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INSTRUCTIONS FOR AUTHORS

AIM AND SCOPE

The Journal will not consider manuscripts any that have been published elsewhere, or manuscripts that are being considered for another publication, or are in press. Studies previously announced in the congresses are accepted if this condition is stated. If any part of a manuscript by the same author(s) contains any information that was previously published, a reprint or a copy of the previous article should be submitted to the Editorial Office with an explanation by the authors

A technical review is performed to confirm that all of the required documentation has been submitted and to conduct a preliminary evaluation of the manuscript and supplementary files to assess suitability for the Journal. The manuscript will be returned to the Author in the event of any deficiency.

Pediatric Practice and Research Journal operates a blind review process. Contributions deemed suitable are then typically sent to a minimum of two independent expert reviewers in the field of study to assess the scientific quality of the paper.

The Editor/Editors are responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. If necessary, author(s) may be invited to submit a revised version of the manuscript. This invitation does not imply that the manuscript will be accepted for publication. Revised manuscripts must be sent to the Editorial Office within 4 (four) weeks, otherwise they will be considered as a new application. The corresponding author will be notified of the decision to accept or reject the manuscript for publication.

Statements and suggestions published in manuscripts are the authors' responsibility and do not reflect the opinions of the Editor, Associate Editors and the Editorial Board members.

The manuscript will not be returned to the authors whether the article is accepted or not. Copyright fee is not paid for the articles published in the journal. A copy of the journal will be sent to the corresponding author.

Language of the Journal

The official languages of the Journal are Turkish and English. The manuscripts that are written in Turkish have abstracts in English, which makes the abstracts available to a broader audience.

Authorship Criteria

After accepted for publication, all the authors will be asked to sign "Coyright Transfer Form" which states the following: " This work is not under active consideration for publication, has not been accepted for publication, nor has it been published, in full or in part (except in abstract form). I confirm that the study has been approved by the ethics committee. " All authors should agree to the conditions outlined in the form.

Pediatric Practice and Research Journal has agreed to use the standards of the International Committee of Medical Journal Editors. The author(s) should meet the criteria for authorship according to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. It is available at www.icmje.org.

Ethical Responsibility

The protocol of clinical research articles must be approved by the Ethics Committee.

In all studies conducted on humans, the "Material and Method" section was approved by the relevant committee or the Helsinki Declaration of Principles (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/).

It should be stated in the text that all persons included in the study signed the am Informed Consent Form ".

The articles submitted to the Pediatric Practice and Research Journal will be deemed to have been conducted in accordance with the Helsinki Declaration of Principles, and have received ethical and legal permissions and will not be held responsible.

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.

If Ethics Committee Approval is required in the article; the received document should be sent with the article.

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The manuscript should be submitted to the Academic Plagiarism Prevention Program by the authors.

It is the authors' responsibility to ensure that the article complies with the ethical rules.

Policy of Screening for Plagiarism

The manuscripts are scanned by the Journal using the iThenticate program for determination of plagiarism and non-ethical situations. Pediatric Practice and Research Journal will immediately reject manuscripts leading to plagiarism.

TYPES OF MANUSCRIPT

Manuscripts should be submitted online via www.pprjournal.com

Original Articles should not exceed 3000 words and should be arranged under the headings of Abstract (not more than 300 words), Introduction, Materials and Methods, Results, Discussion, Conclusion and References.

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.

Letter to the Editor should not exceed 500 words. Short relevant comments on medical and scientific issues, particularly controversies, having no more than five references and one table or figure are encouraged. Where letters refer to an earlier published paper, authors will be offered right of reply.

Reviews are not accepted unless written on the invitation of the Editorial Board.

PREPARATION OF MANUSCRIPTS

All articles submitted to the Journal must comply with the following instructions:

a) Submissions should be doubled-spaced and typed in Arial 10 points.

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.

Title

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

Abstract

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.

Keywords

Not more than five keywords in order of importance for indexing purposes should be supplied below the abstract and should be selected from Index Medicus Medical Subject Headings (MeSH), available at www.nlm.nih.gov/meshhome.html.

Text

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.

References

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.

References should be listed in the following form:

Journal article

Teke Z, Kabay B, Aytekin FO et al. Pyrrolidine dithiocarbamate prevents 60 minutes of warm mesenteric ischemia/reperfusion injury in rats. Am J Surg 2007;194(6):255-62.

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

Sample1: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Sample 2: Sümbüloğlu K, Akdağ B. Regresyon Yöntemleri ve Korelasyon Analizi. Hatiboğlu Yayınevi: Ankara; 2007.

Chapter in a book

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

An organization as an author

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.

Tables

Tables should be complementary, but not duplicate information contained in the text. Tables should be numbered consecutively in Arabic numbers, with a descriptive, self-explanatory title above the table. All abbreviations should be explained in a footnote. Footnotes should be designated by symbols in the following order: *,†, ‡, §, ¶.

Figures

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.

Figure Legends

Legends should be self-explanatory and positioned on a separate page. The legend should incorporate definitions of any symbols used and all abbreviations and units of measurements should be explained. A letter should be provided stating copyright authorization if figures have been reproduced from another source.

Measurements and Abbreviations

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.

Editorial Correspondence

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YAZARLARA BİLGİ

AMAÇ ve KAPSAM

Pediatric Practice and Research 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.

Pediatric Practice and Research Dergisi, bilimsel yayınlara açık erişim sağlar. Dergi basımından hemen sonra, makalelerin tam metinlerine ücretsiz ulaşılabilir.

Dergide yayımlanmak üzere gönderilen yazıların daha önce başka bir yerde yayımlanmamış veya yayımlanmak üzere gönderilmemiş olması gerekir. Daha önce kongrelerde sunulmuş çalışmalar, bu durum belirtilmek koşuluyla kabul edilir. Makale, yazar(lar) ın daha önce yayımlanmış bir yazısındaki konuların bir kısmını içeriyorsa bu durum belirtilmeli ve yeni yazı ile birlikte önceki makalenin bir kopyası da Yayın Bürosu'na gönderilmelidir.

Gerekli tüm belgelerin sunulduğunu teyit etmek ve dergiye uygunluğunu değerlendirmek için makale ve ek dosyaların ön değerlendirmesini yapmak üzere teknik bir inceleme yapılır. Herhangi bir eksiklik olması halinde makale yazara iade edilecektir. Pediatric Practice and Research Dergisi kör bir inceleme süreci yürütmektedir. Uygun görülen yazılar daha sonra makalenin bilimsel kalitesini değerlendirmek için çalışma alanında en az iki bağımsız uzmana gönderilir. Editör / Editörler makalelerin kabulü veya reddi ile ilgili nihai karardan sorumludur.

Editörün kararı kesindir. Gerekli olduğu durumlarda, yazar(lar) dan düzeltme istenebilir. Yazardan düzeltme istenmesi, yazının yayımlanacağı anlamına gelmez. Bu düzeltmelerin en geç 21 gün içinde tamamlanıp dergiye gönderilmesi gereklidir. Aksi halde yeni başvuru olarak değerlendirilir. Sorumlu yazara yazının kabul veya reddedildiğine dair bilgi verilir.

Dergide yayımlanan yazıların etik, bilimsel ve hukuki sorumluluğu yazar(lar)a ait olup Editör, Editör Yardımcısı ve Yayın Kurulu'nun görüşlerini yansıtmaz.

Dergide yayımlanması kabul edilse de edilmese de, yazı materyali yazarlara geri verilmez. Dergide yayımlanan yazılar için telif hakkı ödenmez. Bir adet dergi, sorumlu yazara gönderilir.

Derginin Yazı Dili

Derginin yazı dili Türkçe ve İngilizcedir. Dili Türkçe olan yazılar, İngilizce özetleri ile yer alır. Yazının hazırlanması sırasında, Türkçe kelimeler için Türk Dil Kurumundan (www.tdk.gov.tr), teknik terimler için Türk Tıp Terminolojisinden (www.tipterimleri.com) yararlanılabilir.

Yazarlık Kriterleri

Dergide yayınlanması uygun bulunan tüm yazıların araştırma ve yayın etiğine uygun hazırlandığı, varsa sağlanan fonun kaynağının tanımlandığı, başka yerde yayımlanmadığı veya yayımlanmak üzere gönderilmediği, çalışmaya katılan tüm yazarlar tarafından yazının son halinin onaylandığı, yayımlanacak yazı ile ilgili telif haklarının dergiye devredildiği, tüm yazarların imzaları ile "Yayın Hakkı Devir Formu"nda belirtilmesi gerekir.

Pediatric Practice and Research Dergisi, Uluslararası Tıp Dergileri Editörleri Kurulu'nun (International Committee of Medical Journal Editors) "Biyomedikal Dergilere Gönderilen Makalelerin Uyması Gereken Standartlar: Biyomedikal Yayınların Yazımı ve Baskıya Hazırlanması (Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication)" standartlarını kullanmayı kabul etmektedir. Bu konudaki bilgiye www.icmje.org adresinden ulaşılabilir.

Etik Sorumluluk

Etik Sorumluluk / Kurallar: Klinik araştırma makalelerinin protokolü Etik Komitesi tarafından onaylanmış olmalıdır.

İnsanlar üzerinde yapılan tüm çalışmalarda "Gereç ve Yöntem" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklarasyonu'na (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır.

Çalışmaya dahil edilen tüm kişilerin Bilgilendirilmiş Onam Formu'nu imzaladığı metin içinde belirtilmelidir.

Pediatric Practice and Research Dergisi'ne gönderilen makalelerdeki çalışmaların Helsinki İlkeler Deklarasyonu'na uygun olarak yapıldığı, kurumsal etik ve yasal izinlerin alındığı varsayılacak ve bu konuda sorumluluk kabul edilmeyecektir.

Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntem bölümünde hayvan haklarını Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda koruduklarını, çalışmalarında ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.

Olgu sunumlarında hastanın kimliğinin ortaya çıkmasına bakılmaksızın hastalardan "Bilgilendirilmiş rıza" alınmalıdır.

Makalede ticari bağlantı veya çalışma için maddi destek veren kurum (doğrudan veya dolaylı) mevcut ise yazarlar; kullanılan ticari ürün, ilaç, firma ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar vs.), editöre sunum sayfasında bildirmek zorundadır.

Makalede Etik Kurul Onayı alınması gerekli ise; alınan belge makale ile birlikte gönderilmelidir.

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Makale yazarlar tarafından akademik intihal önleme programından geçirilmelidir.

Makalenin etik kurallara uygunluğu yazarların sorumluluğundadır.

İntihal Taraması Politikası

Makaleler, intihal ve etik olmayan durumların belirlenmesi için iThenticate programı kullanılarak Journal tarafından taranır. Pediatric Practice and Research Dergisi intihallere yol açan makaleleri derhal reddedecektir.

YAZI TÜRLERİ

Yazılar, elektronik ortamda www.pprjournal.com adresine gönderilir.

Orijinal makaleler, 3000 sözcük sayısını aşmamalı, "Öz (en fazla 300 kelime), Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç, Kaynaklar" bölümlerinden oluşmalıdır.

Olgu Sunumu, "Öz, Giriş, Olgu Sunumu, Tartışma, Kaynaklar" şeklinde düzenlenmelidir. En fazla 1000 sözcük ile sınırlıdır. Sadece bir tablo veya şekil ile desteklenebilir.

Editöre Mektup, yayımlanan metinlerle veya mesleki konularla ilgili olarak 500 sözcüğü aşmayan ve beş kaynak ile bir tablo veya şekil içerecek şekilde yazılabilir. Ayrıca daha önce dergide yayınlanmış metinlerle ilişkili mektuplara cevap hakkı verilir.

Yayın Kurulu'nun daveti üzerine yazılanlar dışında derleme kabul edilmez.

MAKALENİN HAZIRLANMASI

Dergide yayınlanması istenilen yazı için aşağıdaki kurallara uyulmalıdır.

a) Yazı; iki satır aralıklı olarak, Arial 10 punto ile yazılmalıdır.
b) Sayfalar başlık sayfasından başlamak üzere, sağ üst köşesinde numaralandırılmalıdır.
c) Online makale sistemine yüklenen word dosyasının başlık sayfasında (makalenin adını içeren başlık sayfası), yazarlara ait isim ve kurum bilgileri yer almamalıdır.
d) Makale, şu bölümleri içermelidir: Her biri ayrı sayfada yazılmak üzere; Türkçe ve İngilizce Başlık Sayfası, Öz, Abstract, Anahtar Sözcükler, Keywords, Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç, Açıklamalar (varsa), Kaynaklar, Şekil Alt Yazıları, Tablolar (başlıkları ve açıklamalarıyla beraber), Ekler (varsa).

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.

Metin

Yazı metni, yazının türüne göre yukarıda tanımlanan bölümlerden oluşmalıdır. Uygulanan istatistiksel yöntem, Gereç ve Yöntem bölümünde belirtilmelidir.

Kaynaklar

Pediatric Practice and Research Dergisi, Türkçe kaynaklardan yararlanmaya özel önem verdiğini belirtir ve yazarların bu konuda duyarlı olmasını bekler.

Kaynaklar metinde yer aldıkları sırayla, cümle içinde atıfta bulunulan ad veya özelliği belirten kelimenin hemen bittiği yerde ya da cümle bitiminde noktadan önce parantez içinde Arabik rakamlarla numaralandırılmalıdır. Metinde, tablolarda ve şekil alt yazılarında kaynaklar, parantez içinde Arabik numaralarla nitelendirilir. Sadece tablo veya şekil alt yazılarında kullanılan kaynaklar, tablo ya da şeklin metindeki ilk yer aldığı sıraya uygun olarak numaralandırılmalıdır. Dergi başlıkları, Index Medicus'ta kullanılan tarza uygun olarak kısaltılmalıdır. Kısaltılmış yazar ve dergi adlarından sonra nokta olmamalıdır. Yazar sayısı altı veya daha az olan kaynaklarda tüm yazarların adı yazılmalı, yedi veya daha fazla olan kaynaklarda ise üç yazar adından sonra et al. veya ve ark. yazılmalıdır. Kaynak gösterilen derginin sayı ve cilt numarası mutlaka yazılmalıdır.

Kaynaklar, yazının alındığı dilde ve aşağıdaki örneklerde görüldüğü şekilde düzenlenmelidir.

Dergilerdeki yazılar

Teke Z, Kabay B, Aytekin FO et al. Pyrrolidine dithiocarbamate prevents 60 minutes of warm mesenteric ischemia/reperfusion injury in rats. Am J Surg 2007;194(6):255-62.

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Ek sayı (Supplement)
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Henüz yayınlanmamış online makale
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

Kitap
Örnek 1: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.
Örnek 2: Sümbüloğlu K, Akdağ B. Regresyon Yöntemleri ve Korelasyon Analizi. Hatiboğlu Yayınevi: Ankara; 2007.

Kitap bölümü
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.

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

Açıklamalar
Varsa finansal kaynaklar, katkı sağlayan kurum, kuruluş ve kişiler bu bölümde belirtilmelidir.

Tablolar
Tablolar metni tamamlayıcı olmalı, metin içerisinde tekrarlanan bilgiler içermemelidir. Metinde yer alma sıralarına göre Arabik sayılarla numaralandırılıp tablonun üstüne kısa ve açıklayıcı bir başlık yazılmalıdır. Tabloda yer alan kısaltmalar, tablonun hemen altında açıklanmalıdır. Dipnotlarda sırasıyla şu semboller kullanılabilir: *, †, ‡, §, ¶.

Şekiller
Şekil, resim, grafik ve fotoğrafların tümü "Şekil" olarak adlandırılmalı ve ayrı birer .jpg veya .gif dosyası olarak (yaklaşık 500x400 piksel, 8 cm eninde ve en az 300 dpi çözünürlükte) sisteme eklenmelidir. Şekiller metin içinde kullanım sıralarına göre Arabik rakamla numaralandırılmalı ve metinde parantez içinde gösterilmelidir.

Şekil Alt Yazıları
Şekil alt yazıları, her biri ayrı bir sayfadan başlayarak, şekillere karşılık gelen Arabik rakamlarla çift aralıklı olarak yazılmalıdır. Şeklin belirli bölümlerini işaret eden sembol, ok veya harfler kullanıldığında bunlar alt yazıda açıklanmalıdır. Başka yerde yayınlanmış olan şekiller kullanıldığında, yazarın bu konuda izin almış olması ve bunu belgelemesi gerekir.

Ölçümler ve Kısaltmalar
Tüm ölçümler metrik sisteme (Uluslararası Birimler Sistemi, SI) göre yazılmalıdır. Örnek: mg/kg, µg/kg, mL, mL/kg, mL/kg/h, mL/kg/min, L/min, mmHg, vb. Ölçümler ve istatistiksel veriler, cümle başında olmadıkları sürece rakamla belirtilmelidir. Herhangi bir birimi ifade etmeyen ve dokuzdan küçük sayılar yazı ile yazılmalıdır.

Metin içindeki kısaltmalar, ilk kullanıldıkları yerde parantez içinde açıklanmalıdır. Bazı sık kullanılan kısaltmalar; iv, im, po ve sc şeklinde yazılabilir.

İlaçların yazımında jenerik isimleri kullanılmalıdır.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Çocukluk Çağında Karaciğer Hemanjiyomu Tanısıyla Takip Edilen Hastaların Tiroit Fonksiyon Testlerinin Değerlendirilmesi

Evaluation of Thyroid Function Tests in Patients Followed Up with the Diagnosis of Liver Hemangioma in Childhood

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Öz

Amaç: Bu çalışmanın amacı hemanjiyom tanısı alan hastalarda tiroit fonksiyon testlerinin değerlendirilmesidir.

Gereç ve Yöntem: Ekim 2010-Ekim 2022 yılları arasında hemanjiyom tanısı ile takibe alınan ve tanı anında tiroit fonksiyon testleri bakılmış olan 20 hastanın dosyaları retrospektif olarak incelendi. Hastaların demografik ve klinik özellikleri ile görüntüleme ve laboratuvar bilgileri not edildi.

Bulgular: Çalışmaya dahil edilen 20 hastanın 13'ü (%65'i) kız ve 7'si (%35'i) erkekti. Hastaların yaşı 4 gün ile 16,5 yıl arasında değişiyordu (ortanca, 20 ay). 10 hasta (%50) infanttı. 3 hasta (%15) preterm iken, 17 hasta (%85) termdi. Karaciğer hemanjiyomu 17 hastada tesadüfen bulunurken (%85), 2 hastada (%10) karın ağrısı ve 1 hastada (%5) ise antenatal tanı ile saptanmıştı. Karaciğerdeki hemanjiyom boyutları 4 ile 50 mm arasında değişiyordu (ortanca 10 mm). Hastaların tiroit fonksiyonları incelendiğinde 19 hastada (%95) tiroit fonksiyonları normal iken 1 hastada (%5) subklinik hipotiroidi olduğu saptandı.

Sonuç: İnfantil hepatik hemanjiyoma bağlı hipotiroidizm için çalışmalar yetersiz olup hangi tip infantil hepatik hemanjiyomda hipotiroidinin görülme riskinin arttığı tam olarak belirlenene kadar takipte hipotiroidi gelişebileceği akılda tutulmalıdır.

Anahtar Kelimeler: Çocukluk çağı, hemanjiyom, hipotiroidi

Abstract

Aim: The aim of this study is to evaluate the thyroid function tests in patients diagnosed with hemangioma.

Material and Method: Between October 2010 - October 2022 ; the files of 20 patients who were followed up with the diagnosis of hemangioma and whose thyroid function tests were also checked at the time of diagnosis were retrospectively analyzed. Patients demographic and clinical characteristics, imagings and laboratory results were noted.

Results: Of the 20 patients included in the study; 13 (65%) were female and 7 (35%) were male. The age of the patients ranged from 4 days to 16.5 years (median, 20 months). 10 patients (50%) were infants. While 3 patients (15%) were preterm, 17 patients (85%) were term. Liver hemangioma was found incidentally in 17 patients (85%); 2 patient (10%) diagnosed with abdominal pain and antenatal diagnosis in 1 patient (5%). Hemangiomas in the liver ranged in size from 4 to 50 mm (median 10 mm). When the thyroid functions of the patients were examined; thyroid functions were normal in 19 patients (95%), and subclinical hypothyroidism was found in 1 patient (5%).

Conclusion: Studies for hypothyroidism due to infantile hepatic hemangioma are insufficient, but it should be kept in mind that hypothyroidism may develop in the follow-up until it is fully determined which type of infantile hepatic hemangioma has an increased risk of hypothyroidism.

Keywords: Childhood, hemangioma, hypothyroidism

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GİRİŞ

İnfantil hemanjiyom çocukluk çağının en sık görülen vasküler tümörüdür. İnsidansı tam olarak bilinmemekle beraber muhtemelen %4 ile 5 civarında olduğu tahmin edilmektedir (1). Kızlarda, prematürelerde, çoğul gebeliklerde, progesteron tedavisi alan anne bebeklerinde, aile öyküsü olanlarda görülme ihtimali daha fazladır. Ayrıca ileri anne yaşı, annenin gebelikte sigara içmesi, in vitro fertilizasyon gebelikleri, amniyosentez, koryon villus örneklemesi, plasenta anomalileri, preeklampsi durumlarında da infantil hemanjiyom görülme ihtimalinin arttığını gösteren çalışmalar vardır (2-4).

Karaciğer infantil hemanjiyom için en yaygın cilt dışı yerleşim yeridir; bunu gastrointestinal sistem, beyin, mediasten ve akciğerler takip eder (5). İnfantil hepatik hemanjiyom, infant dönemin en sık görülen iyi huylu karaciğer tümörüdür. Çoğu asemptomatik olmasına rağmen vakaların küçük bir kısmında kanama, hipotiroidizm, abdominal kompartman sendromu ve konjestif kalp yetmezliği gibi hayatı tehdit eden komplikasyonlar meydana gelebilir. Diffüz veya büyük multifokal infantil hepatik hemanjiyomlar daha yüksek komplikasyon riski altındadır (6).

İnfantil hepatik hemanjiyom, komplikasyonu olarak hipotiroidi ilk kez 2000 yılında bildirilmiştir. Hemanjiyomda artmış tip 3 iyodotironin deiyodinaz aktivitesi sebebiyle tiroit hormonunun hızlandırılmış inaktivasyonunun buna sebep olduğu düşünülmektedir (7).

Bu çalışmanın amacı karaciğer hemanjiyomu tanısı konulan hastaların dosyalarının retrospektif olarak incelenmesi ve tanı aşamasında yapıldıysa tiroit fonksiyonlarının retrospektif olarak değerlendirilmesidir.

GEREÇ VE YÖNTEM

Bu çalışma, Selçuk Üniversitesi Tıp Fakültesi Yerel Etik Kurulundan (Tarih: 03.01.2023, Karar No: 2023/13) izin alındıktan sonra Helsinki Bildirgesi ilkelerine uygun bir şekilde yapıldı. Retrospektif bir çalışma olduğu için hasta ya da hasta yakınlarından onam alınmadı. Ekim 2010-Ekim 2022 tarihleri arasında karaciğer hemanjiyom tanısı alan ve takibe alınan tanı anında tiroit fonksiyon testleri de bakılmış olan 1 gün ile 18 yaş arasındaki 20 hastanın dosyaları retrospektif olarak tarandı. Hastaların tıbbi bilgilerine; Çocuk Onkoloji takip dosyalarından ulaşıldı.

Çalışmaya alınan hastaların yaşı, cinsiyeti, doğum zamanı (preterm/term), doğum ağırlığı, şikâyetleri, fizik muayene bulguları, karaciğer hemanjiyom tanısı konulduğundaki görüntüleme bulguları ve tiroit fonksiyon testleri geriye dönük olarak incelendi.

Tiroit fonksiyonları, yaşa göre normal referans aralıklarına göre değerlendirildi. Buna göre:

- Aşikar hipotiroidi: Serbest tiroksin (sT4) seviyesi düşükken, tiroit uyarıcı hormon (TSH) seviyesinin yüksek olması (TSH > 10)
- Subklinik hipotiroidi: Serum sT4 düzeyi normal ancak serum TSH düzeyinin yüksek olması (TSH 5-10)
- Ötiroidi: Hem serum sT4, hem de serum TSH düzeyi normal sınırlarda olanlar
- Hipertiroidi: Serum TSH düzeyi baskılanmış, serum sT4 düzeyi yüksek olanlar

olarak sınıflandırıldı.

Çalışmaya lezyonları hemanjiyom tanımına uyan, başvuru esnasında yaşı 1 gün ile 18 yaş arasında olan hastalar dâhil edildi. Çalışma dışlama kriterleri; hemanjiyom haricinde tanı alanlar, dosyalarında eksik bilgi olanlar ve başvuru anında tiroit fonksiyon test değerlendirmesi olmayan hastalar olarak belirlenmiştir.

İstatiksel Değerlendirme

Kategorik değişkenler için tanımlayıcı istatistik olarak frekans ve yüzde değerleri kullanıldı. Sürekli değişkenler için ise en düşük ve en yüksek değerle beraber ortanca değer verildi.

BULGULAR

Bu çalışmaya karaciğerde hemanjiyomu olan ve tiroit fonksiyon testlerine bakılan 20 çocuk dâhil edildi. Bu hastaların 13'ü (%65'i) kız ve 7'si (%35'i) erkekti. Hastaların yaşı 4 gün ile 16.5 yıl arasında değişiyordu (ortanca, 20 ay). 10 hasta (%50) infanttı. 3 hasta (%15) preterm iken, 17 hasta (%85) termdi.

Karaciğer hemanjiyomu 17 hastada tesadüfen bulunurken (%85), 2 hastada (%10) karın ağrısı ve 1 hastada (%5) ise antenatal tanı ile saptanmıştı. Bir hastada (%5) fizik muayenede karaciğerdeki hemanjiyoma ek olarak sol meme altında da 3x4 cm boyutlarında kapiller hemanjiyomu vardı. Hemanjiyom tanılarında hepsinde tanı ultrasonografi ile konurken 5 hastada (%25) dinamik MRG ile tanı desteklendi. Karaciğerdeki hemanjiyom boyutları 4 ile 50 mm arasında değişiyordu (ortanca 10 mm).

Hastaların tiroit fonksiyonları incelendiğinde 19 hastada (%95) tiroit fonksiyonları normal iken sadece miad doğum olan 1 hastada (%5) subklinik hipotiroidi olduğu saptandı. Subklinik hipotiroidi saptanan tek hasta 2 aylık erkek bebekti. Medikal tedavi başlanması gerekmeyen hastanın poliklinikte tiroit fonksiyon testlerinin kontrolü düzenli aralıklarla devam ediyor.

TARTIŞMA

Hemanjiyomlar çocukluk çağının en sık görülen yumuşak doku tümörleridir. Yaşam döngüleri proliferasyon ve involüsyon olarak iki evreden meydana gelir. Proliferasyon evresi hızlı büyüme ile karakterizedir ve yaşamın ilk

aylarında başlayıp yaklaşık bir yaşa kadar sürebilir. Daha yavaş olan involüsyon evresi %69 hastada 9 yaşına kadar tamamlanır (8, 9). Karaciğer en sık deri dışı yerleşim yeridir. Fokal olanların konjenital olduğu düşünülmektedir (10). Çoğu asemptomatik olan infantil hepatik hemanjiyomların diffüz veya büyük multifokal olanlarında komplikasyon görülme ihtimali artmıştır (6). Hipotiroidi ilk defa Huang ve arkadaşları (7) tarafından 2000 yılında tanımlanmıştır. Beş hepatik hemanjiyom hastasından alınan doku biyopsilerinin 3'ünde artmış tip 3 deiyodinaz aktivitesi saptanmıştır. Hemanjiyomların proliferatif fazı, temel fibroblast büyüme faktörü gibi anjiyojenik faktörlerin artan ekspresyonu ile karakterize edilir (11). Hemanjiyomlarda tip 3 iyodotironin deiyodinazın yüksek düzeyde ekspresyonunun, temel fibroblast büyüme faktörü veya diğer büyüme faktörleri tarafından endotelyal hücrelerde enzimin endokrin veya parakrin indüksiyonundan kaynaklanması muhtemel görünmektedir.

Hipotiroidizmin klinik bulguları büyük dil, kaba ses, kabızlık, üfürüm, uyku halinde artış olarak bilinmektedir fakat bu klinikler çoğunlukla görülmemektedir. İnfant dönemde klinik tanı %3 olarak görülmekle birlikte en sık büyüme-gelişme geriliği, konuşma problemleri, yürümede gecikme ile hastalar getirilmektedir. Başvurularda en sık rastlanan bulgular ise hipotoni, kabızlık, kaba yüz, büyük dil olarak bildirilmektedir(12). Yaşamın ilk yılında hipotiroidizmin geç klinik bulgu vermesi, tanısının koyulmasındaki gecikmeler mental gelişme geriliği gibi ağır komplikasyonlara yol açmaktadır (13). Gelişimsel olarak kritik olan bu dönem, hemanjiyomların proliferatif fazına karşılık gelir ve bu tümörlü bebeklerin kalıcı nörolojik hasar riski altında olabileceğini gösterir.

Japonya'da bazı kurumlarda anket yoluyla yapılan 19 soliter ve multifokal karışık İHH hastasının dâhil edildiği bir çalışmada %5.3 oranında hipotiroidizm saptanmıştır (14). 2018 yılında Şimşek ve arkadaşları (13) tarafından karında şişlik ile başvuran bir infantil hepatik hemanjiyoma bağlı şiddetli hipotiroidizm vakası sunulmuştur (15). Bir başka çalışmada 3 aylık kabızlık ile başvuran bir hastanın etyolojisinde infantil hepatik hemanjiyoma bağlı hipotiroidizm bildirilmiştir (16). Ülkemizde, 2016 yılında konjenital hipotiroidi ile takip edilen bir vakanın tedaviye yanıt vermemesi sonrasında etyolojisinde infantil hepatik hemanjiyom saptanıp sekonder kalp yetmezliği geliştiği bildirilmiştir (17).

Bizim çalışmamızda iki aylık miad doğum olan bir bebek hastada subklinik hipotiroidi saptadık. Diğer hastalarımızda tiroit fonksiyonları normaldi.

Çalışmamızda limitasyonlarımız, retrospektif bir çalışma olması ve toplam hasta sayımız ile infant olan hastalarımızın sayısının düşük olmasıdır.

SONUÇ

İnfantil hepatik hemanjiyoma bağlı hipotiroidizm için çalışmalar yetersiz olup hangi tip infantil hepatik hemanjiyomda hipotiroidinin görülme riskinin arttığı tam olarak belirlenene kadar takipte hipotiroidi gelişebileceği akılda tutulmalıdır.

ETİK BEYANLAR

Etik Kurul Onayı: Bu çalışma, Selçuk Üniversitesi Tıp Fakültesi Yerel Etik Kurulundan (Tarih: 03.01.2023, Karar No: 2023/13) izin alınmıştır.

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

Effect of Different Bacterial Contamination on Experimental Adhesive Intestinal Obstruction in Rats

Sıçanlarda Farklı Bakteriyel Kontaminasyonun Deneysel Adeziv Barsak Obstrüksiyonuna Etkisi

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ABSTRACT

Aim: Postoperative peritoneal adhesions (PPA) cause pain, intestinal obstruction and infertility after abdominal surgery and to date there is no shown pathogenesis or definitive treatment. Intestinal flora and its effect on infection is one of the most serious factors that influence the morbidity during intraabdominal surgeries. Different microorganisms found in intestinal flora or added ones as hospital flora might be the reason of the inflammatory processes and cause PPA formationThere are a lot of tegorizedstudies showing intraabdominal infections cause PPA but there is no study comparing the effect of different bacterial strains on PPA formation. That is why we designed this study using the most common microorganisms isolated in intraabdominal infections and hospital flora. In our study, investigating the impact of different bacterial strains on the nascency and degree of PPA in adhesion formation in rats.

Material and Method: In this this experimental study, subjects were divided into five groups, each one obtaining 12 rats. Groups were categorized as; *E. coli* group, *Klebsiella* group, *Bacteriodes fragilis* group, Sham and Control groups. after the scarification on the 14th day, re abdominal exploration was performed. The results were exmained according to the previously mentioned microscopic-macroscopic classifications.

Conclusion: Microorganisms have been found to have an important role in PPA formation in the experimentally created adhesion model. But there was no significant difference between bacterial strains on PPA formation.

Keywords: Postoperative peritoneal adhesions (PPAs), bacteria, adhesion in rats

ÖZ

Amaç: Postoperatif peritoneal adezyonlar (PPA) abdominal cerrahi sonrası ağrı, intestinal obstrüksiyon ve infertiliteye neden olabilir. Bugüne kadar kanıtlanmış bir patogenezi veya kesin tedavisi yoktur Karın içi girişimlerde en önemli noktalardan biri barsak folarası ve enfeksiyona etkisidir. Florada bulunan veya sıklıkla hastane florası olarak eklenen farklı mikroorganizmaların inflamatuvar süreçlere ve PPA oluşumuna neden olabileceği düşünülmüştür. Karın içi enfeksiyonların PPA'ya neden olduğunu gösteren birçok çalışma vardır. Ancak farklı bakteri suşlarının PPA oluşumu üzerindeki etkisini karşılaştıran bir çalışma yoktur. Bu nedenle çalışmayı intraabdominal enfeksiyonlarda en sık izole edilen mikroorganizmalar ve hastane florası kullanarak tasarladık. Farklı bakteri suşlarının (*Klebsiella* spp, *E. coli* spp, anaerob) sıçanlarda PPA oluşumu ve adezyon derecesi üzerine etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Denekler 12 rattan oluşan beş gruba ayrıldı. Gruplar *E. coli*, *Klebsiella*, *Bacteriodes fragilis*, Sham ve Kontrol grupları olarak adlandırıldı. Sıçanlar 14. Günde sakrifiye edildi ve relaparatomi uygulandı. Sonuçlar daha önce belirlenen sınıflamalara göre makroskopik ve mikroskopik olarak değerlendirldi

Bulgular: Bakteriyel enfeksiyonlu gruplar sham ve control grupları ile karşılaştırıldığında, PPA'da hem mikroskopik hem de makroskopik olarak anlamlı artış gözlemlendi

Sonuç: Çalışmamızda kullanılan mikoorganizmaların PPA oluşumunda rol oynadığı deneysel olarak oluşturulan adezyon modeli ile gösterilmiştir. Ancak bakteri suşları arasında PPA oluşumu üzerinde anlamlı bir fark yoktur

Anahtar Kelimeler: Postoperatif peritoneal adezyon (PPA), bakteri, sıçanlarda adezyon

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INTRODUCTION

PPAs may lead many clinical problems such as intestinal obstruction, severe abdominal pain, intestinal dysfunction and infertility (1). In Pediatric Surgery Clinics, PPAs have an important place in terms of morbidity and hospitalization. In Western countries, PPAs are the most common cause of intestinal obstructions (1). Following abdominal surgery, approximately two-thirds of patients develop PPA, but symptoms are observed in only one-fifth of the patients. Adhesion-induced intestinal obstruction is most common in the pediatric age group. Eight percent of newborns undergoing laparotomy undergo relaparotomy in the future (2). Adhesive obstruction can occur at any time in one-third of patients within one year after the first surgery, and in the remaining one at any time within a long period of 20 years (2,3). Although our knowledge about PPA is gradually increasing, PPA continues to be a problem for surgeons from different disciplines. Many materials and different techniques have been tried to prevent peritoneal adhesions but have not been fully successful to date. Despite all these mechanisms of occurrence, the fact that PPA does not develop at the same level in every patient is a sign that host factors are also important. Intestinal flora and its effect on infection formation are very important in intraabdominal surgical procedures. Different microorganisms found in flora or often added as hospital flora can lead to different levels of inflammatory processes in individuals, causing PPA formation (4).

There are not enough studies in the literature showing how different microorganism presence affects PPA. In our study, we aimed to evaluate whether there is a difference in the formation of peritoneal adhesion in rats contaminated with three different microorganisms that can be found in the gastrointestinal tract.

MATERIAL AND METHOD

After receiving institutional Animal Experiments Ethics Committee approval (2017-42). Before the study, all rats were weighe done by one, their weights were recorded and 60 Wistar-Albino mixed rats, each weighing approximately 200-300 g, wereused in thestudy. In this study, rats were divided into 5 groups, 12 rats each.These groups are;

- Group 1: The group transmitted with *E. coli*,
- Group 2: The group infected with *Klebsiella* spp.
- Group 3: Anaerobic strain (*Bacteriodes fragilis*) infected group,
- Group 4: Control group,
- Group 5: The Sham group.

All rats to be used in the study were kept in the same laboratory environment for 1 week before the experiment. All rats were fed with standard pellet feed and water and were monitored in metabolic cages in standard laboratory conditions (day/night=12/12 hours, temperature 21±2°C, humidity 50%) in isolated environment.

Surgical procedures were applied in sterile atmosphere. Intraabdominal ketamine (Ketalar®, Parke Davis and Co. Inc., 50 mg/kg) and xylazine (Rompun®, Bayer 5 mg/kg) were given as an anaesthetic agent. For the rats to be normothermic (37°C), the temperature of the environment was maintained with a heating lamp. After the abdominal surface was washed and shaved with 10% poviiodin, and sterile covering, laparotomy was performed with an aseptic surgical technique and approximately 3 cm midline incision.

After examing that there was no adhesion in the abdomen, the cecum was observed. As a well-defined adhesion model in all rats; after the parietal area of the cecum was deserosalized and abrasion was formed with dry gauze on the the cecum's antimezenteric surface (4). This treat was continued until focal petechial bleeding was seen on serosal surfaces. Subsequently, the standard *E. coli* spp. coded ATCC 25922, standard *Klebsiella* spp. strains obtained from the Department of Microbiology of Ankara University Faculty of Medicine, the standard *Klebsiella* spp. strains coded ATCC 22914, and the standard anerob (*Bacteriodes fragilis* spp) strain from the Ministry of Health Refik Saydam Hygiene Institute; 1×10^4 'Colony Forming Unit' (CFU) was applied to the pre-determined groups under the supervision of a specialist by the microbiology specialist at the University of Health Sciences Ankara Hospital SAUM Clinical Microbiology Laboratory. (**Figure 1**) To create the sham group, the abdominal walls of 12 rats, which were found to have no adhesion following a 3 cm midline incision after anaesthesia, were continuously covered with 3/0 vicryl and their skin was individually followed by 3/0 silk sutures. In the control group, adhesion model was applied to 12 rats without any drug or bacterial strain. Then all the rats were followed.

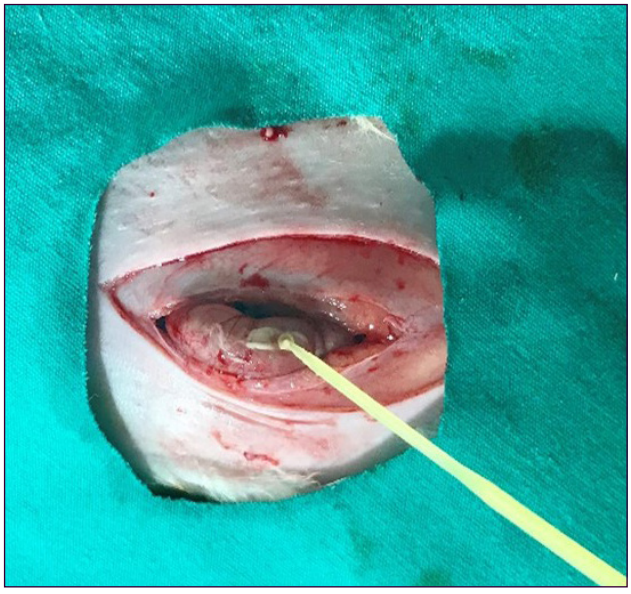

Figure 1. Bacteria planting process in the abdomen)

On the fourteenth postoperative day, all rats were weighed again, and their weights were recorded again. In the post-operative period, 4 rats were lost in 2 different groups due to surgery or anaesthesia. In accordance with the Helsinki contract, all rats were sacrificed on the fourteenth day with a high dose of ether. Then, maximum visibility was achieved by making U incision (it extends from the right epigastric region to below the umbilicus and from there to the left epigastric region) on the abdomen of the subjects. Adhesions were interpreted quantitatively with the classification defined by Nair et al. (5) The evaluation was carried out by two separate persons in accordance with the classification previously described and double-blind (**Table 1**).

Table 1: 'Nair' macroscopic adhesion classification

	Grade	
No adhesion	Grade 0	No adhesion
Adverse adhesion	Grade 1	One band between organs or between the organ and the abdominal wall
Pronounced adhesion	Grade 2	Two band structures; bands between organs and bands between organs and abdominal wall
Pronounced adhesion	Grade 3	Adhesion of intestinal loops between organs or between the organ and the abdominal wall, with no more than two adhesive band
Severe adhesion	Grade 4	Viscera adheres to the abdominal wall directly

During the exploration for adhesions the bands were resected together with the affected organs and only the parietal peritoneum was resected in those who did not have adhesions. The pathological specimens were fixed in 10% formol. The preparations were embedded in paraffin blocks. Five micrometers thick sections were taken on the slide and stained with Hematoxylin-Eosin and examined by light microscopy. Histopathological examination was interpreted in OLYMPUS brand, BX51TF model ×4, ×10, ×20, ×40 lenses. After histopathological evaluation, the preparations were exposed to microscopic grading as defined by Zühlke (6) (**Table 2**). While evaluating the findings statistically, IBM SPSS (Statistical Package for the Social Sciences, version 22.0; SPSS Inc., Chicago, IL) program was used in the study. When comparing the data, Pearson chi-square test was used.

Table 2: The grading system of microscopic adhesion (Zühlke classification)

Grade 0	Normal Findings
Grade 1	Mild connective tissue, fibrin stuctures, thin fibrils of reticulin
Grade 2	Connective tissue consisting of diffuse cells and capillaries, and small amounts of collagen fibers
Grade 3	Thickened connective tissue, decreased cell count, decreased elastic and smooth muscle fibers, increased vasculature
Grade 4	Former granulation tissue, poorly differentiated serosal layers, and cell-poor structure

RESULTS

Macroscopic findings of rats according to Nair classification are shown in **Table 3**. In addition, macroscopic views after sacrification are available in **Figure 2** . According to the microscopic adhesion grading system (Zuhlke) the structural changes in the samples of the intestinal wall were evaluated (**Table 4**).

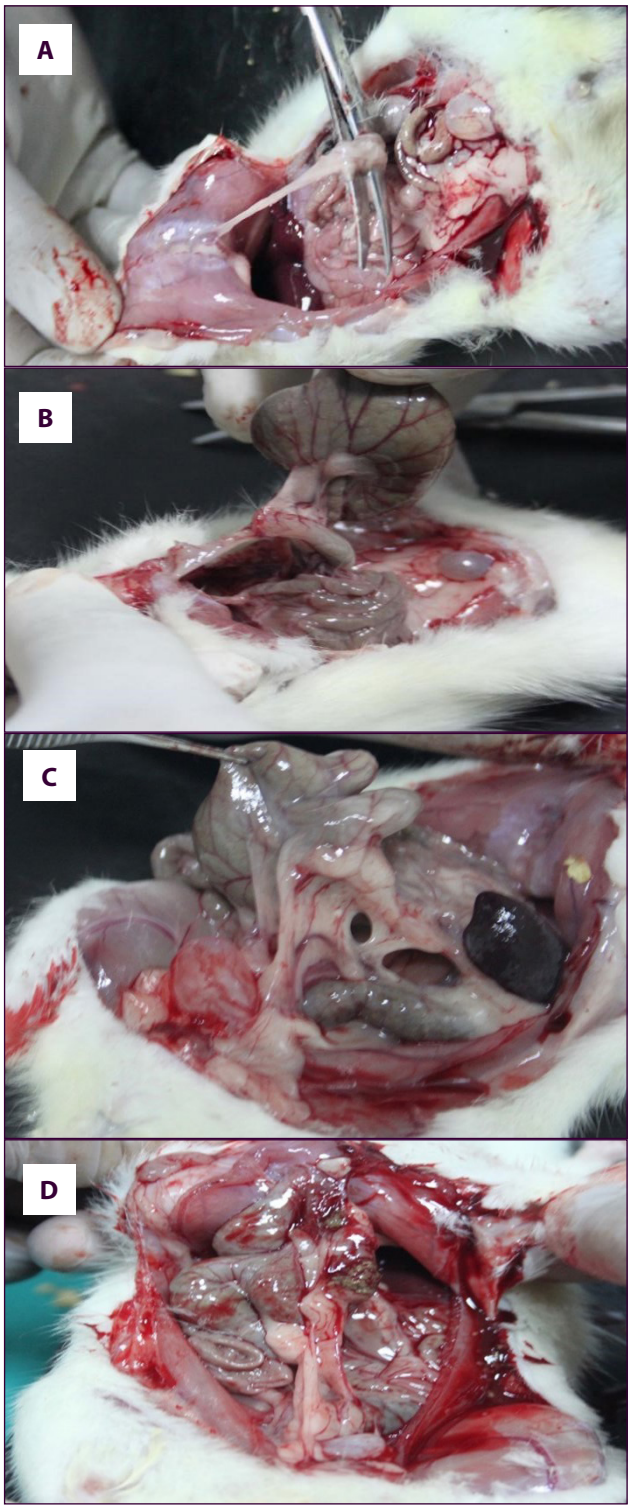

Figure 2. A Macroscopic Grade 1 image, B Macroscopic Grade 2 image, C Macroscopic Grade 3 image, D Macroscopic Grade 4 image

Table 3: Macroscopic adhesion grading by groups

Rats	*E. coli* (Grade)	*Klebsiella* (Grade)	Anaerob (Grade)	Sham (Grade)	Control (Grade)
1.	2	3	4	1	0
2.	2	3	4	4	4
3.	4	4	Ex	0	0
4.	4	3	3	0	0
5.	4	4	3	0	0
6.	3	0	3	1	0
7.	3	4	4	2	0
8.	0	3	4	1	0
9.	1	2	4	1	1
10.	4	3	Ex	1	0
11.	3	Ex	4	1	1
12.	4	Ex	4	1	0

Table 4 Histopathological classification (microscopic adhesion grading) according to groups:

Rats	*E. coli* (Grade)	*Klebsiella* (Grade)	Anaerob (Grade)	Sham (Grade)	Control (Grade)
1.	3	3	2	2	2
2.	3	3	3	4	4
3.	3	3	Ex	1	2
4.	3	3	3	0	1
5.	3	4	3	0	1
6.	4	2	3	1	1
7.	3	3	3	1	1
8.	3	3	4	0	1
9.	3	2	3	1	3
10.	4	4	Ex	2	2
11.	3	Ex	3	1	4
12.	4	Ex	3	1	1

When control, sham and *E. coli* groups are compared; significant difference was found both on Nair classification and Zuhlke classification (p=0.001 according to Pearson chi-square test). When the control, sham and *Klebsiella* groups are compared; there was a significant difference on both Nair classification (p<0.001 according to Pearson chi-square test) and Zuhlke classification (p=0.005 according to Pearson chi-square test). When control, sham and *Bacteriodes fragilis* groups are compared; there was a significant difference both on Nair classification and Zuhlke classification (p<0.001 according to Pearson chi-square test). When *E. coli*, *Klebsiella* and Bacteriodes groups are compared; there was no statistically significant difference (p=0.525 according to Pearson chi-square test).

DISCUSSION

PPA is the one of the most serious cause of long-dated morbidity (7). Therefore, efforts on preventing PPAs are increasing day by day in the recent literature. PPAs may provoke recurrent abdominal pain, intestinal obstructions, and infertility (2). There is a repeated need for outpatient or inpatient treatment. Some patients even must undergo surgery. This situation is reflected as a serious burden on health expenditures as well as the additional morbidity brought to the patients. A process that deactivate PPA formation will prevent repetitive surgeries and the morbidity and financial burden it brings (8).

The widely accepted idea is that careful surgical technique can limit postoperative adhesions. However, increased surgical trauma, unnecessary and excessive manipulations, foreign body and necrotic tissues not being removed from the surgical area and minimally invasive procedures are the reasons causing an increase in PPA formation (9). However, the inflammatory process that develops due to infection or bacterial exposure is an important reason that increases the formation of PPA (10,11).

According to the findings obtained from the results of the study, PPA formation in infected groups was significantly higher than in the control and sham groups. However, information on the effect differences of different microbiological agents on PPAs could not be obtained. Considering that there may be different microorganisms in individuals and each surgery room has its own flora; It was concluded that PPA can be monitored in different degrees and incidence. In our study; Three different bacterial strains were used: *E. coli* spp, *Klebsiella* spp. and *Bacteriodes fragilis* spp. Serious PPA was observed in all groups, and both microscopic and macroscopic differences were found in PPA formation when compared to control and sham groups. However, there was no significant difference between the 3 bacterial groups in terms of PPA formation and severity. Thus, it was found that the infection itself is an important factor in PPA formation, but it has no effect on the degree of adhesion of different bacterial groups. Therefore, we think that the use of antibiotics for the dominant flora before the procedure will significantly decrease the formation of PPA. Also, we can reduce the rate of PPA with surgery to minimize tissue damage with methods that will prevent infection and bacterial translocation.

CONCLUSION

Microorganisms have been found to act a considerable role in PPA construction. But there is no significant difference was noted between *E. coli*, *Klebsiella* and Bacteriodes groups.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by University of Health Sciences Ankara Hospital SAUM Experimental Animals Laboratory (Protocol: 2017-42).

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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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Evaluation of Demographic, Clinical Characteristics and Laboratory Values of Pediatric Patients Followed in Palliative Care

Palyatif Bakımda Takip Edilen Pediatrik Hastaların Demografik, Klinik Özellikleri ve Laboratuar Bulgularının Değerlendirilmesi

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ABSTRACT

Aims: The importance of pediatric palliative care centers, which we think is insufficient both in the world and in our country, is increasing. The aim of this study is to reveal the demographic, clinical and laboratory characteristics of pediatric patients followed in a palliative care center.

Material and Method: In this retrospective study, demographic data (age, gender), laboratory findings (platelet, mean platelet volume, lymphocyte, neutrophil counts, glucose, sodium, potassium, urea) of pediatric patients followed up in an adult palliative care center between 18.10.2018 and 15.01.2023, creatinine, albumin and the C-reactive protein, CRP/albumin ratio, platelet/lymphocyte ratio and neutrophil/lymphocyte ratio) and clinical features (length of stay in PCU and survival) were evaluated.

Results: It was determined that 61 pediatric patients between the ages of 2-17 were followed up in the palliative care center between 18 October 2018 and 15 January 2023. 65.6% of the patients were male and 6.6% were Syrian citizens. The duration of stay in the palliative care center was between 1-64 days. While 16.4% of the patients had tracheostomy, 14.8% needed home mechanical ventilator. Only 3 (4.9%) patients received parenteral nutrition. The diagnosis of admission to the palliative care center of 47 (77.0%) patients included in the study had neurological sequelae after head trauma. The mortality rate was 1.6%.

Conclusion: It is obvious that the centers are insufficient in the face of the increasing need for pediatric palliative care. Although adult palliative care centers are compensating for this deficiency at this stage, it is clearly seen that the number of pediatric palliative care centers should be increased in the future.

Keywords: Palliative Care, pediatric, laboratory values.

ÖZ

Amaç: Hem dünyada hem de ülkemizde sayısı yetersiz olduğunu düşündüğümüz pediatrik palyatif bakım merkezlerinin önemi giderek artmaktadır. Bu çalışmanın amacı, palyatif bakım merkezinde takip edilen çocuk hastaların demografik, klinik ve laboratuvar özelliklerini ortaya koymaktır.

Gereç ve Yöntem: Bu retrospektif çalışmada 18.10.2018-15.01.2023 tarihleri arasında bir erişkin palyatif bakım merkezinde takip edilen çocuk hastaların demografik verileri (yaş, cinsiyet), laboratuar bulguları (trombosit, ortalama trombosit hacmi, lenfosit, nötrofil sayısı, glikoz, sodyum, potasyum, üre, kreatinin, albümin ve C-reaktif protein, CRP/albümin oranı, trombosit/lenfosit oranı ve nötrofil/lenfosit oranı) ve klinik özellikleri (palyatif bakım merkezinde kalış süresi ve mortalite) değerlendirilmiştir.

Bulgular: 18 October 2018 and 15 January 2023 tarihleri arasında 2-17 yaşları arasında 61 pediatrik hastanın palyatif bakım merkezinde takip edildiği tespit edilmiştir. Hastaların %65,6'sı erkek, %6,6'sı Suriye vatandaşıydı. Palyatif bakım merkezinde kalış süresi 1-64 gün arasındaydı. Hastaların %16.4'ünde trakeostomi mevcutken %14,8'inin home mekanik ventilatöre gereksinimi mevcuttu. Sadece 3 (%4,9) hasta parenteral beslenme almaktaydı. Çalışmaya dahil edilen 47 (%77,0) hastanın palyatif bakım merkezine kabul tanısı kafa travması sonrası nörolojik sekeldi. Mortalite %1.6 olarak gerçekleşmiştir.

Sonuç: Pediatrik palyatif bakım ihtiyacının giderek artışı karşısında merkezlerin yetersiz olduğu aşikardır. Şu aşamada erişkin palyatif bakım merkezleri bu yetersizliği kompanse ediyor olsa da ilerleyen zamanlarda pediatrik palyatif bakım merkezlerinin sayılarının arttırılması gerekliliği açıkça görülmektedir.

Anahtar Kelimeler: Palyatif Bakım, pediatrik, laboratuvar değerleri.

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INTRODUCTION

The World Health Organization (WHO) recommends that everyone with life-threatening diseases should receive palliative care and that this care should be started early according to the course of the disease. The interest and need for palliative care is increasing worldwide. However, pediatric palliative care emerges as a newly developing scientific field that has not yet been standardized. Palliative care is defined by WHO as the prevention and alleviation of adult and pediatric patients and their families from facing problems associated with life-threatening diseases (1). The effects of the developing and changing world have led to an increase in the number of individuals with chronic diseases, along with the prolongation of life expectancy. This change not only causes an increase in life expectancy, but also a significant increase in the number of children and families with chronic, life-threatening or life-limiting diseases (2-4). The life expectancy of patients with genetic diseases, events resulting in neurological sequelae, congenital anomalies, neurometabolic diseases and cancer is prolonged. As a result of all these, the need for pediatric palliative care centers is increasing day by day. However, as in the whole world, pediatric palliative care centers are still new in our country, and as a result, the number of pediatric palliative care centers and clinical experience are limited. Therefore, we believe that it is important to reveal the demographic, clinical and laboratory characteristics of patients in palliative care centers.

The aim of the present study is to reveal demographic, clinical and laboratory characteristics of pediatric patients hospitalized in a palliative care center.

MATERIAL AND METHOD

The present retrospective study was approved by the ethics committee of Selçuk University Medical Faculty (Approval date and number: 31.01.2023 and 2023/69) and the medical records of the hospitalized patients in Selçuk University Medical Faculty Hospital palliative care unit between 18.10.2018-15.01.2023 were reviewed. The present study was conducted in accordance with the principles of the Declaration of Helsinki. Patients older than 18 years of age were excluded from the study. In addition, patients with more than one admission were also excluded from the study. The following variables evaluated at admission to PCU were obtained from medical records: Age, gender, platelet, mean platelet volume (MPV), lymphocyte, neutrophil counts, glucose, sodium, potassium, urea, creatinine, albumin and the C-reactive protein (CRP). CRP/albumin ratio, platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) were calculated from the data obtained from medical records. Apart from these data, length of stay in PCU and survival were also obtained from medical records. The starting point for survival was evaluated for the date of first admission to the PCU and continuing for three months.

Statistical Analysis

Statistical analysis was performed using the SPSS Version 22.0 (IBM, Chicago, IL, USA). Evaluation of data in terms of normality was performed with Shapiro–Wilk and Kolmogorov–Smirnov tests. Categorical data were expressed as number (percentages). The numerical data resulting from the descriptive statistics were expressed as the median [interquartile range (IQR)].

RESULTS

In the medical records of the palliative care center, it was determined that 61 children received palliative care services between 18 October 2018 and 15 January 2023. The general characteristics of these pediatric patients in the palliative care center are presented in Table 1. The laboratory values at admission to the palliative care center of pediatric patients are presented in Table 2.

Table 1. General Characteristics of Patients

Variable	Total Patients (n=61) Median (IQR), n (%)
Age, year	12 (9-16)
Gender, (M/F) n (%)	40 (65.6) / 21 (34.4)
Nationality, n (%)	
Turkey	57 (93.4)
Syria	4 (6.6)
Length of Stay, day	5 (2-9)
Tracheostomy presence, n (%)	10 (16.4)
Home mechanical ventilator requirement, n (%)	9 (14.8)
Nutritional status, n (%)	
Enteral nutrition	58 (95.1)
Parenteral nutrition	3 (4.9)
Admission diagnosis, n (%)	
Neurological sequelae after head trauma, after intensive care	47 (77.0)
Chronic disease terminal stage	12 (19.7)
Other (Drowning in water, intoxication after intensive care)	2 (3.3)
Mortality, n (%)	1 (1.6)

IQR: Inter Quantile Range, M: Male, F: Female.

Table 2. Laboratory Values of Patients.

Variable	Total Patients (n= 61) Median (IQR), n (%)
Blood Glucose, mg/dL	103.00 (89.00-120.00)
Blood Urea, mg/dL	24.00 (18.00-33.00)
Blood Creatinine, mg/dL	0.37 (0.27-0.49)
Blood Sodium, mEq/L	138.00 (136.00-141.00)
Blood Potassium, mmol/L	4.12 (3.80-4.35)
Neutrophil count, (109 /L)	6.25 (4.67-9.23)
Lymphocyte count, (109 /L)	1.83 (1.23-2.32)
Platelet count, (109 /L)	286000 (231000-400000)
Mean Platelet Volume, fl	8.15 (7.60-9.50)
Neutrophil to lymphocyte ratio	3.46 (1.98-6.25)
Platelet to lymphocyte ratio	164.75 (123.52-254.75)
C-reactive protein, mg/L	20.00 (5.86-67.45)
Albumin, g/dL	3.50 (3.10-3.90)
C-reactive protein/Albumin Ratio	5.52 (1.62-19.42)

IQR: Inter Quantile Range.

The age range of the patients included in the study was between 2-17 yrs and the median (IQR) age was 12 (9-16) yrs. In the present study, 65.6% of all patients in the palliative care center were male. While 57 (93.4%) of the 61 patients were Turkish citizens, 4 (6.6%) of them were Syrian citizens. While the minimum length of stay in the palliative care center was 1 day, the maximum length of stay was 64 days. In the present study, 16.4% of pediatric patients in the palliative care center had tracheostomy. The number of patients who needed a home mechanical ventilator was 9 (14.8 %). While 95.1% of all patients received enteral nutrition, only 3 (4.9%) patients received parenteral nutrition. Hospitalization diagnosis of 47 (77.0%) patients included in the study was neurological sequelae after head trauma. These patients consisted of patients who needed palliative care after intensive care treatment was completed. Twelve patients were admitted to the palliative care center with a diagnosis of chronic disease terminal stage.

Only 1 of the 61 patients died during the study follow-up period. The patient were male, 17 yrs, and nationality was Turkey. Admission diagnosis of the patient was neurological sequelae after head trauma and length of stay of this patient is 64 days. The patient had tracheostomy, needed a home mechanical ventilator and was receiving enteral nutrition. The abnormal laboratory values of our only patient who died during the follow-up period were as follows: Albumin 2.4 g/dL, CRP; 37.7 mg/L, Lymphocyte count; 0.8 (109 /L), Neutrophil to lymphocyte ratio; 6.25.

DISCUSSION

In this retrospective study, demographic, clinical characteristics and laboratory findings of pediatric patients followed up in an adult palliative care center between 18.10.2018 and 15.01.2023 were evaluated.

Infant and child mortality rates have gradually decreased in the last century due to many factors such as developments in intensive care and surgery, advances in treatment methods, and increase in the number and quality of staff. However, as a result of the increase in the survival rate, the number of children living with chronic diseases is also increasing rapidly. The increase in the number of children living with chronic diseases has led to an increase in the need for pediatric palliative care centers in our country as well as all over the world. Although a few pediatric palliative care centers have been opened in Turkey since 2015, the number of pediatric palliative care centers and clinical experience is still less than expected and the need is expected to increase over time (5). Although the palliative care center including the pediatric patients evaluated in this study is an adult palliative care center, patients are admitted to this center because there is no pediatric palliative care center in the province.

Turkey-based pediatric palliative care reports are limited. In one of these studies, a total of 145 patients from 2 centers were evaluated, and in the other, the data of 98 patients in a single center were reported (6,7). The ages of the patients in these two studies were younger than the present study, and we think that the reason for this is that the palliative care center in the present study was essentially an adult palliative care center. While 67.2% of the pediatric patients in the present study were over the age of 10, 26.1% of the patients in the study of Ayar et al. were over the age of 10 (6). In 2 studies from the USA, the rate of patients over the age of 10 was relatively higher (36%, and 45.5%, respectively) (8,9), although not as much as in the present study.

In the present study, it was determined that 65.6% of the pediatric patients followed in the palliative care center were male. In many studies in the literature, it has been stated that the male/female ratio is almost equal or very close to each other (6,8). We believe that the reason for this difference in the present study is that most of the paltative care patients followed due to the need for palliative care after posttraumatic processes.

As the effects of Turkey's immigration after the Syrian war, it is seen that 6.6% of the patients in our study are Syrian citizens. In the studies of Ayar et al., it was stated that 9.7% of the patients were Syrian (6). It was stated that the number of applications to the emergency service of Syrian refugees in Turkey increased by 8% in 2015 compared to 2010 (10). It is obvious that the increase in emergency service applications will also have a counterpart in intensive care units (11).

In the literature, the length of stay of pediatric patients in palliative care centers varies (6-8).

It was observed that 14.8% of our patients needed a home type mechanical ventilator. There are different results in the literature on this issue. In publications from Turkey and other countries, the need for mechanical ventilators has been stated in a wide range of 8-77% (6,7,12,13).

Adequate and balanced nutrition is an important element that increases the quality of life in palliative care patients (14). Only 4.9% of our patients were receiving parenteral nutrition, which was considerably lower than the rates of parenteral nutrition reported in palliative care (15).

Although pediatric palliative care first came to the fore in oncological patients, it is now applied in a wide variety of diseases. In the present study, the majority of our patients consisted of patients admitted after intensive care. In the literature, 20% of oncological patients are reported (16,17). It is obvious that oncology patients are incompatible with the literature, since the palliative care center where this study was conducted was originally an adult palliative center.

The limitations of our study are that it is a retrospective study, the use of data obtained from an adult palliative care center and the small number of cases. However, it should be noted that many cities in Turkey do not have pediatric palliative care centers.

CONCLUSION

Today, the need for pediatric palliative care centers is increasing day by day. Although the number of adult palliative care centers has gradually increased in our country, it cannot be said that this situation is also valid for pediatric palliative care centers.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was conducted by ethics committee approval obtained from Selçuk University Faculty of Medicine (Approval number:2023/69).

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

The Effect of Rosmarinic Acid Against Ovarian and Lung Injuries Induced by Ovarian Torsion Detorsion in Rats

Over Torsiyon Detorsiyon Kaynaklı Over ve Akciğer Hasarına Karşı Rosmarinik Asidin Etkisi

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ABSTRACT

Aim: Here, we purposed to find out the effects of two different doses of Rosmarinic acid (RA) against ovarian and lung injury caused by ovarian ischemia-reperfusion.

Material and Method: We planned the groups as sham, ovarian torsion detorsion (O/TD; 3hours torsion/3hours detorsion), RA 40 mg/kg (40 mg/kg RA+O/TD), and RA 80 mg/kg (80 mg/kg RA+O/TD) groups. Following the experimental procedure, we sacrificed the rats and then, collected the lung and ovarian tissues for biochemical evaluations.

Result: Total oxidant status (TOS), myeloperoxidase (MPO) activity, malondialdehyde (MDA) levels, and oxidative stress index (OSI) were elevated in the O/TD group compared to the sham group. These parameters declined due to low and high doses of RA administration. Total antioxidant status (TAS) level and superoxide dismutase (SOD) activity diminished in the O/TD group while increasing in RA treatment groups. However, the high dose of RA treatment group enhanced the antioxidant activity further and reduced the oxidant parameters compared to the low dose RA treatment group.

Conclusion: In this study, RA treatment reduced O/TD-induced ovarian and lung injuries in the experimental animals.

Keywords: Ovary, rat, rosmarinic acid, torsion detorsion

ÖZ

Amaç: Bu çalışmada over torsiyon detorsiyonunun neden olduğu over ve akciğer hasarına karşı iki farklı Rosmarinic asit (RA) dozunun etkilerini bulmayı amaçladık.

Gereç ve Yöntem: Grupları sham, over torsiyon detorsiyon (O/TD; 3 saat torsiyon/3 saat detorsiyon), RA 40 mg/kg (40 mg/kg RA+O/TD) ve RA 80 mg/kg (80 mg/kg RA+O/TD) olarak planladık. Deneyin ardından sıçanları sakrifiye edip biyokimyasal değerlendirmeler için akciğer ve over dokularını aldık.

Bulgular: Total oksidan durum (TOS), myeloperoksidaz (MPO) aktivitesi, malondialdehit (MDA) seviyeleri ve oksidatif stres indeksi (OSI), O/TD grubunda sham gruba kıyasla yükselmişti. Bu parametreler, düşük ve yüksek doz RA uygulaması sonucunda azalma gösterdi. Total antioksidan durum (TAS) düzeyi ve süperoksit dismutaz (SOD) aktivitesi, RA tedavi gruplarında artarken O/TD grubunda azaldı. Ancak, yüksek doz RA tedavi grubu, düşük doz RA tedavi grubuna kıyasla antioksidan aktiviteyi daha da arttırıp oksidan parametreleri azaltmıştır.

Sonuç: Mevcut çalışmada RA tedavisi sonucu deney hayvanlarında O/TD'nin neden olduğu over ve akciğer hasarı azalmıştır.

Anahtar Kelimeler: Over, rat, rosmarinik asit, torsiyon detorsiyon

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INTRODUCTION

Different conditions such as a prolonged mesovarium and adnexal venous obstruction may cause ovarian torsion and occlusion of ovarian vessels. This condition leads to a critical decrease in blood flow to the tissues resulting in permanent injury (1). Thereby, ovarian torsion should be diagnosed and treated immediately to maintain ovarian function and fertility (2). Ovarian torsion composes nearly 3% of acute abdominal pain cases applying to emergency department (3). Ovarian torsion may be observed for all age groups in women, but mostly between the ages of 29 to 34 (4), which makes it a serious health condition in terms of fertility. Besides torsion and ischemia, detorsion also causes tissue damage during reperfusion through the overproduction of reactive oxygen species (ROS) (5). ROS contributes to ischemic injury at the cellular level during reperfusion (6).

High ROS levels and leukocyte deposition are observed at the reperfusion stage. Ovarian injury develops unless the intracellular antioxidants prevent ROS (7). Oxidative stress occurs when the oxidant mechanisms (ROS, free radical generation, etc.) overcome the antioxidant systems (8). During the reperfusion stage neutrophil recruitment induces ROS release and thus, plays a key role in tissue injury (9). Activated neutrophils release the myeloperoxidase (MPO) enzyme, which contributes to forming ischemia and reperfusion (10). ROS and malondialdehyde (MDA) accumulation and decreased superoxide dismutase (SOD) levels lead to oxidative stress injury (11).

Rosmarinic acid (RA) has antioxidant, anti-angiogenic, and anti-inflammatory functions (12). Fonteles et al. found that RA demonstrates anti-inflammatory features in ischemic mice. (13). It has been shown that RA protects the ischemic liver and cardiovascular systems through anti-inflammatory and antioxidant functions (14, 15).

Various agents have been examined against ovarian torsion detorsion (O/TD) in previous studies (16). Here, we searched the potential beneficial effects of RA on ovarian and lung tissues in an O/TD model.

MATERIAL AND METHOD

Experimental Animals and Ethical Approval

The current search was confirmed by Atatürk University Local Ethics Council of Animal Experiments (protocol number: 28.06.2018/141). Animal procurement and experimental procedure were carried out at Medical Experimental Application and Research Center of Atatürk University. Rats were put in standard rat cages with regular laboratory conditions. They were fed with regular rat feed and supplied tap water. Feeding was prohibited 12 hours before the experiment, but the water was allowed. to drink.

Groups and Torsion/Detorsion Model

32 Sprague Dawley female rats were weighted (240-250 g). Four groups were created (n=8) randomly as sham, O/TD (3hours torsion/3hours detorsion), RA 40 mg/kg (40 mg/kg RA+O/TD), and RA 80 mg/kg (80 mg/kg RA+O/TD) groups. The animals were immobilized in the supine position and then, the abdominal regions were shaved and disinfected. 10% povidone-iodine was preferred for disinfection. 10 mg/kg intraperitoneal (i.p.) xylazine hydrochloride and 60 mg/kg i.p. ketamine were used for anesthesia during the procedures (17, 18).

A 1-2 cm sized median laparotomic incision was established in the sham group, but no T/D model or medication was performed. The incision was repaired via silk 3/0 suture. In the O/TD group, following the incision, ovaries, ovarian vessels, and fallopian tubes were spun 360 degrees clockwise. They were fixed for 3 hours with atraumatic microvascular clamps, and thus, bilateral torsion was created. In the detorsion period, blood circulation was available for 3 hours by removing the clamps, and the incision was sutured. The O/TD model was preferred from previous studies (16, 19, 20). In low dose and high dose RA treatment groups, following the torsion phase, RA was applied to the rats i.p. at the doses of 40 mg/kg and 80 mg/kg just before detorsion, respectively. Then, the detorsion stage was carried out. The RA doses were based on a previous study (21).

Following the experiment, a high dose of anesthesia was performed for the sacrifice of the rats. The ovarian and lung tissues were removed. They were cleaned by washing and maintained frozen until the biochemical analysis.

Biochemical Analysis

Various parameters were examined in lung and ovarian tissue samples. MDA levels (µmol/g protein) were measured due to the methods explained by Ohkawa et al. (22) to determine the lipid peroxidation status. SOD (U/mg protein) and MPO (U/g protein) activities were evaluated as defined by Sun et al. (23) and Bradley et al. (24), respectively. TAS and TOS levels were gauged through commercially available kits (Rel Assay Diagnostics). OSI is the ratio of TOS to TAS (25), and is measured for the oxidative stress evaluation.

Statistical analysis

We analyzed the data using One-way ANOVA and demonstrated as Mean±Standard Error of Mean (SEM) through SPSS software. We used the Tukey test for the group pairwise comparisons. We admitted the differences as significant if $p<0.05$.

RESULTS

TAS, TOS, and OSI values of ovarian and lung tissues were shown in **Figures 1** and **2**, respectively. A significant raise occurred in the O/TD group compared to the sham group for the TOS and OSI levels, while the TAS value was diminished. Besides, the TAS value elevated significantly while TOS and OSI parameters declined in high and low dose RA groups compared to the O/TD group.

Results of MDA, SOD, and MPO activities in ovarian and lung tissues are presented in **Figure 3** and **Figure 4**, respectively. When the O/TD group was compared to the sham group, MPO activity and MDA levels were increased significantly, but SOD activity was decreased. Besides, when the RA treatment groups were compared to the O/TD group, MPO activity and MDA levels declined, but SOD activity was raised.

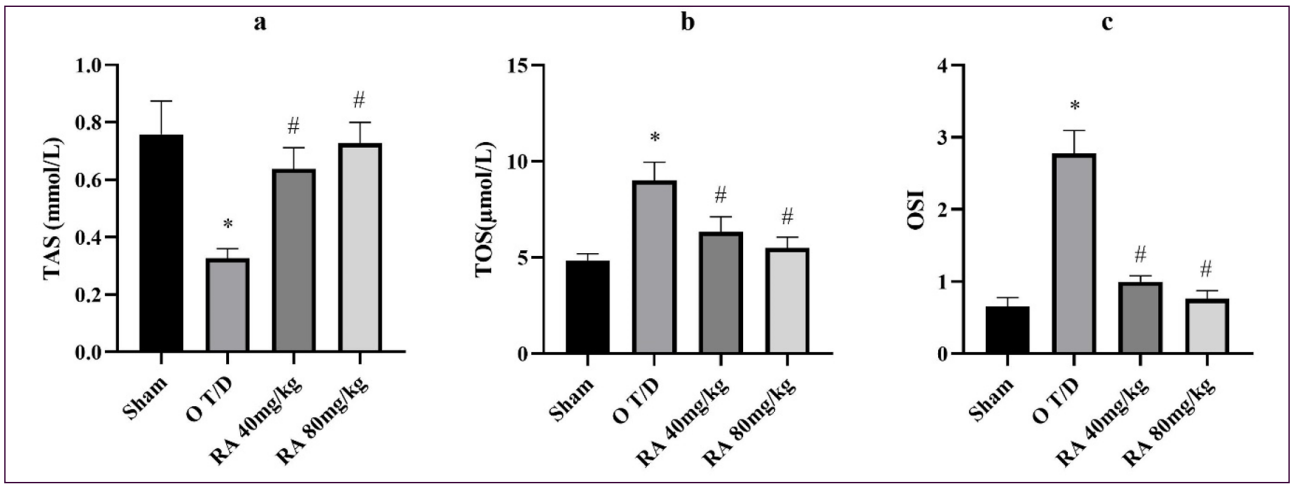

Figure 1. (a) TAS, (b) TOS, and (c) OSI values of ovarian tissue. *p<0.05 compared to sham group. #p<0.05 compared to O/TD group

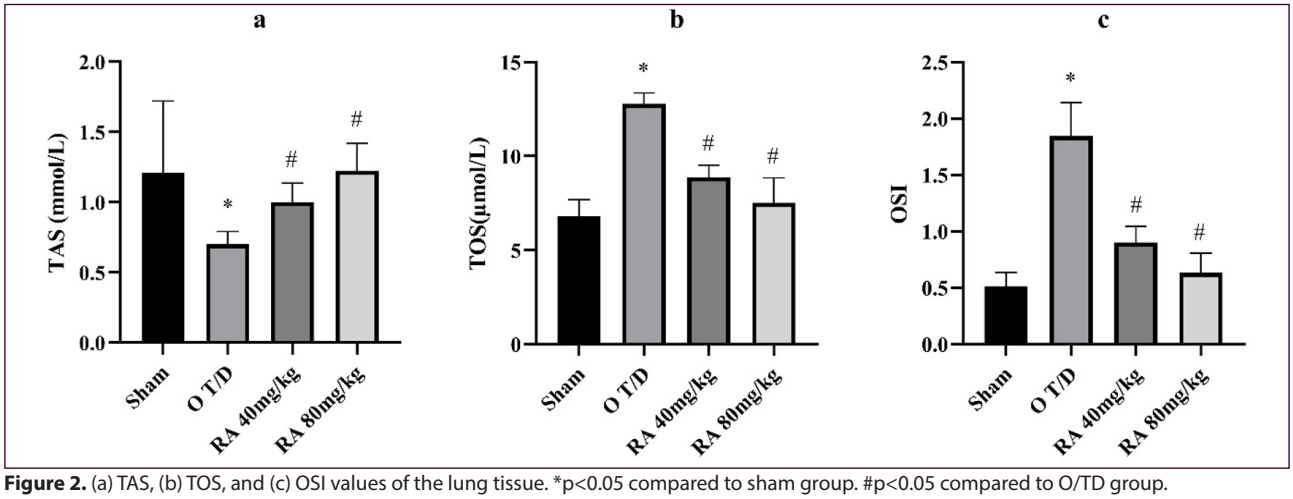

Figure 2. (a) TAS, (b) TOS, and (c) OSI values of the lung tissue. *p<0.05 compared to sham group. #p<0.05 compared to O/TD group.

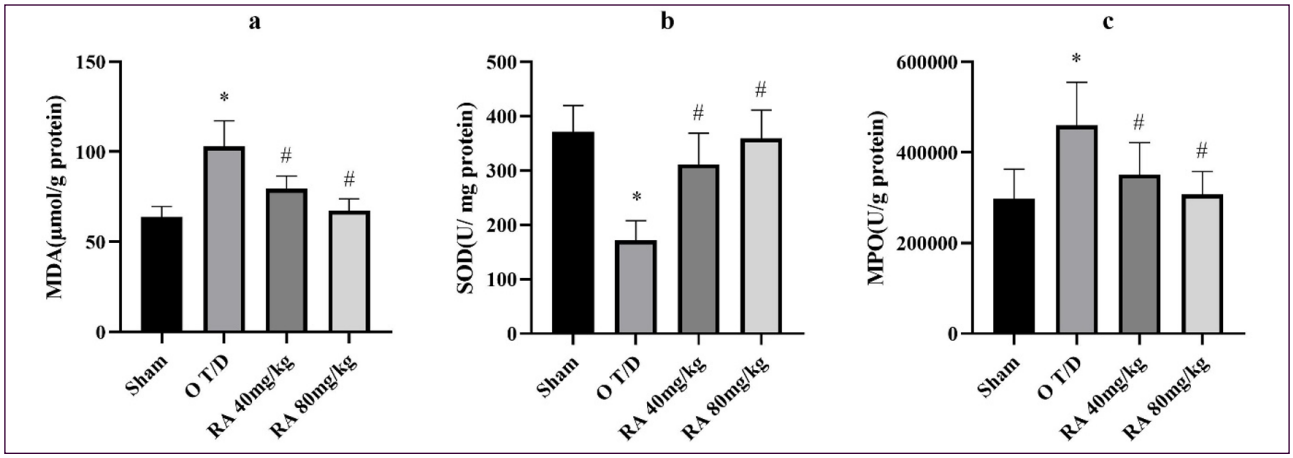

Figure 3. (a) MDA, (b) SOD, and (c) MPO values of ovarian tissue. *p<0.05 compared to sham group. #p<0.05 compared to O/TD group.

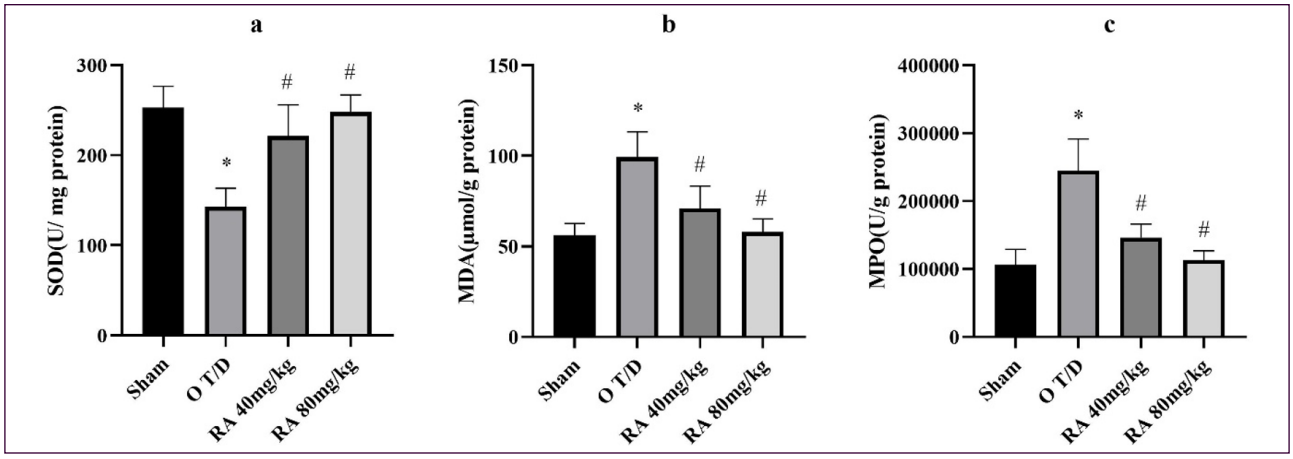

Figure 4. (a) SOD, (b) MDA, and (c) MPO values of the lung tissue. *p<0.05 compared to sham group. #p<0.05 compared to O/TD group.

DISCUSSION

Ovarian torsion affects all women of different ages. It is the rotation of the ovaries around utero-ovarian and infundibulopelvic ligaments (26). Once the ovarian torsion is diagnosed, detorsion of the twisted adnexa is vital to prevent infertility (2, 27). This O/TD process is named ischemia-reperfusion (I/R) injury (28). Ischemia leads to hypoxic injury. During the detorsion phase, even though blood flow may alleviate the injury, reperfusion stimulates the overexpression of reactive oxygen species (ROS) (29, 30). ROS enhances oxidant molecule production and decreases antioxidant levels, including SOD (31). SOD protects against the undesirable effects of ROS, and it is a part of TAS (32).

OSI is a sensitive rate for the oxidative stress assessment (33). The measurement of TAS and TOS levels preferred for the evaluation of I/R injuries (34). High ROS levels and decreased antioxidant activity negatively affect the oxidative–antioxidative balance in favor of oxidative stress (30). ROS enhances MDA production. MDA is a toxic lipid peroxidation product and may alter the membrane structure and cell functions (10). Therefore, it is an indicator of the stress levels both in vitro and in vivo (35). MPO is an enzyme located in neutrophils and is a marker of neutrophil infiltration (36). MPO activity increases during I/R-induced ovarian injury (37).

RA is a phenolic compound (38) with various pharmacological properties, including anti-inflammatory (39), anticancer, and antioxidant activities (40). RA alleviated renal I/R injury with its anti-inflammatory and antioxidant effects in a previous rat study (41). Another study showed that RA protects against cerebral ischemia in diabetic rats with its anti-inflammatory properties (42). RA treatment has been reported to prevent sepsis-induced oxidative damage by raising the SOD levels while diminishing the MDA values in rats. (43). It has been shown that RA increases antioxidant enzyme activity (SOD, etc.) and decreases MDA levels in renal and liver tissues of elderly mice (44).

RA administration performed a renoprotective effect against gentamicin-induced renal cortical oxidative stress in rats by increasing SOD levels and decreasing MDA values (45). Previous research has established that RA reduces spinal cord damage by reducing ROS and lipid peroxidation while increasing antioxidant parameters (46). In a rat model, RA administration alleviated O/TD-related damage in ovarian tissues (47) in harmony with our results. In addition, we also examined the lung tissues and here, we investigated RA to find out the possible protective effects against O/TD in both ovarian and lung tissues.

Understanding the injury pathways of O/TD is vital for new treatment methods. O/TD studies represented that the suppression of oxidative stress might contribute to the treatment. Here, oxidative stress parameters were suppressed, and antioxidant activity enhanced by RA administration, which encourages hope in the treatment of O/TD.

CONCLUSION

In this study, RA treatment reduced O/TD-induced ovarian and lung injuries in the experimental animals. Further research are necessary to find out the possible preventive mechanisms against ovarian and lung injuries induced by O/TD.

ETHICAL DECLARATIONS

Ethics Committee Approval: The current search was confirmed by Atatürk University Local Ethics Council of Animal Experiments (protocol number: 28.06.2018/141).

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

Evaluation of *Staphylococcus aureus* Infections in Children

Çocuklarda *Staphylococcus aureus* Enfeksiyonlarının Değerlendirilmesi

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Abstract

Aim: *Staphylococcus aureus* is the most common infectious agent worldwide which leads to morbidity and mortality. Community and hospital acquired infections can range from skin infections to life-threatening infections. In our study, we evaluated demographic, clinical, and laboratory parameters and the prognosis of children with *S. aureus* infection.

Material and Method: Children infected with *S. aureus* at the Department of Paediatric Infectious Disease, Selcuk University Faculty of Medicine, from 2014 to 2022 were analysed retrospectively. Patients were evaluated for MRSA, MSSA, and community or hospital-acquired infections.

Results: A total of 116 children's detected specimens were collected; 31.9% contained MRSA and 68.1% contained MSSA. The proportion of community-acquired (CA) infections was 88.8%, while hospital-acquired (HA) infections were 11.2%. MSSA was more common in the CA-*S. aureus* group, while MRSA was more common in the HA-*S. aureus* group (p=.025). The most common clinical manifestations included soft tissue infection, lymphadenitis, cutaneous infection, osteomyelitis, and septic arthritis. Each patient was treated with antibiotics, 77.59% of patients was required hospitalization. In 62.9% of the patients, surgical intervention (drainage or debridement) was performed. Despite 86.2% of the patients were cured, infection persisted in nine patients with epidermolysis bullosa, CIPA syndrome, and bone implants. One patient with shunt meningitis died.

Conclusion: *S. aureus* cause both CA and HA superficial or invasive infections, in children. Especially in life-threatening infections, appropriate antibiotic therapy is critical for preventing mortality until an antibiogram culture result is obtained. The patient's clinical condition and regional antibiotic resistance should be considered when prescribing antibiotics empirically.

Keywords: Child, invasive infections, *Staphylococcus aureus*, skin, and soft tissue infections

Öz

Amaç: *Staphylococcus aureus*, dünya çapında morbidite ve mortaliteye yol açan en yaygın enfeksiyöz ajanlardandır. Toplumdan ve hastaneden edinilen enfeksiyonlar cilt enfeksiyonlarından hayatı tehdit eden enfeksiyonlara kadar değişebilmektedir. *S. aureus* enfeksiyonlarının tedavisi, antibiyotik direnci ve aşı eksikliği nedeniyle zordur. Çalışmamızda *S. aureus* enfeksiyonu olan çocukların demografik, klinik ve laboratuvar parametrelerini ve prognozunu değerlendirmeyi amaçladık.

Gereç ve Yöntem: Selçuk Üniversitesi Tıp Fakültesi Çocuk Enfeksiyon Hastalıkları Bölümünde 2014-2022 yılları arasında, *S. aureus* ile enfekte çocuklar retrospektif olarak analiz edildi. Hastalar MRSA, MSSA ve toplumdan veya hastane kaynaklı enfeksiyonlar açısından değerlendirildi.

Bulgular: Toplam 116 çocuk örneğinin %31,9'u MRSA ve %68,1'i MSSA idi. Toplum kökenli (TK) enfeksiyonlar %88,8 iken, hastane kaynaklı (HK) enfeksiyonların oranı %11,2 idi. MSSA, TK enfeksiyonda daha yaygınken, MRSA ise HK enfeksiyonda daha yaygındı (p=.025). En sık klinik belirtiler yumuşak doku enfeksiyonu, lenfadenit, cilt enfeksiyonu, osteomiyelit ve septik artritti. Her hastaya antibiyotik tedavisi uygulandı, hastaların %77.59'unun hastaneye yatırılması gerekti. Hastaların %62,9'una cerrahi girişim (drenaj ve debridman) uygulandı. Hastaların %86.2'sinin iyileşmesine rağmen, epidermolizis bülloza, CIPA sendromu veya kemik implantları olan dokuz hastada tekrarlayan enfeksiyonlar saptandı. Şant menenjiti olan bir hasta öldü.

Sonuç: *S. aureus*, çocuklarda hem toplumdan hem de hastane kaynaklı yüzeysel veya invaziv enfeksiyonlara neden olmaktadır. Özellikle yaşamı tehdit eden enfeksiyonlarda, antibiyogram kültür sonucu çıkıncaya kadar uygun antibiyotik tedavisi mortalitenin önlenmesi açısından kritik öneme sahiptir. Ampirik antibiyotik başlanırken hastanın klinik durumu ve bölgesel antibiyotik direnci göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Çocuk, invaziv enfeksiyonlar, *Staphylococcus aureus*, deri ve yumuşak doku enfeksiyonları

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INTRODUCTION

Staphylococcus aureus is a Gram-positive bacterium that colonizes healthy individuals' skin and mucous membranes of the nose, throat, gastrointestinal tract, and urogenital tract without causing disease. Infections may result from injuries to the skin, mucous membranes, or invasive medical devices. When bacteria enter internal tissues and the bloodstream, they can induce a variety of severe infection. *S. aureus* is the most common invasive bacterial pathogen infecting children in many parts of the world. Both methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA) strains can cause hospital- acquired (HA) or community-acquired (CA) infection (1-2).

The bacteria, depending on their strains, can induce toxin-mediated diseases or invasive infections. Toxins such as alpha-hemolysin and Panton-Valentine leucocidin (PVL), superantigens, phagocytosis inhibitors (such as polysaccharide capsule and protein A), biofilm formation, intracellular survival, and blocking the chemotaxis of leukocytes all contribute to the pathogenesis of *S. aureus* (3-5). PVL toxin is primarily associated with CA-MRSA strains, cause of the skin and soft tissues infections, and pneumonia. PVL can also induce life-threatening infections in healthy individuals (6).

Based on antibiotic sensitivity, *S. aureus* is subdivided into MSSA and MRSA. The mec-A gene, which is located on the bacterial chromosome and codes for penicillin-binding protein-2a (PBP-2a), is responsible for penicillin resistance in MRSA strains. PBP-2a is an important bacterial cell wall enzyme that catalyses the synthesis of peptidoglycan in the bacterial cell wall. Strains of *S. aureus* that produce PBP-2a are typically resistant to penicillin (methicillin, dicloxacillin, nafcillin, oxacillin, etc.) and cephalosporins (2-3,7).

The disease spectrum can range from skin infections (such as abscesses, furuncles, and cellulitis) to life-threatening invasive infections, such as bloodstream infections, endocarditis, meningitis, toxic shock syndrome, necrotic pneumonia, osteomyelitis, septic arthritis, deep neck space infections, pyomyositis, necrotizing fasciitis, lymphadenitis, orbital cellulitis, and urinary tract infections (1-2).

The infectious agent is responsible for both CA and HA infection. HA-*S. aureus* is defined as cases with a positive culture result from a normally sterile site obtained more than 48 hours following hospital admission. At the time of infection onset, the presence of an invasive device, a history of surgery, hospitalization, or dialysis are risk factors for HA-*S. aureus* infections (8).Most of HA-MRSA strains were found to be prevalent in healthcare settings, which were associated with high rates of morbidity and mortality. In addition to causing HA infections, MRSA can also result in CA infections in healthy individuals (9).

In our research, we evaluated the demographic, clinical, and laboratory characteristics and outcomes of *S. aureus* infections in children.

MATERIAL AND METHOD

We reviewed the medical records of children who were diagnosed with *S. aureus* infection at the Department of Pediatric Infectious Disease at the Selcuk University Faculty of Medicine in Konya, Turkey, between January 2014 and December 2022. The hospital's ethics committee approved the study protocols (approval number: 2023/200).

The patients were separated into categories for MRSA and MSSA infections. Demographic data of the patients, underlying diseases, source of infection (community or hospital), clinical findings, laboratory values, radiological evaluations for abscess, hospitalization rates, and treatments methods (antibiotics, surgery) were evaluated retrospectively. Antibiotic susceptibility and resistance of *S. aureus* strains were recorded. The infection was evaluated whether it was CA or HA.

Infections were categorized as bacteraemia with unknown focus, infective endocarditis, catheter-associated bacteraemia, shunt meningitidis, skin or soft tissue infection, lymphadenitis, acute (hematogenous, non-hematogenous) osteomyelitis, chronic osteomyelitis, septic arthritis (hematogenous, non-hematogenous), bursitis, and lung abscess. Patients without full records were excluded from the study.

The samples taken from the patients were processed in the microbiology laboratory with standard methods suitable for the samples. The identification and antibiotic susceptibility tests of bacteria were performed using conventional methods and VITEK 2 (bio-Mérieux, France) automated system.

Statistical Analysis

All statistical analyses were conducted utilizing R version 4.1.2 Statistical Language (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/). Shapiro-Wilk's normality test and Q-Q diagrams were used to determine the normality of the data. The homogeneity of the variances was evaluated using Levene's test. The numerical variables were presented as mean standard deviation, median with ranges (minimum to maximum), or quartiles. Additionally, categorical variables were described in terms of count (n) and percentage (%). According to the demographical and clinical characteristics of *S. aureus* infections in children, a t-test, Mann-Whitney U test, Chi-square test with Yates continuity correction, or two-proportion Z-test was conducted to determine whether there was a statistically significant difference or association between MRSA and MSSA groups.

In addition, the Two-proportion Z-test was used to determine whether there was a significant difference between MRSA and MSSA in the proportion of *S. aureus* isolates that were resistant or sensitive to antibiotics. A two-tailed p-value of 5% or less is considered statistically significant.

RESULTS

Demographic and clinical features of children:

A total 116 children's specimens were collected, 59 of which were male (50.9%). The median age of the children was 3 years (1 month-18 years). The percentage of MRSA among the isolates was 31.9% (n=37), while the percentage of MSSA was 68.1% (n=79). Epidermolysis bullosa, trauma, congenital heart disease, congenital insensitivity to pain with anhidrosis (CIPA) syndrome, malnutrition, dermoid cyst, and ventriculoperitoneal shunt were identified as predisposing factors for *S. aureus* infection in 39 patients (33.6%). Fever was present in 55 patients (47.4%) at hospital admission. No statistically significant difference about age, gender, underlying diseases and fever were determined between the MSSA and MRSA groups.

Infection with CA-*S. aureus* (88.8%) was more prevalent than infection with HA-*S. aureus* (11.2%). While there were more MSSA isolates in the CA-*S. aureus* group (93.7% vs. 78.4%, p=.025), there were more MRSA isolates in the HA-*S. aureus* group (21.6% vs. 6.3%, p=.025).

The patients presented with mostly skin or soft tissue infections, lymphadenitis and osteoarticular infections. Infection of soft tissue was more frequent in the MRSA group than in the MSSA group (37.84% vs. 18.99%, p=.029), while lymphadenitis was more frequent in the MSSA group (30.3%). The MRSA group had a higher incidence of acute osteomyelitis than the MSSA group (13.5% vs. 1.27%, p=.012), and all cases of hematogenous osteomyelitis (n=3) occurred in the CA-MRSA group. All septic arthritis were due to MSSA and, hematogenous septic arthritis accounted for 66% of cases. One patient was treated for CA-MRSA-related pulmonary abscess. Other clinical presentations demonstrated no statistically significant differences between the MSSA and MRSA groups.

Percentage of HA-*S. aureus* infections were; 30.7% soft tissue infection (n=4), 23% catheter-associated bacteraemia (n=3), 15.3 % shunt meningitidis (n=2), 7.6 % chronic osteomyelitis (n=1), 7.6 % skin infection (n=1), %7.6 bacteraemia unknown focus (n=1), %7.6 infective endocarditis (n=1).

The patient on dialysis for chronic renal failure (HA-MSSA) and the patient with ventricular septal defect (CA-MSSA) were both diagnosed with infectious endocarditis. In one patient, HA-MRSA was identified as a non-focus bacteraemia agent. The 77.59% of patients required hospitalization. The hospitalization rates of the MRSA and MSSA groups did not differ statistically significantly. **Table 1** summarizes the demographic and clinical characteristics of the patients.

II. Laboratory features of children with *S. aureus* infections (Table 2):

There was no statistically significant difference found between MRSA and MSSA acute phase reactant values, radiologic imaging findings, blood culture positivity rates. Hematogenous septic arthritis 50% (n=4), infective endocarditis 25% (n=2), shunt meningitis 12.5% (n=1), and catheter-associated bacteraemia 12.5% (n=1) comprised the percentage of patients with MSSA growth in blood cultures. Hematogenous acute osteomyelitis 60% (n=3), bacteraemia 20% (n=1), and catheter-associated bacteraemia 20% (n=1) comprise the percentage of patients with MRSA growth in blood culture.

III. Antibiogram profile of *S. aureus* isolates from children:

More than 94% of *S. aureus* isolates were resistant to penicillin G, followed by 81.7 % resistant to inducible clindamycin, 31.3 % resistant to cefoxitin, 24.3 % resistant to erythromycin, and 21.7 % resistant to clindamycin, respectively. All *S. aureus* isolates exhibited susceptibility to teicoplanin, vancomycin, and linezolid. Most of *S. aureus* strains were (%95) susceptible to daptomycin. Compared with MSSA isolates, the MRSA isolates in this study exhibited a higher resistance rate to erythromycin, ciprofloxacin, tetracycline, fusidic acid, levofloxacin, TMP-SMX, moxifloxacin, and gentamicin (**Table 3**).

IV. Management of infections and outcomes:

At study assessment, 77.5% of the patients (n=90) were received intravenous antibiotic treatment (78.3% of MRSA; %77.2 MSSA). Teicoplanin, ampicillin-sulbactam and clindamycin combination and clindamycin monotherapy were the most common used antibiotics in both groups and overall (**Table 4**). Patients received teicoplanin (n=3) despite MSSA infection due to severe infections were had hematogenous septic arthritis, catheter-associated bacteraemia, and infective endocarditis.

Twenty-six of the patients were treated orally with antibiotics and were not hospitalized. Most of these patients had skin or soft tissue infections and, less often had chronic osteomyelitis.

Seventy of the patients were discharged with oral antibiotics. Clindamycin and trimethoprim sulfamethoxazole were the most common used oral antibiotics in both groups and overall (**Table 4**). The four patients with septic arthritis or osteomyelitis were discharged with intramuscular teicoplanin.

Infections of the skin (n=8), soft tissue (n=6), septic arthritis (n=2), osteomyelitis (n=5), lymphadenitis (n=6), and bursitis (n=1) were treated orally with TMP-SMX. Oral linezolid was used to treat a patient with CA-MRSA acute osteomyelitis, while oral ciprofloxacin was used to treat a patient with a CA-MRSA skin infection.

In 62.9% (n=73) of the patients, surgical intervention was performed. While patients with osteomyelitis or septic arthritis were debrided (12.9%, n=15), patients with lymphadenitis, soft tissue infection, or lung abscess underwent drainage (50%, n=58).

Only one patient with ventriculoperitoneal shunt meningitis died. Infection persisted in patients with epidermolysis bullosa, CIPA syndrome, bone implants and culture growth was detected in fifteen of these patient's samples (%12.9).

Table 1. Demographic and Clinical Features of *Staphylococcus aureus* Infections in Children

	Overall n=116 (%)	MRSA n=37 (31.9%)	MSSA n=79 (68.1%)	p-value
Age (year), (median)	3 (1-18)	3 (1-18)	3 (1-17)	.9591
Gender (Male/Female)	59/57 (50.9/49.1)	17/20 (45.9/54.1)	42/37 (53.2/46.8)	.5992
Underlying Disease	39 (33.62)	16 (43.24)	23 (29.11)	.135
Fever on Admission	55 (47.4)	18 (48.6)	37 (46.8)	>.999
CA- *S. aureus*	103 (88.8)	29 (78.4)	74 (93.7)	**.025**
HA- *S. aureus*	13 (11.2)	8 (21.6)	5 (6.3)	**.025**
Presence of Central Catheter	4 (3.4)	1 (2.7)	3 (3.8)	>.999
Clinical Presentation				
Bacteraemia unknown focus	1 (0.86)	1 (2.7)	0 (0.0)	.319
Infective endocarditis	2 (1.72)	0 (0.0)	2 (2.53)	.331
Catheter-associated bacteraemia	3 (2.5)	2 (5.4)	1 (1.2)	.238
Shunt meningitidis	2 (1.72)	1 (2.7)	1 (1.27)	.582
Skin Infection	27 (23.28)	5 (13.51)	22 (27.85)	.089
Soft Tissue Infection	29 (25.0)	14 (37.84)	15 (18.99)	**.029**
Lymphadenitis	28 (24.14)	4 (10.81)	24 (30.38)	**.022**
Osteomyelitis	15 (12.93)	8 (21.62)	7 (8.86)	.057
*Acute Osteomyelitis	6 (5.17)	5 (13.51)	1 (1.27)	**.012**
Hematogenous	3 (2.59)	3 (0.81)	0 (0.0)	**.031**
Non-Hematogenous	3 (2.59)	2 (5.41)	1 (1.27)	.193
*Chronic Osteomyelitis	9 (7.76)	6 (16.2)	3 (3.7)	.593
Septic Arthritis	6 (5.17)	0 (0.0)	6 (7.59)	.086
Hematogenous	4 (3.45)	0 (0.0)	4 (5.06)	.165
Non-Hematogenous	2 (1.72)	0 (0.0)	2 (2.53)	.331
Bursitis	2 (1.72)	1 (2.7)	1 (1.27)	.583
Lung Abscess	1 (0.86)	1 (2.7)	0 (0.0)	.144
Treatment Management				
Hospitalization	90 (77.59)	29 (78.38)	61 (77.22)	.889
Outpatient	26 (22.41)	8 (21.62)	18 (22.78)	.889

[1]Mann-Whitney U test, [2]Chi-square test with Yates continuity correction, Abbreviations: CA-*S. aureus*, Community acquired-*Staphylococcus aureus*; HA-*S. aureus*, Hospital acquired-*Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

Table 2. Laboratory Features of Children with *Staphylococcus aureus* Infections

Initial Laboratory Values	Overall (n=116)	MRSA (n=37)	MSSA (n=79)	p-value
Total leukocyte count (K/µL)	12.800 (9.560-18.400)	13.100 (9.700-16.800)	12.550 (9.600-18.850)	.6971
Absolute neutrophil count (K/µL)	8.220 (5.100 -11.030)	8.130 (5.250-11.400)	8.325 (5.137,5-11.000)	.7601
Absolute lymphocyte count (K/µL)	3.380 (2.040- 6.080)	3.080 (2.130-5.340)	3.545 (2.000-6.355)	.6751
Haemoglobin (g/dL)	11.47 ± 1.92	11.60 ± 2.09	11.41 ± 1.84	.623
Platelet (K/µL)	403 (300-513)	391 (309.5-480)	409 (294.5-528.75)	.6681
Sedimentation (mm/h)	27 (11-53)	25 (11.75-54.5)	29 (9.5-51.5)	.8921
C-reactive protein(mg/L)	29 (9.95 -70.5)	25 (8.55 -67.5)	29 (12-70)	.7431
Procalcitonin (µg/L)	0.14 (0.07-0.43)	0.14 (0.07 - 0.30)	0.13 (0.07- 0.50)	.8851
Positive blood cultures n (%)	13 (11.2)	5 (13.5)	8 (10)	.753
Abscess formation on radiological imaging n (%)	53 (45.7)	17 (45.9)	36 (45.6)	.976
ECHO-vegetation n (%)	2 (1.7)	0 (0)	2 (2.5)	.334

[1]Mann-Whitney U test, Abbreviations: ECHO, echocardiography; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-Susceptible *Staphylococcus aureus*

Table 3. Antibiotic resistance and susceptibility profile of *Staphylococcus aureus* isolates from children

Antibiotics	Sensitivity			p-value
	Overall	MRSA	MSSA	
Penicillin G	6 (5.4)	0/37 (0.0)	6/74 (8.1)	.076
Mupirocin	92 (97.9)	26/26 (100)	66/68 (97.1)	.383
Cefoxitin	79 (68.7)	0/36 (0.0)	79/79 (100)	<.001
Erythromycin	87 (75.7)	23/37 (62.2)	64/78 (82.1)	.021
Inducible clindamycin resistance	20 (18.3)	9/34 (26.5)	11/75 (14.7)	.142
Clindamycin	90 (78.3)	25/37 (67.6)	65/78 (83.3)	.057
Fusidic acid	104 (89.7)	29/37 (78.4)	75/79 (94.9)	.007
Ciprofloxacin	77 (88.5)	20/29 (69.0)	57/58 (98.3)	.001
Levofloxacin	106 (92.2)	29/37 (78.4)	77/78 (98.7)	.002
Moxifloxacin	106 (93.8)	28/35 (80.0)	78/78 (100)	<.001
Tetracycline	97 (86.6)	25/35 (71.4)	72/77 (93.5)	.001
Gentamicin	110 (94.8)	32/37 (86.5)	78/79 (98.7)	.006
Trimethoprim-sulfamethoxazole	107 (92.2)	29/37 (78.4)	78/79 (98.7)	<.001
Teicoplanin	101 (99.0)	31/31 (100)	70/71 (98.6)	.509
Vancomycin	96 (100)	30/30 (100)	66/66 (100)	>0.999
Linezolid	116 (100)	37/37 (100)	79/79 (100)	>0.999
Daptomycin	77 (95.1)	23/25 (92)	54/56 (96.4)	.402

Table 4. Management of Children with *Staphylococcus aureus* Infections and Outcomes

	Overall n=116, (%)	MRSA n=37, (%)	MSSA n=79, (%)	p-value
Treatment				
Intravenous Antibiotic	90/116 (77.59)	29/37 (78.38)	61/79 (77.22)	.889
Cephazolin	4/90 (4.44)	0/29 (0.0)	4/61 (6.56)	.161
Ampicillin-sulbactam	9/90 (10.0)	3/29 (10.34)	6/61 (9.84)	.941
Clindamycin	15/90 (16.67)	5/29 (17.24)	10/61 (16.39)	.919
Teicoplanin	28/90 (31.11)	12/29 (41.38)	16/61 (26.23)	.149
Vancomycin	4/90 (4.44)	3/29 (10.34)	1/61 (1.64)	.062
Trimethoprim-sulfamethoxazole	4/90 (4.44)	1/29 (3.45)	3/61 (4.92)	.752
Ampicillin-sulbactam+Clindamycin	25/90 (27.78)	5/29 (17.24)	20/61 (32.79)	.126
Vancomycin+Clindamycin	1/90 (1.11)	0/29 (0.0)	1/61 (1.64)	.490
Oral Antibiotic/OPAT	96/116 (82.76)	32/37 (86.49)	64/79 (81.01)	.468
Cephalexin	2/96 (2.08)	0/32 (0.0)	2/64 (3.13)	.314
Amoxicillin	2/96 (2.08)	0/32 (0.0)	2/64 (3.13)	.314
Amoxicillin-clavulanate	10/96 (10.42)	2/32 (6.25)	8/64 (12.5)	.347
Ampicillin-sulbactam	11/96 (11.46)	1/32 (3.13)	10/64 (15.63)	.071
Clindamycin	37/96 (38.54)	14/32 (43.75)	23/64 (35.94)	.461
Trimethoprim-sulfamethoxazole	28/96 (29.17)	12/32 (37.5)	16/64 (25.0)	.206
Ciprofloxacin	1/96 (1.04)	1/32 (3.13)	0/64 (0.0)	.157
Linezolid	1/96 (1.04)	1/32 (3.13)	0/64 (0.0)	.157
Teicoplanin (Intramuscular)	4/96 (4.17)	1/32 (3.13)	3/64 (4.69)	.719
Additional treatment				
Surgery	73 (62.93)	22 (59.46)	51 (64.56)	.597
Need for debridement	15 (12.93)	4 (10.81)	11 (13.92)	.643
Need for drainage	58 (50.0)	18 (48.65)	40 (50.63)	.843
Outcome				
Cured	100 (86.21)	32 (86.49)	68 (86.08)	.952
Persistent infection	15 (12.93)	4 (10.81)	11 (13.92)	.643
Mortality	1 (0.86)	1 (2.7)	0 (0.0)	.144

Chi-square test with Yates continuity correction, Abbreviations: CA- *S. aureus*, Community acquired-*Staphylococcus aureus*; HA-*S. aureus*, Hospital acquired -*Staphylococcus aureus*; MSSA, Methicillin-Susceptible *Staphylococcus aureus* ;MRSA, methicillin-resistant *Staphylococcus aureus*; OPAT, Outpatient parenteral antimicrobial therapy

DISCUSSION

In this retrospective single-centre study, *S. aureus* infection in children was analysed. Our objective was to inform clinicians about the various clinical manifestations of *S. aureus* infections and the regional pattern of antibiotic susceptibility and resistance.

CA-MRSA infection rate has increased in recent years, healthy children are also susceptible. Infections caused by CA-MRSA are usually related to skin and soft tissues. However, CA-MRSA may associate with life-threatening infections (10-11). Skin trauma, frequent skin-to-skin contact, sharing potentially contaminated personal items or equipment that has not been cleaned, crowded conditions, restricted access to medical care, and frequent exposure to antimicrobial agents are risk factors for CA-MRSA (12).

S. aureus infection affects all ages and genders. Gomes et al. reported CA-*S. aureus* infections (n=90) in patients 20 years old over a period of 11 years. The percentage of CA-MRSA is lower than in our study (6.7% vs. 28%). The median age of the patients was two years old (66% of whom were male). In 27 cases (30%), underlying conditions were identified. The majority involved the skin (44.4%), the heart (25.9%), the respiratory tract (11.1%), and the central nervous system (3.9%). Overall, 34 (37.8%) patients had skin/soft tissue infections;56 (62.2%) patients had deep infection; pneumonia (26.8%), arthritis (17.9%), pyodermatitis (14.3%), osteomyelitis (8.9%), adenitis (5.4%), sepsis (5.4%), endocarditis (3.6%), cellulitis (1.8%), urinary tract infection (1.8%). Two (2.6%) of the four patients who were transferred to the intensive care unit died. Patients with MRSA or MSSA infections showed similar baseline features and therapeutic outcomes. The median length of stay in the hospital was 14 (1–53) days (13). In our study, we found no significant variations in the baseline characteristics or prognosis of patients infected with CA-MRSA or CA-MSSA strains.

S. aureus, colonize the skin in 20–30% of the population and is responsible for 80–90% of all skin and soft tissue infections in people worldwide (14). Although drainage is the mainstay of therapy for purulent skin and soft tissue infections antibiotics are associated with clinical improvement. 1st or 2nd generation cephalosporins are recommended for children at low risk of MRSA infection. If the rate of MRSA is high in the community, oral clindamycin, TMP-SMX and doxycycline are recommended for initial treatment. In severe infections, intravenous vancomycin and clindamycin are recommended (15). In our study, 46% of patients presented with skin soft tissue infection and 33.9% of them had MRSA. Clindamycin (28.5%), TMP-SMX (25%), and amoxicillin-clavulanate (16%) were the most common antibiotics used for treatment.

Acute bacterial lymphadenitis is a common childhood condition. Annaliese R. et al reported (2023) 148 children with lymphadenitis. In culture-positive cases, MSSA (49%) and Group A Streptococcus (43%) predominated, while MRSA was seen in a minority of cases (6%). Cephalexin, clindamycin, amoxicillin-clavulanate, was the most used antibiotics (16). In our study, 28 of the patients (24.1%) had lymphadenitis. 14.3% of the cases were identified as MRSA and 85.7% as MSSA. Of these, 75% received treatment with clindamycin.

The most common pathogenic bacteria associated with osteomyelitis in children are MSSA and MRSA.

Clinically, first- or second-generation cephalosporins are routinely used to treat of MSSA acute osteomyelitis in children (17). Oral clindamycin is commonly used to treat acute CA-MRSA osteomyelitis. Because of inducible clindamycin resistance, TMP-SMX is preferred an alternative therapy (18). In our study, there were 15 patients we followed for osteomyelitis and MRSA was detected in 8 of them. Of these, 53.3% received treatment with clindamycin, 33.3% received TMP-SMX. Arnold SR et al. reported 158 cases of acute osteoarticular infection in children. MRSA infections were associated with increased rate of subperiosteal abscess formation (71% versus 38%), therefore increased needing for surgical drainage (91 versus 62 percent) and increased median hospital stay (10 versus 7 days) (19). In our study, no significant difference was found between the two groups in terms of abscess formation, surgical requirements, or hospitalization.

Septic bursitis is an infection that typically affects the prepatellar and olecranon bursae. *S. aureus* accounts for approximately 80% of cases (20). We detected olecranon bursitis in one patient and suprapatellar bursitis in one patient.

David et al reported 313 patients with bacterial CA pneumonia. *S. aureus* was detected in 10.9% of the patients and, MRSA in 26.5% of them. Patients with *S. aureus* pneumonia had a high prevalence of complications (21). Clindamycin is recommended for MRSA pneumonia without concomitant influenza (22).

Vancomycin or clindamycin is suggested as first-line therapy for nonlife-threatening infections (eg, pneumonia, septic arthritis, osteomyelitis) without signs of sepsis thought to be caused by MRSA. Oxacillin, nafsicillin or cephazolin are recommended in patients with MSSA (22).

Vancomycin plus nafcillin or oxacillin is suggested as first-line therapy for severe infections (sepsis, meningitis, endocarditis) thought to be caused by *S. aureus* (HA/CA) (22). Patients with serious infections received vancomycin or teicoplanin treatment.

Most infective endocarditis is caused by CA-*S. aureus* bacteraemia. Children with congenital cardiac disease and/or indwelling central venous catheters are at higher risk (23-24). In our study, infective endocarditis was detected in one patient who underwent dialysis for chronic renal failure (HA-MSSA) and the one patient with ventricular septal defect (CA-MSSA).

Central nervous system (CNS) infections caused by *S. aureus* are uncommon in children. Vallejo et al reported seventy cases of *S. aureus* CNS infection. Forty-nine cases (70%) were secondary to a CNS device. Forty-seven (67.2%) were caused by MSSA and 23 (32.8%) by MRSA (25). In our study, two patients with ventriculoperitoneal shunts had meningitis. One patient with MRSA meningitidis died.

Forty to fifty percent of *S. aureus* bacteraemia in children is associated with a localized infection source such as bone and joint infections, skin and soft tissue infections, pneumonia, or an invasive device. The account of 10% bacteraemia is without a focus (26-27). Non-focal bloodstream infection detected due to HA-MRSA in one of our patients. Bacteremia was detected in 12 patients with focal infection site.

Infants are more vulnerable to invasive HA-MRSA infections. Risk factors for HA-MRSA infection are; presence of an invasive device at the time of admission, history of MRSA infection or colonization, history of surgery, hospitalization, or dialysis, prolonged hospitalization (>14 days), surgery or surgical site infection (28). In our study HA-*S. aureus* infections were skin and soft tissue infection after surgery (n=5), catheter-associated bacteraemia (n=3), shunt meningitidis (n=2), bacteraemia unknown focus(n=1), and infective endocarditis (n=1), chorionic osteomyelitis (n=1).

In the study of Şanlı et al. (2004) 210 *S. aureus* strains grown in patient cultures in different clinics were evaluated retrospectively. Of the overall strains, 48.1% were MSSA and 51.9% were MRSA; 17.6% (n=37) were CA and 82.3% (n=173) were HA. While 56.1% of MRSA were HA, 67.5% of MSSA were CA. Consistent with our study, vancomycin and teicoplanin internal resistance was not observed (29).

In MRSA strains, resistance to penicillin 100%, gentamicin 83.4%, ciprofloxacin 82.5%, levofloxacin 75.2%, clindamycin 72.4%, erythromycin 71.5% detected. In our study, antibiotic resistance rates were lower (except for penicillin); gentamicin 13.5%, ciprofloxacin 31%, levofloxacin 21.6%, clindamycin 32.4 %, erythromycin 37.8%, detected (29). In MSSA strains, resistance to penicillin 65.3%, gentamicin and ciprofloxacin 21.7%, erythromycin 19.8%, levofloxacin and clindamycin 11.8% was detected. Our research found that resistance to penicillin and clindamycin was higher 16.7% and 91.9%, respectively (29).

Our research had some limitations. This is a single center, retrospective study. Some data were missing in medical charts. Bacterial strain virulence factors were not addressed. Since, in addition to antimicrobial resistance, virulence factors affect the clinical outcome of *S. aureus* infections.

CONCLUSION

Staphylococcal infections are encountered with increasing frequency in the community and hospitals, it is one of the infections that are important in terms of mortality and morbidity. *S. aureus* infections are difficult to treat due to antibiotic resistance and a lack of vaccines. The prevalence of methicillin resistance causes significant treatment challenges. it is important to know the regional antibiotic resistance in empirical antibiotic selection. For one to effectively control *S. aureus* infections, it is essential to use preventive control methods in the community and in hospitals.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocols were approved by Selcuk University Faculty of Medicine ethics committee (approval number: 2023/200).

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

Bibliometric Analysis of Publications on PANDAS Syndrome in Psychiatry Research Area

Psikiyatri Araştırma Alanında Pandas Sendromu ile İlgili Yayınların Bibliyometrik Analizi

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ABSTRACT

Aim: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS syndrome) is a neuropsychiatric disorder whose diagnosis and treatment are controversial. The goal of this study was to highlight trends and discuss problems in PANDAS syndrome research since 1998 and to assist researchers in identifying new avenues for this field of study.

Material and Method: This study entails a bibliometric analysis of academic research papers in the field of psychiatry focusing on the PANDAS literature published between 1998 and May 2023. The Vosviewer program was used to conduct bibliometric analysis on the articles chosen from the Web of Science Core Collection.

Results: The analysis encompassed a total of 361 publications, with the highest number of publications occurring in 2004. In the subsequent years, the publication count exhibited an irregular pattern. The most influential publications, garnering 881 citations, were published in 2021. Among the prominently contributing countries, the United States (n=191, 52.91%) held the majority, followed by Italy (n=43, 11.91%), England (n=32, 8.86%), Germany (n=18, 4.98%), Sweden (n=13, 3.60%), Turkey (n=13, 3.60%), and Spain (n=10, 2.77%). Notably, the United States, the United Kingdom, Italy, and Germany displayed extensive collaboration with numerous other countries. The National Institute of Mental Health, Yale University, and Johns Hopkins University emerged as the most productive institutions.

Conclusion: Through this study, we conducted a review of global studies on PANDAS in the field of psychiatry, aiming to emphasize the identified issues. The findings of this study reveal that the number of publications on PANDAS is still significantly lower than anticipated. Considering the numerous uncertainties surrounding the diagnosis, treatment, and etiology of PANDAS syndrome, there is a pressing need for enhanced global scientific productivity in this area.

Keywords: Bibliometrics, PANDAS syndrome, publications

ÖZ

Amaç: Pediatrik otoimmün streptokok enfeksiyonlarıyla ilişkili nöropsikiyatrik bozukluklar (PANDAS sendromu), teşhisi ve tedavisi tartışmalı bir nöropsikiyatrik bozukluktur. Bu çalışmanın amacı, 1998'den bu yana PANDAS sendromu araştırmalarında görülen eğilimleri vurgulamak ve tartışmak, araştırmacılara bu alan için yeni olanaklar belirlemelerine yardımcı olmaktır.

Gereç ve Yöntem: Bu çalışma, 1998 ile Mayıs 2023 arasında yayınlanmış olan PANDAS literatürüne odaklanan psikiyatri alanındaki akademik araştırma makalelerinin bibliyometrik analizini içermektedir. Web of Science Core Collection'dan seçilen makaleler üzerinde bibliyometrik analiz yapmak için Vosviewer programı kullanılmıştır.

Bulgular: Analiz, toplamda 361 yayını içermektedir. En fazla yayının olduğu yıl 2004'tür. Takip eden yıllarda yayın sayısı düzensiz bir seyir izlemiştir. En çok atıfta bulunan yayınlar ise 2021'de yayınlanmış olup toplamda 881 atıf almışlardır. En çok yayın yapan ülkeler olarak Amerika Birleşik Devletleri (n=191, %52.91), İtalya (n=43, %11.91), İngiltere (n=32, %8.86), Almanya (n=18, %4.98), İsveç (n=13, %3.60), Türkiye (n=13, %3.60) ve İspanya (n=10, %2.77) belirlenmiştir. Amerika Birleşik Devletleri, Birleşik Krallık, İtalya ve Almanya, diğer ülkelerle en çok iş birliği yapan ülkelerdir. Ulusal Ruh Sağlığı Enstitüsü, Yale Üniversitesi ve Johns Hopkins Üniversitesi en üretken kurumlar olarak öne çıkmaktadır.

Sonuç: Bu çalışma kapsamında, psikiyatri alanındaki PANDAS üzerine küresel çalışmaları gözden geçirdik ve vurgulamak istediğimiz konuları belirlemeye çalıştık. Bu çalışmanın bulguları, PANDAS üzerine yapılan yayın sayısının hala beklenenden önemli ölçüde daha düşük olduğunu ortaya koymaktadır. PANDAS sendromunun tanı, tedavi ve etiyolojisiyle ilgili birçok belirsizlik göz önüne alındığında, bu alanda küresel bilimsel üretkenliğin artırılması için acil bir ihtiyaç vardır.

Anahtar Kelimeler: Bibliyometri, PANDAS sendromu, yayınlar

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INTRODUCTION

The autoimmune reaction to infection of group A streptococci (GAS) is assumed to be the cause of PANDAS syndrome (Pediatric Autoimmune Neuropsychiatric Disorders Associated with streptococcal infections) (1). It is proposed that the antigenic structure of Group A streptococci is similar to neuron proteins, which may lead to antibody formation and the inadvertent onset of an autoimmune response. However, over the years, researchers found that the levels of suspected antibodies (such as Anti-streptolysin-O, AntiDNAase B) did not increase in the blood during recurrent disease exacerbations in PANDAS patients, and this deficiency has been found in many studies (2). Numerous studies have examined investigated the link between streptococcal infections and sudden onset of neuropsychiatric symptoms. Initial reports suggested that neuropsychiatric issues could emerge up to 9 months after GAS infection (1,3).

In 1998, Swedo et al. (3) initially reported 50 cases of a specific subtype of pediatric obsessive-compulsive disorder (OCD) characterized by the sudden onset and episodic course of symptoms. Swedo et al. (3) introduced the term PANDAS. OCD is typically characterized by obsessive behaviors and rituals. The projected lifetime prevalence of OCD comorbidity is 2.3%, which is noticeably high (4). PANDAS' initial diagnostic standards were put forth in 1998 (3). In order to elucidate the mechanism of the disease, which is thought to have an autoimmune basis, to form an etiologically homogeneous group, and to conduct scientific research on these patients, patients must meet all established criteria completely (5). A 2012 article outlined the PANDAS definition's shortcomings and expressed concerns about how to classify individuals who met all PANDAS criteria but did not have a GAS infection (6). Despite substantial advancements in the study of OCD, significant concerns about the disorder's importance for public health, proper diagnostic classification, and clinical heterogeneity still need to be answered (3,4). Thus, patients who did not meet all criteria but were clinically very similar were excluded from the classification. The authors of PANDAS recognized the weakness of the classification system in including patients who met most, but not all, of the criteria. Thus, they proposed the PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) classification, aiming to classify in-between cases and adolescent cases that do not meet all PANDAS criteria. The CANS (Childhood Acute Neuropsychiatric Syndrome) classification was later added to the literature. The criteria for diagnosis in both of the new classification systems differ significantly, although they both categorize OCD symptoms and tics along with mental symptoms including anxiety, emotional instability, and irritability. In addition, PANS and CANS have been used to include a wider range of patients in the childhood age group (before the age of 18) by removing the requirement of "pre-adolescence" in PANDAS. Another difference is that there is no requirement to identify the triggering infectious agent or environmental triggers such as GAS. In addition, in the PANS definition, it was stated that restriction of food intake or change in eating behavior alone could meet the criterion that OCD and/or tics should be detected (6).

It is not apparent if the diagnostic standards for PANS are specific enough to identify a separate clinical entity. But adding the sudden development of psychiatric symptoms as a requirement seems to separate certain kids apart from other kids who are referred for PANS screening (7). Even if there isn't enough evidence to prove conclusively that PANDAS is an autoimmune disorder, questions about its diagnosis, management. Also, given that this ailment is now more widely known and that this diagnostic category appears to be being used more frequently, the etiology has to be determined (8). Additionally, PANDAS management literature is ambiguous, and there is no clinical consensus on the best course of treatment (1).

Despite the fact that bibliometric analysis is frequently utilized in numerous aspects of medicine (9-16), there has yet to be a similar examination of PANDAS syndrome in the psychiatry research area. The goal of the present investigation is to identify and analyze the most referenced publications, predominantly published journals, most often occurring keywords, and most recognized countries and organizations on PANDAS syndrome in psychiatry research published between 1998 and May 2023.

MATERIAL AND METHOD

The PANDAS literature, which consists of academic research papers in the fields of psychiatry and closely associated disciplines, was assessed bibliometrically for this study. To lessen bias brought on by database updates, the data from 1998 to May 31, 2023 was retrieved from the Web of Science core collection on June 1, 2023. These keywords were used to pull information from the online Web of Science database: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (Topic) OR PANDAS syndrome (Topic) OR PANDAS/PANS (Topic) OR PANDAS/CANS in Psychiatry; Autism & Development Disorders and Neurodegenerative Diseases research areas. For further examination, all records—including titles, summaries, and citations—were exported. The VOSviewer software (VOSviewer_1.6.19) was also utilized to illustrate the thorough data analysis in addition to the gathering of information. Additionally, we used the bibliometric website (https://bibliometric.com/) to display the evolution of keywords and publisher

countries through time. We also downloaded the data in tab-delimited format, complete with full records with associated references, for use with this bibliometric website.

RESULTS

1. Publication and Citation Characteristics

The first publications on PANDAS were published in 1998 and 7 articles were published in this year. After the first publications (1998), a total of 361 publications on PANDAS in the field of psychiatry were indexed in the Web of Science database until the end of May 2023. In this study, these 361 publications were analyzed in detail. In 2004, 25 publications were published and this was the year with the highest number of publications. In the following years, the number of publications has been irregular. The most cited publications were published in 2021, and these publications received 881 citations. The publications published between 1998 and 2023 received 10,982 total citations (7,175 without self-citation) and the average H index of the publications was 56 according to the analysis of the Web of Science database.

According to our findings, the article published by Swedo et al. (3) in 1998 named 'Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases' was the most cited article with 924 total citations. The top 15 most cited articles on PANDAS in psychiatry research are summarized in **Table 1**.

2. Most productive organizations/countries and funding agencies

By analyzing the country information based on author affiliations, it is possible to gain insights into the distribution of PANDAS research studies across different countries. This research area has seen contributions from numerous institutes or colleges from 35 countries worldwide. The United States (n=191, 52.91%), Italy (n=43, 11.91%), England (n=32, 8.86%), Germany (n=18, 4.98%), Sweden (n=13, 3.60%), Turkey (n=13, 3.60%), and Spain (n=10, 2.77%) have emerged as the leading publishing countries in PANDAS research. **Figure 1** illustrates the changes in the number of articles by country over the years. The United States continually maintained the highest level of productivity among the top 10 countries with the most publications. Spain witnessed a surge in publications between 2008 and 2011, followed by a decline. Notably, between 2014 and 2020, the quantity of articles from Turkey increased, and from Sweden between 2015 and 2023.

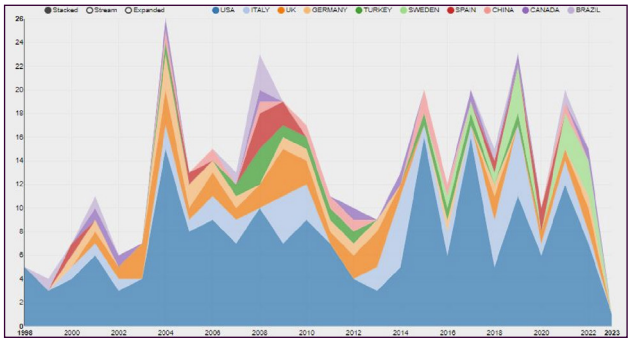

Figure 1. Changes in the number of articles by country over the years

Table 1. Most cited publications about PANDAS syndrome

Title	Authors	Publication Year	Total Citations
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases	Swedo, et al.	1998	924
Tourette's syndrome: from behaviour to biology	Singer, HS	2005	212
The neural bases of obsessive-compulsive disorder in children and adults	Maia, et al.	2008	206
Cognitive impairment in 873 patients with idiopathic Parkinson's disease - Results from the German Study on epidemiology of Parkinson's disease with dementia (GEPAD)	Riedel, et al.	2008	206
Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS)	Murphy, et al.	2002	187
A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections	Garvey, et al.	1999	168
Association between streptococcal infection and obsessive-compulsive disorder, Tourette's syndrome, and tic disorder	Mell, et al.	2005	158
Clinical Evaluation of Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference	Chang, et al.	2015	153
Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders	Snider, et al.	2005	149
Neurobiology of Tourette Syndrome: Current Status and Need for Further Investigation	Felling, et al.	2011	142
Antibody-mediated neuronal cell signaling in behavior and movement disorders	Kirvan, et al.	2006	133
A Dopamine Hypothesis of Autism Spectrum Disorder	Paval, Denis	2017	128
PANDAS: current status and directions for research	Snider, and Swedo, SE	2004	127
Behavioral, Pharmacological, and Immunological Abnormalities after Streptococcal Exposure: A Novel Rat Model of Sydenham Chorea and Related Neuropsychiatric Disorders	Brimberg, et al.	2012	123
Tourette's syndrome: a cross sectional study to examine the PANDAS hypothesis	Church, et al.	2003	123

Regarding funding sources, the majority of PANDAS studies were funded by the National Institutes of Health USA (n=63), the United States Department of Health Human Services (n=63), and the National Institute of Mental Health (n=40). **Table 2** presents the top 10 funding agencies out of a total of 220.

Table 2. The top funding agencies

Funding Agencies	n	% of 361
National Institutes of Health USA	63	17.45
United States Department of Health Human Services	63	17.45
Nih National Institute of Mental Health	40	11.08
Nih National Institute of Neurological Disorders Stroke	12	3.32
Tourette Syndrome Association	6	1.66
Nih Eunice Kennedy Shriver National Institute of Child Health Human Development	5	1.38
Stockholm County Council	5	1.38
Swedish Research Council	5	1.38
Centers For Disease Control Prevention USA	4	1.11
Narsad	4	1.11

* Showing 10 out of 220 funding agencies.

3. Collaboration between Institutions and Countries/ Regions

The United States, with 8,007 citations, 189 documents, and a total link strength of 35, emerged as the country with the highest number of publications and the most collaboration with other countries. The United Kingdom followed with 947 citations, 32 documents, and a total link strength (TLS) of 26. Italy ranked third with 729 citations, 43 documents, and a TLS of 25. Germany came fourth with 609 citations, 17 documents, and a TLS of 15. These countries demonstrated extensive cooperation in PANDAS research (**Table 3**, **Figure 2**).

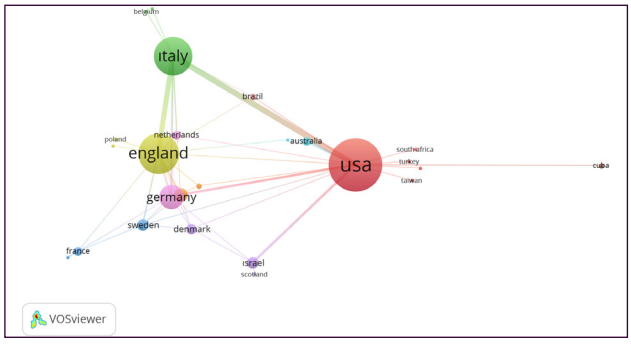

Figure 2. The international collabrations between mostly publishing countries

Among institutions, the National Institute of Mental Health (NIMH) stood out with 2,960 citations, 36 documents, and TLS of 49. Yale University followed with 1,232 citations, 24 documents, and a TLS of 34. Johns Hopkins University ranked third with 1,176 citations, 21 documents, and a TLS of 13. These institutions were identified as the most prolific contributors to PANDAS research (**Figure 3**).

Table 3. Number of documents, citations and total link strength of the most publishing countries

Country	Number of documents	Citations	Total link strength
Australia	6	191	5
Belgium	1	1	1
Brazil	8	259	4
Canada	9	194	3
Croatia	1	0	0
Cuba	2	13	3
Denmark	5	191	6
France	4	41	5
Germany	17	609	15
Japan	3	14	0
Mexico	7	21	3
Netherlands	8	214	5
Norway	3	28	8
Peoples Rebuplic of China	6	67	1
Poland	2	9	1
Portugal	1	0	0
Romania	3	152	0
Russia	1	3	0
Scotland	1	10	1
South Africa	3	50	1
South Korea	1	3	0
Spain	10	107	0
Sweden	13	211	7
Switzerland	2	17	2
Taiwan	4	95	1
Turkey	13	75	1
Ukraine	1	1	0
The United Kingdom	32	947	26
The United States	189	8007	35
India	7	10	2
Iran	3	27	1
Ireland	1	10	1
Israel	6	292	7
Italy	43	729	25

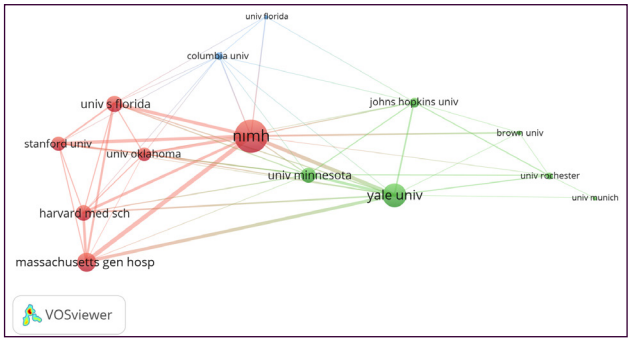

Figure 3 . The co authorship between organisations

4. Keyword's Characteristics

Table 4 shows the total link strength (TLS) of the keywords with more than 10 occurrences. The terms 'PANDAS (130 occurrences, total link strength: 280),

obsessive-compulsive disorder (66 occurrences, TLS: 157), tics (36 occurrences, TLS: 107)' were the keywords with more occurrences. **Figure 4a** shows the keywords by year and **Figure 4b** shows the keyword analysis with the Vosviewer tool.

Table 4. Total link strength of the keywords with more than 10 occurrences

Keyword with more than 10 occurrences	Occurrences	Total Link Strength
Antineuronal antibodies	10	28
Autoimmune	13	31
Autoimmunity	32	95
Group a streptococcus	10	24
Obsessive-compulsive disorder	66	157
OCD	23	58
PANDAS	130	280
Pans	24	61
Pediatric acute-onset neuropsychiatric syndrome	13	26
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections	15	29
Streptococcal infection	22	60
Streptococcal infections	11	23
Sydenham's chorea	11	35
Tic disorders	13	34
Tics	36	107
Tourette syndrome	35	72
Tourette's Syndrome	20	44

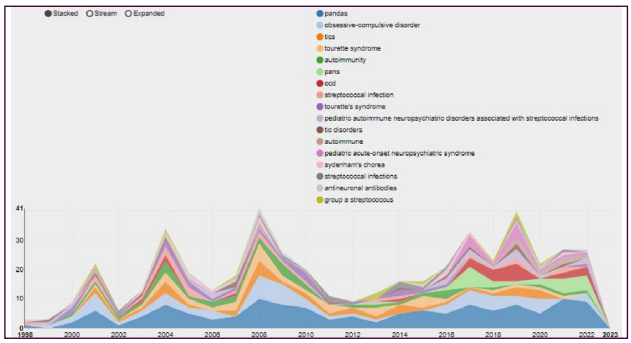

Figure 4 a. Keywords by years

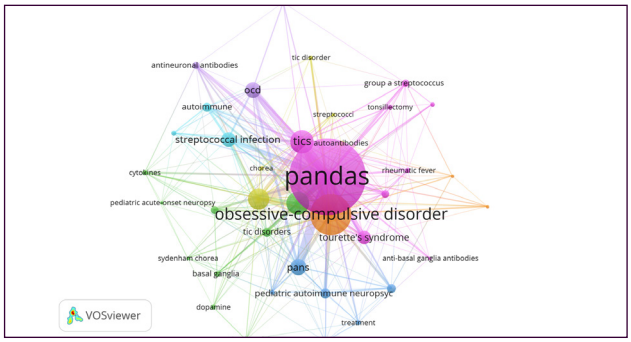

Figure 4 b. Keyword analysis with Vosviewer

5. Mostly publishing journals

Table 5 shows the journals with the most publications on PANDAS. This data is taken from the Web of Science database. Journal of Child and Adolescent Psychopharmacology, Journal of Child Neurology, and the Journal of Neuroimmunology published most of the PANDAS studies.

DISCUSSION

Currently, the PANDAS/PANS syndrome has gained significant attention (8). Since their initial definition, PANDAS and its later version PANS have sparked considerable interest and ongoing debates (20). Numerous cohort studies have established connections between childhood infections and the development of psychiatric disorders, including OCD. However, thus far, biological research has been unable to demonstrate a distinct immunological basis in children meeting PANDAS/PANS criteria. Additionally, there is a lack of solid supporting data for immunotherapy or antimicrobial therapy. The response rates to psychiatric treatment appear to be similar to those observed in OCD cases not associated with PANDAS/PANS. Studies on immunotherapy have produced mixed results, with limited randomized clinical trials suggesting minimal differences in outcomes between IVIG, PLEX, and placebo. Studies on tonsillectomy and antibiotic

Table 5. Mostly publishing journals on PANDAS

Mostly publishing journals	n (%)	Publisher
Journal of Child and Adolescent Psychopharmacology	37 (10.25)	Mary Ann Liebert
Journal of Child Neurology	11 (3.05)	Sage Publications
The Journal of Neuroimmunology	11 (3.05)	Elsevier
Biological Psychiatry	10 (2.77)	Elsevier
Neurology	8 (2.21)	American Academy of Neurology Publications
Pediatrics	8 (2.21)	Amer Acad Pediatrics
Journal of the American Academy of Child & Adolescent Psychiatry	7 (1.94)	Elsevier
American Journal of Psychiatry	6 (1.66)	Amer Psychiatric Publishing
Movement Disorders	5 (1.38)	Wiley
The Pediatric Infectious Disease Journal	5 (1.38)	Lippincott

*Shows 10 out of 191 journals

prophylaxis do not support their use for this specific therapeutic indication (8). In summary, it's crucial to keep in mind PANDAS is a somewhat controversial diagnosis, and there is ongoing research to better understand the condition.

While several bibliometric studies have been conducted on psychiatric disorders (23-26), there is currently no bibliometric analysis available for PANDAS syndrome. Therefore, the objective of this research is to identify and analyze the most frequently mentioned papers, occasionally published journals, highly cited keywords, as well as recognized countries and organizations within the field of psychiatric research between 1998 and May 2023.

The bibliometric technique investigates the structures of document generation, circulation, and application, as well as the structure and evolution of science and technology, by focusing on numerous exterior features of publications such as authors, keywords, abstracts, citations, and so on. Because of its ability to evaluate and anticipate research output, bibliometric analysis has been used for a wide range of topics or fields (17,23-26). Bibliometric analyses are one of the most prevalent ways of assessing the dependability, quality, and effect of scientific investigations. One of the essential factors in this analysis is citation frequency, which is the number of times a publication is cited by other researchers (17). The most frequently referenced publications are the most influential in that particular scientific discipline. It can also be used to prioritize research support organizations and discover areas that have not been sufficiently researched (18,19). Overall, bibliometrics in medicine offers valuable insights into research productivity, impact, trends, and collaboration opportunities. It assists in evaluating the significance of scientific work, informs funding decisions, and contributes to evidence-based medicine practices. Researchers can assess the citation patterns of relevant articles, identify influential studies, and analyze the impact of research on clinical practice. This helps in determining the strength of evidence and making informed decisions about medical interventions. Also, bibliometric analysis enables the identification of emerging trends and areas of research interest. By examining publication patterns and citation networks, researchers and funding agencies can gain insights into the evolving landscape of medical research. This information can guide decisions regarding research prioritization, resource allocation, and strategic planning for future studies (17,23-26).

According to our findings, the article 'Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections' published by Swedo et al. (3) in 1998 named 'Clinical description of the first 50 cases' was the most cited article with 924 total citations. The findings of this investigation corroborate the PANDAS diagnostic criteria's effectiveness in identifying a distinct, clinically homogeneous group of individuals. Furthermore, the unique clinical manifestations identified in this research are not only identical to those documented in the first PANDAS cohort (3).

Susan Swedo specializes as a pediatric and neuropsychiatric researcher. She was Chief of the Pediatrics and Developmental Neuroscience Branch at the United States National Institute of Mental Health beginning in 1998. Swedo was the lead author of a paper in 1994 that described PANDAS disease, a controversial hypothesis (20) that proposed a link between Group A streptococcal infection in children and some rapid-onset cases of OCD or tic disorders such as Tourette syndrome (21). Swedo left the NIH in 2019 and now serves on the PANDAS Physician Network (22). Susan Swedo was also the author who published the most articles (n=31) on PANDAS in the psychiatry research area in our study. Also, advocacy groups have emerged and have made an effort to influence legislation at the governmental level. Examples include the PANDAS Network in the United States and PANDASHELP in Canada (8). The United States (n=191, 52.91%), Italy (n=43, 11.91%), the United Kingdom (n=32, 8.86%), Germany (n=18, 4.98%), Sweden (n=13, 3.60%), Turkey (n=13, 3.60%) and Spain (n=10, 2.77%) were identified as the countries with the highest number of publications on PANDAS. Also, our findings revealed that in terms of international collaboration, two distinct networks emerged: the European network and the worldwide network. In the European network, no single country is distinguished in terms of engagement with others. However, the United States is the hub of the worldwide network, with the greatest cooperation with other linked countries, followed by the United Kingdom and Germany. The United States, United Kingdom, and Germany lead many international collaborations on PANDAS research, in keeping with their high research productivity.

Although previously published cohort surveys have suggested a potential link between infections and OCD and tics, it remains unclear whether ongoing inflammation is the driving factor behind symptoms in these children. Furthermore, there is a lack of evidence supporting the presence of persistent inflammation in biological samples from children with PANDAS/PANS. Research on OCD and tic disorders has yielded diverse but predominantly negative outcomes (20). A systematic analysis investigating the association between cytokines and OCD found a decrease in IL-1, but no clear association between higher levels of cytokines (TNF-α, IL-6) and OCD. It should be noted that confounding factors such as concurrent illnesses, age, and medication usage may have influenced these findings (27). Previous studies have reported fluctuations in serum cytokine levels following exacerbations of Tourette's syndrome/

tics in children (28). Antineuronal antibodies have not been proven to trigger the PANDAS/PANS phenotype, and only a few short trials on psychiatric therapy in the context of PANDAS/PANS have been conducted (20). Keyword analysis can serve as a guide for further research (9, 13). In this study, the analysis of keywords revealed that "PANDAS" (130 occurrences, total link strength: 280), "obsessive-compulsive disorder" (66 occurrences, total link strength: 157), and "tics" (36 occurrences, TLS: 107) were the most frequently mentioned keywords. According to our keyword analysis, we found that researchers are investigating the underlying mechanisms that contribute to the development of PANDAS. This includes exploring the role of streptococcal infections, immune dysregulation, autoimmunity, and the impact on the central nervous system. Studies are being conducted to identify specific antibodies and immune markers associated with PANDAS. Also, efforts are underway to refine and improve the diagnostic criteria for PANDAS. Researchers are exploring the use of biomarkers, such as antibody levels, cytokines, and other immune markers, to aid in diagnosis and distinguish PANDAS from other neuropsychiatric conditions. Another finding of our study that, this research is focused on optimizing treatment strategies for PANDAS. This includes investigating the effectiveness of antibiotics, immune-modulating therapies (such as intravenous immunoglobulin or plasma exchange), and psychiatric interventions (such as cognitive-behavioral therapy and medication management). Studies are being conducted to assess the short-term and long-term outcomes of different treatment approaches. Longitudinal studies are being conducted to evaluate the long-term outcomes of children with PANDAS. Researchers are examining the persistence of symptoms, the impact on cognitive and academic functioning, the risk of developing other psychiatric disorders, and the potential effects on quality of life into adulthood. Understanding the natural course and prognosis of PANDAS is essential for providing appropriate support and interventions. Brain imaging techniques (functional magnetic resonance imaging (fMRI), electroencephalography (EEG), etc.) are being used to study the neurobiological mechanisms associated with PANDAS. These studies aim to identify specific brain regions and neural circuits that are involved in the manifestation of PANDAS symptoms, providing insights into the neurobiology of the disorder. Research is being conducted to detect the prevalence of PANDAS and related factors such as genetic predisposition, environmental influences, infections, or underlying medical conditions in the pediatric population. Studies are exploring the incidence of streptococcal infections and the likelihood of developing PANDAS following an infection. Epidemiological data is important for understanding the scope of the condition and its impact on public health.

The journals that publish the most publications on a topic may also be helpful for researchers to find journals for their publications (29-32). The journals that publish the most publications on PANDAS may also be helpful for researchers in this field to find journals for their publications. The journals that publish the most publications on PANDAS may also be helpful for researchers in this field to find journals for their publications. Journal of Child and Adolescent Psychopharmacology, Journal of Child Neurology, and the Journal of Neuroimmunology published most of the PANDAS studies. Most of these journals were in the field of psychiatry and pediatrics. This may be because PANDAS syndrome is a neuropsychiatric disorder seen in children.

Limitations

This study has several limitations worth noting. Firstly, it was restricted to a specific timeframe and utilized a particular internet portal for data collection, focusing solely on the field of psychiatry. Although no similar study has been published to date, the generalizability of the findings may be limited. Additionally, while visualization and mapping methods were employed in this study, more in-depth analyses such as content analysis or detailed examination of trends, publication numbers of specific journals and institutions over the years, and annual growth rates were not conducted. Future studies could incorporate these aspects for a more comprehensive understanding of the topic.

CONCLUSION

In summary, the study findings highlight that the number of publications on PANDAS remains significantly lower than anticipated. There is a pressing need to enhance global scientific production on PANDAS syndrome, considering the multitude of unknowns surrounding its diagnosis, treatment, and etiology. While there have been contributions from the United States and developed European countries, it is essential to note that the literature on PANDAS involves only 35 countries. Given the severe impact of symptoms on individuals and their families, it is crucial to identify evidence-based and effective interventions, as well as conduct research on the incidence, prevalence, and biological underpinnings of this condition. Collaborative efforts among institutions, detailed clinical phenotyping through collaborative registries, and well-designed investigations into underlying molecular mechanisms are imperative to achieve these objectives. It is important to note that PANDAS research is an ongoing and evolving field. There are varying perspectives and ongoing debates within the scientific community regarding its etiology, diagnosis, and treatment. As a result, further research is needed to address unanswered questions,

establish consensus on diagnostic criteria, and develop evidence-based treatment guidelines for PANDAS. The research conducted in these areas will contribute to a better understanding of PANDAS and improve the care and outcomes for affected children.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval is not required as this study is not a human or animal study.

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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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Relationship Between ABO-Rh Blood Types and Disease Severity in Children with COVID-19 Infection

COVID-19 Tanılı Çocuklarda ABO-Rh Kan Grupları ile Hastalık Şiddeti Arasındaki İlişki

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Abstract

Aim: The purpose of this study was to evaluate correlation between ABO, Rhesus (Rh) blood type and the disease severity status, pneumonia status in children with COVID-19.

Material and Method: The retrospective multicenter study reviewed electronic medical files of all children younger than 18 years old with COVID-19 infection. Patients were divided into three groupas asymptomatic, mild illness and radiologically proven pneumonia. The differences in the ABO and Rh blood group distribution between COVID-19 patients and also the control group were analyzed.

Results: A total of 1026 patients, with a median age of 12 (1-18) years old from 5 different hospitals were included in the study. Of the patients, 32% (n=323), were asymptomatic, 59%(n=607) were mildly symptomatic, and 9%(n=96) were all cases of radiologically proven pneumonia. A total of 1600 children included as the control group. There was no statistically significant difference between the control blood groups and the COVID-19 patients' blood group distribution (p=0.062). When the laboratory characteristics were evaluated, it was determined that as the clinical severity of the patients increased; when age (p=0.012), leukocyte count (p=0.013), CRP (p=0.002), ferritin (p=0.0001) and D-dimer (p=0.049) had increased; and the lymphocyte counts had decreased (p=0.027). There were no istatistically significant difference between blood groups (ABO and Rh), just ABO status and clinical severity condition (respectively p=0.126, p=0.630). When clinical and laboratory data were evaluated according to Rh status, no statistically significant difference was found (p>0.05).

Conclusions: In our study with pediatric population, no difference was detected between blood types and/or Rhesus condition and COVID-19 severity.

Keywords: ABO blood group, COVID-19, risk factors

Öz

Amaç: Bu çalışmanın amacı, COVID-19'lu çocuklarda ABO, Rhesus (Rh) kan grubu ile hastalık şiddet durumu, pnömoni durumu arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Çok merkezli çalışmada COVID-19 enfeksiyonu olan 18 yaşından küçük tüm çocukların elektronik tıbbi dosyalarından retrospektif olarak incelendi. Hastalar asemptomatik, hafif hastalık ve radyolojik olarak kanıtlanmış pnömonisi olanlar olarak üç gruba ayrıldı. COVID-19 hastaları ve kontrol grubu arasındaki ABO ve Rh kan grubu dağılımındaki farklılıklar analiz edildi.

Bulgular: Çalışmaya 5 farklı hastaneden medyan yaşı 12 (1-18) olan toplam 1026 hasta dahil edildi. Asemptomatik hastalar %32 (n=323), hafif semptomatik %59 (n=607) ve radyolojik olarak kanıtlanmış pnömoni tüm vakaların %9'u (n=96) idi. Kontrol grubu olarak toplam 1600 çocuk dahil edildi. Kontrol kan grupları ile COVID-19 hastalarının kan grubu dağılımı arasında istatistiksel olarak anlamlı fark yoktu (p=0,062). Laboratuvar özellikleri değerlendirildiğinde hastaların klinik şiddeti arttıkça; yaş (p=0,012), lökosit sayısı (p=0,013), CRP (p=0,002), ferritin (p=0,0001) ve D-dimer (p=0,049) değerlerinin yüksek olduğuve lenfosit sayılarının azaldığı saptandı. (p=0,027). Klinik şiddet durumu ile kan grupları (ABO ve Rh) ve sadece ABO durumu arasında istatistiksel olarak anlamlı fark yoktu (sırasıyla p=0.126, p=0.630). Klinik ve laboratuvar verileri Rh durumuna göre değerlendirildiğinde istatistiksel olarak anlamlı fark bulunmadı (p>0,05).

Sonuç: Pediatrik popülasyon ile yaptığımız çalışmamızda kan grupları ve/veya Rhesus durumu ile COVID-19 klinik şiddeti arasında fark saptanmadı.

Anahtar Kelimeler: ABO kan grubu, COVID-19, risk faktörleri

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INTRODUCTION

Since the outbreak of coronavirus disease 2019 (COVID-19) started in Wuhan, China in December 2019, the new novel infectious disease has caused serious pandemia infecting thousands of people worldwide (1). The range of disease may vary from asymptomatic to severe acute respiratory syndrome. The severe COVID-19 disease mainly affects adult population with certain risk factors (ie; older age, cardiovascular disease, diabetes mellitus, immune deficiency syndromes, etc) (2). The COVID-19 symptoms appear to be less severe in children than in adults (3,4). Most children may be asymptomatic carriers. Clinical manifestations in children with COVID-19 include fever and cough with some accompanied by fatigue, myalgia, nasal congestion, sneezing, sore throat, headache, dizziness, vomiting and abdominal pain. A few children exhibit pulmonary involvement. Shock, multi-organ failure, encephalopathy, heart failure, abnormal coagulation and acute renal failure have been rarely reported in children with COVID-19. The obvious question why COVID-19 infection in children has a milder course than in adults is not fully understood. It is speculated that repeated viral exposure in early life supports the immune system when it responds to COVID-19 infection. There is also speculation that the COVID-19 protein binds to the angiotensin-converting enzyme (ACE) 2, and that children may be protected against COVID-19 because this enzyme is less mature at a younger age (5,6).

Blood groups have been previously proposed in host susceptibility to infectious diseases (7). Many blood groups are receptors for toxins, parasites and bacteria, where they can facilitate colonization or invasion or evade host clearance mechanisms. Additionally, ABO antibodies can be considered part of the innate immune system against some bacterial pathogens and enveloped viruses that carry ABO-active antigens. Most recently, it is speculated that in adult patients with COVID-19 blood type A is associated with the worst outcome, while blood type O is associated with mild symptoms (8). To our knowledge, there have not been so much data to investigate ABO and Rhesus (Rh) blood group types in children with COVID-19 infection especially on pneumoniae. Therefore, the study aimed to examine if such a correlation exists in children infected with COVID-19.

MATERIAL AND METHOD

We conducted a retrospective multicenter trial in five major hospitals in Turkey to determine whether ABO and Rh blood types carry any risk/beneficial factor among children with COVID-19 infection. The study period consisted between March 2020 and December 2020. Demographic information, clinical symptoms and laboratory results were obtained from each patient's electronic medical files. All children with a documented positive COVID-19 nasal smear real-time reverse-transcriptase polymerase chain reaction (PCR) assay were included. In order to provide a homogeneous study subjects for the aim of trial, patients who had a past medical history of any chronic illness (related to respiratory, cardiology, immunology, neurology, metabolic, etc) were excluded from the study. The children with COVID-19 were classified into 3 groups which include asymptomatic, mild disease (ie; subfebrile fever, fatigue, myalgia, nasal congestion, cough etc), and patients with radiologically proven pneumonia. Control group consisted with children in whom ABO and Rh blood type was available in hospital health files. Those with suspected history for COVID-19 infection were not included in the control group. The study was approved by the Ethics Committee of the Mersin University (2021/53), and the institutional ethics review boards of all participating centers, and also from the government's medical research comittee for COVID-19.

Statistical Analysis

Data were collected from electronic health files and recorded via Statistical Package for Social Science (SPSS). Descriptive statistics were given as mean, standard deviation, median, minimum and maximum. In comparison of the variables of dependent groups, the "Paired Samples T Test" was used for the normally distributed variables, and the "Non-parametric Wilcoxon test" was used for the variables that did not show normal distribution. Comparisons for variables in independent groups, "Independent Samples T Test" was used for normal distributed data, and the"Mann-Whitney U test"in data that did not show normal distribution."Kruskal Wallis Analysis" was used in the analysis of data with more than two not normally distributed groups. "One-way Anova" was used for normally distrubuted more than two groups. In statistical comparisons, the level of significance was determined as $p<0.05$.

RESULTS

A total of 1026 patients from 5 different hospital included in the study. Fifty-one percent of the patients were male and their median age were 12 (1-18) years old. Patients were classified into three groups according to their clinical severity. Accordingly, asymptomatic patients comprised 32% (n=323) of all cases, mildly symptomatic were 59% (n=607), and radiologically proven pneumonia were 9% (n=96).

A total of 1600 children, 60% of whom were male, with a median age of 6.6 (1-18) years were included as the control group. When blood groups were evaluated, 35% (n=566) of the cases were A(+), 30% (n=474) were 0(+), 17% (n=270) were B(+), 8% (n=132) AB(+), 4% (n=65) A(-), 3% (n=54) 0(-), 2% (n=22) were B(-) and 1% (n=17) were

AB(-) (**Figure 1**). When the blood groups of the COVID-19 cases were evaluated, similar to the control group, the most common blood groups were A (+) 41%(n=422), 0(+) 29%(n=298), B (+) 13%(n=139) and AB (+) 7%(n=71). Other blood groups were 0(-) 4% (n=45), A (-) 3% (n=30), B(-) 2% (n=14) and AB(-) 1% (n=7) respectively (**Figure 2**). There was no statistically significant difference between the control blood groups (ABO and Rh) and the blood groups of cases with COVID-19 distribution; the both group were similar (p=0.062). There was no statistical difference between the groups in terms of ABO blood group (p=0.076) and Rh status (p=0.3).

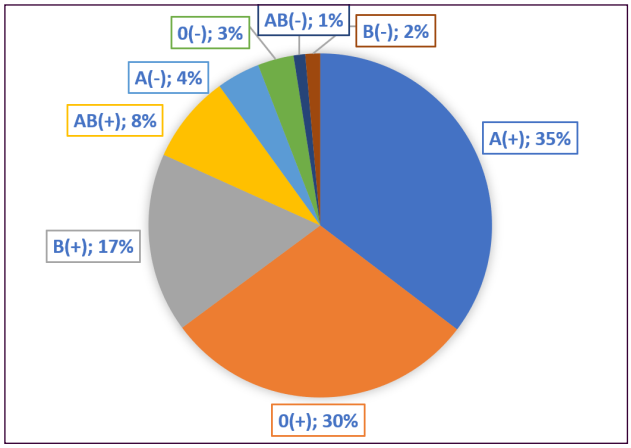

Figure 1: Distribution of the control blood groups.

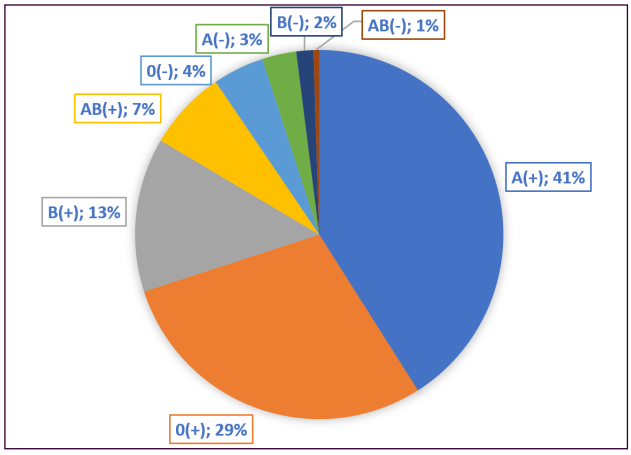

Figure 2: Distribution of the COVID-19 patients' blood groups.

Laboratory and demographic parameters according to the clinical severity of the cases were given in **Table 1**. When we look at the age and clinical severity status, a statistical difference was found between the groups, and it was determined that this difference was between mild symptomatic and asymptomatic groups in the post Hoc evaluation (p=0.007). Age was higher in mildly symptomatic group from asymptomatic ones (p=0.012). No statistical difference was found between the other clinical severity groups (p>0.05). When the laboratory characteristics are evaluated, as the clinical severity of the patients increases; age (p=0.012), leukocyte count (p=0.013), C-reactive protein (CRP) (p=0.002), ferritin (p=0.0001) and D-dimer (p=0.049) values were increased, and the lymphocyte counts were found to decrease (p=0.027) (**Table 1**).

Clinical severity statuses according to blood groups (ABO and Rh) are given in **Table 2**. According to the study, there were no statistically significant difference between blood groups and clinical severity condition (p=0.126).

Table 2: Distribution of blood groups according to COVID-19 clinical severity status

Blood groups	Asymptomatic 32% (n=323) % (n)	Mildly symptomatic 59% (n=607) % (n)	Pneumoniae 9% (n=96) % (n)	p
A(+)	41.8 (135)	40.2 (244)	44.8 (43)	0.126
A(-)	2.2 (7)	3.1 (19)	4.2 (4)	
B(+)	14.9 (48)	13.8 (84)	7.3 (7)	
B(-)	1.2 (4)	1.5 (9)	1 (1)	
0(+)	31.6 (102)	27.8 (169)	28.1 (27)	
0(-)	3.1 (10)	5.1 (31)	4.2 (4)	
AB(+)	5 (16)	7.9 (48)	7.3 (7)	
AB(-)	0.3 (1)	0.5 (3)	3.1 (3)	

* Chi-square test was used for statistical analysis.

Clinical severity statuses according to A, B, O and AB blood groups are given in **Table 3**. In the study, there were no statistically significant difference between ABO blood groups and clinical severity condition (p=0.630).

Table 1: Clinical features of the COVID-19 cases according to their clinical severity condition

	Asymptomatic n=323 (32%)	Mildly symptomatic n=607 (59%)	Pneumoniae n=96 (9%)	p
Age (months)	114 ± 67.1	129 ± 71.5	121 ± 75	0.012
Sex (F/M)	46% F, 54% M	51% F, 49% M	49% F, 51% M	0.251
Leukocyte (/mm3)	6301 ± 3431	6900 ± 3189	7662 ± 5623	0.013
Lymphocyte (/mm3)	2200 (110-12520)	2140 (90-17520)	1770 (10-21200)	0.027
Hemoglobin (gr/dL)	11.8 ± 1.6	11.9 ± 1.3	12.1 ± 1.9	0.197
C-reactive protein (mg/dl)	2±3.6 ; 1(0.3-15)	2.5±4.3 ; 1(0.3-19)	8.5±9.3 ; 5.5(1-31)	0.002
Ferritin (ug/dl)	12 (1-1026)	31 (1-4563)	54 (5-2383)	0.0001
D-dimer (µg/ml)	0.3 (0.1-24)	0.4 (0.1-31)	0.5 (0.2-30)	0.049

F: female, M: male.

Table 3: Distribution of A, B, O and AB blood groups according to COVID-19 clinical severity status						
% (n)	A % (n)	B % (n)	0 % (n)	AB % (n)	Total % (n)	p
Asymptomatic	31.4(142)	34 (52)	32.5 (112)	22.8 (17)	31.5 (323)	
Mildly symptomatic	58.2 (263)	60.8 (93)	58.5 (200)	64.6 (51)	59.2 (607)	0,630
Pneumoniae	10.4 (47)	5.2 (8)	9.1 (31)	12.7 (10)	9.4 (96)	
Total	100 (452)	100 (153)	100 (343)	100 (78)	1026	

When the blood groups of the COVID-19 cases are evaluated, no difference was found between the groups in terms of clinical data, except for D-dimer (p=0.021). D-dimer was highest at AB(-), followed by B(+), A(+), 0(+), A(-), AB(+), B(-), and lowest at 0(-).

When the laboratory data of the cases are evaluated according to the ABO blood groups, the leukocyte count was found to be the highest in the B group, and followed by 0, A and the lowest in the AB groups, respectively; and this difference was found to be statistically significant (p=0.016). No statistical difference was found in other parameters (**Table 4**).

When demographic features and laboratory data are evaluated according to Rh status, no statistically significant difference was found (p>0.05), **Table 5**.

DISCUSSION

The first description with ABO blood type and severe acute respiratory distress syndrome (SARS-1) was an observation of reduced likelihood of infection in patients with blood type O (9). Later, this interesting finding supported with more evidence by the discovery of virion particles replicating in epithelial cells of the respiratory tract in blood type A or B individuals were covered with A or B antigens (10). This provided the shed viral particles easily recognized by type O individuals harboring both anti-A and anti B antibodies in their sera. In addition, similar configuration found between the A antigen and parts of the ACE2 receptor which is the primary site of entry for the virus into the body. Thus, anti-A antibodies circulating in type O individuals might able to prevent the binding and subsequent cellular entry of the virion into the cells. This observation would fulfill the same biologic effect preventing cellular entry of novel COVID-19 (also named SARS-CoV-2). There is also an assumption of increased prevalence of hypercoagulability in individuals carrying blood type A which is linked to the severity of COVID-19 particularly in adults (11,12). In our study, there were not any hypercoagulability condition, but on D-dimer values AB(-) type blood group had the highest value according to the other blood groups.

Most recently, there is growing evidence of ABO and Rh blood groups are associated with risk for COVID-19 illness in adults (13–16). Most studies have concluded a relation between ABO blood groups and COVID-19 infection with respect to blood type O induviduals were less infected than other blood types. In contrast, blood types A and AB found to be a high risk for pneumonia, mechanical ventilation requirement, prolonged intensive care unit admission and death. Additionally, few studies suggested

Table 4: Demographic features and laboratory data of the COVID-19 cases according to ABO blood groups.					
	A	B	O	AB	p
Age (months)	124 ± 71	120 ± 67	125 ± 71	125 ± 72	0.953
Sex (F/M)	46% F, 54% M	55% F, 45% M	46% F, 54% M	47% F, 53% M	0.107
Leukocyte (/mm3)	6254 ± 3391	6900 ± 3189	6865 ± 3287	5661±2825	0.016
Lymphocyte (/mm3)	2000 (10-21000)	2140 (90-17520)	2300 (10-12000)	1737 (10-10170)	0.109
Hemoglobin (gr/dL)	12.3± 1.5	11.9 ± 1.3	12.0 ± 1.4	11.7 ± 2.3	0.117
C- reactive protein (mg/dL)	3.1±5.6 ; 11(0.3-33)	2.5±4.3 ; 1(0,3-19)	3.8±7.6 ; 11 (0.3-55)	4.5±7.2;1.1 (0.2-32)	0.222
Ferritin (ug/dl)	25 (1-2380)	31 (1-4563)	26 (1-4563)	23,5 (12-504)	0.303
D-dimer (µg/ml)	0.3 (0.1-28)	0.4 (0.1-31)	0.34 (0.03-24)	0,3 (0,12-29)	0.332
Abbrevations: F: female, M: male.					

Table 5: Demographic features and laboratory data of COVID-19 cases according to Rh status			
	Rh pozitive	Rh negative	p
Age (months)	114 ± 67.1	129 ± 71.5	0.545
Sex (F/M)	46% F, 54% M	51% F, 49% M	0.872
Leukocyte (/mm3)	6301 ± 3431	6900 ± 3189	0.317
Lymphocyte (/mm3)	2200(110-12520)	2140 (90-17520)	0.387
Hemoglobin (gr/dL)	11.8 ± 1.6	11.9 ± 1.3	0.265
C- reactive protein (mg/dL)	2±3.6;1(0.3-15)	2.5±4.3;1(0.3-19)	0.624
Ferritin (ug/dl)	12 (1-1026)	31 (1-4563)	0.716
D-dimer (µg/ml)	0.3 (0.1-24)	0.4 (0.1-31)	0.076
Abbrevations: F: female, M: male.			

that Rh negatif blood type had more protective effect than Rh positive type in above mentioned morbidity and mortality (17,18). In our study there were not any clinical significant difference between blood types, ABO blood groups or Rh status and clinical severity condition.

Another interesting observation is the proportion of O blood group individuals to non-O blood group individuals may vary in different countries (19,20). It is well known that some countries heavily struck by the morbidity and mortality of COVID-19. Such countries are the United States, Italy, Spain and Brazil which all shared a percentage of group O individuals lower than 40% of the population. While countries showing relatively less COVID-19 mortality such as Saudi Arabia, Egypt, and Singapore all had a percentage of O blood group individuals greater than 40%. Our country appears to be in the lower percentage of blood type O countries with a distrubition of blood type A 39.99%, blood type O 28.26%, blood type B 17.09% and blood type AB 14.66%, respectively (21).

To our knowledge, the current study is the pioneer multicenter trial in investigating the risk ABO and Rh bloods groups in children with COVID-19 with a considerable number of study participants. Importantly, our study control group reflects similar findings of the national blood type research results (22).

In this study, higher age, leucocyte count, CRP, ferritin, D-dimer values were associated with cinical severity. In another studies or meta-analyzes these findings were similar with our study (23–25).

In similar studies, the proportion of blood group A in patients infected with SARS-CoV-2 was significantly higher than that in healthy controls (39.3% vs. 32.3 %, p=0.017), while the proportion of blood group O in patients infected with SARS-CoV-2 was significantly lower than that in healthy controls (13). In our study, especially in pediatric population, there was no any significant difference between blood groups. Both of control and COVID-19 group were similar (p=0.062).

According to population-based cohort study to determine whether ABO and Rh blood groups are associated with risk for SARS-CoV-2 infection and severe coronavirus disease 2019 (COVID-19) illness; there was also a lower risk for severe COVID-19 illness or death associated with type O blood group versus all others (adjusted relative risk-aRR-, 0.87 [CI, 0.78 to 0.97]; Absolute risk differecence (ARD),-0.8 per 1000 [CI, -1.4 to -0.2]). Also with Rh negative versus Rh positive (aRR, 0.82 [CI, 0.68 to 0.96]; ARD, -1.1 per 1000 [CI, -2.0 to -0.2]) status (17). So the O and Rh blood groups may be associated with a slightly lower risk for SARS-CoV-2 infection and severe COVID-19 illness. In our study both of control and COVID-19 blood group distribution were similar (p=0.062). Also there was no statistical difference between the groups distribution in terms of blood group (ABO; p=0.076) and Rh status (p=0.3).

In another study; COVID-19 patients with blood group A or AB required mechanical ventilation (p= 0.02) compared with patients with blood group O or B (15). Also total leucocyte counts, and D-dimer values were higher in A or AB group compared to group O or B (15). In our study, acoording to clinical laboratory results of blood groups, leucocyte count were higher in O or B group contrastly to the similar study (p=0.016). Also D-dimer values were not statistically different between blood groups (p=0.332)

CONCLUSION

In our study with pediatric population, there was no difference between blood types or Rhesus condition and COVID-19 severity. There may be more meaningful results that can be obtained in groups with more participants.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocols were approved by Mersin University Clinical Researches Ethics Committee (Decision No: 2021/53, Date: 01/20/2021).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: 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

Curry-Jones Sendromlu Hastada Anestezi Yönetimi

Anesthesia Management in a Patient the Curry Jones Syndrome

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ÖZ

Curry-Jones Sendromu (CJS), kraniyofasiyal malformasyonlar, polisindaktili, yamalı deri lezyonları, göz ve bağırsak anormallikleri ile karakterize nadir görülen bir hastalıktır. CJS SMO gen mutasyonuna bağlı olmaktadır. Biz vakamızda CJS tanılı çocuk hastaya planlanan operasyon için anestezi yaklaşımından bahsettik.

Anahtar Kelimeler: Curry-Jones sendrom, anestezi, çocuk, polisindaktili

ABSTRACT

Curry-Jones Syndrome (CJS) is a rare disease characterized by craniophacial malformations, polysyndactyly, patched skin lesions, eye and intestinal abnormalities. Curry Jones syndrome depends on SMO gene mutation. In our case, we talked about the anesthesia approach for the planned operation in a pediatric patient with CJS.

Keywords: Curry-Jones syndrome, anesthesia, child, polysyndactyly

GİRİŞ

Curry-Jones Sendromunun(CJS) ana özellikleri sindaktili, polidaktili, kraniosinostoz, korpus callosum agenezisi, cilt anomalileri(artan saç büyümesiyle birlikte yara izi ve atrofik hale gelen karakteristik inci beyazı alanlar), kolobomlar veya mikroftalmi ve bağırsak tıkanıklığıdır (1). SMO geninin tekrarlayan, mozaik bir mutasyonu CJS'ye neden olur (2). Curry ve Jones, bu duruma sahip iki hastayı ilk olarak 1987'de tanımladılar ve CJS terimi ilk olarak 1988'de Cohen tarafından ve ardından 1990'da Gorlin ve arkadaşları tarafından kullanıldı (1). CJS gibi nadir görülen vakada anestezi deneyimimizi paylaşmayı amaçladık.

OLGU

Üç yaşında 18 kg ağırlığında CJS tanısı olan kız çocukta dört ekstremitede de bulunan polidaktili ve sindaktiliye yönelik cerrahi operasyon planlandı. Hastanın preoperatif görüntülenmesinde tespit edilen corpus callosum agenezisi ve glokomu vardı. Fizik muayenesinde makrosefali, frontal kabartı, düz oksiput, yüz asimetrisi vardı. Burnu kısa ve basıktı. Üst göz kapaklarında ektopik kirpikler mevcuttu. Cildinde anormal tüylenme, gövde, sol kol ve sağ bacağında pigmentli ve hipopigmente lezyonlar vardı. Her dört ekstremitede polidaktili ve sindaktilisi vardı (**Resim 1,2**). Preoperatif hazırlığında laboratuar parametreler normal aralıktaydı. Preoperatif değerlendirmede ASA 3 fiziksel status olarak değerlendirildi. Ameliyat odasına alınan hastaya rutin monitörizasyon uygulandı (puls oksimetri, elektrokardiyografi, noninvaziv kan basıncı). Hastanın değerlendirilmesinde zor damar yolu erişim (DIVA)*(3) skoru 4 olarak tespit edildi. Ayrıca cerrahi operasyon 4 ekstremitede de gerçekleşeceği için damar yolu açma konusunda zorluk yaşandı. Kollarda turnike kullanılacağından üst ekstremitede damar yolu açılamadı. Cerrahi operasyon sırasında da yeniden damar yolu açmak zor olacağı için sol ayak sırtından 24 G intraketle damar yolu açıldı. İndüksiyonda propofol 2 mg/kg, fentanyl 1mcg/kg, rokuronyum 0,6 mg/kg iv olarak uygulandı. Yüz anomalilerinden dolayı zor hava yolu ile karşılaşılabileceğinden zor hava yolu hazırlığı yapıldı. Video laringoskop hazırlandı. Maske ventilasyonu kolaydı. 4 numara spiralli tüp ile tek seferde direkt laringoskopla entübe edildi. Anestezi idamesi sevofluran (1 MAC) ve 0.1 µg/kg/dk remifentanil infüzyon ile sağlandı. Vaka boyunca vital bulguları stabil seyretti. 3 saat süren operasyon sonunda hasta ekstübe edildi ve anestezi sonrası bakım

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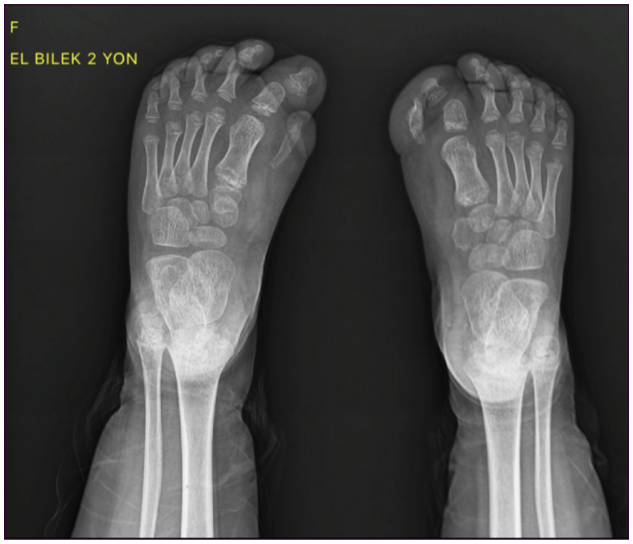
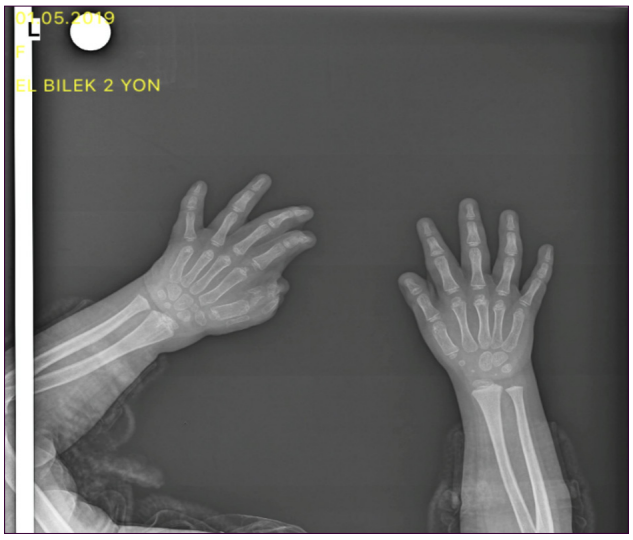
ünitesine devredildi. Anestezi sonrası bakım ünitesinde 35 dakika kalan hastanın vital bulguları stabil seyretti ve hasta servise devredildi.



Resim 1. Ayak grafisi



Resim 2. El grafisi

TARTIŞMA

CJS, kraniyofasiyal malformasyonlar, polisindaktili, yamalı deri lezyonları, göz ve bağırsak anormallikleri ile karakterize nadir görülen bir hastalıktır (4). Bildirilen vakalarda ve bu hastada mevcut olan özellikler sindaktili, polidaktili ve cilt değişiklikleridir. Bizim vakamızda corpus callosum agenezisi ve glokom da vardı. Literatürde CJS ile ilgili veriler sınırlıdır. Yakın zamana kadar CJS'nin genetik etiyolojisi bilinmiyordu (2). Hedgehog (HH) yamalı GLI yolundaki genler, Curry Jones sendromunun patogenezi için önemlidir, çünkü bu genlerdeki daha önce tanımlanmış genetik kusurlar, CJS konjenital anomalileri ve karakteristik neoplazmaları ile ilişkili bulunmuş (5). Kraniosinostoz, beyin malformasyonları, polisindaktili ve medulloblastoma bunlara dahildir (5). Bir çalışmada SMO genindeki mutasyonun HH sinyalinin kurucu aktivasyonuna yol açtığını, dolayısıyla embriyonik gastrointestinal gelişimde HH sinyalini bozarak gastrointestinal malformasyonlara ve bozulmuş peristaltizme neden olduğunu bildirmiştir (2). CJS şüphesi olan çocuklarda gastrointestinal malformasyonlar için abdominal görüntüleme önemlidir. Bizim vakamızda gastrointestinal bir anomali yoktu. Yapılan başka bir çalışmada CJS benzer şekilde SMO gen mutasyonuna bağlı ortaya çıkan Happle Tinschert sendromuyla (HTS) benzerliğinden bahsedilmiştir (6). Her iki sendromda da SMO gen mutasyonuna bağlı ortaya çıkmaktadır. HTS sendromunda bazaloid hamartomlar gözlenirken CJS'da yoktur ve CJS'da olan gastrointestinal sistem bulguları da HTS'de gözlenmemektedir (6). Bir çalışmada CJS'da nadir görülen medullablastom ve trichoblastoma olan 2 ayrı vakadan bahsedilmiştir (5). Trichoblastoma, kollajen stroma ile ilişkili primordial epitelden oluşan kıl germ hücresinin iyi huylu bir deri tümörüdür (5). Trichoblastoma, sebase nevüslerde ortaya çıkan en yaygın tümördür (5). HH sinyal yolunun düzensizliği, bir nevus sebaseusun gelişiminde rol oynar (5). Daha önce bildirilen 9 CJS vakasının hepsi sporadik hem erkek hem de kadınlarda görüldüğü tespit edilmiş (5). Açıklanamayan tekrarlayan gastrointestinal semptomları olan kraniosinostoz, polisindaktili veya yamalı cilt belirtileri olan bebeklerde CJS tanısı düşünülmelidir (2). DIVA skoru, çocuklarda intravenöz erişimin zorluğunu değerlendirmek için kullanılan klinik bir tahmin kuralıdır (7). Yen ve ark., DIVA skoru ≥4 olan çocukların damar yolunun başarısız olma olasılığının daha yüksek olduğunu bulmuşlardır (7). Bizim vakamızda da DIVA skoru 4 olarak değerlendirildi. CJS vakamızda biz damar yolu bulmakta zorlandık. Çünkü damar yol için kullanabileceğimiz alan kısıtlıydı. Üst ekstremitede turnike kullanılacağı için damar yolu açılamadı. Cerrahi operasyon sırasında damar yolunu taşımak zor olacağı için sol ayak sırtından damar yolu açabildik.

SONUÇ

CJS nadir görülen SMO geninde mutasyona bağlı olarak ortaya çıkan bir hastalıktır. Kraniafasyal anomalilere bağlı olarak zor hava yolu ile karşılaşılabilir ve dikkat edilmelidir. Polidaktilil ve sindaktiliye yönelik planlanan cerahi operasyonlarda vakamızda olduğu gibi damar yolu erişiminde zorlukla karşılaşılabilir.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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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