektif olarak incelendi. Gebelik haftasına göre preterm, geç preterm ve term bebek olmak üzere 3 gruba ayrılarak incelendi. Bazı hastaların ilk 7 gün bakılan GGT ve 8-28 gün arası bakılan iki GGT değeri çalışmaya alındı. Bebeklerin 28. günden sonra bakılan GGT değerleri çalışmaya alınmadı.

Bulgular: Bu bebeklerin 95'i kız (% 47,5) ve 105'i erkek idi (% 52,5). Preterm bebek sayısı 32 (%16), term bebek sayısı 73 (%36.5), geç preterm (34-37 gebelik haftası) sayısı 95 (% 47,5) idi. Hastaların 180 (%90) C/S (Sezaryen) ile 20 bebek ise (%10) normal spontan vajinal yol (NSVY) ile doğmuştu. Pretem infantların 1-7 gün arası ortalama GGT (GGT1) değeri 156± 58; 7-28 gün ortalama GGT (GGT2) değeri 132± 48, geç preterm grup GGT1 ortalama değeri 124,9± 74 GGT 2 ortalama değeri 122± 38, term bebek GGT1 ortalama değeri 150± 83 GGT2 ortalama değeri 119± 29 olarak bulundu ve gruplar arası istatistiksel anlamlı fark saptanmadı (P=0,189, P=0,184). Serum GGT1 ve GGT2 değerleri erkek bebeklerde (146±116, 133± 121) kız bebeklerden (135± 80, 114± 64) istatistiksel anlamlı yüksek saptandı (P=0,00, P=0,00). C/S ile doğan bebeklerin GGT1 ve GGT2 ortalama değerleri (141±102, 126± 90); normal vajinal yolla doğan bebeklerin GGT1ve GGT2 ortalama değerlerinden (139± 85, 107±68) istatistiksel olarak anlamlı yüksek saptandı (P=0,00, P=0,00).

Sonuç: Serum GGT değerleri yaş, cinsiyet ve ölçüm tekniğine göre değişkenlik gösterir. Literatürde bulunan çalışmalarda preterm bebeklerde GGT değerleri araştırılmış ama gebelik haftası belirtilmemiştir. Bizim çalışmamızda spesifik gebelik haftası gruplarında GGT değerleri belirlendi ve preterm ve term bebeklerdeki GGT düzeyleri, daha önceki çalışmalara ve kitap bölümlerine göre belirgin olarak yüksek bulundu.

Anahtar Kelimeler: Gama-glutamil transpeptidaz, GGT, neonatal, referans değer

ABSTRACT

Aim: Expected Γ-Glutamyl transferase (GGT) enzyme levels vary by age group; elevated GGT levels are interpreted following age-appropriate values. GGT levels are routinely utilized in neonatal intensive care units (NICU) to eliminate obstructive liver disorders or oxidative liver damage. However, it might be challenging to interpret because typical GGT values have not been established for infants. Therefore, the purpose of our study was to analyze the association between serum GGT levels and gestational age and determine if gestational age, gender, and mode of delivery influence serum GGT levels.

Material and Method: Liver function tests were performed on 200 patients admitted to the neonatal intensive care unit at Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital between January 2021 and December 2022, including GGT levels, weeks of gestation, birth weights, genders, and mode of delivery (cesarean or normal birth). They were classified as preterm, late preterm, or term newborns based on their gestational week. The study includes GGT levels recorded in the first seven days of specific patients and two GGT values measured between 8 and 28 days. The GGT readings of the neonates tested after the 28th day were excluded from the research.

Result: 95 (47.5%) of these infants were female, while 105 (52.5%) were male. There were 32 preterm infants (16%), 73 term infants (36.5%), and 95 late preterm infants (34-37 weeks of gestation). 180 (90%) of the patients were delivered through C/S (Cesarean section), whereas 20 (10%) were born via spontaneous vaginal birth (NSVY). The mean GGT (GGT1) value for preterm infants between 1-7 days was 156±58; GGT (GGT2) value for 7-28 days was 132±48; the GGT1 value for the late preterm group was 124.9 74, GGT 2 mean value was 122 38, term baby GGT1 mean value was 150 83, GGT2 mean value was 119±29. There was no statistically significant difference between the groups (P=0.189, P=0.184). Serum GGT1 and GGT2 levels were substantially higher in male babies (146±116, 133±121) than in female newborns (135±80, 114±64) (P<0.001 for both comparisons). The mean GGT1 and GGT2 values of infants born through C/S were 141±102 and 126±90, respectively, while the mean GGT1 and GGT2 values of infants born via expected vaginal delivery were 139±85 and 107±68, respectively.

Conclusion: Variations in serum GGT levels depend on age, gender, and measuring procedure. In published investigations, GGT levels of preterm infants were examined, but the gestational week was not mentioned. In our investigation, GGT levels in preterm and full-term infants were shown to be much greater than in prior studies and book chapters.

Keywords: Gamma glutamyl transferase, GGT, neonatal, reference value

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GİRİŞ

γ-Glutamil transferaz (GGT) enzimi hepatosit ve biliyer epitelyal hücrelerinde, renal proksimal tübülüslerde, seminal veziküller, pankreas, dalak, kalp ve beyin hücresinde yer alır. Yenidoğanda serum GGT aktivitesi erişkinlere göre 6-7 kat daha fazla olup, 5-7 ay içinde erişkin düzeylerine düşer. (1) Serum GGT aktivitesi çok büyük ölçüde karaciğer GGT aktivitesini yansıtır. Yarı ömrü 28 gündür ve alkalen fosfataz'dan (ALP) daha sensitif bir kolestaz göstergesi olarak kabul edilir. (2) GGT'nin ALP'ye göre daha spesifik olmasının sebebi ise kemik patolojilerinde ALP'nin aksine yükselmemesidir. (3)

Klinikte, pediatrik hastaların artmış GGT değerleri nedeniyle karaciğer fonksiyonları açısından araştırılması sık karşılaşılan bir durumdur. (1) Özellikle yenidoğan yoğun bakım ünitelerinde (YYBÜ), GGT seviyeleri obstruktif karaciğer hastalıkları veya oksidatif karaciğer hasarı ekarte edilmek istendiğinde sık kullanılan bir değerdir, ancak yenidoğan için normal GGT değerleri belirlenmediği için yorum yapmak zor olabiliyor. Yüksek GGT değerleri preterm grupta bir patoloji olmadan da görülebilir, ama bu yüksekliğin anlamlı olup olmadığını belirlemek mümkün değil. Preterm bebeklerde GGT değerlerinin yorumlanması için literatürde az sayıda yayın bulunmaktadır; bunlarda da preterm bebeklerde term bebeklere göre daha yüksek GGT değerleri olduğu bildirilmekle beraber referans değerleri net olarak tanımlanmadı. (3,4)

GGT ölçümü için kullanılan otomatik cihazlar genelde hızlı ve ucuzdur; ama sonuçların yorumlanması için doğru referans aralığı belirlenmezse anormal test sonuçları belirlenemez. (5,6) Yenidoğanlarda GGT düzeyi karaciğer fonksiyon testleri arasında sıklıkla kullanılmakla beraber referans aralığı nispeten düşük hasta sayısı ile yapılmış eski çalışmalar ile hesaplanır.

Çalışmamızda amacımız; serum GGT değerleri ile gebelik yaşı arasında ilişkiyi araştırmak, ve gebelik yaşının, cinsiyetin, doğum şeklinin serum GGT değerlerini etkleyip etkilemediğini incelemekti. Ayrıca yenidoğan bebeklerin ilk bir ayı için referans GGT değerlerini belirlemekti.

GEREÇ VE YÖNTEM

Amasya Sabuncuoğlu Şerefeddin Eğitim ve Araştırma Hastanesinde Ocak 2021 – Aralık 2022 tarihleri arasında yenidoğan yoğun bakım ünitesine 26-41 gebelik hafta arası yatan 200 hastanın karaciğer fonksiyon testlerinden GGT enzim değerleri, gebelik haftaları, doğum ağırlıkları, cinsiyetleri, doğum şekli (sezeyan veya normal doğum) retrospektif olarak incelendi. Gebelik haftası 26-41 gebelik haftası arası preterm, 34-37 hafta arası geç preterm ve >37 gebelik haftası olan bebekler term bebek olmak üzere 3 gruba ayrılarak incelendi. Herhangi bir metabolik veya karaciğer hastalığı, kolestazı, kültürle kanıtlanmış enfeksiyonu, serum aminotranferaz enzim düzeyleri yüksek olan hastalar çalışmaya dahil edilmedi. Bazı hastaların ilk 7 gün bakılan GGT ve 8-28 gün arası bakılan iki GGT değeri çalışmaya alındı. Bebeklerin 28. günden sonra bakılan GGT değerleri çalışmaya alınmadı. GGT değerleri Beckman Coulter AU 5800 Biyokimya Otoanalizörü ile kinetik kolorimetrik yöntem kullanılarak değerlendirildi. Elde edilen verilerin istatistiksel analizi için, SPSS 21 (SPSS Inc. Chicago, Illinois, USA) programı kullanıldı. Datanın dağılım özelliğine göre sürekli değişkenler Student t-test ya da Mann-Whitney U-test ile, kategorik değişkenler ise ki-kare ya da Fisher kesin testi ile değerlendirildi. İkiden fazla grubun incelenmesinde Kruksal Wallis testi kullanıldı. Elde edilen sonuçlar ortalama±standart sapma şeklinde veya n (%) olarak verildi. P değerinin 0.05'in altında olduğu durumlar istatistiksel olarak anlamlı sonuçlar şeklinde değerlendirildi.

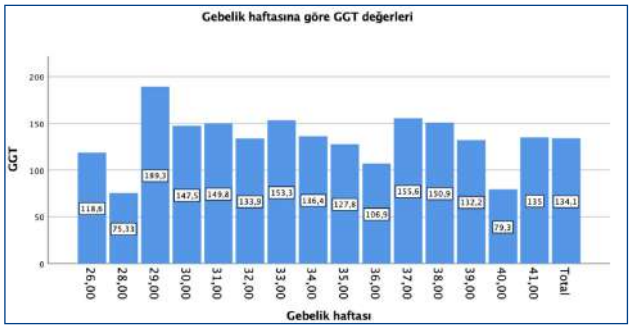
BULGULAR

Ocak 2021 – Aralık 2022 tarihleri arasında YYBÜ'ye yatan 26-42 gebelik arasında doğan bebeğin 200 tanesi, çalışmaya dahil edildi. Bu bebeklerin 95'i kız (% 47,5) ve 105'i erkek idi (% 52,5). Gebelik haftası 3 gruba ayrıldı: preterm (34 > gebelik haftası), geç preterm (34-37 gebelik haftası), term (37< gebelik haftası). Preterm bebek (34 > gebelik haftası) sayısı 32 (%16), term bebek sayısı 73 (%36.5), geç preterm (34-37 gebelik haftası) sayısı 95 (% 47,5) idi. Çalışmaya alınan bebeklerin ortalama doğum ağırlıkları sırası ile preterm bebekler için 1.2009±435 gr geç preterm bebeklerin ortalama ağırlığı 2068±904 term bebeklerin ise ortalama ağılığı 3,435gr± 575 gramdı. Hastaların 180 (%90) C/S (Sezaryen) ile 20 bebek ise (%10) normal spontan vajinal yol (NSVY) ile doğmuştur. Dermografik özellikleri **Tablo 1**'de gösterilmiştir.

Pretem infantların 1-7 gün arası ortalama GGT (GGT1) değeri 156± 58; 7-28 gün ortalama GGT (GGT2) değeri 132± 48 , geç preterm grup GGT1 ortalama değeri 124,9± 74 GGT 2 ortalama değeri 122± 38, term bebek GGT1 ortalama değeri 150± 83 GGT2 ortalama değeri 119± 29 olarak bulundu ve gruplar arası istatistiksel anlamlı fark saptanmadı (P=0,189, P=0,184). Şekil1'de her gebelik haftası için serum GGT değerleri gösterilmektedir.

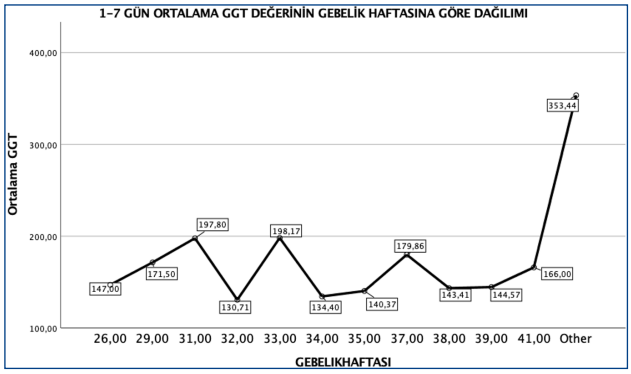
Tablo 1. Hastaların dermografik özellikleri

	Preterm (32)	Geç Preterm (73)	Term (95)	P değeri
Doğum ağırlığı±SD	950±300gr	2000±200	3300±500	P=0.07 P=0.08
Gebelik haftası±SD	29±1,12	35±1,36	39±2,3	P=0.00 P=0.00
Cinsiyet K/E	14/18	38/35	50/45	P=0.08 P=0,06
Doğum Şekli Normal/sezaryan	28/4	7/67	10/95	P=0.03 P=0.00

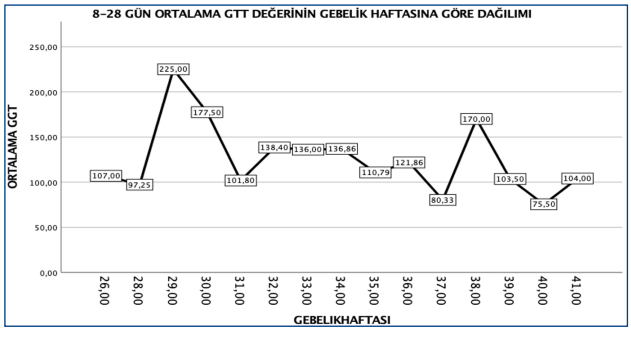


Şekil 1: Her gebelik haftası için serum GGT değerleri

Serum GGT1 ve GGT2 değerleri erkek bebeklerde (146±116, 133± 121) kız bebeklerden (135± 80, 114± 64) istatistiksel anlamlı yüksek saptandı (P=0,00, P=0,00). C/S ile doğan bebeklerin GGT1 ve GGT2 ortalama değerleri (141±102, 126± 90); normal vajinal yolla doğan bebeklerin GGT1ve GGT2 ortalama değerlerinden (139± 85, 107±68) istatistiksel olarak anlamlı yüksek saptandı (P=0,00, P=0,00). Ortalama ilk 7 gün GGT değerlerinin gebelik haftasına göre dağılımı şekil 2'de; 8-28 gün ortalama GGT değerlerinin gebelik haftasına göre dağılımı şekil 3'de gösterildi.



Şekil 2: 1-7 gün ortalama GGT değerlerinin gebelik haftasına göre dağılımı



Şekil 3: 8-28 gün ortama GGT değerlerinin gebelik haftasına göre dağılımı

TARTIŞMA

GGT hücre duvarına bağlı olarak vücutta yaygın bulunan bir enzimdir ama serumda GGT düzeylerinin karaciğer kaynaklı olduğu kabul edilir. (3) Serum GGT değerleri cinsiyet ve ölçüm tekniğine göre değişkenlik gösterir. Ayrıca her yaş grubunda farklı düzeyler tanımlanmıştır. (7) Yenidoğan döneminde genelde GGT serum değerlerinin sınırlarının belirlenmesi yerine referans aralığının 2,5 ve 97,5 persentiller arasında belirtilmesi klinikte serum GGT sonuçlarının yorumlanmasını zorlaştırmaktadır. (3) Literatürde bulunan çalışmalarda preterm bebeklerde GGT değerleri araştırılmış ama gebelik haftası belirtilmemiştir. Bir başka çalışmada ise referans değerleri aylık yaşa göre ayrılmıştır. (1) Bizim çalışmamızda spesifik gebelik haftası gruplarına göre GGT değerleri belirlendi. Preterm bebeklerde yapılan çalışmalarda GGT değerlerinin 1. günde dahi term bebeklere göre 1,5 kat yüksek olabildiği gösterilmiştir. (8)

İlk 28 günde bebeklerde GGT düzeylerinde gebelik haftalarına göre belirgin farklılıklar gözlemlediğimiz için test sırasındaki gebelik haftasının önemi büyüktür. Daha önce yapılan bir çalışmada ilk 5 günde GGT değerlerinin değişmediği gösterilmiş. (9) Bizim çalışmamızda da term bebeklerde benzer bulgular saptandı.

Bizim çalışmamızda preterm ve term bebeklerdeki GGT düzeyleri, daha önceki çalışmalara göre belirgin olarak yüksek bulundu. (1,10-12). Ayrıca önceki çalışmalar ile çelişkili olarak bizim çalışmamızda preterm ve term bebekler arasında belirgin GGT ölçüm farkı bulunmadı. Bunun sebebi, çok düşük doğum ağırlıklı bebeklerin strese daha hassas olmalarına rağmen daha zayıf cevaplarının olması ve beklenen GGT artışından daha düşük yükselme görülmesi olabilir. Gebelik haftası 32 ve 35. haftalar arasında olan bebeklerde GGT seviyeleri belirgin yüksek olabiliyor. (3) Çalışmamızdaki geç preterm bebek sayısının fazla olması ortalama GGT yüksekliğine sebep olmuş olabilir.

Bizim çalışmamızda sezaryan ile doğan bebeklerin GGT düzeyi vajinal yol ile doğan bebeklere göre belirgin yüksekti. Ancak yapılan bir çalışmada vajinal yol ile doğumlarda artmış GGT seviyeleri görülmüş. (4) Bizim çalışmamızda sezaryan oranın çok yüksek olması literatür ile çelişkili bulgulara sebep olmuş olabilir.

Yapılan bir çalışmada 37. gebelik haftasından büyük bebeklerde kızlarda GGT düzeyleri daha düşük bulunmuştur. (4) Erkek bebeklerdeki yüksek GGT düzeyi başka bir çalışmada daha gözlemlenmiştir. (13) Bizim çalışmamızda da literatür ile uyumlu olarak erkeklerde daha yüksek GGT değerleri saptandı.

Güncel yayınlara bakıldığında çeşitli çalışmalarda yenidoğanların dahil olduğu bebeklerde GGT düzeyleri araştırılmış ve üst sınır olarak 100 U/L olarak belirlenmiş. (14,15) Fakat bu çalışmalarda bizim çalışmamızdan farklı olarak araştırılan bebekler izole olarak yenidoğan değil, yaş aralığı geniş (3 ay-1 yıl). Ayrıca son yıllarda yapılan çalışmalarda izole olarak yenidoğanlarda belirlenen GGT düzeyleri ise çalışmalara dahil olan yenidoğanlarda çeşitli karaciğer hastalıkları varlığında araştırılarak bulunmuş. (16,17)

SONUÇ

Sonuç olarak yenidoğan döneminde (0-4 haftalar arası) GGT düzeyleri erişkin düzeylere göre beş ile yedi kat fazla saptanabilir. Bizim çalışmamızda herhangi bir hastalığı olmayan yenidoğanlar için uygun bir referans olmasa bile yoğun bakım ünitelerinde izlenen yenidoğan bebekler için uygun referans aralığı olarak kullanılabileceğini düşünmekteyiz.

ETİK BEYANLAR

Etik Kurul Onayı: Çalışma retrospektif olarak planlanmış ve veriler dijital olarak elde edildiğinden etik kurul onayına gerek yoktur.

Aydınlatılmış Onam: Çalışma retrospektif olarak dizayn edildiği için hastalardan aydınlatılmış onam alınmamıştır.

Hakem Değerlendirme Süreci: Harici çift kör hakem değerlendirmesi.

Çıkar Çatışması Durumu: Yazarlar bu çalışmada herhangi bir çıkara dayalı ilişki olmadığını beyan etmişlerdir.

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Yazar Katkıları: Yazarların tümü; makalenin tasarımına, yürütülmesine, analizine katıldığını ve son sürümünü onayladıklarını beyan etmişlerdir.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

HAV, HBV, HCV and HIV Seroprevalence in Patients Who Requested ELISA Examination in the Emergency Department, a Retrospective Study

Acil Serviste ELISA Tetkiki İstenen Hastalarda HAV, HBV, HCV ve HIV Seroprevalansı, Retrospektif Bir Çalışma

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ABSTRACT

Introduction: The aim of this study is to determine the seroprevalence of HAV, HBV, HCV and HIV in patients who applied to the emergency service for hepatitis viruses and HIV serology, to examine their correlation with their admission complaints, and to document the incidence of positivity in the community cross-sectionally by determining the proportion of risky patients who applied to the emergency department

Material and Method: Among the patients who applied to the emergency department between January 2022 and December 2022, anti-HAV IgM, HBsAg, anti-HBc IgM, HIV Ag/Ab (antigen/antibody) (HIV-1/ HIV-2 IgM and IgG antibodies and HIV-1 antibodies) cases that were requested to be tested for p24 antigen) were included in the study

Results: General characteristics of the patients, Viral markers measured by ELISA method and their distribution by gender, Viral markers measured by ELISA method and their distribution by nationality and Leading search reasons in serology examinations were evaluated.

Conclusion: This study has data that can reflect the society in terms of the place where it was conducted and the number of patients included in the study. With the sensitivity of the Ministry of Health on the subject and the impact of the intensive work of the primary care on vaccination, we have found satisfactory results in terms of transmission and vaccination.

Keywords: Seroprevelance, ELISA, emergency medicine

ÖZ

Giriş: Bu çalışmanın amacı acil servise hepatit virüsü ve HIV serolojisi ile başvuran hastalarda HAV, HBV, HCV ve HIV seroprevalansını belirlemek, başvuru şikayetleri ile ilişkisini incelemek ve pozitiflik insidansını belgelemektir. acil servise başvuran riskli hasta oranını belirleyerek toplum kesitsel olarak

Gereç ve Yöntem: Ocak 2022-Aralık 2022 tarihleri arasında acil servise başvuran hastalarda anti-HAV IgM, HBsAg, anti-HBc IgM, HIV Ag/Ab (antijen/antikor) (HIV-1/ HIV-2 IgM ve IgG antikorları ve p24 antijeni için test edilmesi istenen HIV-1 antikorları) vakaları çalışmaya dahil edildi.

Bulgular: Hastaların genel özellikleri, ELISA yöntemi ile ölçülen viral belirteçler ve cinsiyete göre dağılımı, ELISA yöntemi ile ölçülen viral belirteçler ve uyruğuna göre dağılımı ve seroloji incelemelerinde öne çıkan arama nedenleri değerlendirildi.

Sonuç: Bu çalışma, yapıldığı yer ve çalışmaya dahil edilen hasta sayısı açısından toplumu yansıtabilecek verilere sahiptir. Sağlık Bakanlığı'nın konuyla ilgili hassasiyeti ve birinci basamak sağlık hizmetlerinin yoğun çalışmasının aşılamaya da etkisi ile bulaşma ve aşılama açısından yüz güldürücü sonuçlar bulduk.

Anahtar Kelimeler: Seroprevelans, ELİSA, acil tıp

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INTRODUCTION

Despite the widespread use of screening methods in recent years, the importance given to worker health, the widespread use of workplace medicine, public service announcements and in-service trainings on infectious diseases transmission methods, Hepatitis A (HAV), hepatitis B virus (HBV) transmitted by blood and/or oral route. Transmission is increasing in viral infections such as hepatitis C virus (HCV) and Human immunodeficiency virus (HIV) (1). Due to the increasing population density and immigration, primary care preventive and screening health services are insufficient in some regions.

According to the 2017 World Hepatitis Report, the global prevalence of HBV infection is 3.5% in 2015, and there are 2 billion people who have encountered HBV in the world, approximately 240 million-257 million people live with HBV infection, 2.7 million of them with HIV, 10-15% It is estimated that 1% of them are co-infected with HCV (2). According to the World Hepatitis report, in 2015, 71 million people were living with chronic HCV infection, and 1.75 million new HCV infections were diagnosed. 2.3 million people living with HIV also have HCV infection (2). HIV has reached almost the entire population of the world, and according to the data of The Joint United Nation Program on HIV/AIDS (UNAIDS) for 2022, 38.4 million people were infected with HIV in 2021 and 650000 people died due to HIV/AIDS-related causes (3). There are 30293 HIV-infected individuals and 2083 AIDS cases in our country, from 1985 to 31 December 2021, whose confirmation test was positive and reported. On the other hand, between January 1, 2021 and December 31, 2021, a total of 3002 cases, including 2922 HIV-infected individuals and 80 AIDS cases, were positive for confirmatory tests (4).

Although viral markers are not routinely examined in admissions to the emergency department; It is requested before the operation in the etiology of elevated liver function tests (LFT), workplace accidents by healthcare professionals, resistant fever and unexplained etiology of unconsciousness.

The aim of this study is to determine the seroprevalence of HAV, HBV, HCV and HIV in patients who applied to the emergency service for hepatitis viruses and HIV serology, to examine their correlation with their admission complaints, and to document the incidence of positivity in the community cross-sectionally by determining the proportion of risky patients who applied to the emergency department.

MATERIAL METHOD

The study was carried out with the permission of the İzmir Kâtip Celebi University Non-Invasive Clinical Research Ethics Committee (Date: 21.04.2022 -Decision No: 0188). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Setting

This single-center, retrospective cross-sectional study was conducted in an emergency medicine clinic of a tertiary education and research hospital. Our hospital is one of the hospitals where the most emergency service applications are made in the city center where it is located.

Participants

Among the patients who applied to the emergency department between January 2022 and December 2022, anti-HAV IgM, HBsAg, anti-HBc IgM, HIV Ag/Ab (antigen/antibody) (HIV-1/ HIV-2 IgM and IgG antibodies and HIV-1 antibodies) cases that were requested to be tested for p24 antigen) were included in the study. Patients with missing data were excluded from the study. The demographic characteristics of the patients included in the study, the indications of the examinations (suspicion of viral hepatitis, liver dysfunction, before hemodialysis and interventional procedures, etc.) and examination results were recorded in the study data form.

Outcome Measures

Anti-HAV IgM, HBsAg, anti-HBc Ig M, HIV Ag/Ab results were obtained in the microbiology laboratory with Abbott Architect I2000SR (Architect, Abbott, USA) macro-ELISA device autoanalyzer and chemiluminescence immunoassay (Chemiluminescence) technique. The results were evaluated based on the operating criteria of the commercial kit. 0.80 U/L for anti-HAV IgM, 0.90 U/L for HBsAg, 0.90 U/L for anti-HCV, greater than 1 U/L for HIV Ag/Ab and for anti-HBc IgM If ≥1 U/L samples were considered positive. In addition, confirmatory test results were accepted as definitive results for those who were HIV Ag/Ab positive.

Statistical Analysis

IBM SPSS Statistics 28 (SPSS Inc., Chicago, USA) program was used for data analysis. Descriptive statistics are presented with frequency, percentage, mean and standard deviation values. Whether the data conformed to the normal distribution was evaluated using the Shapiro-Wilk test, skewness- kurtosis values, and Q-Q plots. Independent Samples t-Test was used for data conforming to normal distribution in the comparison of two independent groups. The chi-square test was used to compare two or more categorical groups. A p value of <0.05 was considered significant. All statistics were done at 95% confidence interval.

RESULTS

Considering the sociodemographic characteristics of 4799 patients admitted to the emergency department and included in our study, 2056 (42.8%) were female and 2743 (57.2%) were male. The mean age of women is 54.4±22.8, while that of men is 46.4±20.8. Of the cases, 4622 (96.3%) were citizens of the Republic of Turkey (T.R.), 144 (3%) were Syrian citizens, 8 (0.2%) were from Europe, 16 (0.3%) were from Asia, and 9 (0.2%) were from Africa (**Table 1**).

Table 1. General characteristics of the patients

	Number (n)	Percentage (%)
Age (mean±SD)	50 ± 22	
Gender		
Female	2056	42.8
Male	2743	57.2
Total	4799	100
Nationality		
Turkish	4622	96.3
Syrian	144	3
European	8	0.2
Asian	16	0.3
African	9	0.2
Total	4799	100

The positivity rates in the patients included in the study were 2% (n=95) for Anti HAV IgM and 3.3% (n=159) for Hbs Ag. Anti HBc IgM 0.5% (n=26). 1.2% (n=57) for anti HCV. For HIV Ag/Ab Combo it was 0.6% (n=27). When the differences between the sexes were examined, the rate of HbsAg positivity was found to be statistically significantly higher in men than in women (4%, 2.5%) (p=0.001). No gender difference was found between other markers (**Table 2**).

Table 2. Viral markers measured by ELISA method and their distribution by gender

	Gender		Total	p
	Female	Male		
Anti HAV IgM				0.107
Negative	2023 (98%)	2681(98%)	4704 (98%)	
Positive	33 (2%)	62(2%)	95 (2%)	
Total	2056 (42.8%)	2743 (57.2%)	4799 (100%)	
HBSAg				0.001
Negative	2008 (97.7%)	2632 (96%)	4640(96.7%)	
Positive	48 (2.3%)	111 (4%)	159 (3.3%)	
Total	2056 (100%)	2743 (100%)	4799 (100%)	
Anti HBc IgM				0.212
Negative	2048 (99.6%)	2725 (99.3%)	4773 (99.5%)	
Positive	8 (0.4%)	18 (0.7%)	26 (0.5%)	
Total	2056 (100%)	2743 (100%)	4799 (100%)	
Anti HCV				0.076
Negative	2717 (99.1%)	2025 (98.5%)	4742 (98.8%)	
Positive	26 (0.9%)	31 (1.5%)	57 (1.2%)	
Total	2743 (100%)	2056 (100%)	4799 (100%)	
HIV Ag/Ab combo				0.541
Negative	2046 (99.5%)	2726 (99.4%)	4772 (99.4%)	
Positive	10 (0.5%)	17 (0.6%)	27 (0.6%)	
Total	2056 (100%)	2743 (100%)	4799 (100%)	

Considering the differences according to the nationalities of the patients included in the study, Anti HCV positivity was found in Turkish Residents. It was found to be significant in nationals compared to others (p <0.001). Positive and negative rates by nationality are given in **Table 3**.

Table 3. Viral markers measured by ELISA method and their distribution by nationality

	Nationality						
	Turkish	Syrian	European	Asian	African	Total	p
Anti HAV IgM							0.138
Negative	4534 (94.5%)	137 (2.9%)	8 (0.2%)	16 (0.3%)	9 (0.2%)	4704 (98%)	
Positive	88 (1.8%)	7 (0.1%)	0 (0%)	0 (0%)	0 (0%)	95 (2%)	
Total	4622 (96.3%)	144 (3%)	8 (0.2%)	16 (0.3%)	9 (0.2%)	4799 (100%)	
HBSAg							0.080
Negative	4468 (93.1%)	142 (3%)	8 (0.2%)	14 (0.3%)	8 (0.2%)	4640 (96.7%)	
Positive	154 (3.2%)	2 (0%)	0 (0%)	2 (0%)	1 (0%)	159 (3.3%)	
Total	4622 (96.3%)	144 (3%)	8 (0.2%)	16 (0.3%)	9 (0.2%)	4799 (100%)	
Anti HBS IgM							0.993
Negative	4597 (95.8%)	143 (3%)	8 (0.2%)	16 (0.3%)	9 (0.2%)	4773 (99.5%)	
Positive	25 (0.5%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	26 (0.5%)	
Total	4622 (96.3%)	144 (3%)	8 (0.2%)	16 (0.3%)	9 (0.2%)	4799 (100%)	
Anti HCV							<0.001
Negative	4572 (95.3%)	139 (2.9%)	8 (0.2%)	14 (0.3%)	9 (0.2%)	4742 (98.8%)	
Positive	50 (1%)	5 (0.1%)	0 (0%)	2 (0%)	0 (0%)	57 (1.2%)	
Total	4622 (96.3%)	144 (3%)	8 (0.2%)	16 (0.3%)	9 (0.2%)	4799 (100%)	
HIV Ag/Ab Combo							0.904
Negative	4595 (95.7%)	144 (3%)	8 (0.2%)	16 (0.3%)	9 (0.2%)	4772 (99.4)	
Positive	27 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	27 (0.6)	
Total	4622 (96.3%)	144 (3%)	8 (0.2%)	16 (0.3%)	9 (0.2%)	4799 (100%)	

When positivity rates were compared according to their diagnosis, Anti HAV IgM positivity was found to be statistically significant in hemodialysis patients compared to other diagnoses (p <0.001). No significant difference was found between other markers and indications. (**Table 4**).

Considering the rate of positivity in the tests taken before the emergency operation, incidentally; Anti HAV IgM 1.3% (n=42) Hbs Ag 3.2% (n=102), Anti HBc IgM 0.4% (n=13), Anti HCV 1% (n=33), HIV Ag/Ab Combo 0.3% (n =11).

DISCUSSION

Emergency services are units that provide health care 24 hours a day without any interruption, concern many different disciplines, where patients are admitted at the first application or by referral from another health center, and the exact diagnosis of the patients is mostly unknown at the first stage. Despite the gradual increase in risk groups in communicable diseases and the precautions taken against transmission routes, the incidence of these diseases is still increasing (5).

The first unit that welcomes patients in cases of threats that are noticed or detected for the first time is the emergency services. In this case, the importance of emergency service physicians and managers to take the necessary precautions emerges. Patients and health personnel working in emergency departments where continuous health services are provided are constantly at risk of some infectious diseases (6,7). This situation has also come to the fore in the COVID-19 case we have experienced in recent years (8). Despite these known facts, it was observed in the study that the number of applications by the health personnel in the emergency department of our hospital was very low. The low number of occupational accidents shows that the educational and practical process in in-service training and prevention methods is successful.

However, the prevalence of being positive was found to be compatible with the prevalence of the population in patients who applied to the emergency department and did not have active complaints for infectious diseases and were requested to have hepatitis and HIV serology tests (4,9). The proportions of patients who were taken in this cross-sectional preoperative or unexplained condition and found to be positive vary between 1.4% and 0.4%. Although these rates show that the ministry of health is working effectively in public health, it is of great importance that newly detected cases are directed to appropriate treatment in order to prevent new transmissions.

The fact that the number of patients included in the study was 4799 and the female-male ratios were equal, we think that it is generally adaptable for a cross-sectional study. Considering the immigration status from foreign countries for the last 5 years, it is observed that the patients who applied to the emergency department did not differ much in terms of sociodemographic nationality.

Except for the Hbs Ag positivity rate (males are statistically more numerous), there is no statistical difference between the sex ratios in other markers. Similar results were found in other studies (10).

Table 4. Leading search reasons in serology examinations

	Anti HAV IgM		HBsAg		Anti HBc IgM		Anti HCV		HIV Ag/Ab		Total
	Neg n (%)	Pos n (%)	Neg n (%)	Pos n (%)	Neg n (%)	Pos n (%)	Neg n (%)	Pos n (%)	Neg n (%)	Pos n (%)	n (%)
Acute viral hepatitis	167 (97.1%)	5 (2.9%)	166 (96.5%)	6 (3.5%)	171 (99.4%)	1 (0.6%)	170 (98.8%)	2 (1.2%)	171 (99.4%)	1 (0.6%)	172 (100%)
LFT Augmentations	820 (96.1%)	33 (3.9%)	821 (96.2%)	32 (3.8%)	845 (99.1%)	8 (0.9%)	837 (98.1%)	16 (1.9%)	843 (98.8%)	10 (1.2%)	853 (100%)
Gallbladder diseases	95 (100%)	0	94 (98.9%)	1 (1.1%)	94 (98.9%)	1 (1.1%)	93 (97.9%)	2 (2.1%)	94 (98.9%)	1 (1.1%)	95 (100%)
Preoperative	3130 (98.7%)	42 (1.3%)	3070 (96.8%)	102 (3.2%)	3159 (99.6%)	13 (0.4%)	3139 (99%)	33 (1%)	3161 (99.7%)	11 (0.3%)	3172 (100%)
Hemodialisis	183 (95.3%)	9 (4.7%)	188 (97.9%)	4 (2.1%)	191 (99.5%)	1 (0.5%)	191 (99.5%)	1 (0.5%)	189 (98.4%)	3 (0.6%)	192 (100%)
Endoskopy	224 (97.4%)	6 (2.6%)	219 (95.2%)	11 (4.8%)	228 (99.4%)	2 (0.9%)	228 (99.1%)	2 (0.9%)	229 (99.6%)	1 (0.4%)	230 (100%)
Malignity	13 (100%)	0	13 (100%)	0	13 (100%)	0	13 (100%)	0	13 (100%)	0	13 (100%)
Cirrhosis	26 (100%)	0	26 (100%)	0	26 (100%)	0	26 (100%)	0	26 (100%)	0	26 (100%)
Work accident	29 (100%)	0	28 (96.6%)	1 (3.4%)	29 (100%)	0	28 (96.6%)	1 (3.4%)	29 (100%)	0	29 (100%)
Substance abuse	17 (100%)	0	15 (88.2%)	2 (11.8%)	17 (100%)	0	17 (100%)	0	17 (100%)	0	17 (100%)
p value*	<0.001		0.373		0.843		0.578		0.177		

Considering the differences according to nationalities, Anti HCV positivity T.C. It was found to be significant in nationals compared to others (p <0.001), but it is controversial whether it is clinically significant due to the large differences between the number of patients in the groups compared. More research is needed on this subject.

CONCLUSION

This study has data that can reflect the society in terms of the place where it was conducted and the number of patients included in the study. With the sensitivity of the Ministry of Health on the subject and the impact of the intensive work of the primary care on vaccination, we have found satisfactory results in terms of transmission and vaccination.

Limitations

The most important limitation of this study is that it did not include all patients who applied to the emergency department, but only those who were requested to be tested. Second important limitation of this study is that its an retrospectiv studies. Study was conducted through patient records.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the İzmir Kâtip Celebi University Non-Invasive Clinical Research Ethics Committee (Date: 21.04.2022 -Decision No: 0188).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Çocuklarda Ewing Sarkom Ailesi Tümörler: Tek Merkez Sonuçları

Ewing's Sarcoma Family of Tumors in Children: The Results from A Single Center

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ÖZ

Amaç: Bu çalışmanın amacı, Ewing sarkom ailesi tümörlü (EFT) çocukların klinik özelliklerini ve sonuçlarını gözden geçirmektir.

Gereç ve Yöntem: Patolojik olarak EFT tanısı alan çocukların onkoloji dosyaları retrospektif olarak incelendi. Hastaların klinik özellikleri, tedavi yaklaşımları ve tedavi sonuçları kaydedildi. Ayrıca, hastaların tam kan sayımlarından nötrofil/lenfosit oranları (NLR) ve platelet/lenfosit oranları (PLR) da hesaplandı.

Bulgular: Çalışmaya 50 hasta dâhil edildi. Hastaların yaşı 9,6 ay ile 17,5 yıl arasında değişiyordu (ortanca, 10,1 yıl). Erkek/kız oranı, 25/25 idi. En sık başvuru şikâyet ağrıydı (n= 43, %86). Ekstraosseoz tutulum yapan 16 hasta (%32) vardı. Bölgesel lenf nodu metastazı yapan 6 hasta (%12) vardı. On iki hastada uzak metastaz saptandı. Altı hastada uzak metastaz yeri akciğerken altı hastada diğer uzak organ metastazı vardı. Genel ve olaysız sağ kalım oranları, sırasıyla %60,1±8,9 ve %52,5±8,2 idi. Hastaların izlem süreleri 0,2 yıl ile 15,7 yıl arasında değişiyordu (ortanca, 3 yıl). Kız cinsiyet, ileri evre hastalık, laktat dehidrogenaz değerinin yüksek olması, tümör volümü > 10 cm3, yaş ≥ 12, anemi varlığı, nötrofil lenfosit oranı sağ kalım üzerine negatif prognostik etkide bulunmuş olsa da istatistiksel olarak anlamlı bulunmadı. Metastatik hastalığın olması ve PLR > 150 olması olaysız sağ kalım üzerindeki negatif etkisi istatistiksel olarak anlamlı bulundu.

Sonuç: Ewing sarkom ailesi tümör tedavisinde multidisipliner yaklaşım oldukça önemlidir. Bizim çalışmamızda her ne kadar yaşam oranları üzerine etki etmese de (hasta sayımızın az olması ile ilişkili olabilir) yüksek riskli hastalarda yeni tedavi yaklaşımlarına ihtiyaç vardır.

Anahtar Kelimeler: Ewing sarkom ailesi tümör, çocuk, prognoz

ABSTRACT

Aim: The aim of this study is to review of the clinical characteristics and outcome of children with Ewing' sarcoma tumors of family (EFT).

Material and Method: Oncology charts of children who were pathologically diagnosed with EFT were reviewed retrospectively. The clinical features, treatment approaches and treatment results of the patients were recorded. In addition, neutrophil/lymphocyte ratios (NLR) and platelet/lymphocyte ratios (PLR) were calculated from the complete blood counts of the patients.

Results: Fifty patients were included in the study. The age of the patients ranged from 9.6 months to 17.5 years (median, 10.1 years). The male/female ratio was 25/25. The most common complaint was pain (n= 43, 86%). There were 16 patients (32%) with extraosseous involvement. There were 6 patients (12%) with regional lymph node metastasis. Distant metastases were detected in 12 patients. Six patients had distant metastases in the lung, while six patients had other distant metastases. Overall and event-free survival rates were 60.1±8.9% and 52.5±8.2%, respectively. The follow-up period of the patients ranged from 0.2 years to 15.7 years (median, 3 years). Although female gender, advanced disease, high lactate dehydrogenase value, tumor volume > 10 cm3, age ≥ 12, presence of anemia and neutrophil lymphocyte ratio had a negative prognostic effect on survival, it was not statistically significant. The negative effect of metastatic disease and PLR > 150 on event-free survival was found to be statistically significant.

Conclusion: A multidisciplinary approach is very important in the treatment of EFT. Although it did not affect survival in our study (may be related to the small number of patients), new treatment approaches are needed in high-risk patients.

Keywords: Ewing sarcoma family of tumor, children, prognosis

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GİRİŞ

Ülkemizde, kemiğin primer tümörleri tüm çocukluk çağı tümörlerinin yaklaşık %6,5'uğunu oluşturmaktadır (1). Ewing sarkom ailesi tümörler, çocukluk çağının primer kemik tümörlerinin yaklaşık %34'ünü oluşturmaktadır (2). Ewing sarkom ailesi tümörler (EFT), Ewing sarkomu (ES), ekstraosseöz Ewing sarkomu, primitive nöroektodermal tümör ve Askin tümörlerini kapsar.

Hastaların genellikle başvuru şikâyetleri ağrı, şişlik ya da ele gelen kitle, ateş ve patolojik kırıklardır. Ewing sarkomu sıklıkla alt ekstremitede uzun kemikler etkilenmektedir (2,3). Uzun kemiklerde ise diyafizde yerleşmektedir. Göğüs duvarını içeren torakopulmoner bölgenin EFT'si Askin tümörü olarak da bilinmektedir (2).

Ewing sarkomu ailesi tümörlerinin tedavisinde, multidisipliner yaklaşımlarla son 3-4 dekat içerisinde yaşam oranlarında oldukça yüz güldürücü sonuçlar elde edilmiştir. Burada özellikle lokal kontrolün sağlanmasında cerrahi ve/veya radyoterapinin kullanılması, intensif kemoterapilerin kullanılması ve destek tedavilerinde gelişmeler önemli rol oynamıştır (2). Günümüzde, genel olarak metastatik olmayan EFT'de 5-yıllık hastalıksız yaşam oranları %60-70'lerde iken, ne yazık ki tanı anında metastazı olan hastalarda bu oran %10-30'lara düşmektedir. Prognozu olumsuz yönde etkileyen faktörler genellikle büyük yaş, pelvis, kosta, vertabra, skapula, kafa kemikleri, klavikula gibi aksiyal kemik yerleşimli olması, büyük tümör volümü ve tanı anında serum laktat dehidrogenaz enzim yüksekliğidir (2).

Bu çalışmada, kliniğimizde izlenen EFT'si olan çocuk hastalarımızın, klinik bulguları, tedavi yaklaşımları ve tedavi sonuçları ve tedavi sonuçlarına etki eden faktörlerin araştırılması amaçlanmıştır.

GEREÇ VE YÖNTEM

Bu çalışma için Selçuk Üniversitesi Tıp Fakültesi, Yerel Etik Kurul'undan 29.03.2022 tarihli 2022/07 sayı ile izin alınmıştır. Retrospektif bir çalışma olduğu için hasta ve hasta yakınlarından onam alınmamıştır.

Selçuk Üniversitesi Tıp Fakültesi, Çocuk Onkoloji ve Hematoloji Bilim Dalı'nda 2006 ile 2021 yılları arasında EFT tanısı alan veya izlenen hastaların dosyaları retrospektif olarak incelendi. Hastaların dosyalarından;

Demografik bilgi olarak: yaş ve cinsiyet

Klinik bulguları olarak: başvuru anındaki şikâyetleri ve şikayet süreleri, fizik muayene bulguları, tam kan sayımları (tam kan sayımlarından NLR ve PLR hesaplandı), tümör volümü, başvuru anındaki laktat dehidrogenaz (LDH) düzeyleri (LDH için referans aralığı: 125-222 U/L'dir). Hem NLR hem de PLR için Vasquez ve arkadaşlarının (4) çalışmasında değerler referans değer olarak alınmıştır.

Tümörün yerleşim yerleri aksiyal kemikler (pelvis, kosta, vertabra, skapula, kafa kemikleri, klavikula), apendiküler kemikler (femur, fibula, tibia, humerus, ayak kemikleri, radius, ulna, el kemikleri), diğer kemikler, ekstraosseoz olarak sınıflandırıldı.

Hastalar lokal ya da metastatik olarak iki gruba ayrıldı.

Tedavileri: Uygulanan kemoterapi protokolü, radyoterapi uygulanıp / uygulanmadığı, cerrahi girişim uygulanıp / uygulanmadığı ya da uygulanamadığı kaydedildi.

Hastalarda yıllara göre ve ilaç teminindeki güçlüklere göre, AEWS 0031 isimli kemoterapi protokolü (5), EICESS-92 isimli kemoterapi protokolü (6), PIAV kemoterapi protokolü (sisplatin, ifosfamid, adriamisin ve vinkristin) ve Euro-Ewing-99 isimli kemoterapi protokolü (7) uygulandı.

Tedavi sonuçları: hastalık sonucu (yaşıyor/kaybedildi), genel yaşam oranı ve süresi, ve olaysız yaşam oranı ve süresi hesaplandı ve kaydedildi.

İstatistiksel Analiz

İstatistiksel analizler için, GraphPad Prisim 9 (GraphPad, San Dieogo, USA) ve SPSS 22.0 paket programı kullanıldı. Tanımlayıcı istatistiklerde, kategorik veriler (nominal ya da ordinal veriler) için frekans ve yüzde değerleri kullanılırken numerik verilerde önce dağılımın normal olup olmamasını değerlendirmede D'Agostino & Pearson testi (GraphPad software'in önerisi) kullanıldı. Eğer dağılım normal ise aritmetik ortalama ± standart sapma; dağılım normal değilse en düşük ve en yüksek değerle beraber ortanca değer verildi. Yaş grupları (ordinal veri) ve cinsiyete göre iki kategorik değişken arasındaki ilişkiler ki-kare testi trend ile analiz edildi. Genel ve olaysız yaşam oranları için Kaplan Meier Survival analizi kullanıldı. Sağ kalım analizlerinin karşılaştırılmasında Log Rank testi kullanıldı. P değeri < 0,05 ise istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Çalışmaya, EFT'si olan 50 çocuk hasta dâhil edildi. Hastaların yaşları 9,6 ay ile 17,5 yıl arasında değişiyordu (ortanca, 10,1 yıl). Erkek ve kız oranı eşitti (25/25). Hastaların demografik ve klinik özellikleri Tablo 1'de görülmektedir. En sık başvuru şikâyeti ağrıydı (n: 43, %86).

Tümörlerin yerleşim yerleri incelendiğinde 18 hastada apendiküler kemik (%36), 16 hastada aksiyal kemik (%32) ve 16 hastada ise ekstraosseöz yerleşimliydi (%32) (**Tablo 1**).

Tanı anında, LDH yüksekliği 35 hastada (%70) saptandı (**Tablo 1**).

On iki hastada (%24) ise uzak organ metastazı vardı ve en sık uzak organ metastazı 6 hastada akciğerdi (%12).

Tablo 1: Hastaların demografik ve klinik özellikleri

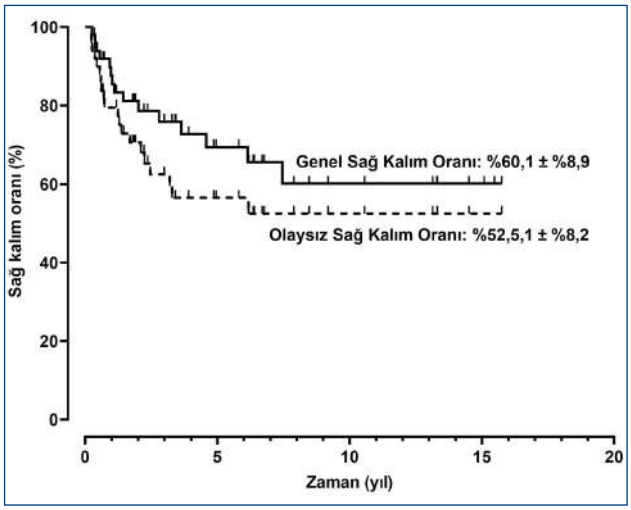
Özellik	n,(%)
Yaş, ortanca (en düşük-en büyük)	10,1 yıl (9,6 ay-17,5 yıl)
Cinsiyet	
Erkek	25, (%50)
Kız	25, (%50)
Şikayetler	
Ağrı	43, (%86)
Şişlik	36, (%72)
Hareket kaybı	24, (%48)
Kilo kaybı	6, (%12)
Ateş	5, (%10)
Enürezis	2, (%4)
Hemoglobin düzeyi	
Normal	43, (%86)
Düşük	7, (%14)
Lökosit değeri	
Normal	42, (%84)
Düşük	5, (%10)
Yüksek	3, (%6)
Nötrofil değeri	
Normal	44, (%88)
Yüksek	3, (%6)
Düşük	3, (%6)
Lenfosit değeri	
Normal	45, (%90)
Düşük	5, (%10)
Platelet değeri	
Normal	43, (%86)
Yüksek	7, (%14)
Platelet lenfosit oranı	
≤ 150	31, (%62)
> 150	19, (%38)
Nötrofil lenfosit oranı	
≤ 2	33, (%66)
> 2	17, (%34)
Serum laktat dehidrogenaz düzeyi, (Normal: 125-222 U/L)	
Normal	15, (%30)
Yüksek	35, (%70)
Yerleşim yeri	
Apendiküler kemikler	18, (%36)
Aksiyal kemikler	16, (%32)
Ekstraosseöz	16, (%32)
Tümör volümü	
≤10 cm3	10, (%20)
>10 cm3	40, (%80)
Hastalığın yaygınlığı	
Lokalize	38, (%76)
Metastatik	12, (%24)
Kemoterapi rejimleri	
AEWS 0031 isimli kemoterapi protokolü	17, (%34)
EICSS-92 isimli kemoterapi protokolü	16, (%32)
PİAV	10, (%20)
Euro-Ewing protokolü	7, (%14)
Cerrahi	
Uygulandı	37, (%74)
Uygulanmadı ya da uygulanamadı	13, (%26)
Radyoterapi	
Uygulandı	28, (%56)
Uygulanmadı ya da uygulanamadı	22, (%44)

Tedavi yaklaşımları

Hastalara en çok AEWS-0031 isimli protokol uygulandı (n: 17, %34). Bunu sırasıyla EICESS-92 isimli protokol (n:16, %32), PIAV isimli protokol (n: 10, %20) ve Euro-Ewing 99 isimli protokol (n: 7, %14) uygulandığı görüldü. Otuz yedi hastaya (%74) cerrahi girişim uygulanırken, 13 hastaya uygulanmadı ya da uygulanamadı (%26). Radyoterapi ise 28 hastaya uygulandığı görüldü (%56).

Tedavi sonuçları

Ewing sarkom ailesi tümörlü hastaların yaşam analizleri değerlendirildiğinde, genel ve olaysız sağ kalım oranları, sırasıyla %60,1±8,9 ve %52,5±8,2 idi (**Şekil 1**). Hastaların izlem süreleri 0,2 yıl ile 15,7 yıl arasında değişiyordu (ortanca 3 yıl). Genel ve olaysız sağ kalım oranları üzerine etki eden faktörler **Tablo 2**'de verilmiştir.



Resim 1. Hastaların genel ve olaysız sağ kalımları

TARTIŞMA

Ewing sarkom ailesi tümörler, çocuklarda osteosarkomdan sonra en sık görülen primer kemik tümörüdür. Tüm EFT'nin yaklaşık %80'i 20 yaşın altındadır. Küçük yuvarlak mavi hücreli tümörlerden biri olan Ewing sarkom, siyah ırk ve Asyalı çocuklarda daha az beyaz ırkta daha sık görülür. Çoğu hasta, genellikle kemik büyümesi veya çocuklarda meydana gelen sporla ilgili yaralanmalarla ya da büyüme ağrısı karıştırılan, aralıklı veya değişken yoğunlukta lokalize ağrı ve şişlik ile başvururlar. Diğer başvuru yakınmaları ise, ateş ve patolojik kırıklardır (2, 3).

Bizim hastalarımızda, en sık başvuru şikâyeti ağrı ve şişlik olduğu görülmektedir. Bir diğer önemli semptom hareket kaybı olurken kilo kaybı ve ateş gibi sistemik semptomlar hastaların yaklaşık %10'unda olduğu görülmektedir. Bir diğer semptom ise özellikle pelvik yerleşimli EFT'li hastalarda enürezis varlığıdır ki bizim hastalarımızda %2'sinde enürezis hastaların olduğu gözlendi.

Tablo 2: Genel ve olaysız sağ kalım oranları üzerine etki eden faktörler

	GENEL SAĞ KALIM ORANI					OLAYSIZ SAĞ KALIM ORANI				
	Genel sağ kalım oranı (%)	Standart hata (%)	Log Rank Testi (Mantel Cox)			Olaysız sağ kalım oranı	Standart hata	Log Rank Testi (Mantel Cox)		
			X2	df	p			X2	df	p
Cinsiyet			1,546	1	0,214			2,541	1	0,111
Kız	55,1	12,3				44,2	11,5			
Erkek	62,9	14,1				61,1	11,2			
Hastalık yaygınlığı			1,578	1	0,209			6,129	1	0,013
Lokalalize	70,7	8,6				66,7	8,5			
Metastatik	39,4	16,7				14,6	12,4			
Laktat dehidrogenaz düzeyi			0,922	1	0,337			0,266	1	0,606
Normal	75,8	12,7				58,3	15,2			
Yüksek	53,7	11				49,7	9,6			
Tümör volümü			2,497	1	0,114			2,588	1	0,108
≤ 10 cm3	85,7	13,2				75	15,3			
> 10 cm3	53,9	10,3				46,9	9,3			
Hemoglobin düzeyi			0,05	1	0,822			2,585	1	0,108
Normal	60,1	10,5				57	9,1			
Düşük	57,1	18,7				28,6	17,1			
Platelet lenfosit oranı*			1,475	1	0,224			6,290	1	0,012
≤150	65,8	10,9				66,9	9,4			
>150	48,8	15,2				21,9	12,8			
Nötrofil lenfosit oranı*			2,675	1	0,102			2,291	1	0,130
≤ 2	67,4	10,4				56,3	9,9			
>2	47,6	14,8				48,5	12,9			

* Sınır değerleri Vasquez ve arkadaşlarının (4) çalışmasından alınmıştır.

Ewing sarkomu en sık alt ekstremite yerleşimli iken ikinci en sık tutulum yeri pelvis kemikleridir (2, 3). Kemik tutulumu olmayan ES vakalarını "ekstraosseöz" olarak tanımlanmaktadır. Hastaların %20'sinden azında, EFT herhangi bir kemiği tutmaz, ancak doğrudan ekstremitelerin ve gövdenin yumuşak dokularından veya viseral bölgelerden kaynaklanır (8, 9). Bizim çalışmamızda, femur, fibula, tibia, humerus, ayak kemikleri, radius, ulna, el kemikleri gibi apendiküler kemikler en sık tutulurken, pelvis, kosta, vertabra, skapula, kafa kemikleri, klavikula gibi aksiya kemiklerde tutulum oranı %32 idi. Bizim çalışmamızda ilginç olarak ekstraosseöz EFT'li hasta oranın yüksek bulundu fakat bu durumu açıklayamadık.

Günümüzde, cerrahi, radyoterapi ve kemoterapinin birlikte olduğu multidisipliner yaklaşımlarla lokalize olan EFT'li hastalarda 5-yıllık hastalıksız yaşam oranları %60-70'lere ulaşmıştır. Ancak benzer başarı oranları maalesef tanı anında metastatik olan hastalarda elde edilememiştir. Tanı anında metastatik hastalığı olan hastalarda bu oran sadece %10-30'lardadır (2). Metastatik hastalık bilinen en önemli prognostik faktör olsa da ayrıca tanı anındaki yaşın büyük olması, tümörün aksiyal kemik yerleşimli olması, tümör boyutunun büyük olması ve tanı anındaki serum LDH düzeyinin yüksek olması diğer kötü prognostik faktörler olarak bilinmektedir. Ayrıca bildirilen diğer prognostik faktörler arasında ateş, anemi varlığı, proliferatif indeks ve kemoterapiye cevap olarak nekroz oranları da diğer prognostik faktörlerdir (2, 3, 10-13).

Ülkemizde yapılan bir çalışmada, Kutluk ve arkadaşları (14), 1972 ile 1999 yılları arasında, 133 ES'li çocuk hastada, 5-yıllık genel sağ kalım oranı lokalize hastalığı olan hastalarda %42 ve tanı anında metastazı olan hastalarda ise %15 bulmuşlardır. Kutluk ve arkadaşları (14) çalışmalarında ayrıca, uzak metastazların varlığı, büyük primer tümörler (primer tümör çapının <8 cm olması) ve pelvik lokalizasyon kötü prognozla ilişkili olduğunu bulmuşlardır. Bu çalışmada, 1990'lı yıllarda genel yaşam oranlarının %60'lara ulaştığı görülmektedir.

Ülkemizde yapılan bir başka çalışmada ise, Sarı ve arkadaşları (15), 1992-2005 yılları arasında 98 ES'lu hastayı incelemişlerdir. Yazarlar, 5-yıllık genel ve olaysız sağ oranlarını %47 ve %40 bulmuşlardır. Metastatik hastalığı olmayan hastalar için bu oranlar sırasıyla %51 ve %45 iken, metastatik hastalığı olan hastalarda %27 ve %18 olarak bulunmuştur. Kızlarda 5 yıllık genel ve olaysız sağ kalım oranları sırasıyla %30 ve %17 iken, erkeklerde %48 ve %45 bulunmuştur. Metastaz varlığı metafiz tümörleri ile yakından ilişkiliydi. Tümörün kemikteki lokalizasyonu (diyafiz veya metafizyal) ve hastaların cinsiyeti prognostik öneme sahip olduğunu bildirmişlerdir.

Bizim çalışmamızda, EFT'li hastaların yaşam analizleri değerlendirildiğinde, genel ve olaysız sağ kalım oranları, sırasıyla %60,1±8,9 ve %52,5±8,2 idi. Hastaların izlem süreleri 0,2 yıl ile 15,7 yıl arasında değişiyordu (ortanca 3 yıl). Kız cinsiyet, ileri evre hastalık, LDH değerinin yüksek olması, tümör volümü > 10 cm3, yaş ≥ 12, anemi varlığı,

nötrofil lenfosit oranı sağ kalım oranları üzerine negatif prognostik etkide bulunmuş olsa da istatistiksel olarak anlamlı bulunmadı. Ancak, hem metastatik hastalık olması hem de PLR'nin 180 üzerinde olması olaysaız sağ kalım üzerine olumsuz bir etkisi vardı.

Son yıllarda NLR ve PLR gibi bazı biyolojik belirteçlerin çocukluk çağı kanserlerinde de kullanımı artmıştır. Vasquez ve arkadaşlarının (4) medyan takip süresinin 17 ay olduğu çalışmada yüksek NLR değerinin ES prognostik bir faktör olmadığını saptamışlardır. Li ve arkadaşlarının (16) yaptıkları çalışmada NLR ve PLR'nin ES'li hastaların sağ kalımı ile anlamlı şekilde ilişkili olduğunu göstermiştir. Xu ve arkadaşlarının (17) spinal EFT'sinde inflamatuar biyobelirteçlerin prognostik değerini araştıran çalışmasında NLR'nin ve PLR'nin hastaların prognozu ile ilişkili olmadığını göstermiştir. Çalışmamızda, NLR'nin prognoz üzerine bir etkisinin olmadığını saptadık. PLR'nin ise genel sağ kalım oranları üzerine etkisi yokken, PLR > 150 olması olaysız sağ kalım üzerindeki negative etkisi istatistiksel olarak anlamlı bulundu.

SONUÇ

Son üç dört dekatta lokalize EFT tedavisnde oldukça yüz güldürücü sonuçlar elde edilmiş olsa da metastatik EFT tedavisinde yeni tedavi yaklaşımlarına ihtiyaç vardır.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Can Inflammatory Markers Measured before Total Knee Replacement be an Early Indicator of Revision?

Total Diz Protezi Öncesi Ölçülen İnflamatuar Belirteçler Revizyonun Erken Belirteci Olabilir Mi ?

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ABSTRACT

Aim: Knee replacement is one of the most commonly performed orthopedic surgeries today. Various prognostic markers are being investigated to reduce the revision rate. In this study, inflammatory markers measured from preoperative blood were evaluated in terms of revision.

Material and Method: 100 patients who underwent Total Knee prosthesis between January 2017 and December 2021 (50 revisions and 50 non-revisions) were included in the study. Systemic immune-inflammatory index (SII), neutrophil-lymphocyte ratio(NLR), lymphocyte-monocyte ratio(LMR) and platelet-lymphocyte ratios(PLR) calculated from the hemograms taken before the first surgery of these patients; were evaluated comparatively between those with and without revision surgery.

Results: The mean age of the patients was 63.98±9.30 (38-80) in patients who underwent revision, and 65.64±9.45 (46-87) in patients who did not undergo revision. There was no significant difference in age and gender distribution between the revised and non-revisioned groups (p>0.05). No significant difference was observed in the number of neutrophils, lymphocytes, and monocytes between the revised and non-revisioned groups (p>0.05). There was no significant difference in SII, NLR, LMR and PLR values between the revised and non-revisioned groups (p>0.05)

Conclusion: SII, NLR, LMR and PLR calculated from the preoperative hemogram taken before total prosthesis surgery, and no significant relationship was found between revision of the knee prosthesis.

Keywords: total knee arthroplasty, Systemic immune-inflammatory index, revision, neutrophil-lymphocyte ratio

ÖZ

Amaç: Diz protezi günümüzde en sık uygulanan ortopedik ameliyatlardan biridir. Revizyona gitme oranını düşürmek için çeşitli prognostik belirteçler araştırılmaktadır. Bu çalışmada da ameliyat öncesi alınan kanlardan ölçülen inflamatuar belirteçlerin revizyona gitme açısından değerlendirmesi yapılmıştır.

Gereç ve Yöntem: Çalışmaya Ocak 2017-Aralık 2021 tarihleri arasında Total Diz protezi yapılan 100 hasta(50 revizyona giden 50 revizyona gitmeyen) dahil edilmiştir. Bu hastaların ilk ameliyatları öncesi alınan hemogramlarından hesaplanan Sistemik immün-inflamatuar indeks (SII), nötrofil lenfosit oranı(NLR), lenfosit monosit oranı(LMR) ve platelet lenfosit oranları (PLR); revizyon ameliyatı olan ve olmayanlar arasında karşılaştırmalı olarak değerlendirilmiştir.

Bulgular: Hastaların yaş ortalaması revizyon yapılan hastalarda 63,98±9.30(38-80), revizyon yapılmayan hastalarda ise 65,64±9.45(46-87) olarak bulundu. Revizyon yapılan ve yapılmayan grup arasında yaş ve cinsiyet dağılımı anlamlı farklılık gözlenmedi(p>0.05). Revizyon yapılan ve yapılmayan grup arasında nötrofil, lenfosit, monosit sayısında anlamlı farklılık gözlenmedi(p>0.05). Revizyon yapılan ve yapılmayan grup arasında SII, NLR, LMR ve PLR değerlerinde anlamlı farklılık gözlenmedi(p>0.05)

Sonuç: Total protez ameliyatı öncesi alınan preop hemogramdan hesaplanan Sistemik immün-inflamatuar indeks (SII), nötrofil lenfosit oranı, lenfosit monosit oranı ve platelet lenfosit oranı ile diz protezinin revizyona gitmesi arasında anlamlı bir ilişki bulunamamıştır.

Anahtar Kelimeler: total diz artroplastisi, Sistemik immün-inflamatuar indeks, revizyon, nötrofil-lenfosit oranı

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INTRODUCTION

The knee joint is the largest joint of the human body and has complex movements. The joint most affected by degenerative diseases like osteoarthritis is the knee. Osteoarthritis (OA) is the most common disease of the musculoskeletal system (2). OA; It is a complex disease that causes degeneration of joint components through a combination of structural, mechanical and biological pathways (3). There are many factors in the etiology, and it is the result of the interaction of systemic and local factors (4,5).

The history of total knee arthroplasty, which has been successfully applied for many years in the treatment of knee joint osteoarthritis (gonarthrosis), dates back to the middle of the 19th century. In addition to clinical and functional positive results, loosening due to long years of use of the prosthesis is an absolute result. The need for revision knee arthroplasty arises as a result of the instability that develops due to the decrease in the adhesion between the bone and the prosthesis (6).There are many factors in the loosening of knee arthroplasty components. Overuse, obesity, implant design, surgical technique and infection are some of these factors (6). Miller et al. reported that the first step of the mechanism that causes prosthesis loosening is micro-movements between the prosthesis and bone(7). Other mechanisms are osteolysis, component collapse, inflammatory response to microparticles formed as a result of polyethylene insert abrasion, and inflammation that develops in infective conditions (7).The basic mechanism underlying osteolysis, which is the first condition for the development of non-septic loosening, is the biological response to microparticles formed as a result of prosthesis wear. As a result of phagocytosis of these particles in the joint by macrophages, it initiates the inflammatory process. It has been shown that mediators such as IL-1, IL-6, TNF, PGE2 and metalloproteinase are secreted in the inflammatory process (9-11).

It has been shown that inflammation markers such as C-reactive protein (CRP), IL-6 and TNF-α, which are widely used, are significant in the prognosis of OA and the level of pain due to arthrosis (12,13). On the other hand, parameters such as systemic immune-inflammatory index (SII), neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio and platelet-lymphocyte ratio are practical and innovative biomarkers that are developing in cancer and inflammatory diseases(14).

In this study, we aimed to examine whether the Systemic immune-inflammatory index (SII), neutrophil lymphocyte ratio, lymphocyte monocyte ratio and platelet lymphocyte ratio measured before knee replacement surgery can be used as a prognostic marker for revision.

MATERIAL AND METHOD

This study was approved by the local ethics committee and complies with the Helsinki Declaration. The informed consent was waived due to the retrospective nature of the study and the assessment utilized anonymous research findings.

In this study, the data of 164 patients who applied to the Orthopedics and Traumatology outpatient clinic with the complaint of pain between January 2017 and December 2021 were retrospectively analyzed. 42 patients who were found to have septic loosening as a result of the examinations were excluded from the study.

Twenty-two patients with known autoimmune disease, acute and chronic infectious disease, systemic inflammatory disease, current immunosuppressive drug use, anti-inflammatory drug use in the last 15 days, chronic liver disease, history of malignancy, and disease causing coagulation disorder were excluded. As a result of physical examination and imaging, 50 patients who were diagnosed with aseptic loosening in knee prosthesis, underwent revision total knee arthroplasty and had at least 1 year of regular follow-up were selected. Fiftypatients undergoing total knee arthroplasty and not undergoing revision knee arthroplasty were selected as the control group. As a result, a total of 100 patients were included in the study. It was observed that total knee prosthesis was applied in various brands and models in line with the physician's preference in the patients. All of the patients were selected from those who had a total knee prosthesis that PCL-Substituting Knee Prosthesis

Neutrophil, lymphocyte, platelet and monocyte values obtained from CBC tests performed within 10 days before surgery in the included patients were used. Systemic Inflammatory Index (SII)(Neutrophil *Platelet/Lymphocyte), Neutrophil-Lymphocyte ratio (NLR), Lymphocyte-Monocyte ratio (LMR) and Platelet-Lymphocyte ratio (PLR) parameters were calculated.

Statistical analysis

IBM SPSS version 26.0 software program (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Mean, standard deviation, minimum and maximum values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov test. Mann-Whitney U test and independent sample test were used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and Fischer test was used when the chi-square test conditions were not met. A P value of <0.05 was considered statistically significant.

RESULTS

The study included 100 patients, 50 revisions (41 Female, 9 Male) and 50 non-revision (41 Female, 9 Male) patients between 2017-2021.

The mean age of the patients was 63.98±9.30 (38-80) in patients who underwent revision, and 65.64±9.45 (46-87) in patients who did not undergo revision.

There was no significant difference in age and gender distribution between the revised and non-revisioned groups (p>0.05).

No significant difference was observed in the number of neutrophils, lymphocytes, and monocytes between the revised and non-revisioned groups (p>0.05). There was no significant difference in SII, NLR, LMR and PLR values between the revised and non-revisioned groups (p>0.05) (**Table 1**).

DISCUSSION

A hemogram is a laboratory evaluation performed before almost all surgeries. It is frequently used for many evaluations because it is both cheap and easy to access (14). It has been shown in many studies that there is a correlation between the proportional relationship between the blood markers in the hemogram and the prognosis of some diseases (15-18). No relationship was found between the indicators and revision.

Recent studies have shown that the SII value calculated by peripheral lymphocyte, neutrophil and platelet counts is a good index for demonstrating local immune response and systemic inflammation. SII is an index of inflammation that is easy to calculate and can be reproduced from CBC results. It has been found to be significant in the prediction of prognosis and in patient follow-up in conditions such as various malignancies (hepatocellular cancer, esophageal cancer, small cell lung cancer), cardiogenic shock, adult Still's disease, ankylosing spondylitis (15-20).

Although there are many studies on the cancer prognosis of emerging and innovative biomarkers with parameters such as systemic immune-inflammatory index (SII), neutrophil lymphocyte ratio, lymphocyte monocyte ratio and platelet lymphocyte ratio (14), no significant difference was observed in our study in terms of the prognosis of total knee prosthesis (p>0.05).

It has been found that these parameters, which have significant results as inflammatory markers in many malignant and inflammatory diseases, do not give significant results as early markers of knee replacement revision. This may be because the inflammation that develops in aseptic knee arthroplasty is not at a level to affect systemic blood parameters. Also, the small number of patients in the study may have affected the statistical analysis. In addition, patients with autoimmune diseases, a history of acute and chronic infections, systemic inflammatory diseases, a history of malignancy and coagulation disorders were not included in the study. However, a similar trial was conducted in this group of patients and it was likely that a statistically significant change in the parameters studied could be detected.

Our study had several limitations. Our study included only a limited number of patients and is single centered. Future multicenter studies with higher patient numbers will provide more accurate information.

CONCLUSION

No significant correlation was found between the Systemic immune-inflammatory index (SII), neutrophil lymphocyte ratio, lymphocyte monocyte ratio and platelet lymphocyte ratio calculated from the preop hemogram taken before the total prosthesis surgery and revision of the knee prosthesis.

Table 1. Relationship with demographic data and hematological parameters of patients

Descriptive Statistics							
	Revised			Non-revised			p
	Mean±SD	Minimum	Maximum	Mean±SD	Minimum	Maximum	
NEU	4,50±1.8	2,31	10,86	4,87±2.13	1,90	12,90	0,23
LYM	2,01±0.73	0,70	3,84	2,19±0.77	0,50	4,30	0,19
MONO	0,47±0.17	0,02	0,93	0,48±0.18	0,20	1,30	0.7
SII	732,50±629.91	257,83	3173,63	687,01±553.02	163,00	3168,00	0,98
NLR	2,62±1.98	1,17	11,63	2,90±3.58	0,98	24,00	0,63
LMR	8,01±26.58	1,20	192,00	4,90±1.91	1,08	10,75	0,13
PLR	156,47±89.55	61,39	590,14	133,61±48.93	66,25	271,33	0,29
AGE	63,98±9.30	38	80	65,64±9.45	46	87	0,55
Gender		Female 41 Male 9			Female 41 Male 9		1.00

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the local ethics committee and complies with the Helsinki Declaration.

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

Referee Evaluation Process: Externally peer-reviewed.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Ailevi Akdeniz Ateşi ile İlişkili Renal Amiloidozu Değerlendirmede Renal Dupleks Doppler Ultrasonografinin Tanısal Değeri

Diagnostic Value of Renal Duplex Doppler Ultrasonography in the Evaluation of Renal Amiloidosis Associated with Familial Mediterranean Fever

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ÖZ

Amaç: Ailevi Akdeniz Ateşi (AAA), otoinflamatuvar sendromlar arasında en sık görülen periyodik ateş sendromudur. Bu hastalığın en ağır komplikasyonu, amiloidoz gelişimidir. Çalışmamızda; AAA tanısı almış, proteinürisi mevcut, kolşisin kullanan çocuk hastalarda, renal ve intrarenal vasküler yapılardaki hemodinamik değişikliklerin renal renkli dupleks Doppler ultrasonografi (RDDUS) ile değerlendirilmesi amaçlandı.

Gereç ve Yöntem: AAA tanısı almış olup düzenli aralıklarla izlenen ve kolşisin kullanan 43 hasta ile 20 sağlıklı çocuktan oluşan kontrol grubu çalışmaya dahil edildi. Hasta çocuk grubu ve kontrol grubunun genel özelikleri ile spot idrarda protein, kreatinin, protein/kreatinin oranları incelendi. Her iki gruba renal RDDUS incelemesi yapılarak her iki böbrek üst pol, orta kesim ve alt polü ile her iki ana renal arterden elde edilen rezistivite indeksi (Rİ) ve pulsatilite indeksi (Pİ) değerleri kaydedildi. Bu parametreler, istatiksel analiz ile karşılaştırıldı.

Bulgular: Hasta çocuk grubundan elde edilen RDDUS analizi ölçümleri ile proteinürinin indirekt göstergesi olan spot idrarda protein/kreatinin oranı arasında istatistiksel olarak anlamlı farklılık saptanmadı (p>0.05). Kontrol çocuk grubunda RDDUS analizi ölçümlerinde, sağ böbrek üst polünden elde edilen Rİ değerleri, hasta grubundan elde olunan Rİ değerlerinden anlamlı olarak daha yüksek bulundu (p=0.002). Diğer incelenen RDDUS parametrelerinde, her iki grup arasında istatiksel olarak anlamlı farklılık saptanmadı (p>0.05).

Sonuç: Renal vasküler tutulum yapabilen AAA'da, RDDUS, kolay uygulanabilir bir tetkik olmasına rağmen, renal hasara sebep olabilecek amiloidozu engelleyen bir tedavi yöntemi olan kolşisin kullanan hastalarda, RDDUS bulguları silik olabilir.

Anahtar Kelimeler: Ailesel Akdeniz ateşi (FMF), renal dupleks Doppler ultrasonografi (RDDUS), Kolşisin

ABSTRACT

Aim: Familial Mediterranean Fever (FMF) is the most common periodic fever syndrome among autoinflammatory syndromes. The most severe complication of this disease is the development of amyloidosis. Our aim was to evaluate the hemodynamic changes in renal and intrarenal vascular structures by renal duplex Doppler ultrasonography (RDDUS) in pediatric FMF patients with proteinuria who were using colchicine.

Material and Method: 43 children with FMF who were followed up regularly and using colchicine and 20 healthy children were included in the study. The patient characteristics and protein, creatinine and protein/creatinine ratios in the spot urine were analyzed of the patient and control groups. RDDUS examination was performed in both groups, and resistivity index (RI) and pulsatility index (PI) values obtained from the upper pole, middle section, lower pole and main renal arteries of both kidneys were recorded.

Results: There was no statistically significant difference between the RDDUS analysis measurements obtained from the patient group and the protein/creatinine ratio in spot urine, which is an indirect indicator of proteinuria (p>0.05). RI values obtained from the upper pole of the right kidney were found to be significantly higher in control group compared to patinet group in RDDUS analysis (p=0.002).There was no significant difference in the other RDDUS parameters between the two groups (p>0.05).

Conclusion: Although RDDUS is an easily applicable test in FMF with renal vascular involvement, RDDUS findings may be indistinct in patients using colchicine, which prevents amyloidosis that may cause renal damage.

Keywords: Familial Mediterranean fever (FMF), renal duplex Doppler ultrasonography (RDDUS), Colchicine

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GİRİŞ

Ailevi Akdeniz Ateşi (AAA) ya da benign rekürren poliserozit, otoinflamatuvar sendromlar arasında en sık görülen periyodik ateş sendromudur (1). AAA, serozal membranların inflamasyonu ile karakterize peritonit, plörit, perikardit, sinovit-artrit ve yüksek ateşe neden olan, otozomal resesif geçiş gösteren herediter bir hastalıktır (2,3). AAA sıklığı, çocuklukta her iki cinste eşit olmasına rağmen, erişkinde erkeklerde 1.5-2 kat daha fazladır (4). AAA'da esas klinik bulgu, rekürren ve kendini sınırlayan ateş ataklarıdır. Periton, sinoviyum veya plevra inflamasyonuna bağlı ağır abdominal ağrı, artiküler veya göğüs ağrısı, ateş epizotlarına eşlik eder (2). Ateş ve karın ağrısı hastaların %90'ında, göğüs ağrısı %40'ında görülür. Asimetrik non-destrüktif artrit %75, kronik destrüktif artrit %2-5, sakroileit %0-4 oranında görülmektedir. Özellikle çocuk ve genç erişkin hastaların %5'inde ortaya çıkan febril skrotal atak, testis torsiyonu ile karışabilir ve gereksiz cerrahi operasyonla sonuçlanabilir (5-6). Ataklar arasında hastalar semptomsuzdur.

AAA hastalarında sekonder amiloidoz gelişimi, prognozda belirleyici olan hastalığın en kritik komplikasyonudur (7). Amiloid fibriller, renovasküler yapılar ve parankimal tutulum yoluyla doku ve organın morfolojik bütünlüğünü bozar. Vasküler tutulum renal arterler ve arteriyollerde olabileceği gibi parankimin glomerüler ve tubulointerstisyel alanlarında da olabilir (8). Amiloidoz gelişimi ile semptomların süresi, ağırlığı ve başlangıç yaşı arasında herhangi bir korelasyon bulunamamıştır (5-6). Böbrek tutulumu asemptomatik mikroalbuminüri, makroalbüminüri, üremi ve son dönem böbrek yetmezliği ile kendini gösterebilir (7).

AAA'da hastalığın ağırlığını belirleyebilmek amacıyla; hastalığın başlangıç yaşı, atak sıklığı, kullanılan kolşisin dozu, eklem tutulumu, erizipel benzeri semptom varlığı ile amiloidoz varlığı olup olmamasına göre kriterler ve Tel Hashomer ağırlık skoru puanlama sistemi geliştirilmiş olup, bu kriterlere göre hastalık hafif, orta ve ağır olarak sınıflandırılmıştır (9). AAA tedavisinde kullanılan kolşisin, nötrofillerde konsantre olarak atak sırasında meydana gelen kemotaktik aktivite artışını inhibe eder ve uzun dönemde amiloidoz gelişiminin önlenmesinde, hastalığın tedavisi ve akut rekürren alevlenmelerinin önlenmesinde etkilidir (5-6).

İnflamatuvar atak ağırlığı ile amiloidoz varlığı arasında belirgin bir ilişki yoktur. Günlük kolşisin tedavisi, hem atakları hem de amiloid depozisyonunu önleyebilir. Ancak AAA ile ilişkili amiloidoz, henüz eradike edilememiş olup; amiloidoz hala hem çocuk hem de erişkinlerde kronik renal yetmezlik nedenidir. İlk defa 1955 yılında tanımlanan AAA ilişkili amiloidozun gerçek prevalansı bilinmemesine rağmen kolşisinle düzenli bir şekilde takip edilen hastaların %5'inde amiloidoz geliştiğine inanılmaktadır (10).

RDDUS hem ana renal arteri hem de intra-renal arteriyel yapıları değerlendirebilen noninvaziv bir görüntüleme yöntemidir (11). Biz bu çalışmada; AAA tanısı almış ve kolşisin kullanan farklı yaş grubu çocuk hastalarının renal renkli dupleks Doppler ultrasonografi (RDDUS) bulgularını, sağlıklı bireyler ile karşılaştırmayı amaçladık.

GEREÇ VE YÖNTEM

Hasta çocuk grubu, Temmuz 2008-Eylül 2008 tarihleri arasında "Tokat Gaziosmanpaşa Üniversite" hastanesi çocuk polikliniğinde AAA tanısı almış olup düzenli aralıklarla izlenmekte olan ve proteinürisi olan 43 çocuktan oluşturuldu. Kontrol grubu ise aynı tarihler arasında hastaneye başvuran 20 sağlıklı çocuktan oluşturuldu. Hasta grubundaki çocukların yaş, cinsiyet, kilo ve boyları ile AAA tanı süreleri sorgulandı. Ayrıca bu çocukların AAA için Tel Hashomer ağırlık skorları ve spot idrarda protein, kreatinin ve protein/kreatinin değerleri kaydedildi. Kontrol grubundaki çocukların ise yaşları, cinsiyetleri, kilo ve boyları sorgulandı.

Hasta ve kontrol grubunun tüm ultrasonografik incelemeleri renkli Dupleks Doppler US cihazı ile (Logic 9, GE Medical Systems, Milwaukee USA) konveks 2–5 Mhz transduser kullanılarak gerçekleştirilmiştir. İşlem aynı radyolog tarafından ve hastalar açken yapıldı. İncelemede her iki böbreğin üst pol, orta kesim ve alt pollerindeki arkuat arterlerinden ve her iki ana renal arterin hilus düzeyinden elde edilen rezisitivite indeksi (Rİ), pulsatilite indeksi (Pİ) değerleri ölçüldü. Her bir böbrek için üst pol, orta kesim ve alt polden en az 3 ölçüm yapılarak ortalamaları alındı. Ardışık en az 3-5 benzer görünümde dalga formları elde edildiğinde herhangi bir dalga formundan ölçüm alındı. Bu parametreler, istatiksel analiz ile karşılaştırıldı.

İstatistiksel değerlendirme

Sürekli değişkenler ortalama standart sapma (SD), nitel değişkenler yüzde veya oran olarak ifade edildi. İki grup arasında sürekli değişkenler "Student's T" veya "Mann-Whitney U" testi ile nitel değişkenler ise "Ki kare" testi ile karşılaştırıldı. Nitel değişkenler karşılaştırılırken çapraz tablolarda (2x2) beklenen değerlerin 5' ten küçük olduğu durumlarda "Fisher's Exact" testi kullanıldı. Protein/kreatinin oranı ile RDDUS parameterleri arasındaki ilişki "Pearson correlation coefficient" korealasyon testi kullanılarak değerlendirildi. Tüm istatistiksel analizlerde hesaplanan p değeri<0.05 ise fark istatistiksel olarak anlamlı kabul edildi. Tüm istatistiksel analizler için SPSS programı (Version 11: SPSS Inc, Chicago, IL, USA) kullanıldı.

BULGULAR

Hasta grubu yaş ortalaması 12±3 olan 23 erkek (%53.5), 20 kız (%46.5) olmak üzere toplam 43 hastadan, kontrol grubuysa yaş ortalaması 11±2 olan 8 erkek (%40), 12 kız (%60) olmak üzere toplam 20 sağlıklı çocuktan oluşturuldu.

Hasta grubunun genel özellikleri **Tablo 1'**de gösterilmiştir. Belirlenen AAA skor yüzdeleri; grade 1 %47, grade 2 %50, grade 3 %3 idi.

Tablo1. Hasta Grubunun Genel Özellikleri	
Değişkenler	
Hasta sayısı (n)	43
Yaş (yıl)	12±3
Erkek (n, %)	23 (%53.5)
Kadın (n, %)	20 (%46.5)
Boy (cm)	1.42±0.16
Kilo (kg)	35±12
Vücut kitle indeksi (kg/m2)	17.1±2.5
Tanı süresi (yıl)	5±4
Spot idrarda Protein (mgr/dl)	216±257
Spot idrarda Kreatinin (mgr/l)	103±60
Spot idrarda Protein/kreatinin oranı (dl/l)	2.25±1.47
AAA skoru	
Grade 1 (hafif)	18 (%47)
Grade 2 (orta)	19 (%50)
Grade 3 (ağır)	1 (%3)

Hasta grubundaki çocuklarda RDDUS incelemesi ile tespit edilen her iki böbreğe ait intrarenal üst pol, orta kesim ve alt polden elde edilen Rİ ve Pİ değerleri ile ana renal arterlere ait ortalama Rİ, Pİ değerleri **Tablo 2**'de gösterildi.

Tablo 2. Hasta grubundan elde edilen renal renkli Doppler ultrasonografik veriler		
	Sağ Böbrek (ortalama±standart sapma)	Sol Böbrek ortalama±standart sapma)
Üst pol intrarenal Rİ	0,59±0,06	0,58±0,06
Orta kesim intrarenal Rİ	0,58±0,05	0,57±0,05
Alt pol intrarenal Rİ	0,58±0,06	0,56±0,04
Üst pol intrarenal Pİ	0,99±0,33	0,98±0,37
Orta kesim intrarenal Pİ	0,94±0,26	0,90±0,15
Alt pol intrarenal Pİ	1,01±0,40	0,93±0,36
Ana renal arter Rİ	0,62±0,06	0,63±0,06
Ana renal arter Pİ	1,11±0,27	1,16±0,35
Rİ: Rezisitivite indeksi, Pİ: Pulsatilite indeksi		

AAA skoru hafif, orta ve ağır olanlar arasında iki grup oluşturuldu. AAA skoru hafif olanlar 1.grup, orta ve ağır olanlar 2. grup olarak kabul edildi. Yaş, cinsiyet, vücut kitle indeksi, tanı süresi, spot idrarda protein, kreatinin miktarı, protein/kreatinin oranı ve her iki böbreğin RDDUS parametreleri iki grup arasında karşılaştırıldı. Tanımlanan bu parametrelerde her iki grup arasında istatistiksel olarak anlamlı bir farklılık saptanmadı (**Tablo 3**).

Hasta grup ile kontrol grubu arasında yaş, cinsiyet, vücut kitle indeksi arasında anlamlı farklılık saptanmadı (p>0.05). Her iki grup arasında sağ böbrek üst polünden alınan Rİ değerleri dışında istatistiksel olarak anlamlı bir farklılık saptanmadı (**Tablo 4**). Sağ böbrek üst polden elde edilen RI değerleri ise kontrol grubunda hasta gruba göre anlamlı olarak daha yüksek bulundu P=0.002).

Tablo 3. Hastalığın ağırlığına göre renal renkli Doppler ultrasonografi bulgularının ve hasta özelliklerinin karşılaştırılması			
	Hafif AAA skoru	Orta-Ağır AAA skoru	P değeri
Hasta sayısı (n)	18	19	p>0.05
Yaş (yıl)	12±4	12±3.5	p>0.05
Erkek (n,%)	9 (%50)	12 (%60)	p>0.05
Boy (cm)	1,4±0,2	1.5±0,2	p>0.05
Kilo (kg)	34±12	36±14	p>0.05
Vücut kitle indeksi (kg/m2)	16,8±2,5	16,5±2,8	p>0.05
Spot idrarda protein (mgr/dl)	197±93	250±364	p>0.05
Spot idrarda kreatinin (mgr/l)	115±53	100±70	p>0.05
Spot idrarda protein/kreatinin oranı (dl/l)	1,9±1,2	2,4±1,7	p>0.05
Sağ üst pol intrarenal Rİ	0,57±0,05	0,58±0,06	p>0.05
Sağ orta kesim intrarenal Rİ	0,57±0,03	0,57±0,05	p>0.05
Sağ alt pol intrarenal Rİ	0,59±0,07	0,57±0,06	p>0.05
Sağ üst pol intrarenal Pİ	0,90±0,14	1,07±0,50	p>0.05
Sağ orta kesim intrarenal Pİ	0,90±0,10	0,96±0,40	p>0.05
Sağ alt pol intrarenal Pİ	1,23±0,65	0,89±0,16	p>0.05
Sol üst pol intrarenal Rİ	0,57±0,03	0,58±0,05	p>0.05
Sol orta kesim intrarenal Rİ	0,56±0,03	0,56±0,05	p>0.05
Sol alt pol intrarenal Rİ	0,57±0,04	0,56±0,03	p>0.05
Sol üst pol intrarenal Pİ	0,99±0,38	1,05±0,53	p>0.05
Sol orta kesim intrarenal Pİ	0,87±0,31	0,88±0,13	p>0.05
Sol alt pol intrarenal Pİ	0,94±0,21	1,02±0,60	p>0.05
Sağ ana renal arter Rİ	0,64±0,08	0,62±0,06	p>0.05
Sağ ana renal arter Pİ	1,19±0,40	1,08±0,20	p>0.05
Sol ana renal arter Rİ	0,65±0,08	0,63±0,06	p>0.05
Sol ana renal arter Pİ	1,21±0,54	1,16±0,23	p>0.05
Rİ: Rezistivite indeksi, Pİ: Pulsatilite indeksi, AAA skoru: Ailevi Akdeniz Ateşi Skoru			

Tablo 4. Çalışma Gruplarının Genel Özellikler ve RDDUS Parametreleri Bakımından Karşılaştırılması			
	Hasta	Kontrol	P değeri
Hasta sayısı (n)	43	20	p>0.05
Yaş (yıl)	12±4	11±2	p>0.05
Erkek (n, %)	23 (%54)	8 (%40)	p>0.05
Boy (cm)	1,4±0,2	1.5±0,2	p>0.05
Kilo (kg)	35±13	36±8	p>0.05
Vücut kitle indeksi (kg/m2)	16,6±2,6	17,6±2,3	p>0.05
Sağ üst pol intrarenal Rİ	0,58±0,06	0,63±0,06	P=0.002*
Sağ orta kesim intrarenal Rİ	0,57±0,05	0,59±0,06	p>0.05
Sağ alt pol intrarenal Rİ	0,57±0,07	0,60±0,07	p>0.05
Sağ üst pol intrarenal Pİ	0,99±0,37	0,98±0,23	p>0.05
Sağ orta kesim intrarenal Pİ	0,93±0,29	0,96±0,20	p>0.05
Sağ alt pol intrarenal Pİ	1,03±0,46	0,96±0,23	p>0.05
Sol üst pol intrarenal Rİ	0,58±0,05	0,59±0,07	p>0.05
Sol orta kesim intrarenal Rİ	0,56±0,04	0,59±0,06	p>0.05
Sol alt pol intrarenal Rİ	0,57±0,04	0,56±0,05	p>0.05
Sol üst pol intrarenal Pİ	0,99±0,44	0,96±0,18	p>0.05
Sol orta kesim intrarenal Pİ	0,88±0,11	0,96±0,21	p>0.05
Sol alt pol intrarenal Pİ	0,98±0,43	0,85±0,16	p>0.05
Sağ renal arter Rİ	0,62±0,07	0,61±0,06	p>0.05
Sağ renal arter Pİ	1,19±0,40	1,08±0,24	p>0.05
Sol renal arter Rİ	0,65±0,08	0,61±0,08	p>0.05
Sol renal arter Pİ	1,12±0,29	1,07±0,28	p>0.05
Rİ: rezistivite indeksi, Pİ: pulsalite indeksi			

TARTIŞMA

AAA, herediter rekürren ateşin en sık tipidir. AAA hastalarında sekonder amiloidoz gelişimi, prognozda belirleyici olan hastalığın en kritik komplikasyonudur (7). Amiloid fibriller, renovasküler yapılar ve parankimde birikir. Vasküler tutulum hem renal arterlerde hem de arteriyollerde olabilir (9).

RDDUS, renal ve intrarenal arterlerde kan akımını görüntüler. Spektral analiz ise akım hakkında kantitatif bilgi verir. RDDUS, renal vasküler rezistansın non-invaziv olarak değerlendirilmesine olanak sağlar. Doppler bulguları, erişkin ve çocuklarda renal arter stenozu, renal ven trombozu, böbrek biyopsisi sonrası komplikasyonların değerlendirilmesi, akut ve kronik böbrek inflamasyonunda kan akımının değerlendirilmesi, obstrüktif ve non-obstrüktif toplayıcı sistem dilatasyonu ayrımının yapılmasında, çeşitli parankimal böbrek hastalıklarında renal vasküler rezistansın değerlendirilmesinde yararlıdır (11).

Renal vasküler rezistans, sistol/diastol oranı, Rİ ya da Pİ gibi parametreler ölçülerek değerlendirilebilir. Birçok çalışmada pediyatrik renal vasküler rezistansın değerlendirilmesinde en sık Rİ değeri kullanılmaktadır (13). Platt ve arkadaşlarının yaptığı bir çalışmada renal biyopsi yapılmış 41 hastanın Rİ değerleri analiz edilmiştir. İzole glomerüler hastalığı olan hastalarda normal Rİ değerleri (0,58) gözlenmişken, vasküler veya interstisyel hastalığı olan hastalarda ise belirgin yükselmiş Rİ değerleri (0.75-0.87) bulunmuştur (14). Mostbezk ve arkadaşları histopatolojik olarak tanısı konmuş renal hastalık bulguları olan 34 hastayı RDDUS ile perkutan biyopsi öncesi değerlendirmiştir. Renal parankimal hastalıklar ile RI arasında istatiksel olarak anlamlı farklılık saptanmamıştır. Ancak RI, arterioskleroz, glomeruler skleroz, ödem, fokal interstisyel fibrozis gibi nonspesifik vasküler ve glomeruler patolojiler ile ilişkili bulunmuş. RI, arterioskleroz insidansının yüksek olması nedeniyle hastanın yaşı arttıkça artmıştır (15).

RDDUS, renal biyopsinin yerini almamakla birlikte birçok çalışmada, Doppler sonografinin bilinen renal hastalık takibinde kullanılabileceği önerilmektedir. Patriquin ve arkadaşlarının yayınladıkları bir seride, Doppler sonografinin hemolitik üremik sendromlu hastalarda klinik düzelmeden önce renal düzelmeyi öngörebileceği bildirilmiştir (16). Doppler sonografinin ayrıca non-obstrüktif akut renal yetmezlik ve diyabetik nefropatinin değelendirilmesinde yararlı olduğu gösterilmiştir (13).

Kolşisin, AAA'ya bağlı gelişen amiloidozun tedavisinde ve önlenmesinde etkili bir tedavi yöntemidir (17). Zemer ve arkadaşları, bir çalışmada ise uzun dönem devamlı ve günlük kolşisin tedavisinin amiloidoz sebebiyle gelişen renal hastalık nefrotik sendrom döneminde tanı konulsa bile böbrek hasarını azaltacağını göstermişlerdir. Kolşisin tedavisinin gerilettiği 3 nefrotik sendromlu olgu da bildirmişlerdir (18). Livneh ve arkadaşlarının bir çalışmasında, amiloidoza bağlı böbrek hastalığı geliştikten sonra düzenli kolşisin tedavisi başlanan 68 AAA hastasının 22'sinde renal hastalığın stabil kaldığı, 15'inin düzeldiği ve 31'inin kötüleştiği gösterilmiştir. Hastalığın kötüleşmesi, başlangıç kreatinin değerlerinin 1.5mgr/dl üzerinde olması ve ortalama kolşisin dozajı ile ilişkili bulunmuş fakat tedavi öncesi hastalığın şiddeti, proteinüri süresi, nefrotik sendrom varlığı, febril atakların persistansı ya da cinsiyetle ilişkisi bulunmamıştır (19). Kolşisinin terapötik etkisi ilk prezentasyonda renal hastalık evresi, ilaç dozu ve tedavi başlandığı andaki histopatolojik bulgular ile ilişkilidir (20).

Bizim çalışmamızda, takip süresi ve atak şiddeti farklı AAA tanısı konulmuş çocuk hasta grubunda renal ve intrarenal vasküler yapılardaki hemodinamik değişikliklerin RDDUS ile değerlendirilmesi amaçlandı. Renal parenkimal hastalığın değerlendirilmesinde incelediğimiz parametreler renal ve intrarenal arteriyel yapılardan elde olunan Rİ, Pİ parametreleriydi. Her iki böbrekten yapılan ölçümlerle elde edilen Rİ, Pİ değerleri ile proteinüri göstergesi spot idrarda protein/kreatinin oranı arasında istatistiksel anlamlı bir ilişki bulunmamıştır. 2016 yılında Sezer ve arkadaşlarının AAA hastaları ile sağlıklı bireylerin RDDUS bulgularını karşılaştırdığı çalışmasında; mikroalbuminürisi bulunan AAA hastalarından elde edilen RI değerlerinin hem normoalbuminürik hasta grubuna göre hem de kontrol grubuna göre anlamlı olarak daha yüksek olduğunu göstermişlerdir (20). Aynı çalışmada bizim çalışmamıza benzer şekilde hasta grubu ve sağlıklı kontrol grubu arasında elde edilen Pİ değerleri arasında anlamlı farklılık saptanmamıştır. Bizim çalışmamızda hasta ve kontrol grubu arasında hem Rİ hem de Pİ değerleri arasında anlamlı farklılık olmaması hastaların çoğunluğunun hafif ve orta AAA skoruna sahip olmasına veya hastaların tanı anından itibaren renal amiloidozu engelleyen kolşisin kullanımına bağlı olabilir. Bu konuyu aydınlatmak amacıyla daha geniş ve daha homojen hasta gruplarında kolşisin kullanan ve kullanmayan hastaları da içerecek şekilde yeni çalışmalar yapılması gereklidir.

Rezistivite indeksi, RDDUS spektrumundan elde edilebilen basit bir parametredir. Bu indeks, maksimal sistolik kan akımı ile ilişkili olarak end-diyastolik kan akımı azalmasını yüzde olarak ifade eder. Böbrek kompresyonu gibi ekstrensek faktörler, valsalva manevrası boyunca nefes tutma, aşırı bradikardi Rİ değerlerini arttırabilir (12). Bizim çalışmamızda hasta çocuk grubu ile kontrol grubu arasında yapılan RDDUS analizi ölçümlerinde sağ böbrek üst polünden elde edilen Rİ değerleri, kontrol grubunda hasta grubuna göre literatürden farklı olarak anlamlı olarak daha yüksek bulundu. Bu durumun inceleme esnasında kompresyon gibi teknik nedenlere bağlı olabileceği düşünüldü.

Çalışmamızın belirtilmesi gereken bazı kısıtlılıkları bulunmaktadır. Hasta sayımız kısıtlı idi. Hastalarımızın tamamı kolşisin kullanıyordu, kolşisin kullanmayan hastalar çalışmaya dahil edilmemişti. Ölçümler tek radyolog tarafından yapılmıştı, bu nedenle gözlemciler arası uyum analizi

yapılamamış olması diğer bir kısıtlılıktı. Ayrıca proteinürisi mevcut hastaların amiloidoz gelişiminin ortaya konulması için histopatolojik değerlendirilmesi yoktu.

SONUÇ

RDDUS, renal vasküler yapıları değerlendiren invaziv olmayan, ucuz ve operator bağımlı bir tekniktir. AAA gibi amiloidoza bağlı renal vasküler tutulum yapan bir hastalıkta kolaylıkla uygulanabilmesine rağmen, amiloidozu engelleyen bir tedavi yöntemi olan kolşisin kullanan hastalarda, renal hasar gelişmemesine bağlı olarak RDDUS bulguları silik olabilir. Bu nedenle RDDUS'nin AAA izleminde klinik pratikte kullanımı yaygın değildir. AAA'da RDDUS'nin etkinliğini göstermek amacıyla çok merkezli, geniş hasta serili, prospektif çalışmalara ihtiyaç vardır.

ETİK BEYANLAR

Etik Kurul Onayı: Çalışma retrospektif olarak planlanmış ve veriler dijital olarak elde edildiğinden etik kurul onayına gerek yoktur.

Aydınlatılmış Onam: Çalışma retrospektif olarak dizayn edildiği için hastalardan aydınlatılmış onam alınmamıştır.

Hakem Değerlendirme Süreci: Harici çift kör hakem değerlendirmesi.

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Yazar Katkıları: Yazarların tümü; makalenin tasarımına, yürütülmesine, analizine katıldığını ve son sürümünü onayladıklarını beyan etmişlerdir.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Evaluation of the Factors Affecting the Clinical Course and Prognosis in a Group of Patients with Transverse Myelitis

Transvers Miyeliti Olan Bir Grup Hastada Klinik Seyir ve Prognozu Etkileyen Faktörlerin Değerlendirilmesi

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ABSTRACT

Aim: Acute transverse myelitis is a spinal cord inflammatory disease that can occur at various spinal levels. It is extremely rare but can cause severe disability and even death. In this study, we aimed to evaluate the clinical findings, etiologic factors, and their effects on prognosis in a group of patients with acute transverse myelitis.

Material and Method: The study included 30 patients with acute transverse myelitis who were hospitalized at our clinic between January 2012 and December 2018. Hospitalization and discharge modified Rankin Scales, basic demographic data, treatments, lesion level, imaging, and CSF findings were recorded.

Results: Sixteen (53%) of the patients were male and 14 (47%) were female. The mean age was 54 years (16-84 years). While 13.3% of the cases developed into multiple sclerosis during follow-up, the etiology was malignancy in 16.6%, neuromyelitis optica in 6.6%, and infectious pathologies in 6.6%. Gender, age, parity of sphincter involvement, CSF protein, high hospitalization MRS score, and number of hospitalization days were identified as prognostic factors (p values were p=0.017, p=0.002, p=0.0013, p=0.019, p=0.001, p=0.002, respectively). High hospitalization rankin score and increased number of hospitalization days were correlated with poor prognosis at discharge (Pearson correlation coefficient r=0.886, p<0.001; r=0.675, p<0.001, respectively).

Conclusion: Acute transverse myelitis may have many different etiologies. Even in patients who meet the diagnostic criteria, multiple sclerosis can develop during follow-up. Long-term monitoring and paraneoplastic processes should be considered in myelitis. Furthermore, determining the factors affecting prognosis is useful in predicting the long-term clinical course of patients and guiding treatment.

Keywords: Clinical findings, etiology, prognosis, transverse myelitis

ÖZ

Amaç: Akut transvers miyelit omuriliğin çeşitli spinal seviyelerinde görülebilen enflamatuvar bir hastalığıdır. Oldukça nadir rastlanmakla beraber ağır engellilik ve hatta ölüme neden olabilir. Bu çalışmada akut transvers miyelit ile takip edilen bir grup hastanın klinik bulguları, etiyolojide yer alan faktörlerin değerlendirilmesi ve prognoza etkilerinin araştırılması planlandı.

Gereç ve Yöntem: Kliniğimizde Ocak 2012-Aralık 2018 tarihleri arasında yatırılarak incelenen 30 akut transvers miyelit hastası çalışmaya dahil edildi. Hastaların yatış ve taburculuk modifiye rankin skalaları, temel demografik verileri, uygulanan tedaviler, lezyon seviyesi, görüntüleme ve BOS bulguları kayıt edildi.

Bulgular: Hastaların 16'sı erkek (%53), 14'ü (%47) kadındı. Yaş ortalaması 54 (16-84 yıl) bulundu. Vakaların %13.3'ü takipte multiple skleroza dönüşürken, %16.6'sında etiyolojide malignite, % 6.6'sında nöromyelitis optika, % 6.6'sında ise enfeksiyöz patolojiler tespit edildi. Prognoza etkili faktörler cinsiyet, yaş, sfinkter tutulumu eşlikçiliği, BOS proteini, yatış MRS skorunun yüksek olması ve yatış gün sayısı olarak belirlendi (p değerleri sırasıyla p=0.017, p=0.002, p=0.013, p=0.019, p=0.001, p=0.002). Yüksek yatış Rankin skoru ve yatış gün sayısının artışı taburculukta kötü prognozla korele bulundu (r=0.886, p<0.001; r=0.675, p<0.001).

Sonuç: Akut transvers miyelitin etiyolojisinde birçok farklı neden bulunabilmektedir. Tanı kriterlerini tam olarak karşılayan hastalarda dahi takipte multiple skleroza dönüşüm olabilmektedir. Miyelitte uzun süreli takip ve paraneoplastik süreçlerin yer alabileceği akılda tutulmalıdır. Ayrıca prognoz üzerine etkili faktörlerin belirlenmesi uzun vadede hastaların klinik seyrini öngörmede ve tedaviyi yönlendirmede değer taşımaktadır.

Anahtar Kelimeler: Etiyoloji, klinik bulgular, prognoz, transvers miyelit

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INTRODUCTION

Acute Transverse Myelitis is a spinal cord inflammatory disease that can develop from a variety of causes and manifests as a wide range of clinical findings ranging from non-specific mild sensory symptoms to severe paralysis (1). This extremely rare disease has an annual incidence of 1-8/1.000.000. (2). The thoracic spinal cord is the most commonly affected spinal cord region (3).

A variety of factors could be involved in the etiology of acute transverse myelitis. These generally include parainfectious, paraneoplastic, drug/toxin-induced, systemic autoimmune diseases, and acquired demyelinating diseases of the central nervous system (2). When an underlying cause is discovered, it is referred to as secondary transverse myelitis; otherwise, it is referred to as idiopathic transverse myelitis. In 15-30% of the cases, no etiologic cause can be found. Today, the idiopathic group is gradually decreasing as a result of advanced diagnostic tests and increased recognition of NMO (4).

The clinical presentation of acute transverse myelitis syndromes may occasionally cause diagnostic difficulties (1). Back pain, paraparesis, paresthesia, level sensory deficit, and bladder-bowel symptoms are the most common symptoms (3). A thorough history, neurological examination, cerebrospinal fluid (CSF) examination, and neuroimaging are all important in making a diagnosis. CSF examinations play an important role in understanding demyelinating disorders and inflammatory processes (5). Since the condition can cause severe disability, both early diagnosis and effective treatment are important.

The purpose of this study was to retrospectively evaluate the demographic, etiologic, and clinical characteristics of patients with acute transverse myelitis in the light of imaging and laboratory findings, to investigate the underlying pathologies, to examine them in terms of follow-up and treatment, and to determine the associated factors that may affect the prognosis in the short term.

MATERIAL AND METHOD

In this study, 45 medical epicrisis documents of patients between the ages of 16 and 85 years who were hospitalized at Erciyes University, Faculty of Medicine, Department of Neurology between January 2012 and December 2018 and whose neurologic system examination findings were suggestive of inflammatory processes with spinal cord involvement were retrospectively reviewed. Ten patients were excluded from the study because they had previously been diagnosed with MS. Three patients were excluded due to a spinal cord infarction, and two patients were excluded due to existing spinal cord involvement caused by a tumoral lesion. Thirty patients with no prior neurologic symptoms or history and who met the diagnostic criteria for acute transverse myelitis according to the transverse myelitis consortium working group (TMCWG) criteria were included in our study. These diagnostic criteria were as follows: (1)- sensory, motor, or autonomic dysfunction attributable to the spinal cord; (2)- symptoms must be bilateral (not necessarily symmetrical); (3)- clearly defined level of sensory deficit; (4)- progression to the worst level in less than 21 days after onset of symptoms; (5)- T2 hyperintense signal change on neuroimaging (MRI or myelography), brain abnormalities suggestive of MS, and exclusion of extra-axial compressive etiology (6)- pleocytosis or increased Immunoglobulin G (IgG) index in CSF (4).

Patients with MS diagnosed at follow-up were diagnosed according to the 2018 McDonald criteria. MS patients with a first episode of myelitis were included in our study.

Gender, age, presenting complaints, medical history, season of presentation, blood tests, presence of autonomic symptoms, treatments and clinical improvement were all studied retrospectively. The time to diagnosis was defined as the interval between the onset of the first symptom after hospitalization and the clinical diagnosis of ATM. Sphincter involvement was questioned. Lumbar puncture (LP) was performed on all patients. The value of CSF protein, viral serology, oligoclonal band positivity, immune globulin G index, and CSF cytology were all evaluated. Blood tests included serologic tests, vasculitis, celiac disease, and cancer markers in addition to routine complete blood and biochemistry examinations. All patients underwent Aquaporin-4 Antibody IgG test for NMO diagnosis. Viral serology was performed in CSF, and the Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV), Herpes Simplex Virus (HSV Types 1–2), and Varicella Zoster (VZV) were tested. In addition, VDRL and TPHA for Neurosyphilis, Borrelia Burgdorferi IgM for Lyme disease, Neurobrucellosis examinations, as well as CSF PCR, and CSF culture for tuberculosis were performed.

All patients underwent 1.5 T brain and spinal MRI. The location and distribution of lesions, the extent of lesions, the number of involved segments, and the presence of gadolinium contrast enhancement were recorded. A sagittal spinal examination defined long segment spinal involvement as involvement of three or more vertebral segments and short segment spinal involvement as involvement of one or two vertebral segments.

Based on hospitalization and discharge examination findings, the clinical prognosis of the patients was evaluated using the Modified Rankin Scale (MRS). As a result, those with an MRS score of less than 2 were considered to have a good prognosis, while those with an MRS score of 2 or higher were considered to have a poor prognosis.

Approval for the study was obtained from Erciyes University Ethics Committee. (2018/40)

Statistical Analysis

Statistical analyses were performed using the SPSS (Statistical Package for The Social Sciences) program version 26 (Armonk, NY, IBM Corp.,released 2019). Categorical measurements were summarized as numbers and percentages, and numerical measurements as mean and standard deviation (median, minimum, and maximum as needed). A chi-square test was used to compare categorical data. In the comparison of two independent groups, Student's t-test was used for the data fitting the normal distribution, and the Mann-Whitney U test was used for the data not fitting the normal distribution. In correlation analysis, the Pearson correlation coefficient was applied to normally distributed data. The statistical significance value was accepted as $p < 0.05$.

RESULTS

The study included 30 patients, ranging in age from 16 to 84 years old. Sixteen (53%) of the patients were male and 14 (47%) were female. The mean age was 54 years (16-84 years). The average length of hospitalization was 19.73 (7-42) days. **Table 1** displays the basic demographic data for the entire patient group.

Table 1: Basic demographic data of the patients

Variables	N(%)
Age, mean±Std (min-max)	53.3±16.0(16-84)
Days of hospitalization, mean±Std (min-max)	19.7±11.9(7-62)
Season of hospitalization	
Spring	9(30.0)
Summer	11(36.7)
Autumn	4(13.3)
Winter	6(20.0)
Symptom at hospitalization	
Sensory deficit	4(13.3)
Motor deficit	3(10.0)
Both motor and sensory deficits	23(76.7)
CSF protein (mg/dL), mean±Std (min-max)	52.0±32.7(25-170)
CSF glucose, mean±Std (min-max)	76.4±24.4(28-139)
Blood WBC at hospitalization, mean±Std (min-max)	9426±3706(4140-18400)
Blood Hgb at hospitalization, mean±Std (min-max)	12.9±1.7(9,3-16,4)
Blood PLT at hospitalization, mean±Std (min-max)	259.000±92.648(117.000-471.000)
Number of segments retained, mean±Std (min-max)	3.8±2.2(2-10)
MRS score at hospitalization, mean±Std (min-max)	3.5±1.3(1-5)
MRS score at discharge, mean±Std (min-max)	2.6±1.5(0-5)

The average length of stay in the intensive care unit for one patient hospitalized there was 16 days. In terms of hospitalization season, 11(36.7%) patients were admitted during the summer, 9(30%) in the spring, 6(20%) in the winter, and 4(13.3%) in the autumn. The symptoms at hospitalization were motor loss and numbness in 23 patients (76.7%), numbness in 4 patients (13.3%), and motor loss in 3 patients (10%). Loss of strength was symmetrical in 22(73.3%) patients and asymmetrical in 8(26.7%) patients. The average time between symptom onset and admission was 3 months in two patients and 8 (1-15 days) days in the other patients.

Respiratory distress was observed in 1 patient who was hospitalized in the intensive care unit. The patient was in respiratory distress, and the lesion began at the C3 level, was contrast-enhancing, expansile, and extended up to the T8 level. In the following period, the patient's CSF examinations revealed that the condition was associated with TB. The patient had pulmonary involvement. He was extubated and discharged without respiratory distress after receiving appropriate treatment. None of our patients had excitus. Before the disease, four (13.3%) patients had a history of upper respiratory tract infection. Three (10%) patients had autonomic dysfunction. Two of these patients had ileus, and one had orthostatic hypotension. During the subsequent period, one patient who was diagnosed with ileus was later diagnosed with rectal cancer. The other orthostatic hypotensive patient had diffuse medulla spinalis involvement, and the etiology was TB. Sphincter involvement was found in 10 (33.3%) of the patients.

All patients underwent LP. The mean CSF protein value was 52.0 (25-170) mg/dL. The normal CSF protein values in our laboratory were 15–45 mg/dL. Values above 45% were considered high. 10 (33.3%) patients had high protein values. CSF OCD was analyzed in all patients. CSF OCD Type 1 was found in 5 patients, Type 2 in 3 patients, and Type 4 in 1 patient. Anti-aquaporin-4 antibodies were analyzed for NMO and found positive in one patient.

While 4 (13.3%) patients were diagnosed with Multiple Sclerosis, 5 (16.6%) patients were diagnosed with malignancy (1 with laryngeal cancer, 1 with ovarian cancer, 1 with renal cell carcinoma, 1 with metastasis of an undetermined primary, and 1 with lymphoma). Antigliadin antibodies were found to be positive in 1 patient, and celiac disease was diagnosed as a result of further investigations, while Behcet's (beh-CHETS) disease was detected in 1 patient and NMO was detected in 2 patients. In 1 patient, TB infection was identified as the etiologic cause, and in 1 patient, HSC-2 type 2 was. In 15 out of 30 patients, an etiologic cause could be identified (50%).

When screenings were analyzed, it was observed that all patients underwent cranial and spinal magnetic resonance imaging (MRI). Cervical involvement was observed in 4 (13.3%) patients, cervicothoracic in 6 (20%) patients, thoracic in 9 (29.7%) patients, thoracolumbar in 1 (3.3%) patient, lumbar in 8 (26.7%) patients, sacral in 1 (3%) patient and conus medullaris in 1 (3%) patient. Contrast enhancement was observed in 19 (53.3%) patients. An MRI of 2 patients with NMO revealed long segment spinal involvement beginning at C2 and extending to the T3 level. Contrast uptake was present in 1 patient and absent in the other. All 4 patients with MS had short-segment cervical spinal involvement. Contrast uptake was observed in 2 patients. Long segment spinal involvement was detected at various spinal levels in 14 of the remaining 26 patients. Three of these patients were diagnosed with malignancy, one with celiac disease, one with TB, and one with HSV-2. Contrast enhancement was observed in all patients with malignancy.

It was determined that 4 patients received pulse steroid alone, 10 patients continued oral steroid for one month after pulse steroid, 9 patients underwent plasmapheresis due to lack of clinical improvement after pulse steroid, one patient received pulse steroid, then PF, then IVIG, 4 patients underwent plasmapheresis alone, one patient received pulse steroid after IVIG, and one patient continued with oral steroid after IVIG.

Patients were also evaluated with MRS for short-term hospitalization and discharge prognosis. As a result, MRS less than 2 was considered good prognosis, while MRS 2 and above was considered poor prognosis. The parameters that made a significant difference in prognosis were gender, age, parity of sphincter involvement, CSF protein, high hospitalization MRS score, and the number of hospitalization days (p values were p=0.017, p=0.002, p=0.0013, p=0.019, p=0.001, p=0.002, respectively) (**Table 2**).

Table 2: Comparison of variables that may be effective in myelitis prognosis according to the results of the Modified Rankin Scale

Variables	Modified Rankin below 2	Modified Rankin above 2	p
Gender F/M, n (%)	8/1(50/7.1)	8/13(50/92.9)	0.017
Age, mean (SD)	38.7 (4.2)	59.7 (12.4)	0.002
Autonomic Finding Exist, n%)	0(0)	3(14.3)	0.534
Sphincter Involvement Exist, n(%)	0 (0)	10 (47.6)	0.013
History of previous infection exist, n(%)	0 (0)	4 (19)	0.287
Etiology idiopathic, n(%)	3(33.3)	12(57.1)	0.427
CSF protein, mean (SD)	40.7 (11.0)	56.9 (37.6)	0.019
MRS score at hospitalization, mean (SD)	2.0 (0.7)	4.2 (0.8)	0.001
Days of hospitalization, mean (SD)	12.2 (4.7)	22.9 (12.6)	0.002
Number of involved segments, mean (SD)	3.7 (2.2)	4.0 (2.5)	0.814
Contrast-enhanced, n(%)	5(55.6)	12(57.1)	0.936

High hospitalization rankin score and increased number of hospitalization days were correlated with poor prognosis at discharge (Pearson correlation coefficient r=0.886, p<0.001; r=0.675, p<0.001, respectively).

DISCUSSION

The adult age group has a much higher incidence of ATM than the pediatric age group. Approximately 20% of cases are seen in the pediatric age group, while 80% are in adults (6). The mean age of transverse myelitis in our study, which included adults, was 53.3±16.0 years. The mean age in the Chaves et al. study was found to be 45.8 years, 43 years in another study including a large series, and 39.4 years in a study conducted in our country (7,8). The disease shows a bimodal distribution. It tends to peak in the 2nd and 4th decades of life (3).

The study included 30 patients, 16 of whom were male (53%) and 14 of whom were female (47%). In terms of gender, there are comparable rates in the literature. Despite a slight female predominance, the frequency of men and women being affected is close to each other (3). Our patients were mostly hospitalized in the spring and summer seasons. Although no significant seasonal increase in myelitis has been reported, it is known that it may occur more frequently, particularly during the summer and fall (9). While numbness alone (13.3%) and motor deficit alone (10%) were uncommon presenting symptoms, the onset of both motor and sensory deficits was the most common complaint. Only about 15% of cases are expected to have sensory deficits. Both motor and sensory involvement is the most common presentation (10).

Four of our patients had a history of infection in the two weeks preceding the disease, and they all presented with various upper respiratory tract symptoms. Bacterial and viral serologic tests, as well as CSF cultures, were performed on all patients, and TB was detected in 1 patient and HSV-2 was detected in 1 patient. A positive CSF PCR reaction is used in the diagnosis of transverse myelitis due to HSV-2. HSV-2 can cause radiculomyelitis and necrotizing myelitis. It is a very rare etiology of myelitis (11). It is most commonly seen in immunocompromised patients. Our patient was not immunocompromised, so antiviral treatment with acyclovir was continued. Significant clinical improvement was observed. Tuberculosis was discovered, but brain imaging revealed no pathology. However, he had pulmonary involvement and respiratory distress. In addition, CSF glucose was very low and CSF protein was high. CSF was dominated by polymorphonuclear cells. The diagnosis was confirmed by CSF culture. This patient's lesion showed a long spinal involvement in the cervicothoracic region and was edematous and contrast-enhanced. Spinal neurologic manifestations due to

tuberculosis are mostly intramedullary tuberculoma, leptomeningitis, and extradural involvement. Although transverse myelitis is a rare complication of tuberculosis-related neurologic involvement, it should be considered in the differential diagnosis.

Gastrointestinal dysfunction may be observed in myelitis due to the involvement of autonomic pathways. During the acute phase of spinal shock, gastroparesis, paralytic ileus, and acute gastric dilatation may be observed (3). In our series, two patients developed ileus, and one was later diagnosed with colon cancer. Autonomic involvement may also be seen as orthostatic hypotension. If the lesion is large and edematous, the possibility of occurrence increases, particularly in cervical spinal segments above T6. In these patients, a combination of orthostatic hypotension in the acute phase, also known as autonomic dysreflexia, and sudden hypertensive episodes in the later phase may be seen. Meanwhile, a sudden change in heart rate and accompanying piloerection, sweating, and facial flushing may be observed (13). Our patient with orthostatic hypotension had extensive spinal involvement, with an expansile lesion above the T6 level. No cause of myelitis was found in the etiology of this patient.

Urethral and/or anal sphincter involvement was detected in 10 (33.3%) patients. Sphincter involvement is a common complication of transverse myelitis and may persist even after motor recovery (3). According to the report of Cobo Calvo et al., 68% of 85 patients had anal and/or urethral sphincter involvement (14). Sphincter involvement did not occur in any of the MS patients in our study. Of the 10 patients with sphincter problems, 8 had long segment spinal involvement, 3 had cervicothoracic lesions, 4 had thoracic lesions, 1 had conus medullaris, 1 had sacral lesions, and 1 had lumbar lesions.

Three of the three patients with oligoclonal band type 2 positivity were diagnosed with MS. One of our MS patients had an oligoclonal band type 1 detected. Type 2 oligoclonal band positivity in CSF examination was thought to be an important marker in the investigation of MS. NMO was detected in 2 patients and was negative in the other patients. While lesions involving 8 and 9 cervical spinal segments were detected in our patients with NMO, one had contrast enhancement and the other did not. Aside from the NMO patients, 14 others had longer segmental spinal involvement, 6 of whom had no etiologic cause and the others did. Long spinal involvement was thus discovered in a total of 16 patients, with an etiology identified in 8 of them. Long segment spinal involvement is particularly associated with NMO, and NMO is detected in 60% of these cases, according to the literature, and it is emphasized that it is associated with non-idiopathic transverse myelitis in cases where NMO is not found (7). However, only 50% of the long segment spinal involvement in our patient series had an etiology.

Although the TMCWG criteria allow for a more objective diagnosis of myelitis, conversion to MS is expected in around 10% of patients, even in those who fully meet the criteria. The number of cases included in our study was limited, and the follow-up period was brief. Nevertheless, 4 patients were diagnosed with MS during follow-up. Patients who are followed up according to the diagnostic criteria in the studies are expected to show an average of 3–14% MS transformation in a 5-year follow-up, although different rates have been reported in different publications (15).

The rankin scale was noted for short-term prognosis at both hospitalization and discharge. Accordingly, male gender, advanced age, sphincter involvement, high Bos protein level, high MRS scale at admission, and long hospitalization were found to be higher in the poor prognosis group.Many factors have been identified as contributing to a poor prognosis in myelitis. These include motor involvement, rapid progression, relapse, severe functional deficit, sphincter involvement, and involvement of a long spinal segment (15,16,17). The bad prognostic markers discovered in our study back up the literature. When we evaluated the prognosis in terms of long spinal segment involvement, we found a higher MRS score even though there was no statistically significant difference. We discovered no link between the presence of contrast enhancement and progosis. We think that evaluation in large series with a large number of cases will be useful in this regard. In addition, although we could not detect statistical significance in some data, such as the presence of autonomic symptoms, respiratory distress, and a history of previous infection due to the limited number of patients in our study, we found that the discharge MRS score was higher in the presence of these findings.

One of the limitations of our study is that, despite being one of the most important centers where patients with the diagnosis of radiculomyelitis are referred from many cities in the Central Anatolia Region, our hospital is a single center with a limited number of patients. As a result, it can be considered limited in terms of generalizing the data. Nonetheless, it is significant in terms of describing the clinical course and disease characteristics of a group of patients who were hospitalized, followed, and investigated over a long period of time in a single center. Another limitation is that the study was retrospective and evaluated short-term treatment responses, with no long-term regular follow-up examination results.

In conclusion, our study demonstrated that there may be many different causes in the etiology of myelitis, and some markers may guide the prognosis. The number of spinal segments and the location of the lesion, as well as CSF findings, were among the markers in our case series that shed light on the transformation to MS and

NMO during the follow-up period. Another important point has been paraneoplastic processes in the etiology of myelitis. Our case series demonstrated that different types of underlying malignancies may cause similar myelitis symptoms, and that long-term follow-up and detailed examinations are critical for early diagnosis and treatment in this patient group. In this regard, large-scale multicenter epidemiologic studies are required.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was obtained from Erciyes University Ethics Committee (2018/40).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Does Carpal Tunnel Syndrome Affect Disease Activity in Patients with Fibromyalgia?

Karpal Tünel Sendromu Fibromiyaljili Hastalarda Hastalık Aktivitesini ve Yaşam Kalitesini Etkiler mi?

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ABSTRACT

Aim: A high prevalence of carpal tunnel syndrome (CTS) in patients with fibromyalgia has been reported and this seems to affect patients' quality of life. This study aimed to investigate whether there is any relationship between disease activity and quality of life (QoL) in fibromiyalgia patients with CTS and electrophysiological and ultrasonographic measurement values.

Material and Method: The cross-sectional study included 102 fibromyalgia patients with CTS symptoms and 102 healthy control subjects. Tender Points Count, Pain Location Inventory, and Symptom Impact Questionnaire were recorded for the FM group. Overall disease impact was assessed with the Fibromyalgia Impact Questionnaire and quality of life with the Nottingham Health Profile. The median nerves of all participants were evaluated electrophysiologically and ultrasonographically. The electrophysiological and ultrasonographic measurements were compared between the groups, then the electrophysiological and ultrasonographic measurements of the fibromyalgia patients were compared with disease activity and QoL.

Results: Compared to the control group and the fibromyalgia group with no CTS determined electrophysiologically, the distal median nerve was found to be enlarged in the fibromyalgia group on ultrasonography (p=0.001). The distal median nerve area was determined as a factor with an effect on QoL and disease severity (p=0.037, p=0.041).

Conclusion: Fibromyalgia patients with CTS symptoms but electrophysiologically normal results can be evaluated with US. CTS severity affects quality of life and disease severity in fibromyalgia. These results, which have been previously shown electrophysiologically, are now supported by US. Further studies are required to confirm these results.

Keywords: Fibromyalgia, quality of life, carpal tunnel syndrome, electrophysiology, ultrasonography

ÖZ

Amaç: Fibromiyalji ve karpal tünel sendromu birlikteliği sık görülmektedir ve bu durumun hastaların yaşam kalitesini etkilediği düşünülmektedir. Bu çalışmada, karpal tünel sendromu olan fibromiyalji tanılı hastalarda elektrofizyolojik ve ultrasonografik ölçüm değerleri ile hastalık aktivitesi ve yaşam kalitesi arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya karpal tünel sendromu semptomları olan 102 fibromiyalji hastası ve 102 sağlıklı kontrol katıldı. Fibromiyalji grubu için hassas nokta sayımı, ağrı yeri envanteri ve semptom etki anketi kaydedildi. Hastalık aktivitesi Fibromiyalji Etki Anketi ile, yaşam kalitesi ise Nottingham Sağlık Profili ile değerlendirildi. Tüm katılımcıların median sinirleri elektrofizyolojik ve ultrasonografik olarak değerlendirildi. Gruplar arasında elektrofizyolojik ve ultrasonografik ölçümler karşılaştırıldı, ardından fibromiyalji hastalarının elektrofizyolojik ve ultrasonografik ölçümleri hastalık aktivitesi ve yaşam kalitesi ile karşılaştırıldı.

Bulgular: Elektrofizyolojik olarak karpal tünel sendromu saptanmayan fibromiyalji grubu ve kontrol grubu hastaları karşılaştırıldığında, ultrasonografide fibromiyalji grubunda distal median sinir alanının genişlemiş olduğu görüldü (p=0.001). Ayrıca distal median sinir alanı, yaşam kalitesi ve hastalık şiddetini etkileyen bir faktör olarak belirlendi (p=0.037, p=0.041).

Sonuç: Karpal tünel sendromu semptomları olan ancak elektrofizyolojik bulguları normal olan fibromiyalji hastaları ultrasonografi ile değerlendirilebilir. Karpal tünel sendromu şiddeti, fibromiyaljide yaşam kalitesini ve hastalık şiddetini etkilemektedir. Daha önce elektrofizyolojik olarak gösterilen sonuçlar ultrason bulguları ile desteklenebilir. Bu sonuçları doğrulamak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Fibromiyalji, yaşam kalitesi, karpal tünel sendromu, elektrofizyoloji, ultrasonografi

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INTRODUCTION

Fibromyalgia (FM) is a rheumatic disease of the soft tissues, the etiology of which isnot exactly known. It is characterized by widespread musculoskeletal pain and tender points, sleep disturbance, morning stiffness, fatigue, irritable bowel syndrome, complaints of paresthesia, pain and a subjective sense of swelling in the hands, as well as frequent psychological distress (1). Paresthesia and sensory alterations are seen in 80% of patients diagnosed with FM (2). Although the mechanism of this symptom in FM is not exactly known, paresthesia is thought to be a result of abnormal sensory perception occurring due to central sensitization (3).

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy and has been reported to affect one in ten people (4). It is caused by compression of the median nerve inside the carpal tunnel in the wrist region as it passes through the carpal tunnel leading to changes in the endoneural blood flow, oedema formation, and ultimately ischemia and nerve injury (5). CTS is generally characterised by sensory abnormalities including neuropathic pain symptoms such as paresthesia and dysesthesia, numbness, tingling and hyperalgesia (6).

Electrodiagnostic testing is currently considered the gold standard for confirmation of a clinical diagnosis of CTS, but nerve conduction studies (NCS) remain normal in 15% of patients with characteristic clinical features of CTS (7).

Ultrasonography (US) has been shown to be a useful diagnostic tool in CTS (8), with reports in literature showing that the median nerve cross-sectional area (CSA) in the wrist is strongly associated with clinical and electrophysiological severity (9).

There are some studies on the co-existence of these two diseases, which have similar symptoms and affect the same age and gender group, but these studies have only evaluated CTS electrophysiologically (10,11).

The first aim of this study was the evaluation of the median nerve with electrophysiological and ultrasonographic measurement methods in patients with FM with complaints of paresthesia and weakness in the hands and investigate the relationship between these measurement results and disease activity and quality of life. The other aim of this study was to compare electrophysiological and ultrasonographic measurements in FM patients with no CTS and in control group with no CTS.

MATERIAL AND METHOD

Participants

The cross-sectional study included 102 patients attending our outpatient clinic with complaints of CTS such as paresthesia and weakness in the hands between 2019 and 2020, who were diagnosed with FM according to the American College of Rheumatology (ACR) 2013 diagnostic criteria (12), and 102 age-and gender, body mass index (BMI), and education status-matched healthy control subjects with convenience sampling method.

The voluntary participants in the control group were selected from staff and the relatives and/or caregivers of the patients without any musculoskeletal symptoms or signs. Patients <18 years and >65 years of age and with a history of inflammatory, autoimmune, endocrine, severe renal disease, central nervous system disease were excluded from the study. Patients with a history of trauma, surgery, ganglion cyst, tenosynovitis, tendinitis, peripheral nerve damage or radiculopathy and patients treated with drugs for FM and vitamin deficiency were also excluded. Pregnant and nursing women were not included in the study.

The study protocol was approved by the Local Ethics Committee (Date: 07.01.2019 No:58/23) and all procedures were performed in compliance with the Helsinki Declaration. The protocol was explained to all the study participants, and informed consent was obtained at the beginning of the study.

Demographic characteristics

Age, gender, dominant hand, BMI and education status of both the FM group and the control group were recorded. Education status was classified in 5 groups as illiterate, literate, 5 years education, 8 years education, 11 years education, and more than 11 years education.

Clinical parameters

Symptomatic hand, comorbid diseases, duration of disease, Tender Points Count (TPC), Pain Location Inventory (PLI), and Symptom Impact Questionnaire (SIQR) were recorded for the FM group. Overall disease impact was assessed with the Fibromyalgia Impact Questionnaire (FIQ) and quality of life with the Nottingham Health Profile (NHP).

TPC (tender point count) was determined by applying pressure of <4 kg to 18 symmetrical points on both sides of the body. If the participants felt pain, the tender point was considered positive. The total number of tender points was recorded as the TPC score. The maximum score of TPC was 18 (13).

The PLI score was recorded as the number of the pain locations of 28 points (jaw, neck, mid-upper back, front of chest, mid lower back, upper back, lower back, shoulders, arms, hands, wrists, hips, thighs, knees, ankles, feet) over the past 7 days (0-28) (12).

SIQR evaluates the intensity of 10 common symptoms (pain, energy, stiffness, sleep, depression, memory, anxiety, tenderness, balance, sensitivity to loud noises,

bright lights, odors and cold) over the last 7 days. Each symptom is scored between 0-10, and the total score range is 0-100) (13).

FIQ is a self-reported questionnaire which assesses the impact of FM symptoms on the physical and mental health of patients. Physical impairment, number of days feeling good, work missed, ability to do work, pain, fatigue, rest, stiffness, anxiety, and depressive symptoms are measured with the FIQ. Each subscale has a maximum score of 10, and these are added to give the total score, with higher scores indicating a negative impact (0-100) (14).

NHP was used to evaluate the quality of life in patients. NHP is a patient-reported scale, comprising 38 items and 6 subscales: physical mobility (8 questions), pain (8 questions), sleep (5 questions), emotional reactions (9 questions) social isolation (5 questions), and energy level (3 questions). It measures the distress of patients in physical, emotional, and social domains (15).

Electrophysiological evaluation

Both the FM group and control group underwent motor and sensory NCS of the median and ulnar nerves, using Medelec Synergy 10 channel ENMG (Oxford, U.K.) equipment applied by the same observer. The NCS were performed using the technique described by Oh S (16). The upper extremities were placed in a relaxed and comfortable position with the arm extended, palm up. Sensory nerve action potential (SNAP), sensory nerve velocity (Vsens), common nerve action potential (CMAP), distal motor latency (DML), and motor nerve velocity (Vmotor) were measured using supramaximal stimulation and surface electrode adjustment for skin temperature. CTS was diagnosed electrophysiologically if the median sensory velocity recorded from digit 2 was <41.25 m/s, common nerve velocity recorded from the palm was <34 m/s or the median DML measured from the beginning of the stimulus artifact to the onset of the action potential by stimulating the median nerve at the wrist (5 cm proximal to the active recording electrode placed on the abductor pollicis brevis muscle) was >3.6 ms. The severity of CTS was evaluated in three groups as mild, moderate, or severe. Mild CTS was defined as decreased sensory nerve velocity (with or without SNAP below the lower standard limit, no conduction block or mild conduction block, and no thenar electromyography (EMG) abnormalities (if tested). Moderate CTS was defined as abnormal median sensory velocity as above and (relative or absolute) prolongation of the DML, conduction block may be present, and minor thenar EMG abnormalities may be present; Severe CTS was defined as decreased median CMAP and sensory nerve velocity, with either an absent SNAP or mixed NAP, or a low-amplitude or absent thenar CMAP, conduction block may be present, and thenar EMG abnormalities are often present (17).

Ultrasound evaluation

All ultrasound evaluations were performed by the same experienced observer using a high resolution 12 mHz linear probe (GE Logiq P5, General Electric Korea). After all participants were positioned with the arm in extension, forearm in supination and wrist in a supine neutral position, CSA was measured at two different levels using a continuous tracing method along the inner border of the epineurium (18). Proximal CSA of the median nerve was measured at the radiocarpal joint, and the distal CSA of the median nerve was measured at the level of the proximal carpal bones.

Comparisons

Electrophysiological and ultrasonographic evaluations of both extremities were applied to all the subjects in both the FM and control groups by the same physician on the same day. In the FM group, the electrophysiological, and ultrasound results were compared with clinical parameters, disease severity and quality of life.

Statistical analysis

The power of the study was calculated using the G Power 3.1.8 analysis method. The minimum number of participants required for a 15% change in the fibromyalgia impact questionnaire was 98 for each group.(at 80% power level, statistical significance $p<0.05$). The study was planned with a minimum of 196 participants, 98 patients in each group.

Data obtained in the study were analyzed statistically with SPSS vn.25.0 software. Descriptive statistics were presented as mean±standard deviation for continuous variables and percentages (%) for nominal variables. The Kolmogorov-Smirnov test was used to assess the conformity of data to normal distribution. In the comparisons between the groups, mean values were compared with the Independent simple t-test for continuous variables. Fisher's Exact test was used to compare categorical values between groups. Correlations between electrophysiological and ultrasound evaluations and clinical parameters were analyzed with the Pearson's correlation test. Then a simple linear regression analysis was applied for statistical significance. (Dependent variable: median nerve distal CSA) (Independent variable; sleep subscale and total scores of SIQR, FIQ, energy, sleep subscales and total score of NHP). Accordingly, the regression equation model was created as $y= mx+b$ (m=slope, b=intercept). m and b values were calculated with the Least squares estimation (19). Values of $p<0.05$ were considered statistically significant.

RESULTS

The demographic characteristics of the FM and control groups are presented in **Table 1**. All participants in both

the FM (n=102) and control groups (n=102) were female. The mean age of the FM group was 44.50±8.31 years and the mean age of the control group was 46.10±5.65 years. There was no significant difference between the two groups in respect of gender, age, dominant hand, education status and BMI (p>0.05).

Table 1. Comparison of demographic characteristics of FM and control group

Demographic Parameters	FM Group n=102	Control Group n=102	P
Age (years)mean±SD	44.50±8.31	46.10±5.65	0.07**
Dominant hand n (%)			0.74*
Right	97 (95.1)	99 (%97.1)	
Left	5 (4.9)	3 (2.9)	
Education status n (%)			0.22*
Not illiterate	0	3 (2.9)	
Literate	4 (3.9)	8 (7.8)	
5 years education	68 (66.7)	63 (61.8)	
8 years education	10 (9.8)	18 (17.6)	
11 years education	13(12.7)	7 (6.8)	
Over 11years education	7 (6.9)	3 (2.9)	
BMI (kg/cm2)mean±SD	29.11±7.34	27.58±4.61	0.07**

SD:Standard deviation, BMI:body mass index, FM: Fibromyalgia *= Fisher's Exact test, **=Independent simple T test,

The clinical parameters and quality of life scores of the FM group are shown in **Table 2**. In the FM group, all participants complained of paresthesia and weakness in both the right and left hands. Electrophysiological examinations were performed on 204 hands of 102 FM patients and 204 hands of the control group. Normal electrophysiological studies were detected in 93 (45.6%) hands in the FM group. Mild CTS was determined in 77 (37.7%) hands and moderate CTS in 34 (16.7%) hands in the FM group. There was no patient with severe CTS in the FM group according to the electrophysiological studies. Although there were no complaints of paresthesia and weakness in the control group, CTS was detected in 3 hands in the control group. Therefore, the study continued with 201 hands in the control group.

The comparisons of the electrophysiological and ultrasound evaluation results between the groups are shown in **Table 3**. The values of median SNAP, median Vsens, median DML, proximal CSA median, distal CSA median were determined to be significantly different between the two groups (p=0.012, p=0.018, p=0.015, p=0.001, p=0.001, respectively).

The clinical parameters and quality of life showed no significant difference between those without CTS, or with mild CTS and moderate CTS in the FM group (p>0.05) (**Table 4**).

Compared to the healthy control group and FM patients with CTS symptoms but electrophysiologically normal results, the distal CSA on USG was found to be wider in the FM group (p=0.001) (**Table 4**).

Table 2. Disease characteristics in FM group

Parameters	FM Group n=102 mean±SD
Disease duration (years)	2.19 ±1.65
Tender Point Count (0-18)	14.79 ±3.45
Pain location inventory	24.99±5.69
Symptom Impacy Questionare (0-10 cm)	
Pain	6.95 ±1.72
Energy	6.39 ±2.07
Stifness	5.45 ±2.48
Sleep	6.03 ±3.16
Depression	4.80 ±2.96
Memory	5.42 ±2.84
Anxiety	5.38 ±3.19
Tenderness	5.06 ±3.17
Balance	3.35 ±2.94
Enviromental sensivity	6.23±2.69
Total score	28.83 ±12.05
Fibromiyalgia Impact Questionnare	59.27 ±15.90
Nottingham Health Profile	
Pain	72.66 ±27.01
Energy	81.10 ±21.15
Sleep	40.69 ±35.36
Physical mobility	34.45 ±19.33
Emotionalreaction	50.16 ±26.83
Social isolation	29.99 ±32.45
Total score	51.33 ±16.07

SD:Standard deviation, FM: Fibromyalgia

Table 3. Comparison of electrophysiologic and ultrasound measurement values between FM and control group

Parameters	FM Group n=204 mean±SD	Control Group n=201 mean±SD	P*
Median SNAP (μV)	44.81±15.51	47.15±11.67	0.012
Median Vsens (m/s)	39.86±5.05	44.27±6.11	0.018
Median CMAP (mV)	10.77±2.84	12.24±2.64	0.012
Median DML (ms)	3.01±0.75	2.55±1.02	0.015
Median Vmotor (m/s)	59.83±6.04	58.68±7.12	0.093
Proximal CSA median (cm2)	0.25±0.26	0.10±0.03	0.001
Distal CSA median (cm2)	0.23±0.27	0.09±0.06	0.001

SD: Standard deviation, , μV=mikrovolt, mV=milivolt, cm2:square centimeter, m/s: meter/second, ms: millisecond FM: fibromiyalgi, SNAP: sensory nerve action potential, Vsens: sensorial nerve conduction velocity, CMAP: compound nerve action potential, DML:distal motor latency, Vmotor: motor nerve conduction velocity, CSA: cross section area, p*: Paired simple T test, Bold p values are statistical difference

Table 4: Comparisons between control and FM group with normal electrophysiology (No CTS)

Parameters	FM group (No CTS) n=93 hands mean±SD	Control Group n=201 hands mean±SD	p
Median SNAP(μV)	46.50±12.54	47.15±11.67	0.822*
Median Vsens(m/s)	43.07±6.17	44.27±6.11	0.561*
Median CMAP (mV)	11.60±2.36	12.24±2.64	0.128*
Median DML (ms)	2.64±0.42	2.55±1.02	0.643*
Median Vmotor(m/s)	58.71±4.60	58.68±7.12	0.939*
Proximal CSA median (cm2)	0.11±0.01	0.10±0.03	0.548*
Distal CSA median (cm2)	0.15±0.08	0.09±0.06	0.013*

SD: standard deviation, μV= mikrovolt, mV= milivolt, cm2:square centimeter, m/s: meter/second, ms: millisecond FM:fibromiyalgia, CTS:carpal tunnel syndrome, SNAP: sensory nerve action potential, Vsens: sensorial nerve conduction velocity, CMAP: compound nerve action potential,DML:distal motor latency Vmotor: motor nerve conduction velocity, CSA: cross section area, p*: Paired simple T test, Bold p values are statistical difference

Correlations of the electrophysiological and ultrasound findings with clinical parameters and quality of life in the FM group are shown in **Table 5**. There were no significant correlation between disease characteristics and, electrophysiologic severity and proximal CSA in FM group (p>0.05). Positive moderate correlation was detected between distal CSA and sleep subscale and total scores of SIQR, FIQ, energy, sleep subscales and total score of NHP (p<0.05).

Table 5: Correlation of electrophysiologic and ultrasound values with disease evaluation parameters in FM Group

Parameters	Electrophysiologic severity		Proximal CSA		Distal CSA	
	r	P*	r	P*	r	P*
Disease duration (years)	0.102	0.697	0.361	0.339	0.190	0.555
Tender Point Count (0-18)	0.136	0.377	0.244	0.527	0.424	0.215
Pain location inventory	0.227	0.381	0.277	0.471	0.239	0.352
FIQ	0.231	0.889	0.488	0.220	0.515	0.045
Nottingham Health Profile						
Pain	0.088	0.745	0.335	0.417	0.369	0.176
Energy	0.031	0.910	0.494	0.214	0.513	0.041
Sleep	0.266	0.320	0.272	0.328	0.692	0.047
Physical mobility	0.470	0.066	0.511	0.195	0.147	0.600
Emotional reaction	0.031	0.910	0.494	0.214	0.204	0.466
Social isolation	0.055	0.839	0.825	0.094	0.429	0.110
Total score	0.070	0.795	0.633	0.049	0.154	0.044
SIQ (0-10 cm)						
Pain	0.112	0.668	0.293	0.445	0.369	0.159
Energy	0.458	0.064	0.146	0.708	0.128	0.636
Stifness	0.165	0.526	0.322	0.399	0.387	0.138
Sleep	0.124	0.636	0.074	0.785	0.658	0.048
Depression	0.361	0.236	0.191	0.622	0.162	0.550
Memory	0.090	0.730	0.169	0.664	0.230	0.391
Anxiety	0.057	0.828	0.166	0.669	0.109	0.688
Tenderness	0.406	0.106	0.400	0.287	0.390	0.136
Balance	0.254	0.326	0.390	0.327	0.400	0.125
Enviromental sensivity	0.059	0.823	0.271	0.480	0.124	0.647
Total score	0.637	0.124	0.399	0.287	0.442	0.046

FM: Fibromyalgia, FIQ: Fibromiyalgia Impact Questionnaire, SIQ: Symptom Impacy Questionnare r: correlation coefficient, *: Pearson's correlation test

According to the regression analyses, an increase in the SIQR total score and high disease severity were factors effective on increasing distal CSA (p=0.037, p=0.041). (**Table 6**)

Table 6: Simple Linear Regression Analysis between Median Nerve distal CSA and sleep

	R2	B	SE	95%CI (lower-upper) for B	p
Sleep (SIQR)	0.186	1.714	0.569	0.584-2.843	0.037
Total SIQR score	0.067	0.860	0.367	0.072-1.647	0.058
FIQ	0.189	2.561	0.836	0.901-4.220	0.041
Energy (NHP)	0.263	0.923	0.337	0.506-1.461	0.052
Sleep (NHP)	0.074	0.402	0.157	0.063-0.742	0.124
Total NHP score	0.021	0.337	0.379	0.482-1.157	0.190

CSA: cross section area, SIQ: Symptom Impacy Questionnare, FIQ: Fibromiyalgia Impact Questionnaire, NHP: Nottingham Health Profile, R2 : R squared, B:unstandardized regression coefficient, SE:coefficients standard error, CI: confidence interval.

DISCUSSION

This study was designed to evaluate the median nerve with electrophysiological and ultrasonographic measurement methods in FM patients with complaints of CTS symptoms and to investigate if these results had an effect on disease activity and quality of life.

No matter how much contradictory data have been published in recent years, there are increasing numbers of studies reporting a correlation between FM and CTS. Some studies have supported the idea that the rate of CTS is higher in patients with FM compared with that in the normal population (20).

However, Sarmer et al reported CTS at the rate of 10% in FM patients and 4% in control subjects, and the difference did not reach statistically significant levels (21). In another study, electrodiagnostic findings of CTS were detected in 24% of FM subjects and in %29 of the control group (22). Silva et al. studied CTS with ultrasonography only in 41 FM patients and 42 healthy control subjects and found no statistically significant difference between the groups, and concluded that it would be difficult to clinically distinguish FM patients with CTS from those without it (23). The high prevalence of CTS in the fibromyalgia population is thought to be associated with the common underlying mechanisms. Currently, there is no study explaining the mechanisms of why CTS is frequently seen in patients with fibromyalgia. CTS is an associated condition that represents the peripheral nociceptive mechanisms in fibromyalgia. Although the dominant mechanism in fibromyalgia is thought to be central sensitization, peripheral nociceptive mechanisms such as peripheral ischemia, microtrauma, and increased nociceptor activity can lead to central pain sensitization (24).

Unlike other studies, in the current study, CTS was evaluated both electrophysiologically and ultrasonographically. The results of this study showed that compared to the healthy control group, the distal CSA measured on USG was significantly larger in patients who had CTS symptoms but were electrophysiologically evaluated as normal.

This could be attributed to the common pathophysiology of CTS and FM. In a study by Chinn et al, it was reported that cytokines and chemokines led to the neuroinflammation, which can be described as classic (involving a mechanical nociceptive stimulus) or neurogenic in FM (25). In a study that investigated the immune profile of patients diagnosed with CTS and compared with healthy control subjects, Moalem-Taylor et al found that CTS is associated with an increase in systemic inflammatory modulating cytokines/chemokines, which potentially regulate neuropathic symptoms. In addition, a significant relationship was found between CTS severity and serum levels of inflammatory mediators (26). There may be

another reason for this result. In the literature, it has been shown that electrodiagnostic testing for CTS may be normal in some patients who have typical clinical features of CTS, but sonographic abnormalities (diagnostic of CTS) may be seen in up to 50% of this population. Borrire et al evaluated the differences in sonographic parameters of CTS patients with normal and mildly abnormal NCS. Evaluation was made of 169 wrists (101 patients) with a clinical diagnosis of CTS, and 40 wrists of 20 healthy control subjects. 49 wrists were classified as mild NCS-positive and 38 as NCS-negative based on the laboratory NCS normal values. It was found that 26% of the NCS-negative group had abnormal CSA and the CSA also differed significantly between the two groups (27).

Another study proved that the rate of undiagnosed CTS in women with FM is much higher than that reported in the general population (28). Therefore, it can be recommended that symptomatic patients should be evaluated ultrasonographically in addition to electrophysiologically.

In this study, the majority of patients diagnosed with CTS electrophysiologically were of mild severity, and there were no patients with severe CTS. This could be due to the fact that electrophysiological findings do not have a significant relationship with other parameters. However, low Vsens and CMAP, which are sub-parameters of NCS, are associated with increased CTS severity. These sub-parameters were found to have an effect both on the increase in the pain subscale of quality of life and disease severity.

The median CSA size has been found to be an effective factor on the SIQR total score and high disease severity. In a study by Fahmi et al. electrophysiological evaluation was made of 40 FM patients and 60 healthy control subjects and the frequency of CTS was found to be higher in the FM patients than in the control group. That study also reported a highly statistically significant correlation between the severity of CTS and the FIQ scores of FM patients (29). The correlation between electrophysiological findings and disease severity and pain scores in the current study was similar to these previous results.

To the best of our knowledge, this is the first study to have evaluated FM patients with CTS symptoms with both US and NCS in respect of disease severity and quality of life.

This study had some limitations. First was that only patients with CTS symptoms were included in the patient group and asymptomatic subjects in the control group. Secondly, it is an important deficiency that the occupational status of the participants is not questioned. Because, occupational status is an important factor in the etiology of CTS. Another limitation was that this study did not contain long-term follow-up of FM patients.

CONCLUSION

CTS is more frequent in patients with FM than in the normal population. FM patients with CTS symptoms but electrophysiologically normal results can be evaluated with US. CTS severity affects quality of life and disease severity in fibromyalgia. These results, which have been previously shown electrophysiologically, are now supported by US. Further studies are required to confirm these results.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the University/local human research ethics committee (Date: 07.01.2019, Decision No: 58/23).

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

Referee Evaluation Process: Externally peer-reviewed.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Long-Term Prognostic Evaluation of Patients Presenting to the Emergency Department with a Pre-Diagnosis of Sepsis

Acil Servise Sepsis Ön Tanısı İle Başvuran Hastaların Uzun Dönem Prognostik Değerlendirilmesi

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ABSTRACT

Aim: The aim of this study was to evaluate the 90-day post-discharge mortality and rehospitalization rates of patients hospitalized in the emergency department with a preliminary diagnosis of sepsis.

Material and Method: Among the patients who applied to our hospital's emergency department between January 1, 2020 and January 1, 2022 with fever, chills, shivering, confusion, nausea and vomiting, patients over the age of 18 who met the criteria for sepsis-3 and were hospitalized or referred to the intensive care unit were included in the study. Age, gender, acute physiological and chronic health evaluation scores of the cases meeting these diagnostic criteria were recorded.

Results: 176 patients were admitted to the Emergency Department with the diagnosis of sepsis 58.44% (n=137) of the patients were male and 41.56% (n=39) were female. 15.78% (n=28) of 176 patients died in the emergency department, 32.44% (n=57) died after ICU admission, and 26.44% (n=47) were discharged.

Conclusion: This study shows that all patients need professional care within 90 days of intensive care discharge. It may be recommended to establish a separate unit in the hospital on this subject.

Keywords: Sepsis, emergency service, prognosis, post discharge care

ÖZ

Amaç: Bu çalışmanın amacı, sepsis ön tanısı ile acil servise yatırılan hastaların taburculuk sonrası 90 günlük mortalite ve yeniden yatış oranlarını değerlendirmektir.

Gereç ve Yöntem: Hastanemiz acil servisine 1 Ocak 2020-1 Ocak 2022 tarihleri arasında ateş, titreme, titreme, konfüzyon, bulantı ve kusma şikayetleri ile başvuran hastalardan sepsis kriterlerini karşılayan 18 yaş üstü hastalar; 3 hastaneye yatırılan veya yoğun bakıma sevk edilenler çalışmaya dahil edildi. Bu tanı ölçütlerini karşılayan olguların yaş, cinsiyet, akut fizyolojik ve kronik sağlık değerlendirme puanları kaydedildi.

Bulgular: Acil Servise sepsis tanısı ile başvuran 176 hasta %58,44 (n=137) erkek, %41,56 (n=39) kadındı. 176 hastanın %15,78'i (n=28) acil serviste, %32,44'ü (n=57) yoğun bakım ünitesine kabul edildikten sonra öldü ve %26,44'ü (n=47) taburcu edildi.

Sonuç: Bu çalışma, tüm hastaların yoğun bakımdan taburcu olduktan sonraki 90 gün içinde profesyonel bakıma ihtiyacı olduğunu göstermektedir. Bu konuda hastanede ayrı bir birim kurulması önerilebilir.

Anahtar Kelimeler: Sepsis, acil servis, prognoz, taburculuk sonrası bakım

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INTRODUCTION

Sepsis is a chain of reactions of the body against the infection that prevents the functioning of more than one organ, which develops due to the infection, can go as far as shock (1-3).

Shock is circulatory failure that causes an imbalance between tissue oxygen demand and oxygen transported to the tissue. Whatever the cause, this situation, which develops as a result of hypoperfusion, results in cellular dysfunction (4).

The causes of shock in patients who apply to the emergency department and have shock symptoms at the time of admission or during follow-up should be quickly identified and treatment should be initiated for the cause (5,6).

Most patients who survive sepsis have neuromuscular weakness, persistent neurocognitive deficits, symptoms of depression, and poor quality of life. (7-11). With the developments in health and the increase in hospital modernization, sepsis have become a disease that can be diagnosed quickly and can be cured with early interventions. Of the surviving cases; The rates of admission to health institutions and re-hospitalizations are high due to reasons such as newly developed sepsis-related organ failure, relapse or newly developed infections, planned controls, together with existing comorbidities (12).

Although studies on sepsis is increasing in our country, there is not enough information about post-survival. In our study, we aimed to evaluate the 90-day mortality and rehospitalization rates after discharge of patients hospitalized in the emergency department with a preliminary diagnosis of sepsis.

MATERIAL AND METHOD

This study was approved by the University/local human research ethics committee (Date: 16.06.2022, Decision no: 0349). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

Our study was carried out retrospectively and observationally in a single center in a tertiary university hospital. For the study, patients who were diagnosed with sepsis in the emergency department of our hospital between January 1, 2020 and January 1, 2022 and meeting the study criteria were included.

Among the patients who applied to our hospital's emergency department between January 1, 2020 and January 1, 2022 with fever, chills, shivering, confusion, nausea, and vomiting, patients over the age of 18 who met the criteria for sepsis-3 and were hospitalized or referred to the intensive care unit were included in the study (13). Cases under the age of 18, pregnant, hospitalization diagnosis other than sepsis were not included in the study.

Age, gender, Acute Physiology And Chronic Health Evaluation Score II (APACHE II), estimated mortality rate, Glasgow Coma Score (GCS), SOFA score, serum lactate level, and C-reactive protein (CRP) values were recorded. By examining the patient registration documents, the number of days of intensive care hospitalization, whether mechanical ventilator (MV) support was available, the number of MV days if MV was needed, the type of ICU discharge (exit, discharge, transfer to another clinic, transfer to the palliative care unit) were recorded.

Sepsis-related organ failures of the survivors were examined. For patients discharged from the hospital; Using the hospital patient registration and information system (Probel), re-admissions to the hospital due to sepsis-related conditions within 90 days after ICU discharge were checked, the reasons for coming back to the hospital, re-admissions to the ICU, if any, and the number of days of hospitalization were recorded. Patients who were not registered in the patient registry and information system after discharge from ICU were called by phone and their health status (living/deceased) at 30 and 90 days after discharge, their application to health institutions and their re-admissions to ICU were questioned. The data were recorded in the SPSS (Statistical Package for the Social Sciences Inc.) program and statistical analyzes were made.

RESULTS

Between 01 January 2020 and 01 January 2022, 176 patients were admitted to the Emergency Department with the diagnosis of sepsis. 57.95% (n=102) of the patients were male and 42.05% (n=74) were female.

When the prognoses of the patients who entered the shock state were examined, 15.78% (n=28) of 176 patients died in the emergency department, 32.44% (n=57) died after ICU admission, and 26.44% (n=47) were discharged. Outcome information was not available for 25.33% (n=44) due to referral.

The pathologies that cause shock in the sepsis patients included in the study are shown in the table. Accordingly, pneumonia was the most common underlying cause in shock patients with a rate of 36.36% (n=64). When we examined the other underlying causes of shock, 17.04% (n=30) had urinary tract infection (UTI), 9.09% (n=16) gastroenteritis, 8.52% (n=15) soft tissue infection, 7.95%. (n=14) oral intake disorder, 3.97% (n=7) trauma, 1.70% (n=3) anaphylaxis, 1.13% (n=2) gastrointestinal system bleeding, and 14.20% (n=25) appear to be other causes (**Table 1**).

Table 1. Etiological comparison of sepsis status		
Disease Causing Sepsis	**%**	**n (number of patients)**
Pneumonia	36.36	64
Urinary tract infection	17.04	30
Oral intake disorder	7.95	14
Trauma	3.97	7
GI bleeding	1.13	2
Gastroenteritis	9.09	16
Soft tissue infection	8.52	15
Anaphylaxis	1.70	3
Other	14.20	25

The data of 132 patients who were not referred but whose outcome information could be accessed were analyzed. According to these data, the survival rate was 35.41% (n=47), and 64.58% (n=85) of the cases died. The age of surviving patients was 66.4±13.4, while those who died were 71±10.6 years. A significant correlation was found between advanced age and mortality (p=0.021). Although the GCS score was 10.9±4.3 in surviving patients and 7.1±5.1 in patients with ex, GCS was found to be correlated with survival (p=0.018). The APACHE II score was found to be 21.7±6.9 in survivors and 34.1±9.2 in those who died, and it was associated with mortality (p=0.026). The SOFA score, lactate and CRP values calculated at the time of hospitalization of the patients were found to be statistically significantly higher in patients with ex (p<0.001) (**Table 2**).

Table 2. Effect of some parameters on mortality			
	Survivor (n=47)	**Exitus (n=85)**	**p**
Age	66.4±13.4	71±10.6	0.021
GCS	10.9±4.3	7.1±5.1	0.018
SOFA	5.9±2.7	10.7±3.3	<0.001
APACHE II	21.7±6.9	34.1±9.2	0.026
Lactate	3.3±2.1	8.4±5.2	<0.001
CRP	113±46.7	221±61.9	<0.001

When the antecedents of all patients are evaluated; It was observed that 89.1% of the cases had at least 1 chronic disease. DM was detected in 39.1%, CHF in 15.7%, COPD in 22.8%, CAD in 19%, CRF in 13.9%, HT in 30.4%, and CVO in 21.5%. In the evaluation of the patients who were admitted to the hospital again after discharge, DM is the most common with 41% and HT is the second with 24% in terms of comorbidity, followed by CHF in the third place. When we look at the re-admission rates of the patients, general condition disorder and oral intake disorder are the most common reasons for admission (33% CRF).

If we look at the 90-day re-admissions of the discharged patients to the emergency department, 27 (58%) of 47 patients had re-admissions. While 16 (34%) of these applications were hospitalized again, 9 (19%) were admitted to the intensive care unit. Among the discharged patients, 2 (5%) of the patients who applied to the emergency department again died (**Table 3**).

Table 3. Prognosis of patients re-admitted to the emergency department within 90 days of discharge		
90-day analysis of discharged patients	**%**	**n (number of patients)**
Number of patients discharged	100	47
Re-admission to the emergency department	58	27
Hospitalization from Emergency again	34	16
Intensive care hospitalization from Emergency	19	9
Exitus (From those who applied to the emergency department)	5	2

Mortality rates are similar to diagnoses in the etiology of sepsis. However, considering the discharges, there are etiologically similar diagnoses and they do not have numerical superiority over each other.

DISCUSSION

Timely management of sepsis reduces morbidity and mortality, as well as lowers healthcare costs (14-16). With the 2-year analysis of our hospital's Emergency Service Sepsis record, we aim to determine where and how we can improve our sepsis-fighting operations. Sepsis; It is a health problem that is difficult to recognize, diagnose and treat. Timely and rapid diagnosis is essential for successful treatment. In order to minimize mortality in sepsis, it is necessary to apply prompt, appropriate and intensive treatment. Delays in diagnosis are often seen due to different clinical findings and clinical courses.

As seen in this study, sepsis is primarily a disease of the elderly population; however, we could not obtain data from pediatric emergency services. The reason is the lack of availability of branches related to pediatric emergency care in our hospital. According to our data, there is no age or gender-related severity in sepsis according to the population studied (p= 0.021)

During the time period of this study, 36.44% of the patients with sepsis who applied to the emergency department could be explained by Pneumonia. Comparing the etiology of septic patients admitted to the hospital's emergency department with sepsis in line with the literature, it was observed that it was one of the most common septic conditions secondary to pneumonia, the second most common secondary to urinary tract infection. Pneumosepsis and urosepsis are the conditions that we encounter most frequently in the advanced age group according to Madkour et al. (17)'s research.

In a study by Baykara N,et al. (18), the presence of infection was detected in 57.7% (n=863) of 1499 patients included in the study, and 6.9% (n=104) of these patients were evaluated as sepsis according to the sepsis diagnostic criteria. The mortality rate has been reported as 75.9%. Mortality rate in sepsis diagnosis and sepsis in

this study is similar to Turkish data (18). In the study of Baykara et al., high mortality rates; Age, APACHE 2 score, diagnosis of ICU admission, SOFA score were found to be correlated. SOFA score, Lactate level and CRP are correlated with mortality correlated with literatüre (19). The mortality rates in our study may also be associated with the advanced age (71±10.6) of the cases.

According to Prescott HC et al.'s research (19); They apply to health institutions again with physical problems, cognitive disorders, recurrent infections or sepsis, sepsis-related chronic organ failures after discharge. Despite the improved health awareness and the ease of access to health, the rate of re-admissions to the hospital within 90 days after discharge was found to be 58%. Prescott HCet al. 's (20) another research found that, 42.7% of the surviving cases applied to health institutions again in the first 90 days after discharge. The most common reason for admission was determined as recurrent infections (urinary system, skin or soft tissue infections and pneumonia). We can interpret this as the fact that home care services are still not at an adequate level. Of the re-admissions, 34% were re-admitted to the service, and 19% re-admitted to the intensive care unit.

In the analysis of the effect of patient characteristics on mortality, 64.58% of the patients whose data could be accessed completely died. Fleischmann C et al. In his study on sepsis patients, the in-hospital mortality rate was reported as 24.3%, which is not consistent with our findings. We think that this is due to the exclusion of patients whose data could not be fully evaluated (21). The age of the surviving patients was 66.4±13.4, while the age of the deceased was 71±10.6. A significant correlation was found between advanced age and mortality (p=0.021). This may be explained by the tendency for older patients to have more comorbidities and less physiological reserves. Our result is compatible with the literatüre (22). The APACHE II score was found to be 21.7±6.9 in survivors and 34.1±9.2 in ex patients, which was associated with mortality. Our result is compatible with the literatüre (23). In this study, the SOFA score, lactate and CRP values of the patients were found to be statistically significantly higher in patients with ex. Balcan et al. found that increased APACHE-II score, increased SOFA score and increased CRP were associated with mortality in their study. The results are consistent with our study (24).

Limitations

It was done with a limited number of cases in a single center. The fact that the ICD-10 diagnosis codes of sepsis cases were entered differently in the data system of our hospital caused the patients to be excluded from the study.

CONCLUSION

This study shows that all patients need professional care within 90 days of intensive care discharge. It may be recommended to establish a separate unit in the hospital on this subject. Future studies and pilot applications will determine the need on the subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the University/local human research ethics committee (Date: 16.06.2022, Decision no: 0349).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Efficacy of Acetic Acid and Lugol's Iodine Assisted Colposcopic Imaging in Cases with Anormal Pap Smear Test Results

Anormal Pap Smear Testi Sonucu Olan Olgularda Asetik Asit ve Lugol İyot ile Kolposkopik Görüntülemenin Etkinliği

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ABSTRACT

Aim: This study was conducted to investigate the diagnostic efficacy of colposcopic imaging with Acetic Acid and Lugol's Iodine in cases with abnormal pap smear test results.

Material and Method: Hundred and five patients who presented to the Maltepe University Medical Faculty Hospital Gynecology Outpatient Clinic between 2017 and 2020 with abnormal pap smear results and whose biopsy was taken using colposcopic imaging were evaluated retrospectively. The study included patients with Pap smear results indicating atypical squamous cells of undetermined significance (ASCUS), low grade squamous intraepithelial lesion (LSIL), or high grade squamous intraepithelial lesion (HSIL).

Result: 19% (n=20) of the patients with abnormal pap smear test results were diagnosed with HGSIL, 43.8% (n=46) were diagnosed with LGSIL, and 37.1% (n=39) were diagnosed with ASCUS. As a result of the biopsy performed on these patients, chronic cervicitis was diagnosed in 48.6%, CIN 1 in 28.6%, and CIN 2-3 in 22.9%. Initially, Acetic Acid was applied during colposcopy. In detecting premalignant cervical lesions, aceto-white areas were determined to have a sensitivity of 74.1%, a positive predictive value of 65.6%, a specificity of 58.8%, and a negative predictive value of 68.2%. Upon application of Lugol's Iodine, the sensitivity of areas with no uptake in detecting premalignant cervical lesions was 83.3%, while the positive predictive value was 61.6%, the specificity was 45.1%, and the negative predictive value was 71.9%.

Conclusion: We determined that colposcopic imaging with Acetic Acid is more accurate than Lugol's Iodine for detecting cervical premalignant lesions in patients with abnormal pap smear test results.

Keywords: Acetic acid, cervical cancer, colposcopy, hpv, lugol's iodine

ÖZ

Amaç: Bu çalışma anormal pap smear test sonucu olan olgularda asetik asit ve lugol iyot ile kolposkopik görüntülemenin tanısal etkinliğini araştırmak amaçlı yapılmıştır.

Gereç ve Yöntem: Maltepe Üniversitesi Tıp Fakültesi Hastanesi Jinekoloji Polikliniği'ne 2017-2020 yılları arasında başvuran hastalara yapılan pap smear testinde anormal sonuç saptanan ve kolposkopik görüntüleme yapılarak biyopsi alınan 105 hasta retrospektif olarak değerlendirildi. Pap smear test sonuçları; önemi belirlenemeyen atipik skuamoz hücreler (ASCUS), düşük dereceli skuamöz intraepitelyal lezyon (LSIL) ve yüksek dereceli skuamöz intraepitelyal lezyon (HSIL) olarak saptanan hastalar çalışmaya alındı.

Bulgular: Anormal pap smear test sonucu olan hastaların %19'u (n=20) HGSIL, %43.8'i (n=46) LGSIL ve %37.1'i (n=39) ASCUS tanısı aldı. Bu hastalara yapılan biyopsi sonucunda hastaların %48.6'sında kronik servisit, %28.6'sında CIN 1, %22.9'unda CIN 2-3 patolojik tanıları tespit edildi. Kolposkopik görüntüleme esnasında öncelikle asetik asit uygulaması yapıldı. Aseto-beyaz alanların premalign servikal lezyonları saptamadaki duyarlılığı %74.1, pozitif prediktif değeri %65.6, özgüllüğü %58.8, negatif prediktif değeri %68.2 olarak tespit edildi. Ardından yapılan lugol iyot uygulaması sonrası tutulum izlenmeyen alanların premalign servikal lezyonları saptamadaki duyarlılığı %83.3, pozitif prediktif değeri %61.6, özgüllüğü %45.1, negatif prediktif değeri %71.9 olarak bulundu.

Sonuç: Anormal pap smear testi sonucu olan hastalarda servikal premalign lezyonlarını saptamada asetik asit kullanarak yapılan kolposkopik görüntülemenin lugol iyota göre daha yüksek tanısal doğruluğa sahip olduğunu saptadık.

Anahtar Kelimeler: Asetik asit, lugol iyot, kolposkopi, serviks kanseri

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INTRODUCTION

Cervical cancer, the fourth most prevalent cancer in women, is responsible for 8% of all cancer-related fatalities (1,2). In the development of invasive cervical cancer, a protracted phase of preinvasive disease is observed, characterized by the progression of precursor lesions from cellular atypia to varying degrees of cervical intraepithelial neoplasia (CIN).

Epidemiological studies have identified many risk factors for the development of CIN and cervical cancer. These include human papillomavirus (HPV), early sexual activity, multiparity, multiple sexual partners, long-term use of combined oral contraceptives, smoking, and low socioeconomic status. HPV types are highly associated with CIN and invasive cancer (3). CIN is the abnormal growth of cells on the surface of the cervix that may have the potential to cause malignancy. CIN, which refers to potential precancerous transformation of cervical cells, most commonly occurs at the squamocolumnar junction of the cervix. It is rated from 1 to 3.

According to the American Society of Colposcopy and Cervical Pathology (ASCCP) guidelines, the standard screening method for cervical cancer is the pap smear test. Screening programs for women should begin at the age of 21 and be repeated every three years. In women over the age of 30, screening strategies differ. According to the ASCCP guidelines, both pap smear test and HPV-DNA test (co-test) are recommended every 5 years after the age of 30 (4). With HPV-DNA testing, it is possible to detect high-risk HPV genotypes that can cause cervical cancer. The addition of HPV testing to screening programs after the age of 30 is due to the fact that, after this age, the likelihood of HPV infection clearance decreases and the persistence of HPV increases (5, 6).

The incidence of cervical cancer has decreased by more than 50 percent in the last 30 years as a result of the implementation of screening programs. This rate decreased from 14.8 per 100,000 women in 1975 to 6.7 per 100,000 women in 2011. The disease's mortality rate decreased from 5,5 per 100,000 women in 1975 to 2,3 per 100,000 women in 2011 (7). Studies indicate that 50% of women diagnosed with cervical cancer have never undergone a pap smear test, while 10% have not undergone a screening test within 5 years prior to diagnosis (8).

Pap smear test results are reported as normal, atypical squamous cells of uncertain significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL). While the regression rate of CIN 1 cases is 57%, this rate is around 32% in CIN 2-3 cases. The potential of CIN cases to progress to cervical cancer is the most important risk factor to be considered. In the absence of early detection, patients with low- and high-grade squamous intraepithelial lesions have an increased risk of progression to cervical squamous cell carcinoma or invasive carcinoma. CIN 2 cases have a 5% progression rate to cervical cancer, while CIN 3 cases have a 13% progression rate (9). Colposcopic imaging is a procedure performed on women with abnormal pap smear test results to determine the biopsy site and improve diagnostic accuracy (10). Colposcopic imaging is required for patients over the age of 24, who have ASCUS and are infected with oncogenic type HPV virus, as well as women with HGSIL or ASCUS-H, regardless of age (4).

The application of Acetic Acid and Lugol's Iodine to the cervix during colposcopic imaging is crucial for detecting cervical lesions. Studies have shown that colposcopic imaging methods with Acetic Acid and Lugol's Iodine are more sensitive than pap smear tests (11). These applications, which provide easy results and do not require any laboratory support, are frequently used today. Acetic Acid and Lugol's Iodine are used in colposcopic imaging because of the color changes they create in abnormal tissues. While normal tissues are unaffected by the application of Acetic Acid, areas with an increased nuclear/cytoplasmic ratio, such as CIN, become white. Another solution utilized is Lugol's Iodine, which reacts with glycogen in normal squamous epithelium. This solution, which causes browning in normal tissue, cannot stain high-grade CIN lesions brown because they contain low amounts of glycogen and produce negative uptake regions (12). In this study, we aimed to demonstrate the diagnostic effectiveness of Acetic Acid and Lugol's Iodine application in colposcopic imaging.

MATERIAL AND METHOD

The study included 105 patients who underwent a pap smear test at the Gynecology Outpatient Clinics of Maltepe University Medical Faculty Hospital between 2017 and 2020 and whose abnormal cytology results necessitated a colposcopy biopsy. LSIL, HSIL and ASCUS were considered as a result of abnormal cytology.

From the patient files, the age, gradivy, parity, and cervical pathology results of the women were retrospectively analyzed and recorded. In addition, the results of these patients' colposcopic imaging, observation with Acetic Acid and Lugol's Iodine were recorded.

Colposcopic imaging in our clinic includes the use of Acetic Acid and Lugol's Iodine. Positive Acetic Acid uptake was determined by the presence of well-defined, dense, acetowhite lesions near the squacolumnar junction or cervical os one minute after Acetic Acid administration. Following the application of Lugol's Iodine solution, the presence of mustard or saffron yellow areas in the transformation zone was accepted as the evaluation criterion for the presence of Lugol's Iodine negative area (13). The sensitivity, specificity,

positive and negative predictive values of Acetic Acid and Lugol's Iodine applications used during colposcopic imaging were investigated according to biopsy results. The study was approved by the Ethics Committee of the University of Maltepe.

Statistical Method

In order to summarize the study's findings, descriptive statistics for continuous (numerical) variables were tabulated as median, minimum, and maximum, depending on the distribution. Numbers and percentages were used to summarize categorical variables.

Kappa test was used for negative compatibility of Acetic Acid and Lugol's Iodine with pathology. The specificity, sensitivity, negative and positive predictive values were computed based on the pathology and states of Acetic Acid and Lugol's Iodine.

Statistical analysis was carried out using the "Jamovi project (2022), Jamovi (Version 2.2.5.0) and JASP (Version 0.16.1) programs and the level of significance was taken into account as 0.05 (p-value).

RESULTS

The mean age of the 105 patients in the study was 39.1±9.4 years (range: 22-64), and 36.1% were childless. Twenty (19%) of the study's patients were diagnosed with HSIL, forty-six (43,8%) with LGSIL, and thirty-nine (37,1%) with ASCUS. While aceto-white uptake was observed in 61 patients (58.1%) when Acetic Acid was applied, no staining was observed in 73 patients (69.5%) when Lugol's Iodine was applied. According to the results of the colposcopic biopsy, 48.6% were reported to have chronic cervicitis, 28.6% CIN 1, and 22.9% CIN 2-3. (**Table 1**). In terms of age, gravida, and parity distribution, there was no statistically significant difference (p> 0.05) between patients diagnosed with chronic cervicitis, CIN 1, and CIN 2-3.

When the biopsy results were analyzed according to the Pap smear test results, 30% (n=9) of the cases with ASCUS were diagnosed as CIN 1 and 25% (n= 6) of them were diagnosed as CIN 2-3. While 53.3% (n=16) of LGSIL cases were diagnosed as CIN 1 and 41.7% (n=10) CIN 2-3, 16.7% (n=5) of HGSIL cases were diagnosed as CIN 1 and 33.3% (n=8) was diagnosed with CIN 2-3 (**Table 2**).

According to pathology results, the distribution of patients with Acetic Acid uğtake was similar (34.4%, 31.1%, and 34.4% for chronic cervicitis, CIN 1 and CIN 2-3, respectively). The rate of chronic cervicitis, CIN 1 and CIN 2-3 in patients without Lugol's Iodine uptake was calculated as 38.4%, 32.9% and 28.8% (**Table 3**). Statistically significant levels of concordance were observed between the pathology results and the presence of Acetic Acid uptake and the absence of Lugol's Iodine uptake (**Table 4**).

Table 1. Demographic and clinical characteristics

	Mean±SD / n (%)	Median (Min. - Max.)
Age	39.1±9.4	38.0 (22.0- 64.0)
Gravida (%)		
Nulligravida	38 (36.2)	
Primigravida and Multigravida	67 (63.8)	
Parity (%)		
Nulliparous	41 (39.0)	
Primiparous and Multiparous	64 (61.0)	
Pap smear test result (%)		
ASCUS	39 (37.1)	
LGSIL	46 (43.8)	
HGSIL	20 (19.0)	
Acetic Acid uptake (%)		
Yes	61 (58.1)	
None	44 (41.9)	
Lugol's Iodine uptake (%)		
Yes	32 (30.5)	
None	73 (69.5)	
Pathology (%)		
Chronic Cervicitis	51 (48.6)	
CIN 1	30 (28.6)	
CIN 2-3	24 (22.9)	

Table 2. Distribution of pathology results according to Pap smear test results.

Pathology Result	Pap smear test result (%)		
	ASCUS (n=39)	LGSIL (n=46)	HGSIL (n=20)
Chronic Cervicitis (n=51)	24 (47.1)	20 (39.2)	7 (13.7)
CIN 1 (n=30)	9 (30.0)	16 (53.3)	5 (16.7)
CIN 2-3 (n=24)	6 (25.0)	10 (41.7)	8 (33.3)

Table 3. Distribution of pathology results according to Acetic Acid and Lugol's Iodine application results.

	Acetic Acid uptake (+) (n=61)	Lugol's Iodine uptake (-) n=73)
Chronic Cervicitis	21 (34.4)	28 (38.4)
CIN 1	19 (31.1)	24 (32.9)
CIN 2-3	21 (34.4)	21 (28.8)

Table 4. Diagnostic accuracy of Acetic Acid and lugol's iodine in the diagnosis of premalignant cervical lesions

	Sensitivity	Specificity	PPD	NPD	Kappa	p value
Acetic Acid Uptake (+)	74.1%	58.8%	65.6%	68.2%	0.117	0.001
Lugol's Iodine Uptake (-)	83.3%	45.1%	61.6%	71.9%	0.303	0.002

PPD. Positive predictive value, NPD. Negative predictive value

Table 4 summarizes the diagnostic accuracy of Acetic Acid and Lugol's Iodine in the differential diagnosis of cervical premalignant lesions (CIN 1, 2, and 3). The calculated sensitivity and specificity of Acetic Acid in predicting CIN lesions were 74.1% and 58.8%, respectively. The sensitivity of Lugol's Iodine in predicting CIN lesions was 83.3%, while the specificity was 45.5%.

DISCUSSION

Colposcopic imaging is based on the observation that malignant and premalignant epithelium exhibit distinct visual characteristics regarding contour, color, and vascularity. During colposcopic imaging, the transformation zone must be identified. In colposcopic imaging, a broad-band light spectrum is used for visual scanning. In imaging, solutions of Acetic Acid and Lugol's Iodine are used to enhance the detection of differences between normal and abnormal tissues. The most significant advantage of utilizing Acetic Acid and Lugol's Iodine is that they do not require any special procedures (11,13).

The application of Acetic Acid accelerates and reverses the coagulation of cellular proteins. It helps to coagulate and clear mucus secretions from the cervix by causing swelling of columnar and abnormal squamous epithelial areas and dehydration of cells in epithelial tissue. Normal squamous epithelium appears pink, while columnar epithelium appears red due to light reflected from the stroma. Acetic Acid coagulates the cellular proteins in the epithelium and causes the stroma to become discolored. Thus, a color change to aceto-white occurs. Consequently, the action of Acetic Acid is dependent on the quantity of cellular proteins present in the epithelium. Increased nuclear activity and DNA concentration are associated with the most prominent white color change while normal tissues are unaffected by the application of Acetic Acid. Areas with an increased nuclear/cytoplasmic ratio, such as CIN, become white (3).

All patients' cervixes were treated with 3% Acetic Acid in order to highlight suspicious and abnormal areas during colposcopic imaging. Acetic Acid application resulted in aceto-white areas in 41.2% of chronic cervicitis cases, 63.3% of CIN 1 cases, and 87.5% of CIN 2-3 cases (**Figure 1**). The group with CIN 2-3 had a significantly higher rate of Acetic Acid uptake than the group with chronic cervicitis and CIN 1. Similar to our study, another study carried out by Denny et al. determined that Acetic Acid inspection with sensitivity for CIN 2-3 lesions was 74% (14). In a study conducted by Bhattachan et al. in 2019, the sensitivity of observation with Acetic Acid during colposcopy imaging was found to be 80%, and the specificity was 88.5%, for the detection of cervical lesions. (15). Similar to other studies, the negative predictive value of Acetic Acid application was determined to be 68.2% (16, 17).

Lugol's Iodine solution was applied following the application of Acetic Acid. Iodine is glycophilic and iodine uptake occurs in epithelial cells containing glycogen after administration. Columnar epithelium lacks glycogen, while squamous metaplastic epithelium contains abundant glycogen. It is found in very small amounts in CIN and invading cancer cells. As a result, after iodine application, squamous epithelium containing normal glycogen stains brown or black. Columnar epithelium is not stained because it does not retain iodine. Areas of immature squamous metaplastic epithelium may remain only partially iodine-stained. Iodine does not stain inflammatory areas of the squamous epithelium, so they appear colorless against the surrounding black or brown background. CIN and invasive cancer areas do not contain glycogen, so they do not retain iodine and appear as thick mustard-yellow or saffron-colored areas (3).

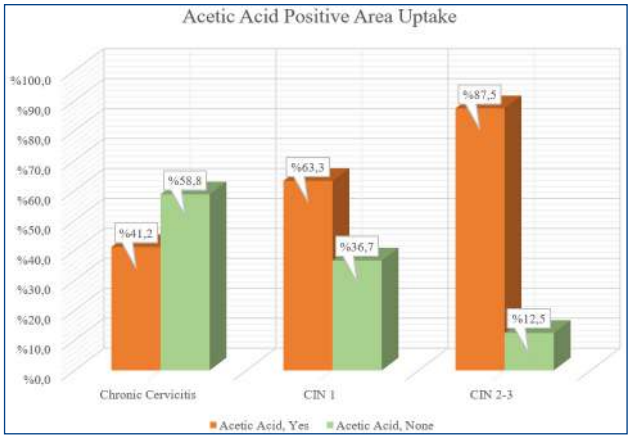

Figure 1. Acetic Acid Positive Area Uptake

The incidence of non-uptake areas after Lugol's iodine application was 54.9% in chronic cervicitis, 80% in CIN 1, and 87.5% in CIN 2-3 (**Figure 2**). Although the presence of Lugol's Iodine negative area in CIN 1 and CIN 2-3 cases was not found to be statistically significant, it was observed to be significantly increased compared to chronic cervicitis cases. While our study found the sensitivity of Lugol's Iodine application to be 84.5%, another study found it to be 92.2%, which is consistent with our findings (18).

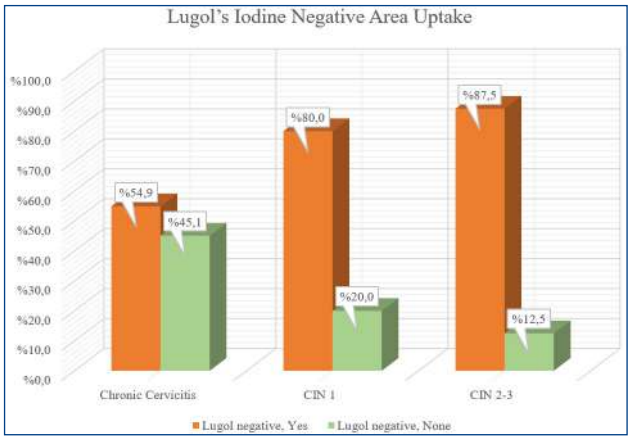

Figure 2. Lugol's Iodine Negative Area Uptake

In a meta-analysis of data from nineteen studies, the sensitivity and specificity for the diagnosis of CIN2+ with Lugol's Iodine were 88.1% (95% CI: 81.5-94.7%) and 85.9% (95% CI: 81.7-90.0%), respectively (19). Meanwhile, the use of different parameters as Acetic Acid uptake criteria can be attributed to the disparities in results in some studies (16).

In our study, 46 patients whose pap smear test results revealed LGSIL had colposcopic imaging and biopsy results reported CIN 2-3 in 21.7% of the cases. Therefore, based on the findings of the current study, we can conclude that colposcopic imaging is more effective than a pap smear test at identifying cervical lesions that are malignant and premalignant.

Studies have shown that an increased number of biopsies increases the diagnostic accuracy of cervical malignancies. During colposcopic imaging, the probability of high-grade lesions in random biopsies taken from nonsuspicious areas ranges from 13% to 37% (20). In our study, we preferred to obtain biopsies from aceto-white regions, Lugol's Iodine-negative regions, metaplastic regions, and suspicious regions. Four quadrant biopsies were taken from the squamocolumnar junction from all patients, even though colposcopic imaging did not reveal abnormal areas. Our study's most significant limitations are its small sample size and retrospective nature.

CONCLUSION

Acetic Acid and Lugol's Iodine applications in colposcopic imaging are effective applications that increase the success rate in the diagnosis of cervical neoplasia. In this study, we demonstrated that the use of Acetic Acid during colposcopic imaging for the detection of premalignant cervical lesions is more accurate than the use of Lugol's Iodine.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Maltepe University Medical Ethics Committee Reference Number: 2020/900/70.

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Survival and Failure Outcomes of Neoadjuvant/Definitive Radiotherapy in Locally Advanced Esophageal and Gastro-Oesophageal Junction Cancer: A Single Institute Experience

Lokal İleri Evre Özofagus ve Gastroözofageal Bileşke Tümörlerinde Neoadjuvan / Definitif Radyoterapinin Sağkalım ve Başarısızlık Sonuçları: Tek Merkez Deneyimi

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ABSTRACT

Aim: The aim of this study was to present our clinical experience as survival and failure outcomes in patients with locally advanced esophageal and gastro-oesophageal junction (GEJ) cancer who received neoadjuvant /definitive radiotherapy (RT).

Material and Method: Twenty-eight patients with locally advanced stage (cT3-T4 any N and any T, N +) esophageal and GEJ cancer who received RT were retrospectively analyzed. Intensity-modulated radiotherapy (IMRT) was implemented to the patients in 25-33 fractions at a total dose of 45-59.4 Gy (median, 50 Gy).

Results: Twelve of 28 patients were alive during up to the four-year follow-up period. The overall recurrence rate was 28% (8/28). The median overall survival (OS) and recurrent-free survival (RFS) were 17 and 8 months, respectively. The one-year OS and RFS were 65% and 28%, respectively. Surgery was performed on only 9 of 28 patients. Pathological complete response (pCR) was observed in 5 (55%) of 9 operated patients. In 19 non-operated patients, local control was achieved with RT/CRT in 90%, only 2 (10%) patients were locally progressed.

Conclusion: Multidisciplinary treatment is crucial in patients with locally advanced esophageal cancer with poor survival rates. Neoadjuvant/definitive RT is an effective treatment option for local control.

Keywords: Esophageal cancer, neoadjuvant treatment, radiotherapy, chemoradiotherapy, survival

ÖZ

Amaç: Bu çalışmanın amacı, neoadjuvan / definitif radyoterapi (RT) alan lokal ileri evre özofagus ve gastroözofageal bileşke (GEJ) tümörlü hastalarda sağkalım ve başarısızlık sonuçlarını ve klinik deneyimimizi sunmaktır.

Yöntem ve Gereç: Lokal ileri evre (cT3-T4 herhangi bir N ve herhangi bir T, N +) özofagus ve GEJ tümörlü, RT alan 28 hasta geriye dönük olarak incelendi. Hastalara 25-33 fraksiyonda toplam 45-59,4 Gy (medyan, 50 Gy) dozda yoğunluk ayarlı radyoterapi uygulandı.

Bulgular: Maksimum dört yıllık takip süresi boyunca 28 hastadan 12'si hayattaydı. Genel nüks oranı % 28 (8/28) idi. Medyan genel sağkalım (OS) ve rekürrensiz sağkalım (RFS) sırasıyla 17 ve 8 aydı. Bir yıllık OS ve RFS sırasıyla% 65 ve% 28 idi. Yirmi sekiz hastanın sadece dokuzu opere oldu. Patolojik tam yanıt (pTY), opere olan 9 hastanın 5'inde (% 55) sağlandı. Opere olmayan hastaların (n=19) % 90'ında RT ile lokal kontrol sağlandı, sadece 2 (% 10) hasta lokal olarak progrese idi.

Sonuç: Kötü prognozlu, lokal ileri özofagus kanserli hastalarda multidisipliner tedavi yaklaşımı önemlidir. Neoadjuvan / definitif RT, lokal kontrol için güvenli ve etkili bir tedavi seçeneği olabilir.

Anahtar Kelimeler: Özofagus kanseri, Neoadjuvan tedavi, Radyoterapi, Kemoradyoterapi, Sağkalım

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INTRODUCTION

Esophageal cancer is one of the most aggressive gastrointestinal system (GIS) malignancies and its long-term prognosis is poor even with multimodal treatments. The 5-year survival rates are around 15-25%. Despite the poor prognosis, approximately 50% of the cases have local or local-advanced disease (1, 2).

In recent years, neoadjuvant chemoradiation (CRT) followed by surgical resection has been determined as the standard treatment for locally advanced esophageal and gastroesophageal junction (GEJ) cancer. Previous studies showed that survival outcomes were worse with surgery alone or radiotherapy alone (3, 4). With recent trials, CRT has been demonstrated to improve survival outcomes (2, 5). It has been reported that neoadjuvant chemotherapy does not improve overall survival (OS) compared to surgery alone (6). However, large randomized trials and meta-analyses illustrated that combined neoadjuvant therapy provided a survival benefit compared to surgery alone or neoadjuvant chemotherapy (2, 5, 7, 8). Phase 3-randomized Cross trial demonstrated neoadjuvant CRT followed by surgery, expressed as trimodal therapy, increased the chance of pathological complete response (pCR), R0 resection and so improved survival (2). Clinical complete response (cCR) and/or pCR, which occurs as a consequence of neoadjuvant treatments, are important prognostic marker in esophageal cancers, as in other GIS malignancies (9-11).

In this retrospective study, we aimed to present our clinical experience as survival and failure outcomes in patients with locally advanced esophageal and GEJ cancer who received neoadjuvant / definitive RT.

MATERIAL AND METHOD

Patient selection

Twenty-eight patients with locally advanced stage (cT3-T4 and any T, N +) esophageal and GEJ cancer who received RT between April 2015 and September 2020 in the Radiation Oncology clinic of Tokat Gaziosmanpaşa University were retrospectively analyzed. The study was conducted in accordance with the Helsinki declaration and this was approved by the ethics committee of our hospital (Decision no: 21-KAEK-089). Patient interview information, patient files and electronic system data were used for the study. Patients who completed their full courses and received definitive or neoadjuvant RT were included. Whereas, patients with unavailable information, metastatic disease, and received palliative RT were excluded from the study.

Treatment details

All patients before treatment were evaluated in a multidisciplinary treatment council. The patients were graded according to the AJCC TNM staging classification (8th edition). Computed tomography (CT), 18F-FDG PET/CT, and endoscopy were used for clinical staging. The gross target volume (GTV) was contoured according to the fusion of CT and PET/CT images, as well as endoscopic examination information. Clinical target volume (CTV) was created by expanding the GTV 3-4 cm from superior-inferior, and 0.5-1 cm margin from radial directions. CTVs are expanded 0.5 cm to accomplish planning target volume (PTV). With the Varian Clinac DHX Linac device, intensity-modulated radiotherapy (IMRT) was implemented to the patients in 25-33 fractions at a total dose of 45-59.4 Gy (median, 50 Gy). Definitive doses of RT (59.4 Gy) were delivered to three patients with cervical localization. Concurrent chemotherapy was applied to 86% of the patients. Weekly carboplatin-paclitaxel was administered to the majority of the patients (83% n: 20). CT and / or PET/CT were repeated 4-6 weeks after RT for re-evaluation. Patients were invited to follow-up visits for the first 1-month and then 3-months after the treatment and their tests were performed.

The primary endpoint of the study was to present data on overall (OS) and recurrent-free survival (RFS). In addition, factors affecting survival were examined. The endpoint for OS was the last control date (for survivors) and date of death (for dead ones). The endpoint for RFS was the date of progression.

Statistical analysis

Analyzes were performed using the SPSS software program (Version 20.0). Categorical variables were defined as absolute numbers. Continuous variables were reported as mean ± standard deviation or median values and ranges. Kaplan-Meier analysis was used for overall survival analysis. Univariate cox-regression analysis was performed to evaluate the effect of available parameters on overall survival. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Of the 28 patients included in the study, 9 (32%) were female and 19 (68%) were male. Their mean age was 63.7 ± 12.3 years. The median follow-up period was 14 months (range, 3-48 months). 7 patients received neoadjuvant chemotherapy. The most common localization of the tumor was distal (14 patients (50%)). The most common clinical stage was T3N0 (10 patients (36%)). The mean SUVmax of the tumor on PET CT before treatment was 15.8 ± 6.6. While 9 patients (32%) were operated after neoadjuvant CRT, 19 (68%) patients did not undergo surgical resection. The histopathology of the patients was SCC in 23 (82%), and adenocarcinoma in 5 (18%). No patient had distant metastases at the time of diagnosis. The demographic and clinical data of the patients are summarized in **Table 1**.

Table 1. Demographic and clinical data of the patients

Characteristics	n (%)
Sex	
Male	19 (68%)
Female	9 (32%)
Tumor location	
upper	3 (10.7%)
middle	7 (25%)
distal	14 (50%)
GEJ	4 (14.3%)
Clinical TN Stage	
T3N0	10 (36%)
T3N1	6 (21%)
T4N0	2 (7%)
T4N1	3 (11%)
T3N2	7 (25%)
Operation	
No	19 (68%)
Yes	9 (32%)
Histology	
Squamous cell carcinoma	23 (82%)
Adenocarcinoma	5 (18%)
Relapse Status	
No	20 (71%)
Yes	8 (29%)
Last Status	
Alive with healthy	9 (32%)
Alive with disease	3 (11%))
Ex	16 (57%)
Neoadjuvant Chemotherapy	
No	21 (75%)
Yes	7 (25%)

During the follow-up period, 16 (57%) patients died. The overall recurrence rate was 28% (8/28). Of the 28 patients, two had loco-regional relapse, five had distant metastasis, and one had local + distant relapse. The median OS was 17 months (95% Confidence interval (CI): 9-24) (**Figure 1**), while the median RFS was 8 months (95% CI: 5-10) (**Figure 2**). The one and two-year OS were 65% and 36%, respectively. The one-year RFS was 28.6%. In 19 non-operative patients following RT, while local control was achieved with RT in 17 (90%) patients (complete or partial response), local progression was observed in only 2 (10%) patients in the last control.

In univariate cox-regression analysis, there was no statistically significant relationship between OS and the factors such as concurrent chemotherapy (p: 0.132), whether or not surgery (p: 0.09), RT dose (0.46), clinical stage (p: 0.672), lymphovascular invasion (LVI) (p: 0.534), perineural invasion (PNI) (p: 0.065), weight loss (p: 0.137), neoadjuvant chemotherapy (p: 0.8), pre-therapy PET/CT SUV max (p: 0.869).

After treatment 6 patients (21%) were evaluated with only PET/CT, 11 (39.5%) with only CT, the remaining 11 (39.5%) with both CT and PET/CT. When they were restaged after treatment, clinical complete response (cCR) was observed in 8 (28.6%) patients, clinical partial response (cPR) in 19 (67.9%) patients and stable response in 1 (3.6%) patient.

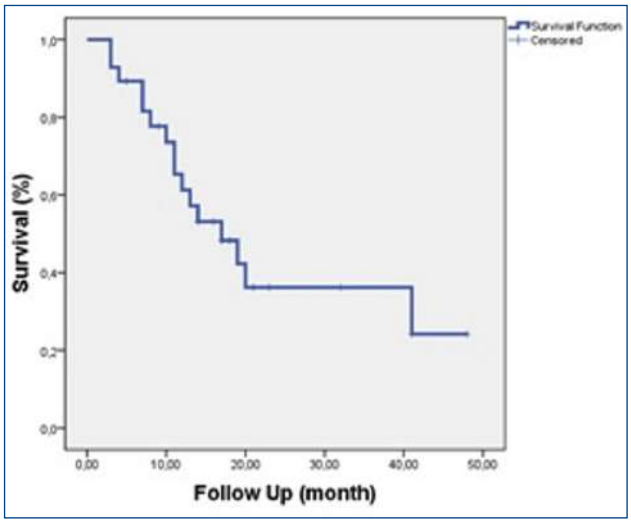

Figure 1. Kaplan-Meier curve for overall survival (OS)

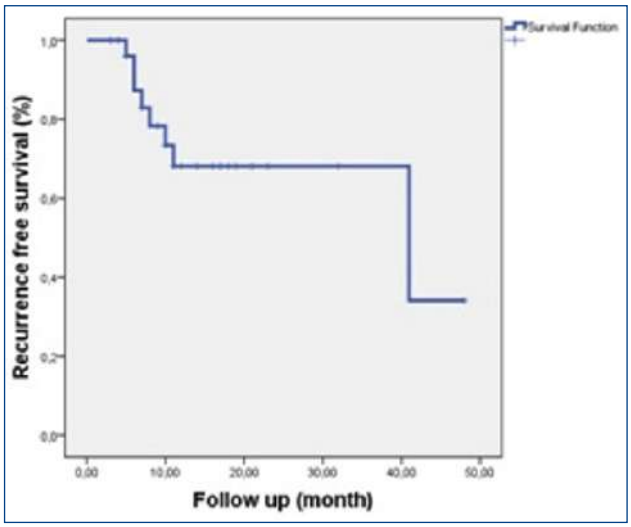

Figure 2. Kaplan-Meier curve for recurrence-free survival (RFS)

Surgery was performed on only 9 of 28 patients. Pathological CR (i.e. pT0N0) was achieved in 5 (55.5%) of 9 operated patients. Of the 5 patients with pCR, 2 had a complete metabolic response on post-RT PET/CT. On the other hand, the remaining 3 patients with pCR did not have post-RT PET/CT. All 4 patients with pPR had a partial response on post-RT PET/CT, as well as correlated with pathology. While only one patient was clinically N0 before neoadjuvant treatment, it was detected that the patient had occult nodal disease at the time of esophagectomy.

DISCUSSION

Esophageal cancer is one of GIS malignancies with a poor prognosis and in which the majority of patients are present at a locally advanced stage at the time of diagnosis. Recently, many phase 3 studies and meta-analyses have revealed that neoadjuvant CRT significantly improved survival in locally advanced esophageal cancer (2, 8, 12). In this study, we aimed to present the survival and local control outcomes of neoadjuvant treatments in patients with locally advanced esophageal cancer. Twelve of 28 patients were alive during up to the four-year follow-up period. The overall recurrence rate was 28% (8/28). The median OS and RFS were 17 and 8 months, respectively. The one-year OS and RFS were 65% and 28%, respectively. Surgery was performed on only 9 of 28 patients. Pathological CR was observed in 5 (55%) of 9 operated patients. In 19 non-operated patients, local control was achieved with RT in 90%, only 2 (10%) patients were locally progressed.

Response to neoadjuvant CRT has been found to be an independent predictor in terms of disease relapse in many studies (9, 14-16). In the literature, there are differences in pCR rates after trimodal treatment (17-20). Cristina et al. reported that the rate of pCR was 28% in patients with esophagus and GEJ tumors diagnosed with adenocarcinoma who underwent neoadjuvant CRT (17). In another retrospective study, consequences of neoadjuvant CRT were investigated in 46 patients with esophageal squamous cell carcinoma (SCC), and they found the pCR rate to be 44% (18). Some researchers reported this rate of around 20% (19, 20). Furthermore, SCC histology has been found to be associated with higher rates of pCR (2, 21). In the current study, although patients with both SCC and adenocarcinoma histology were included, we found the pCR rate to be 55%. Although it seems to be a higher rate compared to the literature, this rate may change downward as the number of patients increases. Unfortunately, due to reasons such as patient preference, comorbidities, socio-economic level, etc. most patients could not undergo surgery.

Some researchers have shown that patients with pCR have better OS as well as less locoregional failure (9, 14-16). No statistically significant relationship was found between pCR and survival in the current study, probably due to the small number of patients included in the study and also undergoing surgery. In the follow-up of five patients with pCR, one died due to post-op complications, one had isolated distant metastasis, and the remaining three patients live disease-free and healthy. As a matter of fact, patients who receive neoadjuvant therapy have a higher risk of postoperative mortality compared to those who receive surgery alone (22).

Masahiro et al. reported the results of CRT with IMRT in 36 patients with cervical esophageal cancer, 3-year-progression-free survival (PFS) and 3-year-OS were 40% and 46%, respectively (23). Cao et al found that 2-year locoregional control (LRC) and 2-year OS were 67.4% and 46% in 101 patients with esophageal cancer as an outcome of definitive CRT, respectively (24). In the phase 3 Cross study, the 1-, 2-, and 3-years OS rates in the preoperative CRT + surgery arm were 82%, 67%, and 58%, respectively (2). In the present study, because of trimodal therapy could not be applied to all patients, our survival rates were lower compared to the literature. Recently, in a study conducted with 769 esophageal cancer patients with N3 diseases, it was reported that surgery after neoadjuvant therapy improved survival (25). In the current study, only 32% of the patients had surgery, however, there was no N3 disease as in the aforementioned study.

In esophageal cancer, 18F-FDG PET/CT has an essential role in staging and re-evaluation after neoadjuvant therapy, as in other malignancies. PET/CT can predict poor response to neoadjuvant therapy and poor prognosis. Moreover, determining the best candidate for surgical resection is possible with PET/CT. Tustumi F et al. (26) examined the prognostic effect of pre-neoadjuvant PET/CT parameters on survival in 113 esophageal cancer patients. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) in the primary tumor; SUVmax in the suspicious lymph node was found to be significantly correlated with survival (26). In another similar study, 43 patients with esophageal cancer were evaluated with PET/CT before and after neoadjuvant therapy. Pathological CR was obtained in 56% of the patients and the predictive value of PET/CT for pCR was examined. The assessment of 18F-FDG PET/CT showed overall sensitivity of 57.9%, specificity of 62.5% (27). In our study, merely 17 of 28 patients had post-treatment PET/CT. Unfortunately, the analysis could not be performed for its effect on predicting the pathological response, as there were few patients whose pathological stage could be determined. However, in pre-treatment PET CT, primary tumor SUVmax was not found prognostic for survival (p: 0.869). We think that the reason for this result may be related to the low number of patients.

CONCLUSION

Multidisciplinary treatment is crucial in patients with locally advanced esophageal cancer with poor 5-year survival rates. Neoadjuvant/definitive radiotherapy may be a safe and an effective treatment option for local control.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of Tokat Gaziosmanpaşa University with the decision no 21-KAEK-089 on 1 April 2021.

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Sağlık Hizmetleri Meslek Yüksekokulu Öğrencilerinin Delici Kesici Alet Yaralanmaları Hakkında Bilgi Düzeylerinin Belirlenmesi

Determination of the Knowledge Levels of The Health Services Vocational School Students about Sharps Injuries

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ÖZ

Giriş: Sağlık Hizmetleri Meslek Yüksekokulu (SHMYO) öğrencileri de diğer sağlık çalışanları gibi delici kesici alet yaralanmaları (DKAY) için risk taşımaktadır. SHMYO öğrencilerinin eğitim programlarında bulaşıcı hastalıklar dersi olmasına karşın DKAY ile ilgili süreç yönetiminde zayıf kaldığı düşünülmektedir. Çalışmamızda öğrencilerin DKAY'a maruz kalma durumları, bilgi düzeyleri ve aldıkları önlemlerin belirlenmesi amaçlandı.

Gereç ve Yöntem: Retrospektif, kesitsel nitelikte tasarlanan çalışma, 15-30 Ekim 2021 tarihleri arasında SHMYO öğrencileriyle yürütüldü. Araştırmanın evrenini Bitlis Üniversitesi SHMYO öğrencileri oluşturdu. Google Forms üzerinden oluşturulan anket formları tüm öğrencilere online olarak iletildi. Öğrencilerin sosyodemografik özelliklerini bildiren "Katılımcı Bilgi Formu" ve araştırmacılar tarafından ilgili literatür incelenerek geliştirilen "Delici Kesici Alet yaralanması Bilgi Değerlendirme Formu" kullanıldı.

Bulgular: Çalışmaya 320 (%83,6)'si kadın ve 63 (%16,4)'ü erkek toplam 383 öğrenci dâhil edildi. Yaş ortalaması 20,5±1,4 olarak bulundu. Katılımcıların %90,6 (347)'sı hasta başı uygulamasına katıldı, %82,2 (n:315)'si DKAY kavramını bilmekteydi. Katılımcıların 38 (%9,9)'inde DKAY öyküsü bulunmaktaydı. Yaralanmaların 26 (%68,4)'sı enjektörle gerçekleşmişti. DKAY öyküsü olan katılımcıların yalnızca 13 (%34,2)'ü yaralanmayı bildirmişti.

Sonuç: Çalışmamız sonucunda; konuyla ilgili eğitim programlarının idealize edilerek SHMYO öğrencilerinin DKAY konusunda bilgi düzeylerini yükseltmeye çalışmanın faydalı olacağı düşünülmektedir. Ayrıca öğrencilerin mevcut bilgiyi gerek simülasyon eğitimleriyle gerekse de staj programlarıyla uygulama becerisine dönüştürmeleri sağlanmalıdır. Bu nedenlerle delici kesici alet yaralanmalarıyla ilgili eğitimlerin eğitim müfredatında daha iyi vurgulanması ve uygulamaya yansıyacak şekilde planlama yapılması önerilir.

Anahtar Kelimeler: Kesici delici yaralanmalar, sağlık meslek okulu öğrencileri, sağlık bilgisi

ABSTRACT

Introduction: Health services vocational school (HSVS) students are also at risk for sharps injuries, just like other healthcare professionals. Our study aimed to determine the healthcare students' exposure to sharps injuries, during their clinical practice, their level of knowledge and the precautions they take in case of injury.

Material and Method: The study, which was designed as descriptive and cross-sectional, was carried out between 15-30 October 2021 among SHMYO students. The study population consisted of Bitlis University HSVS students. In this study, the "Participant Information Form" and the "Sharp Injury Information Evaluation Form" were developed by the researchers by examining the relevant literature.

Results: A total of 383 students, 320 (83.6%) female, and 63 (16.4%) male were included in the study, with a mean age of 20.5±1.4. 90.6% (n:347) of the participants participated in the bedside practice, 82.2% (n:315) of them knew the concept of sharp injury. 38 (9.9%) of the participants had a history of sharp injury. Of these, 26 (68.4%) were performed with an injector. Thirteen (34.2%) of the participants with a history of sharp injury reported this.

Conclusion: As a result of our study, it was determined that the education and knowledge levels of HSVS students about sharp injuries were below the desired level. In addition, the rate of conversion of learned knowledge into practice skills is low. This important issue should be emphasized better in the curriculum and planning should be done to reflect it in practice.

Keywords: Sharp injuries, students health occupations, health knowledge

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GİRİŞ

Sağlık çalışanları, mesleki koşulları nedeniyle delici ve kesici alet yaralanmaları (DKAY) ile sık karşılaşan meslek grubudur (1,2). Sağlık çalışanlarının hastane koşullarında sadece gündelik temasla 20'den fazla patojen mikroorganizma ile karşılaştıkları bildirilmektedir. Bu patojenlerin en sık karşılaşılanları Hepatit B virüs (HBV), Hepatit C virüs (HCV) ve İnsan Bağışıklık Yetmezliği (Human Immunodeficiency Virus- HIV) virüsleridir (2,3).

Sağlık çalışanlarında DKAY'nin yüksek olduğu araştırmalarda belirtilmektedir. Ancak öğrenci sağlık teknikerlerine yönelik literatürde kapsamlı bir veriye ulaşılamamıştır. Tıbbi deneyimlerinin yetersiz olması nedeniyle klinik uygulamalar sırasında öğrenciler, DKAY açısından yüksek riskli grupta yer almaktadır. Literatürde stajer öğrencilerin %80'lere varan oranlarda DKAY'ye maruz kalabildikleri bildirilmiştir (4). Stajer öğrenciler, temas sonrasında HBV, HCV, HIV gibi potansiyel enfeksiyonların bulaşacağı korkusunu yaşadıklarını vurgulamışlardır (5). Sağlık hizmetleri meslek yüksekokulu (SMHYO) öğrencilerinin eğitim programlarında bulaşıcı hastalıklar dersi olmasına karşın DKAY ile ilgili süreç yönetiminde zayıf kaldığı ve bu tür yaralanmalarda öğrencilerin stres ve korku yaşadığı düşünülmektedir.

Çalışmamızda sağlık öğrencilerinin klinik uygulamaları süresince DKAY'ye maruz kalma durumları, bilgi düzeyleri ve yaralanma durumunda aldıkları önlemlerin belirlenmesi amaçlanmıştır.

GEREÇ VE YÖNTEM

Bu araştırma, SHMYO öğrencilerinin DKAY konusunda bilgi ve tutumlarının belirlenmesi amacıyla restrospektif kesitsel bir çalışma olarak dizayn edilmiştir. Araştırma, 15-30 Ekim 2021 tarihleri arasında Bitlis Eren Üniversitesi SHMYO'da yürütüldü. Araştırmanın evrenini Bitlis Eren Üniversitesi SHMYO öğrencileri oluşturdu. Çalışmaya tüm öğrencilerin dahil edilmesi planlandığı için örneklem seçimi yapılmadı, Google Forms üzerinden oluşturulan anket formları tüm öğrencilere online olarak iletildi. Onam formunu kabul etmeyen ve anket formlarını doldurmayan öğrenciler çalışma dışında bırakıldı. Çalışmaya toplamda 383 öğrenci katıldı.

Araştırmada, "Katılımcı Bilgi Formu" ve "Delici Kesici Alet Yaralanması Bilgi Değerlendirme Formu" kullanıldı. "Katılımcı Bilgi Formu" öğrencilerin sosyodemografik özelliklerini, "Delici Kesici Alet Yaralanması Bilgi Değerlendirme Formu" ise delici kesici aletle yaralanma durumlarını ve bilgilerini sorgulayan sorulardan oluştu. "Delici Kesici Alet Yaralanması Bilgi Değerlendirme Formu" araştırmacılar tarafından başta Hastalık Kontrol ve Korunma Merkezleri (Centers for Disease Control and Prevention (CDC))'nin örnek anket formu olmak üzere ilgili literatür incelenerek geliştirildi (6-12).

Etik Kurul: Bitlis Eren Üniversitesi Rektörlüğü etik kurulu'ndan 21/10-2 sayılı ve E.1191 evrak kayıt numaralı kararıyla onay alındı.

İstatistiksel Analiz

Analizler, SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 22 paket programında değerlendirildi. Çalışmada tanımlayıcı veriler kategorik verilerde n, % değerleri; sürekli verilerde ise ortalama ± standart sapma (Ort±SS) değerleri ile gösterildi. Gruplar arası kategorik değişkenlerin karşılaştırılmasında ki-kare analizi (Pearson Chi-kare) uygulandı. Analizlerde istatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edildi.

BULGULAR

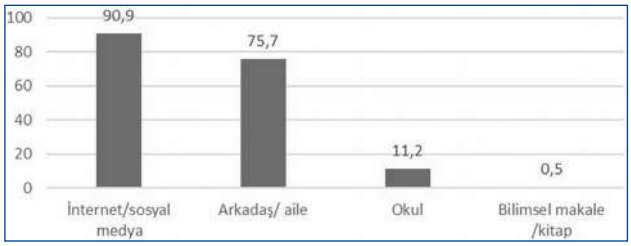
Çalışmaya 320 (%83,6)'si kadın ve 63(%16,4)'ü erkek olmak üzere toplam 383 kişi dâhil edildi. Yaş ortalaması 20,5±1,4 (min=18-maks=28) olarak bulundu. Katılımcıların okuduğu bölümler tablo-1'de verildi. Katılımcıların %90,6 (n:347)'sının hasta başı uygulamasına katıldığı, %82,2 (n:315)'sinin DKAY kavramını bildiği, %11,5 (n:44)'inin ilkokulda DKAY eğitimi aldığı tespit edildi (**Tablo 1**).

Tablo 1. Katılımcıların Sosyodemografik Verileri ve DKAY* Eğitim Durumları

	Sayı	%
Yaş, Ort±SS (min-maks)	20,5±1,4 (18-28)	
Cinsiyet		
Kadın	320	83,6
Erkek	63	16,4
Bölüm		
İlk ve acil yardım programı	51	13,3
Yaşlı bakım programı	40	10,4
Patoloji laboratuvar teknikleri	77	20,1
Çocuk gelişimi programı	168	43,9
Anestezi teknikerliği	47	12,3
Hastabaşı uygulamalara katılma		
Evet	347	90,6
Hayır	36	9,4
DKAY kavramını bilme		
Evet	315	82,2
Hayır	68	17,8
İlkokulda DKAY eğitimi alma durumu		
Evet	44	11,5
Hayır	339	88,5
En son DKAY eğitimi alma zamanı		
Almadım	339	88,5
<6 ay	29	7,6
>6 ay	15	3,9
Eğitim alınan kişi		
Almadım	339	88,5
Birim sorumlusu/klinik sorumlu hocası	35	9,1
Enfeksiyon kontrol hemşiresi	9	2,3

*DKAY: Delici Kesici Alet Yaralanması

Çalışmaya katılanların DKAY bilgi öğrenme yerleri incelendiğinde 348 (%90,9)'inin internet/sosyal medyadan bilgi edindiği görüldü (**Şekil 1**).



Şekil 1. Katılımcıların Delici Kesici Alet ile Yaralanma Bilgi Öğrenme Yerleri

Katılımcıların 38 (%9,9)"inde DKAY öyküsü mevcuttu. Bunların 26 (%68,4)'sı enjektörle, 9 (%23,7)'u bisturiyle, 2 (%5,3)'si makasla, 1 (%2,6)'i ise ilaç flakonuyla olmuştu. Yaralanmalar en sık enjektör kapağını kapatmaya çalışırken meydana gelmişti. DKAY öyküsü ile ilgili özellikler **Tablo 2**'de verildi.

Tablo 2. Katılımcıların DKAY* öyküsü ile ilgili özellikler

	Sayı	%
Öncesinde DKAY öyküsü		
Evet	38	9,9
Hayır	345	90,1
DKAY aleti		
Enjektör	26	68,4
Bistüri	9	23,7
Makas	2	5,3
İlaç flakonu	1	2,6
DKAY oluş şekli		
Enjektör kapağını kapatırken	16	42,1
Kan alırken iğne batması	9	23,7
Delici-kesici alet kutusundan	8	21,1
Pansuman açarken	3	7,9
Seruma ilaç koyarken	1	2,6
İlaç flakonu kırarken	1	2,6
DKAY ilk yapılan şey		
Doktora/ sağlık kuruluşuna başvurma	16	42,1
El yıkama	11	28,9
Dezenfektan kullanma	2	5,3
Herhangi işlem yapmama	9	23,7
Daha önce DKAY olduysa bildirme durumu		
Evet	13	34,2
Hayır	25	65,8
Daha önce DKAY olduysa takiplerine gitme durumu		
Evet	10	26,3
Hayır	20	52,6
Düzensiz	8	21,1

*DKAY: Delici Kesici Alet Yaralanması

Katılımcıların DKAY bilgileri incelendiğinde; katılımcılar, bisturi (%93,7) başta olmak üzere enjektör ve sütur iğnesi ile yaralanmaların başlıca DKAY olduğunu belirttiler. Lanset, ilaç flakonu ya da branül ile olan yaralanmalar ise katılımcılar tarafından daha düşük oranlarda DKAY olarak nitelendirildi. Katılımcılar en fazla oranda HBV, HCV ve HIV enfeksiyonlarına karşı risk altında kaldıklarını ifade etti. Katılımcıların %76,8 (n:294)'i DKAY'nin iş kazası olduğunu, %56,9 (n:218)'u ise adli bir olay olduğunu belirtti. Yaralanma sonrası enfeksiyon komitesine başvurması gerektiğini bildirenlerin oranı %6 (n:23)'ydı. Katılımcıların %5,7 (n:22)'si ise yaralanmayı raporlamak gerektiğini bildirdi. Katılımcıların %6 (n23)'sı DKAY ile ilgili bilgisini yeterli buluyorken; %88 (n:337)'i yeterli bulmadığını belirtti.

Katılımcıların %82,8 (n:317)'i HBV aşısının olduğunu, %28,7 (n:110)'si ise tetanoz aşısı rapel dozunun yapıldığını bildirdi. Klinik uygulamalar öncesi HBV antikor düzeyine bakılanların oranı %67,4 (n:258)'tü. Katılımcıların yalnızca %5,2 (n:20)'si DKAY eğitimlerini yeterli bulurken; %87,7 (n:336)'si DKAY ile ilgili eğitimlerin belirli aralıklarla yapılması gerektiğini ifade etti. Katılımcıların %10,4 (n:40)'ü DKAY'nin önlenmesi için yeterli önlem aldığını ve %9,4 (n:36)'ü çalıştıkları birimde korunmak için fiziksel önlemlerin yeterli olduğunu beyan etti (**Tablo 3**).

Tablo 3. Katılımcıların DKAY* Eğitimleri ve Önlemlerle İlgili Düşünceleri

	Sayı	%
DKAY ile ilgili eğitimleri yeterli bulma		
Evet	20	5,2
Hayır	70	18,3
Kararsız	293	76,5
DKAY ile ilgili eğitimlerin belli aralıklarla tekrarlanması gerektiğini düşünme		
Evet	336	87,7
Hayır	25	6,5
Kararsız	22	5,7
Çalışırken DKAY önlenmesi için yeterli kişisel önlemleri aldığını düşünme		
Evet	40	10,4
Hayır	52	13,6
Kararsız	291	76,0
Çalıştığını birimde DKAY önlenmesi için alınan fiziki önlemlerin yeterli olduğunu düşünme		
Evet	36	9,4
Hayır	43	11,2
Kararsız	304	79,4

*DKAY: Delici Kesici Alet Yaralanması

Hasta başı uygulamalara katılanların %78,1 (n:271)'i; katılmayanların ise %63,9 (n:23)'u DKAY'yi iş kazası olarak görürken; aralarındaki fark istatistiksel olarak anlamlıydı (p=0,013). Hasta başı uygulamalara katılanların DKAY ile ilgili bilgisini yeterli bulma oranı %6,6 (n:23); hasta başı uygulamalara katılmayanların DKAY ile ilgili bilgisini yeterli bulma oranına (%0 (n:0)) göre anlamlı şekilde yüksek bulundu (p=0,003) (**Tablo 4**).

Tablo 4. Hasta Başı Uygulamalara Katılma Durumuna Göre Çeşitli Parametrelerin Karşılaştırılması

	Hasta başı uygulamalara katılma				p**
	Evet		Hayır		
	Sayı	%	Sayı	%	
DKAY* iş kazası mıdır?					0,013
Evet	271	78,1	23	63,9	
Hayır	19	5,5	0	,0	
Fikrim yok	57	16,4	13	36,1	
DKAY* ile ilgili bilgiyi yeterli bulma durumu					0,003
Evet	23	6,6	0	,0	
Hayır	308	88,8	29	80,6	
Kararsız	16	4,6	7	19,4	

*DKAY: Delici Kesici Alet Yaralanması **Kikare analizi yapılmıştır.

TARTIŞMA

Hastalık Kontrol ve Korunma Merkezleri (CDC) verilerine göre hastane personelinde başta enjektörle olmak üzere yılda 385 bin DKAY olmaktadır (6). Ülkemizde de sağlık çalışanları arasında DKAY sıklıkla meydana gelmektedir. Gerek tıp eğitiminde gerekse de hemşirelik ve ebelik başta olmak üzere sağlık alanındaki diğer meslek gruplarının eğitiminde klinik uygulamalar zorunludur. Ancak klinik uygulamalar sırasında öğrenciler, DKAY açısından özellikle risk altındadır. Tıp öğrencilerinin eğitimleri süresince %11-50; hemşirelik öğrencilerinin ise %50-80 arasında DKAY'ye maruz kaldıkları bildirilmiştir (13). Hemşirelik öğrencilerinin eğitimleri süresince DKAY sıklığı %13,9 ile %80 arasında değişmektedir (6,14-17). Irmak ve ark. (15) tarafından yapılan çalışmada hemşirelik öğrencileri arasında (n=310) DKAY oranı %19,4 olarak saptanmıştır. Talas'ın (16) çalışmasındaysa (n=473) bu oran %49 olarak bulunmuştur. Daha yakın zamanlı Kepenek ve ark. (17) tarafından yapılan bir çalışmadaysa 98 DKAY olgusunun %67,3'ünün hemşirelik öğrencisi olduğu bildirilmiştir. Çeşitli araştırmalarda hemşirelik öğrencilerinin DKAY açısından çalışan hemşirelere göre deneyimsizlik, pratik eğitim eksikliği ve kişisel önlemlerin yeterince alınmaması gibi nedenlerden dolayı daha yüksek risk grubunda olduğu bildirilmiştir (10,18–20). Ayrıca yaş ve deneyimsizliğin neden olduğu yüksek anksiyetenin de yaralanmaları artırmış olabileceği düşünülebilir.

Bizim çalışmamızda katılımcıların %9,9'unda DKAY öyküsü mevcuttu. Çalışmamızdaki yaralanma oranı benzer çalışmalara göre daha düşüktü. Bunun nedenleri; öğrencilerin staj yaptıkları hastane ve staj bölümündeki DKAY ile ilgili alınan uygun önlemler ve takipler olabileceği gibi daha kısa staj süreleri, staj yapılan yerde yeterince uygulama yapılmaması, yaralanma beyanının özellikle belirtilmemesi de olabilir. COVID-19 pandemisiyle önemi daha çok anlaşılan kişisel hijyen ve korunma kurallarının da bu farklılıkta rol oynayabileceği düşünülmektedir.

Öncesinde DKAY öyküsü olan 38 öğrenci incelendiğinde; 26'sı (%68,4) enjektörle, 9'u (%23,7) bisturi ile yaralanmıştı ve yaralanmaların çoğunluğunu enjektör ve bistüri yaralanmaları oluşturmaktaydı. Yapılan bir çalışmada da çalışmamıza benzer şekilde öğrencilerde DKAY'ye en çok (%72,1) enjektör iğnesinin neden olduğu belirlenmiştir (21). Sağlık çalışanlarında en fazla yaralanmanın enjektör iğnesi ile gerçekleştiğini bildiren çeşitli yayınlar mevcuttur (10,11).

Çalışmamızda dikkat çekici bir nokta ise yaralanmaların %42'si enjektör kapağını kapatırken, %24'ü kan alırken meydana gelmişti, %21'i ise kesici-delici alet kutusu ile ilişkiliydi. Tüm yaralanmalar göz önüne alındığında DKAY'nin büyük kısmı kontamine aletlerle ilişkiliydi. Çalışmamızın sonucuna benzer şekilde, ülkemizde yapılan bir çalışmada da 231 yaralanmanın 197'sinin (%85) kontamine aletlerle olduğu bildirilmiştir (22). Enjektör uçlarının kapağını kapatmadan uygun seçilmiş kesici delici alet tıbbi atık kutusuna atılması, tek kullanımlık steril tıbbi malzemelerin kullanılması, vakumlu tüple kan alma, damar yolu görüntüleme cihazlarının etkin kullanımı gibi yaklaşımlarla kontamine yaralanmaların büyük kısmı azaltılabilecektir. Bununla birlikte DKAY ve tıbbi atık yönetimiyle ilgili bilgi düzeyini ve tutumu artıracak eğitimlerin düzenlenmesi de çok önemlidir.

Yapılan çalışmalarda yaralanma sonrası ilk müdahale olarak en sık görülen uygulamanın tutumun su ve sabun ile yıkama olduğu bildirilmiştir (12,23). Çalışmamızda ise en sık (%42) olarak yapılan ilk tutum hekime/ilgili sağlık kuruluşuna başvuruydu. Yaralanma sonrası ilk müdahale olarak su ve sabunla yıkama yaptıklarını belirtenlerin oranı %29'du ve %22'si ise yaralandıktan sonra yaralanmayla ilgili herhangi bir şey yapmadığını belirtti. DKAY sonrası uygun müdahale yapılmamasının ve bildirimde bulunulmamasının nedeninin eğitim eksikliği ile birlikte mesleki deneyimsizlik ve benzer olay tecrübesindeki eksiklik olduğunu düşünmekteyiz.

Altıok ve ark. (24) delici kesici aletle yaralanan sağlık personelinin %87,3'ünün yaralanmayı rapor etmediğini bildirmişlerdir. Çalışmamızda yaralanmaya maruz kalan öğrencilerin %65,8'inin olayı bildirmediği görüldü. Ankete katılan tüm öğrencilerin sadece %6'sı DKAY sonrası olayın bildirilmesi gerektiğini düşünmekteydi, geri kalanların hepsi kararsız kaldığını belirtmişti. Yaralanma sonrası enfeksiyon kontrol komitesine (EKK) ya da iş güvenliği ve sağlığı birimine başvurmak gerektiğini bilenlerin oranı da %6'ydı. Bir çalışmada sağlık personellerinin önemli bir kısmının yaralanmayı önemsiz olarak gördüğü, EKK'ye müracaat etmediği ve herhangi bir şey yapmadığı bildirilmiştir (23). En fazla bildirilen rapor etmeme nedenleri ise sırasıyla; ihmalkârlık, risk olarak algılamama düşüncesi, uyarılma korkusu, raporlama prosedürleriyle ilgili süreci bilmeme, gizlilik ile ilgili kaygıların olması ve isteksizlik şeklindedir (14, 25, 26).

Anket sonuçlarına göre öğrencilerin %82,2'si DKAY kavramını bilmekteydi. DKAY ile ilgili bilgi öğrenme yerleri incelendiğinde 348'i (%90,9) internet/sosyal medyadan, 290'ı (%75,7) arkadaş/aileden, 43'ü (%11,2) okuldan ve 2'si (%0,5) ise bilgiyi bilimsel makale/kitaplardan edinmekteydi. Okuldan öğrenme oranlarının düşük olmasını irdelediğimizde; öğrencilerin bir kısmının 1. sınıfta olması nedeniyle henüz eğitim almamaları, verilen eğitime katılmamaları veya eğitimlerini tamamlasalar bile eğitim tekrarı ihtiyacı olabileceğinden kaynaklı olduğunu düşünmekteyiz. Çalışmamızda, en büyük bilgi kaynağının internet/sosyal medya ve arkadaştan edinilen bilgi olduğu görülmekteydi. Burada bu konunun iyi analiz edilmesi gerektiğini düşünmekteyiz. Kaynaklar doğru kullanıldığında bilginin öğrencilere ulaşması için internet iyi bir kaynak olabilir. Ancak konuyla ilgili yanlış ve tutarsız bilginin internet aracılığıyla öğrencilere aktarılmasının hatalı değerlendirmelere ve tıbbi uygulamalara yol açabileceği de unutulmamalıdır.

Hasta başı uygulamalara katılanların %78,1'i, katılmayanların ise %63,9'u DKAY'yi iş kazası olarak görürken aralarında istatistiksel açıdan anlamlı farklılık mevcuttu (p=0,013). Hemşirelik eğitim müfredatında DKAY ile ilgili eğitimler bulunmaktadır. Ancak eğitimlerin uygulama ile pekiştirilmesi, davranışa dönüştürülmesi gerekmektedir. Çalışmamızda hasta başı uygulamalara katılanların DKAY'yi iş kazası olarak görme, raporlama ve alınan eğitimleri yeterli bulma oranları katılmayanlara göre daha yüksek bulundu.

Çalışmaya katılan öğrencilerin %88'si, DKAY ile ilgili bilgisini yetersiz bulmaktaydı, %6'sı ise kararsızdı. Çalışmaya katılan öğrencilerin büyük kısmı (%94) DKAY ile ilgili eğitimleri de yetersiz bulmaktaydı ve belirli aralıklarla eğitimlerin tekrarlanması gerektiğini düşünmekteydi. Bir çalışmada sağlık personelinin yarısının eğitimden sonraki iki yıl içinde DKAY yaşadığı, katılımcıların yarısından fazlasının bu konuda yeterli bilgiye sahip olduğu ancak bu eğitimlerin uygulamaya dönüştürülemediği bildirilmiştir (3). Bu veriler ışığında eğitimlerin uygulamaya yansıması ve tutumları değiştirmesi gerektiği de açıkça görülmektedir.

Staj öncesi değerlendirilen öğrencilerden en az %9'unun HBV aşısı olmadığı ve en az %15'inin staj öncesi HBV antikor düzeyinin ölçülmediği görüldü. Öğrencilerin %64'ü DKAY nedeniyle HBV, HCV ve HIV bulaşabileceğini bilmekteydi. Bulaşıcı hastalıklarla ilgili eğitimler alınmasına rağmen bahsedilen hastalıklarla ilgili bilgi düzeyi istenilen seviyede değildi. Kırım Kongo Kanamalı Ateşi (KKKA) başta olmak üzere diğer kanamalı virüs enfeksiyonları açısından ise bu oran daha da düşük bulundu (<%15). Ülkemizin bazı bölgelerinde daha fazla olmakla birlikte KKKA olguları görülebilmektedir. KKKA, DKAY yoluyla sağlık çalışanlarında enfeksiyona neden olabilir. Öğrencilerin bu konuda düşük bilgi düzeyleri bulaş riskini artırabilir. Eğitimlerin daha etkin ve sık yapılması bu durumların oluşmaması için de uygun olacaktır. Eğitimler sayesinde artan bilgi düzeyinin tutum değişiklikleriyle desteklenmesiyle birlikte DKAY sonrasındaki takiplerin de daha uygun yapılacağını düşünmekteyiz. DKAY sonrasında takibe yüksek uyum sayesinde gelişebilecek hastalıklar engellenebilir ya da erken tanı konulabilir ve gerektiğinde tedavi başlanabilir. HBV aşı eksiği olan öğrencilerin aşılarının tamamlanması ve tetanoz rapel dozu açısından değerlendirilerek gereğinde aşının yapılması sağlanmalı ve staj öncesi gerekli tetkiklerin tamamlanması unutulmamalıdır.

Pandemi dolayısıyla anket formlarının yüz yüze yapılamaması nedeniyle cevapların form üzerinden oluşturulması, katılımcı sayısının görece az olması ayrıca tek merkezli ve kesitsel olarak tasarlanmış olması çalışmamızın kısıtlılıklarını oluşturmaktadır.

SONUÇ

Daha önce yapılan çalışmalar ve çalışmamız birlikte değerlendirildiğinde; öğrenciler, DKAY için riskli bir grubu oluşturmaktadır. Eğitimler; daha etkin, kalıcı ve klinik uygulamalarla pekiştirilecek şekilde düzenlenmelidir. Çalışmamız sonucunda öğrencilerin DKAY ile ilgili eğitim ve bilgi düzeylerinin düşük olduğu saptanmış ve bu yüzden de konunun eğitim müfredatında daha iyi vurgulanması gerektiği düşünülmüştür. Ayrıca eğitimler sık tekrarlanarak, senaryolaştırılarak akılda kalıcı eğitimler şeklinde düzenlenmeli ve tutum değişikliğine fayda sağlamalıdır. Tıbbi malzemelerin doğru, etkin ve güvenli şekilde kullanımı öğretilmelidir. Temas öncesi gerekli aşıların yapılması sağlanmalı ve CDC tarafından önerilen önlemlere uyum arttırılmalıdır. Gereksiz girişimsel işlemlerden kaçınılmalıdır. Enjektör ucunun elle çıkartılmaya çalışılması, kapağının kapatılmaya çalışılması gibi yanlış uygulamalar DKAY'nin büyük kısmını oluşturduğundan bu konuya özellikle dikkat edilmelidir. Özellikle bulaşabilecek enfeksiyonlar ve bu enfeksiyonlara yönelik koruyucu önlemler hakkında bilgi verilmeli ve yaralanma sonrası bildirim yapmanın önemi vurgulanmalıdır.

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Case Report
Olgu Sunumu

Hereditary Spastic Paraparesis Accompanied by Sensorimotor Axonal Polyneuropathy-A Case Report

Sensorimotor Aksonal Polinöropatiye Eşlik Eden Herediter Spastik Paraparezi-Olgu Sunumu

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ABSTRACT

Hereditary Spastic Paraplegias (HSP) are rare, genetically transferred diseases, usually presented with impairment in walking. The coexistence of HSP and polyneuropathy (PNP) in the same patient is much rare and individualized treatment should be taken into account. Here, the rehabilitation results of a case who applied for gait and balance rehabilitation with a combination of HSP and PNP will be presented in light of the literature. A 29-year-old man presented with gait difficulty and balance disorder. The patient had a spastic gait. He had bilateral pes cavus and hammer toe deformities in his feet and tibialis anterior muscles were atrophic bilaterally. Deep tendon reflexes were hypoactive in the upper limbs and hyperactive in the lower extremities. Babinski's sign was bilaterally positive. He also had mental retardation, dysarthria, and bilateral horizontal nystagmus. With all the findings, and examinations the patient was diagnosed with HSP and PNP. After the rehabilitation program, the patient's walking distance and the time to maintain his balance increased. Patients with HSP can be difficult to diagnose because of the diversity in both genetic inheritance and clinical presentation; accompanying sensory symptoms should not be overlooked and treatment should be individualized.

Keywords: Hereditary spastic paraparesis; polyneuropathy; rehabilitation

Öz

Herediter Spastik Parapareziler (HSP), genellikle yürüme bozukluğu ile ortaya çıkan, genetik olarak aktarılan nadir hastalıklardır. Aynı hastada HSP ve polinöropati (PNP) birlikteliği çok nadirdir ve kişiye özel tedavi dikkate alınmalıdır. Burada HSP ve PNP birarada saptanan, yürüme ve denge rehabilitasyonu için başvuran bir olgunun rehabilitasyon sonuçları literatür eşliğinde sunulacaktır. 29 yaşında erkek hasta yürüme güçlüğü ve denge bozukluğu ile başvurdu. Hastanın spastik yürüyüşü vardı. Ayağında bilateral pes kavus ve çekiç parmak deformiteleri vardı ve tibialis anterior kasları bilateral atrofikti. Derin tendon refleksleri üst ekstremitelerde hipoaktif, alt ekstremitelerde hiperaktifti. Babinski bulgusu bilateral pozitifti. Ayrıca zeka geriliği, dizartri ve bilateral horizontal nistagmus vardı. Tüm bulguları ve tetkikleri ile hastaya HSP ve PNP tanısı konuldu. Rehabilitasyon programından sonra hastanın yürüme mesafesi ve dengesini koruma süresi arttı. Hem genetik kalıtımdaki hem de klinik prezentasyondaki çeşitlilik nedeniyle HSP'li hastaların teşhisi zor olabilir; eşlik eden duyusal semptomlar gözden kaçırılmamalı ve tedavi bireyselleştirilmelidir.

Anahtar Kelimeler: Herediter spastik paraparezi; polinöropati; rehabilitasyon

INTRODUCTION

Hereditary Spastic Paraplegias (HSP) are a heterogeneous group of neurodegenerative diseases caused by damage to the pyramidal tract (1). Although HSP is usually inherited in autosomal dominant (AD) form (%70), it can also be inherited as autosomal recessive (AR), X-linked (XL), or mitochondrial (1). HSPs exist in isolated forms (pure HSP), or combined forms associated with neurological or non-neurological manifestations (complex HSP) (2). The features of this syndrome are lower extremity muscle weakness, spasticity, and extensor plantar response. In complicated HSP cases mental retardation, ataxia, amyotrophy, optic atrophy, pigmentary retinopathy, extrapyramidal findings, dementia, deafness, ichthyosis, peripheral neuropathy, and epilepsy can be seen (1,2). HSP is diagnosed by the exclusion of possible acquired causes or the presence of family history in addition to the characteristic clinical features (2).

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Here, a case of HSP accompanied by sensorimotor axonal polyneuropathy (PNP) will be presented since they are rarely observed in the same patient.

CASE REPORT

A 29-year-old male patient was admitted to our clinic for gait and balance rehabilitation. The patient had significant dysarthria and bilateral horizontal nystagmus that started in childhood. He had bilateral pes cavus and hammer toe deformities in his feet (**Figure 1**). Tibialis anterior muscles were atrophic bilaterally. The sensorial deficit was absent. Deep tendon reflexes were hypoactive in the upper extremities and hyperactive in the lower extremities. Babinski's sign was bilaterally positive.

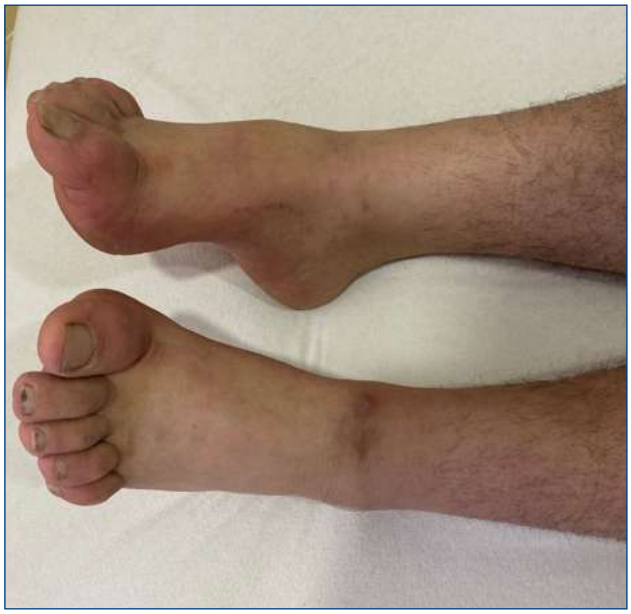

Figure 1. Bilateral pes cavus and hammer toe deformities

He had a scissor-like spastic gait. The patient was able to walk 2-3 meters under the supervision and lost his balance in a short time. The patient did not have a high palate. There was no hearing loss. The patient was evaluated by an ophthalmologist and no pathology was found. Cranial nerve functions were evaluated as normal. Corticobulbar tract involvement and autonomic involvement were not detected. There were no urinary difficulties, defecation difficulties and sexual impairment.

He had no known systemic disease. The patient started walking at the age of four and had gait disturbance and ataxia that started at the age of seven and gradually increased. He had described a slowly progressive deterioration in fine dexterity in the hands. The Intelligence Quotient test of the patient with a learning disability was compatible with moderate mental retardation.

The patient's parents were first-degree relatives and there were no relatives with similar complaints. Cranial and spinal MRIs were normal. Abdominal ultrasonography and blood parameters were normal. All genetic and metabolic tests performed for the differential diagnosis of Friedreich ataxia, Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS), Fragile X, and Niemann Pick Type C were found to be negative. In the electromyography (EMG) test, sensory nerve response amplitudes were found to be low in the sural, ulnar, and median nerves, while no pathology was found in the motor conductions examined. Needle EMG showed long-term motor unit action potentials with a reducing pattern in the bilateral tibialis anterior and gastrocnemius muscles. It has been reported that the findings obtained are compatible with an axonal polyneuropathy syndrome in which sensory and motor fibers are affected.

With all the findings, the patient was diagnosed with HSP and PNP. The patient was included in the rehabilitation program. A pair of orthopedic insoles were prescribed.

After a three-week rehabilitation program, it was seen that the patient was able to ambulate approximately three hundred and forty meters under supervision in the six-minute walking test. He was able to maintain his balance longer. The patient was discharged to be re-evaluated at the follow-up examination.

DISCUSSION

HSP is a clinically and genetically heterogeneous disease. In Europe, the prevalence of HSP is approximately 3~10/100.000 (2).

The first sign of HSP is expressing difficulty in walking. Children may have a walking delay. In addition to clinical features, it can be classified as early-onset (onset age 35 and below) and late-onset (onset age greater than 35) according to the time of onset of symptoms (3).

In pure-type HSP, symmetrical lower extremity spasticity is seen, resulting in a characteristic scissor gait (1-3). Foot deformities such as pes cavus and hammer toe can be seen in 30% of patients. Mild distal weakness and muscle atrophy may be seen in the later stages of the disease (1-3). The upper extremity is typically normal, while the lower extremity has increased tendon reflexes and Babinski sign. However, hyperactive reflexes can be obtained in the upper extremities in some patients (3). Similarly, in our case, there were hyperactive deep tendon reflexes in the lower extremities, whereas hypoactive reflexes were present in the upper extremities. This confirmed the presence of concomitant PNP.

Various genetically transmitted diseases are included in the differential diagnosis of HSP. Arginase deficiency due to spastic paraparesis; ARSACS, in which ataxia, spastic paraparesis and sensorimotor polynoropathy can be seen together, and Friedreich ataxia and Niemann Pick Type C Syndromes due to ataxia are included in the differential diagnosis (1). Brain and spine magnetic resonance imaging, complete ophthalmologic examination and full metabolic screening for inherited neurometabolic disorders, very long chain fatty acid analysis in plasma, serum

vitamin E, cobalamin, copper, ceruloplasmin levels, plasma lipoprotein and amino acid profiles, serological tests for Human Immunodeficiency Virus (HIV), Human T Cell Leukemia Virus Type I (HTLV-I), and Treponema pallidum and all exon genetic examination tests can be used to differentiate HSP from other diseases (1).

Sensory findings such as a mild decrease in vibration sense and paresthesia in the lower extremities can be found in typical HSP patients (1-3). EMG is found to be normal in most of these patients (4). This clinical finding suggests central axonopathy rather than peripheral nerve involvement. Peripheral neuropathy has been described in complicated HSPs, but it can also be detected in electrophysiological pure HSPs (5). Clinically, the level of neuropathy can vary from asymptomatic to severe neuropathy (6). Axonal neuropathy was found in nerve biopsies performed on patients with neuropathy (6). Dyck and Lambert described a form of hereditary motor and sensory polyneuropathy (HMSN) associated with HSP and classified it as "HMSN type V" (7). The loci for HSP and HMSN were analyzed considering the possibility that different mutations in the same gene might cause these two clinical tables, but a clear relationship could not be demonstrated (8). Symptoms usually begin in the second decade of life or later, and the course is usually slow. Similarly, our case underwent an EMG study that was indicative of a motor and sensory peripheral neuropathy of axonal type at the age of 28. It was thought that our patient had early-onset and complex-type HSP accompanied by ataxia, mental retardation, and PNP.

When clinical appearance and genetic features are examined together, it is seen that cases with only spasticity are mostly inherited from AD, and complicated cases are generally inherited from AR. The recessive model of inheritance is known to be common in populations with high rates of consanguineous marriages like our case (9).

There is no treatment to prevent or stop the disease process. The aim of treatment in HSP patients is to reduce spasticity, correct gait disturbance, and increase the functional gain and quality of life of the patient. Antispastic agents or surgery may be beneficial for the symptomatic treatment of HSP (10).

CONCLUSION

In cases presenting with spastic paraplegia during childhood, HSP should also be considered in the differential diagnosis, even at an early stage, consanguineous marriage, family history of walking difficulties, weakness and spasticity should be questioned, and if necessary, they should be referred for further examination and treatment. In conclusion, patients with HSP can be difficult to diagnose because of the diversity in both genetic inheritance and clinical presentation; accompanying sensory symptoms should not be overlooked and treatment should be individualized.

ETHICAL DECLARATIONS

Informed Consent: The patient signed the informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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CASE REPORT
OLGU SUNUMU

Muhtemel COVID-19 Tarafından Tetiklenen Poliarteritis Nodosa Olgusu

A Case of Polyarteritis Nodosa Triggered by Possible COVID-19

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ÖZ

Pandemi COVID-19 dışında kalan bütün hastalıkların bakımını olumsuz etkilemekle kalmamış, kliniğe etki ederek bazı hastalık tablolarını daha karmaşık hale de getirmiştir. Guillain Barre, Sistemik Lupus Eritematozus gibi bazı sistemik hastalıklarda COVID-19 enfeksiyonunun tetikleyici rolü bilinmektedir(1). Bu sunumda COVID-19 enfeksiyonunun PAN vasküliti sistemik hastalığını muhtemel tetikleyici rolünün tartışılması amaçlanmıştır. Öncesinde COVID-19 enfeksiyonu geçiren 26 yaşındaki kadın hastanın şikayetlerinin devam etmesi sebebiyle uzunca bir süre ayırıcı tanı yapıldığı; ultrasonografi, bilgisayarlı tomografi (BT), manyetik rezonans görüntüleme (MRI), positron emisyon tomografi (PET) incelemeleri yanısıra, doku biyopsisi alınarak, medikal tedavisinin metilprednizolon, metotreksat, anti-TNF, sulfasalazin ve siklofosfamid ile yapıldığı ve nihayetinde Poliarterisitis Nodosa (PAN) tanısı ile ayaktan takibe geçilen bir olgu sunulmaktadır. Otoimmün sistemik hastalıkların tanısını koymak zaman alabilir. Pandemi olarak hayatımıza giren COVID-19 enfeksiyonunun diğer viral enfeksiyon etkenlerinde olduğu gibi tetikleyici rolü dikkate alınmalıdır. Bu sunumda HBV örneğinde olduğu gibi COVID-19 tarafından PAN vaskülit kliniğinin belirgin hale getirildiği sonucu çıkarılmıştır.

Anahtar Kelimeler: COVID-19 enfeksiyonu, PAN vasküliti, kanlı ishal, nodüler lezyon

ABSTRACT

The pandemic not only adversely affected the care of all diseases except for COVID-19, but also made some disease tables more complicated by affecting the clinic. The triggering role of COVID-19 infection in some systemic diseases such as Guillan Barre and Systemic Lupus Erythematosus is known(A). In this presentation, it is aimed to discuss the possible triggering role of COVID-19 infection in PAN vasculitis systemic disease. Since the complaints of a 26-year-old female patient who had a previous COVID-19 infection continued for a long time, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) examinations for which differential diagnosis was made, as well as tissue biopsy were taken and medical treatment was methylprednisolone, methotrexate, anti-TNF, sulfasalazine, cyclophosphamide. We present a case that was followed up with the diagnosis of Polyarterisitis Nodosa (PAN). It may take time to diagnose autoimmune systemic diseases. The triggering role of COVID-19 infection, which entered our lives as a pandemic, should be taken into account, as in other viral infection factors. In this presentation, it was concluded that the PAN vasculitis clinic was made evident by COVID-19, as in the HBV example.

Keywords: COVID-19 infection, PAN vasculitis, bloody diarrhea, nodular lesion

GİRİŞ

Pandemiye yol açan COVID-19 enfeksiyonu, bazı hastalıklarla birliktelik göstererek tanı ve tedavilerde beklenenin dışında farklı klinik tablolara yol açabilmektedir. Otoimmünite kökenli hastalıklar bu noktada karşımıza çıkan önemli bir vaka grubudur. PAN'ın klasik başvuru belirtilerini içeren yakınmalar, diğer bazı sistemik hastalıkların belirtileriyle benzer olabildiğinden (2), hastalardaki non-spesifik semptomların varlığında oldukça geniş bir yelpazede ayırıcı tanı yapılması icap edebilmektedir. İlk kez 1852'de tanımlanan PAN (3), 2012'deki son kılavuzda orta veya küçük arterlerin anti-nötrofil sitoplazmik antikorlar (ANCA'lar) ile ilişkisi olmayan nekrotizan arteriti olarak raporlanmaktadır (4). İnsidansı 0-1,6 vaka/milyon, prevalansı 31 vaka/milyon, ortalama tanı yaşı 51 olup, erkek cinsiyette daha fazla görülmektedir. PAN vaskülitinin en önemli klinik belirtileri uyuşma ve yanma şeklindeki periferik sinir ile çoğu zaman nodül olarak görülen cilt bulgularını içermektedir. BT ya da MRI görüntüleme ile elde edilen anjiografilerde renal, me-

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zenterik ve/veya çölyak arterlerde mikroanevrizma tespiti ve lezyondan yapılan doku örneklemelerindeki karakteristik biyopsi bulguları (2) olması klinik belirtiler ile birlikte tanıyı doğrulamaktadır. Biyokimyasal analizler tanısal olmamakla birlikte, organ tutulum düzeyleri hakkında fikir verebilir. PAN vasküliti tedavisinde glukokortikoidler ve siklofosfamidler öncelikli yer alırken, HBV ile ilişkili PAN olduğunda antiviral ajanlar kullanılmaktadır (5).

Bu yazıda klasik olmayan, belirtilerin iç içe geçtiği bir PAN vasküliti olgusunun COVID-19 ile komplike olmuş ayırıcı tanısı ve yapılan hasta yönetimini sunmak amaçlanmıştır.

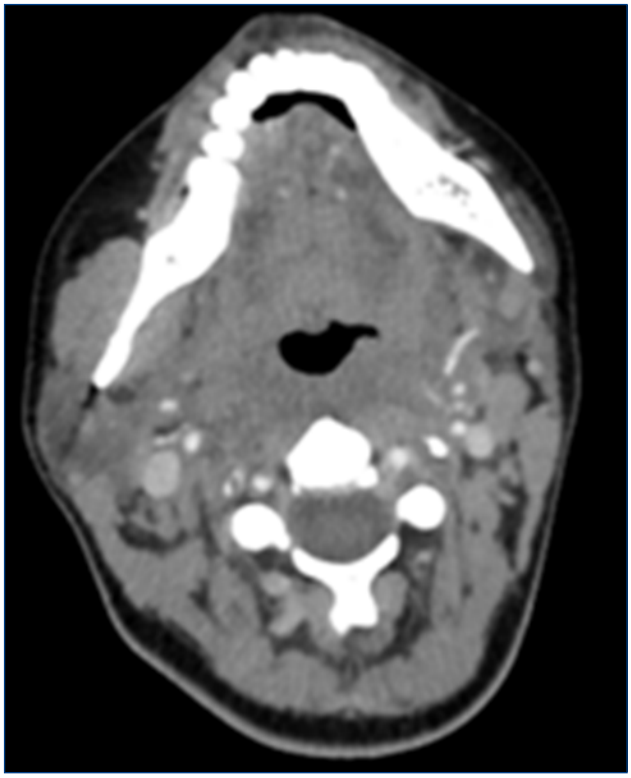
OLGU SUNUMU

Boğaz ağrısı, şişlik ve yutma güçlüğü yanı sıra sol el bileği ve bilateral bacak distalinde inflamasyon izlenimi veren ağrı ve şişlik şikayetleri ile başvuran 26 yaşındaki kadın hastadan, 3 hafta önce COVID-19 enfeksiyonu geçirdiği ancak son iki haftadır yakınmalarının artarak devam ettiği anamnezi alınmıştır. Sorgulamasında göz ve ağız kuruluğu olmadığı gibi başka özellikli bir özgeçmiş bilgisine de rastlanmamıştır.

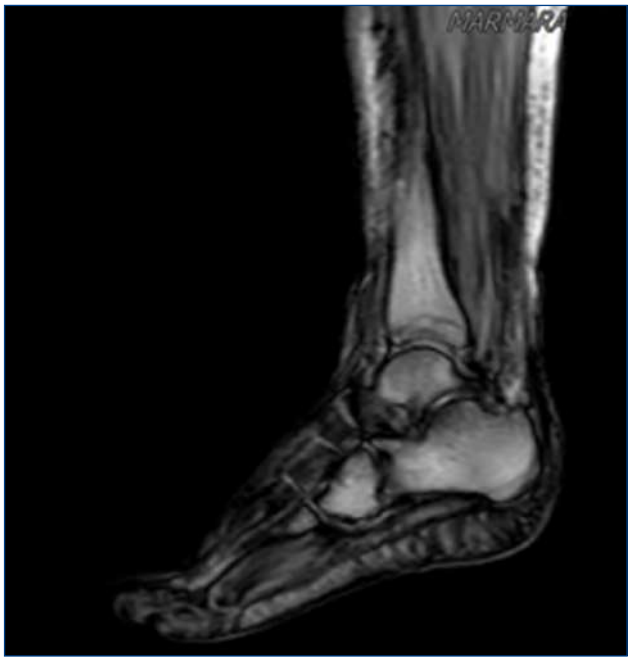
Fizik muayenede ateş (37.5°C), taşikardi (120/dk), sol parotis bölgesine uyan alan ve dilde şişlik, oral mukozada hiperemi ve beyaz plak görünümlü lezyonlar saptanmıştır. Sol el bileğinde ödem ve hareket kısıtlılığı ile bilateral diz tibia şaftına uyan bölgede hassasiyet, şişlik ve ısı artışı saptanmıştır.

USG ile sağ submandibular gland boyutlarında heterojen artma ve iki adet servikal LAP, bilgisayarlı tomografide major tükrük bezlerinde büyüme (**Resim 1**) saptanırken, ekokardiyografi ve alt ekstremite venöz doppler ultrasonografik muayenesinde özellik tespit edilmemiştir. MRI'da 3. metatarsal kemik iliği ödemi ve periost reaksiyonu ile birlikte kemik çevresinde yumuşak doku ödemi izlenmiştir (**Resim 2**). PET incelemesinde malignite lehine bulgu görülmezken, ekstremiteye ait hafif düzeyde enflamasyon tespit edilmiştir. Minor tükürük bezi biyopsisinde özellik bulunmamıştır.

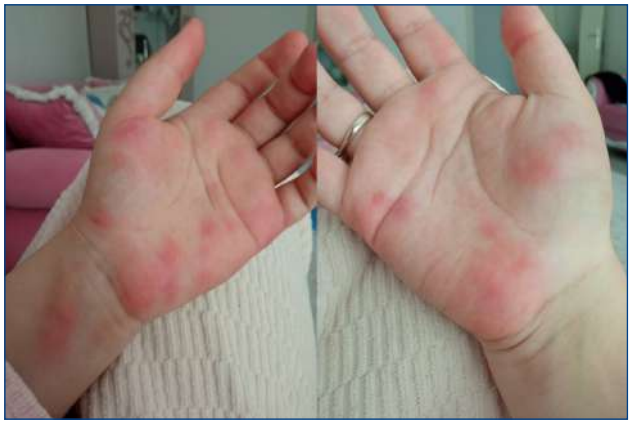
Başvurunun beşinci günü enfeksiyon dışı bir tanı için inceleme başlatılmış ve hastaya 1 g/kg/gün metilprednizolon intravenöz olarak 7 gün uygulandıktan sonra, ilaç dozu 16 mg/gün'e düşürülmüştür. Hastaya parmak uçlarındaki morarma ve şiddetli ağrı sebebiyle antikoagülan olarak düşük molekül ağırlıklı heparin başlanmıştır. Metilprednizolon 32 mg/gün'e çıkarılmış ve haftada 1 gün 15 mg subkutan metotreksat, 4 hafta süreyle verilmiştir. Klinik tabloda iyileşme görülmekle birlikte, beklenen remisyon ve akut faz reaktan cevabı alınmayan hastanın tedavisine anti-TNF eklenmiştir. Bu esnada şiddetli karın ağrısı ve kanlı ishal atakları olması üzerine yapılan batın MRI incelemesinde jejunal anslarda difuz simetrik duvar kalınlığı ve mukozal kontrast tutulumu tespit edildiğinden, kolonoskopi yapılmış ancak patoloji saptanmamıştır. Hastanın takibinin dördüncü ayında el ve ayaklarda nohut büyüklüğünde multipl nodüler lezyonlar ortaya çıkmıştır (**Resim 3**). Lezyonlardan yapılan doku biyopsisinde geç dönem vaskülit bulguları elde edilmiş ve hastada PAN tanısı kesinleştirilmiştir. Bu aşamadan sonra oral 16 mg/gün metilprednizolon tedavisine, 12 saat ara ile oral 2 mg sülfasalazin eklenmiştir. İki hafta sonra yapılan kontrollerde hedeflenen klinik ve laboratuvar remisyon oluşmadığından, intravenöz 500 mg siklofosfamid başlanmış, 15 ve 30. günlerde aynı doz tekrarlanmıştır. Ayaktan tedavi ve takibi devam etmektedir.



Resim 1: Baş Boyun BT'de Major Tükürük Bezlerinde Büyüme



Resim 2: Üçüncü Metatarsal Kemik Çevresi Yumuşak Doku Ödemi



Resim 3: Sol ve Sağ Ellerde Multipl Nohut Büyüklüğünde Nodüler Lezyonlar

TARTIŞMA

Otoimmün hastalıkların tanı ve tedavi süreçlerindeki zorluklar bilinmekle birlikte, güncel ve kademeli algoritmalara uyularak yapılan yönetimler önemini korumaktadır. Erken tanı ve tedavi için yapılan araştırmalara burada sunulan olgunun da katkı sağlayacağı düşünülmektedir. Üstelik COVID-19 pandemisi eşliğinde karşımıza çıkan otoimmün hastalıkların günümüzde, seçimi, tanı alması ve tedavi edilmesinin daha da güçleştiği söylenebilir.

Bakteriyel etyoloji düşünülerek yapılan antibiyoterapiden sonuç alınamadığından, peritonsiller apse düşünülerek baş boyun BT ile yeniden değerlendirilen hastada parotis bezinde görülen diffüz büyüme tanıya ulaşmadaki ilk adım olarak görülmektedir. Serum IgG4 düzeyinin beklenen referans sınırları içerisinde olması, Mikulicz sendromundan uzaklaştırmış olmakla birlikte, tükürük bezi biyopsisi ile kesin olarak ekarte edilmiştir. Bu süreçte yapılan metilprednizolon tedavisine yeterli cevap alınamamış olması daha ileri ayırıcı tanı ihtiyacı olduğunu göstermiştir. Takipler sırasında ortaya çıkan kanlı ishal atakları bu noktada öncelikle inflamatuar bağırsak hastalığı, divertikül ve diğer bazı gastrointestinal patolojiler için şüphe uyandırmış ancak kanlı ishal şikayetinin sebebi yapılan değerlendirmelerde izah edilemediğinden, otoimmün tanı üzerinde yeniden durulmaya devam edilmiştir. Yapılan abdominal MRI ve BT anjiografik incelemelerinde özellik saptanmamış olması, PAN vasküliti için tanısal değeri olan mikroanevrizmaların görülmemesi ile sonuçlanmıştır. Hastanın klinik takipleri devam ederken, yaklaşık dördünce ayında el ve ayaklarında nohut büyüklüğünde nodüllerin ortaya çıkması tanıya giden yoldaki düğümü çözmüş ve nodüllerden biyopsi yapılmıştır. Bütüncül olarak yeniden ele alınan hastanın eklem şikayetleri, kanlı ishal atakları, el ve ayaklarında görülen nodüllerinin PAN vasküliti kaynaklı olduğu sonucuna varılmıştır. Geriye doğru incelendiğinde, takipler sırasında metilprednizolon tedavisine CRP ve sedimentasyon yanıtının alınması da PAN tablosunu destekleyen başka bir bulgu olabileceği değerlendirilmiştir. PAN vaskülitine yönelik steroid ve siklofosfamid verilmesiyle ortaya çıkan klinik ve labaratuvar remisyonu da ayrıca gözlemlenmiştir.

Prediyabetin viral hastalıklar ile bariz diyabete dönüştüğü bilinmektedir (6). Ayrıca, PAN vasküliti hepatit B ilişkili olduğundan (7) ve sunulan vakada hepatit ilişkili testlerin negatif olmasından dolayı, COVID-19'un PAN vaskülitine dair klinik tabloyu ortaya çıkardığı değerlendirilmektedir. Literatürde bu içerikte yeterli bilgi bulunmadığından, COVID-19 ile PAN vasküliti ilişkisinin daha ileri araştırmalarla ele alınması önerilmektedir. Pandemi sırasında tanı alan PAN vaskülitinin, COVID-19 viral enfeksiyonu ile tetiklenmiş olabileceği düşünülmektedir.

ETİK BEYANLAR

Aydınlatılmış Onam: Bu çalışmaya katılan hasta(lar)dan yazılı onam alınmıştır.

Hakem Değerlendirme Süreci: Harici çift kör hakem değerlendirmesi.

Çıkar Çatışması Durumu: Yazarlar bu çalışmada herhangi bir çıkara dayalı ilişki olmadığını beyan etmişlerdir.

Finansal Destek: Yazarlar bu çalışmada finansal destek almadıklarını beyan etmişlerdir.

Yazar Katkıları: Yazarların tümü; makalenin tasarımına, yürütülmesine, analizine katıldığını ve son sürümünü onayladıklarını beyan etmişlerdir.

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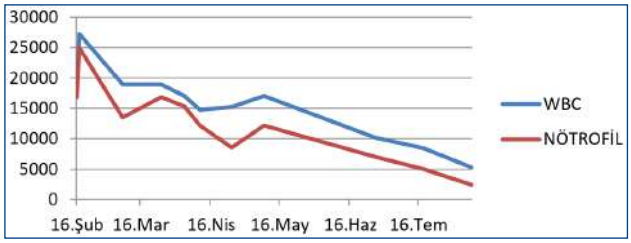
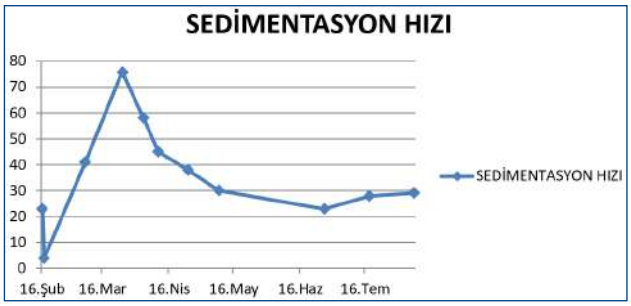
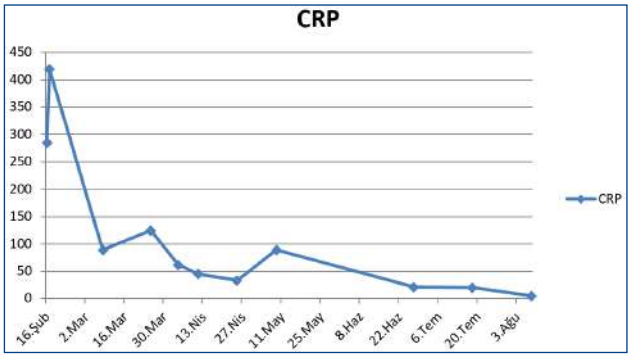


Şekil 1: Başvuru Anından İtibaren WBC-Nötrofil mcL Cinsinden Seyri



Şekil 2: Başvuru Anından İtibaren Sedimentasyon Hızı mm/saat Cinsinden Seyri



Şekil 3: Başvuru Anından İtibaren CRP mg/dL Cinsinden Seyri

Tablo 1: Hastaya Ait Bazı Viral ve Romatolojik Belirteçler

	SONUÇ
HBs Ag	NEGATİF
Anti HBs	NEGATİF
IGG4	NEGATİF
ANA	NEGATİF
ENA Profili	NEGATİF
MPO/PR3	NEGATİF

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CASE REPORT
OLGU SUNUMU

A Case of Deep Thrombocytopenia which had Successfully Received Prolonged Trimethoprim Sulfametaxazole Treatment for Nocardiosis

Derin Trombositopeniye Rağmen Uzun Süreli Trimetoprim Sülfametaksazol Tedavisini Başarıyla Tamamlayan Bir Nokardiyoz Olgusu

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ABSTRACT

Thrimethoprim sulfametaxazole (TMP/SMZ), is usually not preferred to use long time because of its potential to lead thrombocytopenia.But especially in chronic infections which require long lasting treatments, it is an important choice because its oral form is available. We present a case of nocardiosis which had been treated and survived succesfully despite his concomitant deep thrombocytopenia due to idiopathic thrombocytopenic purpura.

Keywords: Trimethoprim/sulfamethoxazole, thrombocytopenia

ÖZ

Trimetoprim sülfometaksazol (TMP/SMZ), trombositopeni yapma potansiyeli nedeni ile kullanımından çekinilen bir antibiyotiktir. Ancak nokardiyoz gibi bazı uzun süreli tedavi gerektiren enfeksiyonlarda, oral kullanılabilmesi nedeni ile vazgeçilmez bir ajandır. Biz de olgumuzda uzun süreli oral tedaviyi eşlik eden, idiyopatik trombositopenik purpura(ITP) tablosuna bağlı bağlı derin trombositopenisine rağmen başarı ile sürdüren ve tamamlayan bir nokardiyoz olgusu sunmaktayız.

Anahtar Kelimeler: Trimetoprim/sülfametoksazol, trombositopeni

INTRODUCTION

Sulfonamides are among the earliest antimicrobials. Today their representative in common practice is the trimethoprim-sulfamethoxazole (TMP/SMZ) compound(1). It is active against many microorganisms, but some serious side effects like renal dysfunction, thrombocytopenia, and dermatological reactions are not rare and make it less prescribed than it could be. In some cases, it can be a great challenge to a clinician when obliged to use TMP/SMZ because of the shortness of other alternatives. We present such a case with prolonged use of TMP/SMZ despite profound thrombocytopenia.

CASE REPORT

A 65 years old male patient, who was followed in hematology clinics for severe thrombocytopenia had been diagnosed with ITP and given 48mg/day methylprednisolone for 2 months. Because his thrombocytopenia did not improve and persisted at the level of 11×10^9/L, He was assessed as a non-responder to steroid treatment and splenectomy was planned after IVIG treatment.

While his platelets returned to normal after discontinuation of steroid treatment, he has been diagnosed with pneumonia plus central nervous system infection due to Nocardia spp unfortunately. He was initially given intravenous triple agents treatment of TMP/SMZ, imipenem, and amikacin for 21 days, and then oral TMP/SMZ as a

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sequential treatment alone. Folinic acid was started simultaneously with TMP/SMZ. But his platelets decreased to 1×10^9/L on the 24th day of treatment and he couldn't tolerate the drug orally because of gastrointestinal discomfort. Again imipenem and amikacin for nocardiosis and thrombopoietin receptor agonist (TRA) for supporting thrombopoiesis were started while TMP/SMZ was stopped. After 1 month of alteration, his platelets were still under 3×10^9/L. This decrease was assessed as due to TMP/ SMZ.

When 2,5 months of the treatment was attained, infection has been recovering, but his platelet levels were still very low despite TRA and other treatments. As good news, the platelets were large at the peripheral blood smear and the patient had no bleeding. He had a persistent demand for discharge and his only reason for hospitalization was nocardiosis treatment which had to continue for at least 6 months.

Because the only oral treatment choice for nocardiosis was TMP/SMZ, the team decided to discharge the patient with that antibiotic. The patient was informed about the importance of regular use of drugs, preventing himself from trauma, and coming to frequent policlinic control and was sent home.

One month later, he was seen in a policlinic control visit at the end of 3,5 months of the nocardiosis treatment. His platelets were determined as 2×10^9/ L but he had no bleeding in this period and his general condition was well with no other symptoms. He told that oral TMP/SMZ had caused a mildly itchy rash but antihistaminics did well. Hematologists had stopped his TRA treatment because they thought it had no benefit.

The next month's control peripheral blood smear showed that platelets couldn't save their large forms without TRA treatment, so it was begun again.

The patients' lung and CNS lesions were seen in resolution at follow-up visits while he had no bleeding despite insisting platelet levels of 3×10^9/L. The treatment was stopped after 6,5 months of total antibiotic use and 4 months of TMP/SMZ alone and continuously; because he was assumed as cured.

The first post-treatment control visit was on the 15th day and his platelets were 2×10^9/L.

Elective splenectomy was made 2 months after nocardiosis treatment had been stopped and his platelets reached to the level of 316×10^9/L.

DISCUSSION

Thrombocytopenia is one of the most recognized adverse events due to TMP/SMZ and is closely related to discontinuation, even exclusion from treatment (2). Although the main mechanism of thrombocytopenia is due to impaired folate use, drug-induced immune thrombocytopenia is also reported (1,3-5). But our patient had received this treatment for a long time despite his thrombocytopenia and survived by partial support of thrombocyte increasing agents and close follow-up. There are some reports of immune thrombocytopenia patients who received TMP/SMZ for infection prophylaxis during rituximab treatment but the dose is low: double-strength (160/800 mg) tablets q12 h, two times a week (6). Another report is about cutaneous nocardiosis of an immune thrombocytopenia patient treated with TMP/ SMZ for three months. The platelet count is mentioned as 35×10^9/L at the beginning of the treatment but there is no information about platelet levels during follow-up (7). Another else report is the treatment of an HIV patient with toxoplasmosis by TMP/SMX+ clindamycin regimen for 4-6 weeks: they report that none of the 25 patients had severe thrombocytopenia during treatment (8). Our patient seems the longest treatment receiving one with the deepest thrombocytopenia.

CONCLUSION

Especially, long-time treatment necessities with no other options may lead to such risky decisions, and in well-chosen patients, this treatment approach may be useful.

ETHICAL DECLARATIONS

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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CASE REPORT
OLGU SUNUMU

The Efficacy of Pazopanib in Ewing Sarcoma

Ewing Sarkomunda Pazopanib'in Etkinliği

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ABSTRACT

Ewing sarcoma is the second most common bone cancer in children, and is an aggressive bone and soft tissue cancer in children and young adults. Extraosseous tumors account for approximately 20% of all tumors, with the pelvis being the most commonly affected bone. The 5-year overall survival rate for localized cancer treated with a multimodal approach such as chemotherapy, radiotherapy, and surgery is 70%, but it is less than 30% for metastatic cancer. Poor prognostic factors include pelvis or sacrum primary localization, age over 18, large tumor size, and elevated lactate dehydrogenase levels. Pazopanib's therapeutic effect in the treatment of metastatic extraosseous Ewing sarcoma is unknown. There are only a few case reports about the effectiveness of pazopanib. We present a case of metastatic extraosseous Ewing sarcoma that was successfully treated solely with pazopanib for 8 years without chemotherapy.

Keywords: Ewing Sarcoma, pazopanib, treatment outcome

ÖZ

Ewing sarkomu çocuklarda en sık görülen ikinci kemik kanseri ve çocuklarda ve genç yetişkinlerde agresif bir kemik ve yumuşak doku kanseridir. Ekstraosseöz tümörler tüm tümörlerin yaklaşık %20'sini oluşturur ve pelvis en sık etkilenen kemiktir. Kemoterapi, radyoterapi ve cerrahi gibi multimodal bir yaklaşımla tedavi edilen lokalize kanser için 5 yıllık genel sağkalım oranı %70'tir, ancak metastatik kanser için bu oran %30'dan azdır. Kötü prognostik faktörler arasında pelvis veya sakrum primer lokalizasyonu, 18 yaş üstü, büyük tümör boyutu ve yüksek laktat dehidrogenaz seviyeleri yer almaktadır. Pazopanib'in metastatik ekstraosseöz Ewing sarkomu tedavisindeki terapötik etkisi bilinmemektedir. Pazopanibin etkinliği hakkında sadece birkaç vaka raporu bulunmaktadır. Bu yazıda, kemoterapi uygulanmaksızın 8 yıl boyunca sadece pazopanib ile başarılı bir şekilde tedavi edilen metastatik ekstraosseöz Ewing sarkomlu bir olgu sunulmuştur.

Anahtar Kelimeler: Ewing Sarkomu, pazopanib, tedavi sonucu

INTRODUCTION

Tumors in the Ewing sarcoma family include Ewing sarcoma (ES), peripheral neuroectodermal tumor (PNET), malignant small cell tumor of the thoracopulmonary region (Askin's tumor), and atypical ES. Because they have similar histopathological and immunohistochemical staining patterns, they are thought to have originated from a single mesenchymal progenitor cell; they also share a common chromosomal translocation (1). The most commonly affected region is the pelvis, followed by the axial skeleton and the femur. Patients present to the clinic with localized swelling and pain, and the majority of patients treated have local recurrence (2). The 5-year overall survival rate for localized cancer treated with a multimodal approach such as chemotherapy, radiotherapy, and surgery is 70%, but it is less than 30% for metastatic cancer (3). In a children's oncology group study, adverse factors included pelvic origin, age over 18 years, tumor size greater than 8 cm, and chemotherapy without ifosfamide/etoposide (IE) (4). The standard treatment for ES is vincristine, doxorubicin, cyclophosphamide (VAC), and IE. VAC/IE for 4-6 cycles preoperatively or before local treatment, then VAC/IE for 14-17 cycles is administered for patients with local presentation (5).

CASE REPORT

A 23-year-old woman presented to our clinic in 2014 with complaints of leg pain, abdominal pain, and an inguinal mass. A mass in the pelvis was discovered using abdominal ultrasonography imaging. 18 FDG-PET/CT imaging revealed a 16x13x17.5 cm mass in the pelvis

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that was destroying the right iliac bone, sacrum, and descending to the right acetabulum. Pathology of a trucut biopsy of the mass revealed small round cells with scant cytoplasm; immunohistochemical staining revealed CD 99 positivity and pan CK, EMA, vimentin, chromogranin, synaptophysin, CD 56, and LCA negativity (**Figure 1**).

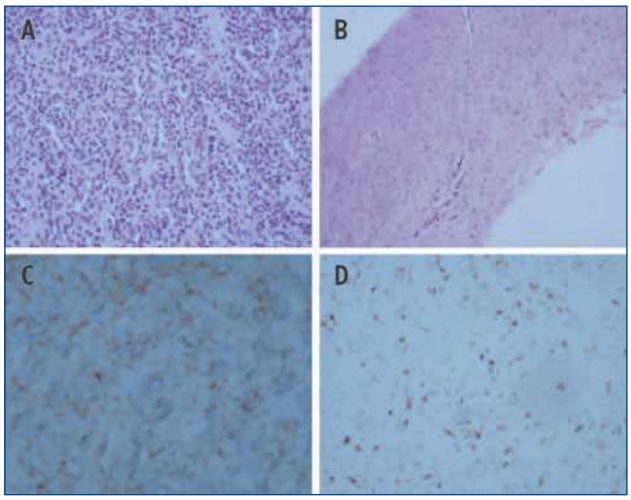

Figure 1. (A) Oval-round shaped hypercellular area consisting of cells with narrow cytoplasm (x20, H&E), **(B)** Area in chondroid structure observed as tumor continuity (x10, H&E), **(C)** Positive staining with CD99 (x40), **(D)** Positive staining with Desmin (x40)

FISH analysis revealed a t(11,22) (q24,p12) fusion transcriptor gene, EWSR 1- FLI1. A VAC/IE chemotherapy regimen of four cycles was planned preoperatively. After four cycles of chemotherapy, 18 FDG-PET/CT imaging revealed stable disease pattern. A multidisciplinary tumor board made the decision to operate on the patient. However, the patient refused the operation. She refused further chemotherapy. Radiotherapy was applied to the pelvic primary tumor. After 6 months of follow-up, a left supraclavicular metastatic lymph node was detected. Biopsy revealed Ewing sarcoma metastasis. Pazopanib 800 mg/day was started orally. After three months, 18 FDG-PET/CT imaging revealed that the primary and the metastatic mass had metabolic response and there were no new lesions. She used pazopanib for 4 years with effective control of the metastatic disease. She stopped using the drug and after 4 months a new 2 cm diameter mass in the lung and new mediastinal lymph nodes thought to be metastatic were detected by contrast-enhanced tomography.. Trucut biopsy of the mass in the lung revealed Ewing sarcoma metastasis. Pazopanib was started again and the metastatic disease was stable after the re-initiation of pazopanib. She was treated with pazopanib 800 mg/day for 4 more years. The only side effect of this long usage of pazopanib was skin depigmentation. She admitted to the emergency clinic with headache and dizziness. Magnetic resonance imaging revealed a 3 cm mass in the occipital lobe. Palliative radiotherapy was applied to the brain metastasis. She refused intravenous chemotherapy. Oral temozolomide was begun. The patient provided informed consent.

DISCUSSION

The cell of origin in ES is thought to have neuroectodermal origin. Almost all cases show reciprocal translocation, including the EWSR 1 gene on chromosome 22. Even if the disease is localized, ES is considered a systemic disease because the majority of patients who do not receive systemic intensive chemotherapy will develop metastases within a year. After receiving localized radiotherapy, our patient refused systemic chemotherapy. Pazopanib 800 mg/day was prescribed to the patient. Pazopanib is a multitargeted tyrosine kinase inhibitor that is taken orally and is approved for the treatment of soft tissue sarcomas other than gastrointestinal stromal sarcoma and liposarcoma. The precise mechanism of action of pazopanib in soft tissue sarcoma is unknown. There are only a few case reports in the literature about the effect of pazopanib in ES patients, and the progression-free survival reported in those studies was only a few months. In our case, the patient has been responding to pazopanib for nearly 8 years.

CONCLUSION

Pazopanib can be used for years with tolerable side effects. It is not known which patients will benefit from pazopanib; a marker or clue is needed for patient selection. For further proof of clinical benefit in patients with soft tissue sarcoma, controlled randomized clinical trials with pazopanib are required.

ETHICAL DECLARATIONS

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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