Pediatric Practice & Research

Journal

ISSN: 2147-6470

Year: 2023 Volume: 11 Issue: 3

Pediatric Practice & Research
Journal

ISSN: 2147-6470

VOLUME 11 ISSUE 3 YEAR 2023

Pediatric Practice and Research Journal is the official journal of the Rumi Pediatric Society. A three annually publication, it has been published continuously since 2013.

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ISSN: 2147-6470

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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.

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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

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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.

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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.

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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.

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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.

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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.
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Yazının Başlığı

Kısa, kolay anlaşılır ve yazının içeriğini tanımlar özellikte olmalıdır.

Özetler

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

Anahtar Sözcükler

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

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

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: *, †, ‡, §, ¶.

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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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Pediatric Practice & Research
Journal

ISSN: 2147-6470

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ORIGINAL ARTICLES

Pediatric Practice & Research
Journal

ISSN: 2147-6470

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ORIGINAL ARTICLES

Pediatr Pract Res 2023; 11(3): 78-85
DOI: 10.21765/pprjournal.1351608

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Clinical Characteristics and Outcomes of Rhabdoid Tumors in Childhood

Çocukluk Çağındaki Rabdoid Tümörlerin Klinik Özellikleri ve Sonuçları

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Abstract

Aims: Pediatric Rhabdoid tumors are highly aggressive tumors with poor prognosis. There is no consensus on standart treatment currently. It was aimed to evaluate the clinical characteristics and outcomes of pediatric rhabdoid tumors.

Material and Method: Eight patients with malignant rhabdoid tumor were evaluated retrospectively from the data set between 2013 to 2020.

Results: Out of 8, 5 patients were male (Male/female: 5/3). Median age was 24 months, (range; 4 months-10 years) 6 patients (75%) were younger than 3 years (4 months-10 years). Localizations of the tumors were heterogeneous: (5 central nervous system, 1 multifocal, 1 kidney, and 1 bladder). Genetic analysis revealed germline heterozygous SMARCB1 mutation in one (12%) patient. Patients experienced various toxicities including Wernicke's-like encephalopathy, vincristine neuropathy, veno-occlusive disease mainly hematologic toxicity/mucositis and febrile neutropenia. Five patients died due to progressive disease (62%). The median follow-up time of all patients was 24.5 months (range 6-41 months). The 2-year-event-free and overall survival rates were 37.5% and 50%, respectively.

Conclusion: It should kept in mind that pediatric rhabdoid tumors may present with various ages and localizations, but mainly under 3 years old and central nervous system. The experience is limited due to rarity, but addition of high-dose chemotherapy with autologous hematopoietic stem cell transplantation could be effective in subset of patients who achieved complete remission before transplantation. The toxicities resulting from intensive treatments could be managable, butnew targeted therapies areneeded to improve survival rates.

Keywords: Children, rhabdoid tumor, atypical teratoid rhabdoid tumor

Öz

Amaç: Pediatrik Rabdoid tümörler oldukça agresif, kötü prognozlu tümörlerdir. Şu anda standart tedaviler hakkında fikir birliği yoktur. Bu çalışmada pediatrik rabdoid tümörlerin klinik özelliklerinin ve tedavi sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 2013-2020 yılları arasındaki veri setinden sekiz malign rabdoid tümör retrospektif olarak değerlendirildi.

Bulgular: 8 hastanın 5'i erkekti (erkek/kadın: 5/3). Ortanca yaş 24 aydı (aralık; 4 ay-10 yaş), 6 hasta (%75) 3 yaşın (4 ay-10 yaş) altındaydı. Tümör lokalizasyonları heterojendi (5 merkezi sinir sistemi, 1 multifokal, 1 böbrek ve 1 mesane). Bir hastada germ line heterozigot SMARCB1 mutasyonunu saptandı (%12). Hastalarda Wernicke benzeri ensefalopati, vinkristin nöropatisi, veno-tıkayıcı hastalık başta olmak üzere hematolojik toksisite/mukozit ve febril nötropeni görülmüştür. Beş hasta progresif hastalık nedeniyle öldü (%62). Tüm hastaların ortanca takip süresi 24,5 aydı (minimum-maximum: 6-41 ay). 2 yıllık olaysız ve genel sağkalım oranları sırasıyla %37,5 ve %50 olarak hesaplanmıştır.

Sonuç: Pediatrik rabdoid tümörlerin çeşitli yaş ve lokalizasyonlarda ortaya çıkabileceği, ancak çoğunlukla 3 yaş altı ve santral sinir sistemi tutulumu olabileceği akılda tutulmalıdır. Nadir görülmesi nedeniyle deneyim sınırlıdır, ancak otolog hematopoietik kök hücre transplantasyonu ile yüksek doz kemoterapinin eklenmesi, transplantasyondan önce tam remisyona ulaşan hasta alt grubunda etkili olabilir. Yoğun tedavilerden kaynaklanan toksisiteler yönetilebilir, ancak hayatta kalma oranlarını iyileştirmek için yeni hedefli tedaviler gereklidir.

Anahtar Kelimeler: Çocuk, rabdoid tümör, atipik teratoid rabdoid tümör

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Başvuru Tarihi/Received: 28.08.2023
Kabul Tarihi/Accepted: 26.09.2023

INTRODUCTION

Rhabdoid tumors are rare and highly aggressive tumors with poor prognosis. They were first described in 1981 by Haas et al. (1). Since their initial description, rhabdoid tumors have been described in multiple localisations including brain, kidney and soft tissue. The common feature of rhabdoid tumors in all localisations is a genetic mutation of SMARCB1. SMARCB1 is a member of the SWI/SNF chromatin-remodeling complex and functions as a tumor suppressor in rhabdoid tumors (2). Despite the heterogeneous morphology and/or immunoprofile, the diagnosis of rhabdoid tumors currently depends on the loss of expression of SMARCB1/INI1 or SMARCA4/BRG1 in the tumor cell. Deletion or mutation of the SMARCB1 locus on 22q11.2 results in loss of the integrase interactor 1 (INI1) protein (3,4). INI1 is expressed in the nuclei of normal cells as well as in most tumors and can be detected by immunohistochemical methods (5). Although there are many ongoing trials related to pediatric rhabdoid tumors, there is no consensus on the standard treatment. In addition, despite multimodal treatments including resection of the tumor mass and chemotherapy and radiotherapy, the prognosis has not improved so far. Although autologous stem cell transplantation has been reported for atypical teratoid/rhabdoid tumor (ATRT), rhabdoid tumor of kidney (RTK) and extrarenal malignant rhabdoid tumor (MRT), experience is limited in developing countries (6,7). The aim of the present study is to evaluate the characteristics, treatments and outcomes of rhabdoid tumors in our pediatric oncology center.

MATERIAL AND METHOD

This study was approved by the Ankara Child Health and Diseases Pediatric Hematology Oncology Training and Research Hospital Ethics Committee (Date: 30.07.2019, Decision No: 2019-229). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The present report was conducted with patients diagnosed with rhabdoid tumors in the Pediatric Oncology Department of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital. A total of 8 patients with rhabdoid tumors followed up between 2013 and 2020 years were retrospectively evaluated using oncology database files. Among them, 5 patients were diagnosed with the AT/RT, 1 with synchronous AT/RT and RTK with metastatic lung nodules, 1 with RTK, and 1 with MRT of the bladder. All patients received multimodal treatments including surgical resection, radiotherapy and chemotherapy. A subset of patients treated with high-dose chemotherapy and autologous stem cell rescue. Carboplatinum and thiotepa were used as the conditioning regimen. All patients were analyzed for clinical characteristics, histopathologic findings, treatment details, genetic testing and prognosis. All patients were diagnosed with malignant rhabdoid tumor by pathology based on the morphological and immunohistochemical evaluation. Staging was performed according to the Chang staging system for AT/RT, SIOP renal tumor staging for malignant rhabdoid tumor of kidney, and TNM staging for malignant rhabdoid tumor of soft tissue.

Statistical Analysis

Statistical Analysis SPSS 22.0 was used as a package program in the analysis. Descriptive statistics were used. Categorical measurements were summarized as numbers and percentages, and numerical measurements were summarized as median and ranges, minimum-maximum. Overall survival (OS) and event-free survival (EFS) were estimated by Kaplan-Meier survival analysis. For OS analysis, survival time was calculated from the date of initial diagnosis to the date of death or last follow-up. For EFS analysis, an event was either relapse (or progression) or death in the absence of relapse (or progression). EFS time was calculated from the date of initial diagnosis to the date of relapse, death in the absence of relapse or progression or last follow-up visit.

RESULTS

Clinical characteristics 8 patients were diagnosed with rhabdoid tumor between 2013-2020 years in a single pediatric oncology clinic. Of the 8 patients, 5 were male and 3 were female. The median age was 24 months (range, 4 months-10 years). Six patients (75%) were below 3 years of age. The most common presenting signs in patients with AT/RT were weakness of extremities (n=3), seizures (n=2) and gait disturbance (n=2). A 10 year-old patient presented with headache, nausea, vomiting ,and gait disturbance. Another patient presented with fever, cough, abdominal distention, ptosis and upward gaze restriction. The others were gross hematuria (n=1) and abdominal pain (n=1). Primary localization of rhabdoid tumors was different inpatients with AT/RT, RTK and MRT. Six tumors were located in the CNS (1 temporal lobe, 1 frontal lobe, 1 intraventricular, 1 posterior fossa, 1 cervical spinal cord and 1 synchronous in frontal lobe, pineal region, lung and kidney), 1 only in kidney (n=1) and 1 in bladder (**Figure 1**-**3**). Three patients had metasthases at initial diagnosis, 1 spinal cord, 1 multifocal involvement and lung nodules and 1 lymph node. The others were localized stages (n=5). All patients were diagnosed as a rhabdoid tumors based on histopathologic and immunohistochemical analysis showing loss of nuclear expression of INI1. Genetic analysis was performed in all patients except the spinal AT/RT. The germline heterozygous SMARCB1 mutation was detected in only one (12%) patient with spinal metasthasis at diagnosis.

All patients with ATRT underwent maximal possible surgical resection of the primary lesion consistent with preservation of neurologic function except for one patient with synchronous rhabdoid tumors in the brain and kidney. One patient who diagnosed with spinal AT/RT underwent C1-3 laminectomy and gross total excision. Unilateral radical nephrectomy was performed in 2 patients with renal tumor; one upfront surgery, the other after neoadjuvant chemotherapy for multifocal tumors in brain and kidney together with lung metastasis. The patient with bladder tumor underwent delayed total surgical resection together with partial cystectomy after 6 cycles of chemotherapy.

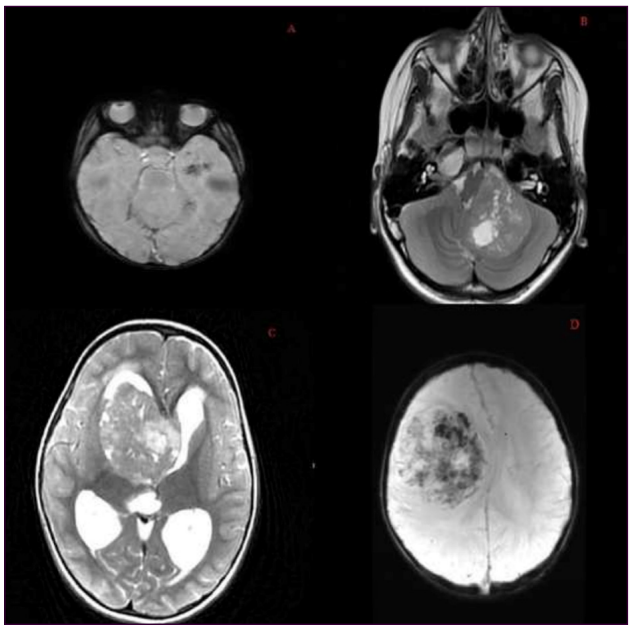

Figure 1: **A:** Magnetic resonance imaging (MRI) of the brain revealed a calcific and partially cystic heterogeneous mass in the left temporal area (2×3 cm) **B:** Magnetic resonance imaging of the brain revealed a mass (3.5 × 2.5cm) in the posterior fossa **C:** Magnetic resonance imaging of the brain revealed a mass in the right lateral ventricle (5×6×6.4) **D:** Cranial MRI showed a mass in the frontal region (7.5×6.2×6.1 cm)

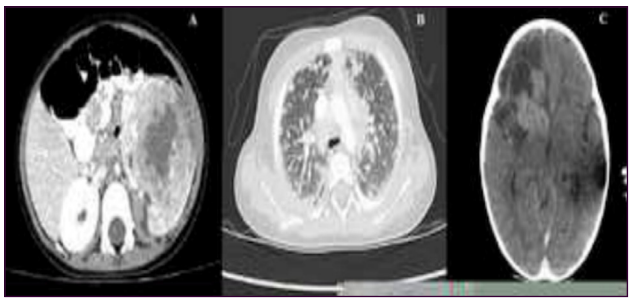

Figure 2 A: Computed tomography showed a heterogeneous mass (6×7×8 cm), centrally hypodense, cystic and necrotic areas in the lower middle pole of the left kidney **B:** Computed tomography showed multiple nodular metastatic lesions and infiltration in the bilateral lung **C:** Computed tomography of brain showed a mass (2×3 cm) in the pineal region and a solid mass (2×2 cm) in the left frontal lobe

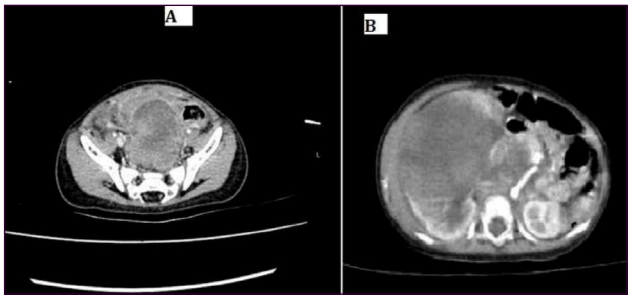

Figure 3 A: Imaging study showed a heterogeneous mass (9x8.7 cm) on the right kidney B: Imaging study showed e pelvic mass (7.9x4.8x4.6 cm) adjacent to posterior wall of bladder

Seven patients were treated according to EU-RHAB protocol consisting of doxorubicin, ifosfamide, carboplatinum, etoposide vincristine, cyclophosphamide and actinomycin-D. One of them (ATRT and RTK) was treated with EU-RHAB protocol after neoadjuvant treatment consisting of doxorubucin, actinomycin-D and vincristine followed by radical unilateral nephrectomy. One patient with spinal AT/RT received vincristine, cyclophosphamide, cisplatin, etoposide. Another patient with intraventricular localization received intraventricular methotrexate therapy via Ommaya reservoir.

All patients received local radiotherapy according to tumor localization. Post-operative radiotherapy to the flank for RTK was given 19.8 Gy for a child >12 months, and 10.8 Gy for another patient.

High-dose chemotherapy followed by autologous stem cell transplantation was performed in 3 patients. Two of them were diagnosed with AT/RT and one patient with malignant rhabdoid tumor of the bladder in the present study. Before transplantation, one patient with AT/RT achieved complete remission, and another partial remission. The patient with bladder rhabdoid tumor also attained complete remission before transplantation. The conditioning regimen consisting of carboplatinum (500mg/m2/day) and thiotepa (300mg/m2/day) was administered from day -6 to -4. The median number of stem cells infused was 4.6x106 /kg (range, 4.25x106 / kg - 5.31x106 /kg) on day 0. The median neutrophil and platelet engraftment days were day +12 (day +11-13) and +15 day +13-17), respectively. Neither toxicity nor delayed engraftment was observed. One of the patients with AT/RT remained in remission for 30 months after transplantation and the other, who was not in complete remission relapsed and died with progressive disease. In addition, a patient with malignant rhabdoid tumor of the bladder achieved remission without any sequelae after high-dose chemotherapy with autologous hematopoietic stem cell transplantation. He is still alive and disease free for 41 months.

Patients have experienced several treatment-related toxicities. The most common toxicities were grade III/IV hematologic toxicity/ mucositis and febrile neutropenia episodes. One patient had infective endocarditis and

Wernicke's-like encephalopathy due to ifosfamide. Magnetic resonance imaging of the brain showed symmetrical T2 hyperintensities in the thalamus, mammillary bodies and tectal plate. He responded to methylene blue and thiamine replacement therapy. Infective endocarditis also responded to antibiotic therapy. Another patient had veno-occlusive disease. She also responded to supportive therapy. Another patient had vincristine neuropathy.

The median follow-up duration of all patients was 24.5 months (range 6-41 months). Three patients are still alive without disease at 28, 30 and 41 months following diagnosis, respectively. Five patients died with progressive disease at 3, 6, 11, 24 and 25 months after initial diagnosis. The median time to death was less than 12 months. The 2-year event-free and overall survival rates fort he entire study population were determined 37.5% and 50%, respectively (**Figure 4**, **5**). The median follow-up duration of patients who underwent autologous hematopoietic stem cell transplantation was 30 months (range, 25-41 months). Of the 3 patients, 1 patient died 25 months after diagnosis, and the other 2 patients are currently disease-free for 30 and 41 months following initial diagnosis, respectively. All patients with metastases at diagnosis (n=3/3) died with progressive disease. Among patients without metastases at diagnosis (n=5), 2 patients died, 3 patients (60%) are currently alive and disease free for median 30 months follow-up duration. Among patients younger than 3 years (n=6), 2 patients (33%) (No# 1 and #8) are still alive and disease-free, others have died. The only one of the 2 patients older than 3 years is still alive with neurological sequale (No#2). The other 5 years old female patient who was diagnosed with spinal AT/RT died with progressive disease (No#5). The clinical characteristics and outcomes of the patients are summarized in the **Table 1**.

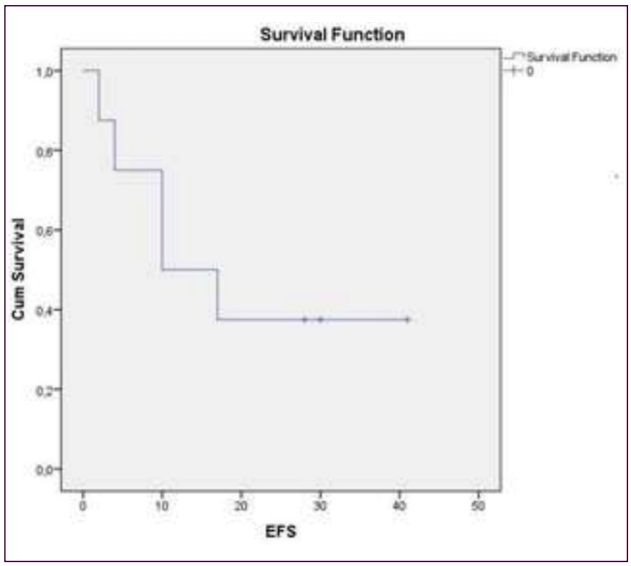

Figure 4: The 2-year event-free survival (EFS) of patients with malignant rhabdoid tumor

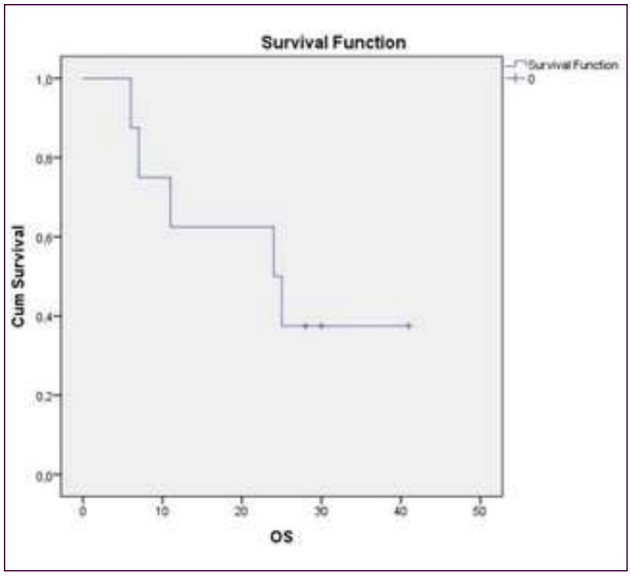

Figure 5: The 2-year overall survival (OS) rates of patients with malignant rhabdoid tumor.

DISCUSSION

In the present study, we described 8 cases diagnosed with rhabdoid tumors. Among 8 cases, the most common type was AT/RT (n=6). Atypical Teratoid Rhabdoid Tumor is an aggressive tumor that was first described in 1996 and included in the World Health Organization classification of the brain tumors in 2000 (8,9). Clinical findings vary with the age of the patients. Signs such as vomiting, lethargy, irritability, weight loss, macrocephaly and seizures are observed in children younger than three years of age. On the other hand, findings of increased intracranial pressure are common in older children similar to our patient (No#2) in the present study (10). Weakness in extremities, walking difficulties and seizures were main complaints at initial presentation of patients with AT/RT in our study. Most ATRTs occur in the posterior cerebral fossa, but can be found anywhere in the central nervous system. Although, it is rare, it may present with multifocal locations (9). In the present study tumors were located differently; 1 patient had spinal mass, 1 patient had intraventricular mass, 1 patient had posterior cerebral fossa mass, 1 patient had frontal mass, 1 patient had temporal mass, and 1 patient had frontal lobe/pineal together with kidney/ lung tumors. Intraventicular and spinal cervical spine locations are very rarely reported and poor prognostic localizations(12-14). Differential diagnosis of AT/RT must be kept in mind in cases of lateral ventricle tumor as well as spinal tumors in pediatric population. In the present study, the number of malignant rhabdoid tumor of kidney(n=2) was less than AT/RT. Malignant rhabdoid tumor of kidney is the most aggressive renal tumor in childhood. They represent 2% of all renal tumors in children and the OS rates ranged from 22% to 42%.

Table 1 The clinical characteristics and outcomes of patients

Patient	Gender	Age	Symptom	Localization	Size (cm)	Metastasis	Immunopathology	SMARC B1	Surgery	RT/ dose	Chemotherapy	Toxicity(Grade III/IV)	Follow up time (month)	Time to relapse (month)	Outcome
1	M	14 months	Seizure	Left temporal lobe	2 x3	No	Beta catenin cytoplasmic +, synaptophysin -, chromogranin -, GFAP +, EMA +, IDH -, CD 56-, loss of INI 1 expression, Ki 67 proliferation index 90%	Negative	Microscopic total excision	54 Gy/ local RT	EU-RHAB regimen and ASCT	Hematological toxicity, mucositis, febril neutropenia	30		Alive
2	M	10 years	Nausea, vomiting	Posterior fossa	3.5 x 2.5	No	Beta catenin cytoplasmic +, synaptophysin -, chromogranin -, GFAP patched +, EMA patched +, IDH -, CD 56-, loss of INI 1 expression	Negative	Microscopic total excision	54 Gy/ local RT	EU-RHAB regimen	Hematological toxicity, mucositis, febril neutropenia, infective endocarditis, Wernicke's- like encephalopathy	28		Alive
3	M	30 months	Impaired walking, convulsion	Right lateral ventricle	5x6x6.4	Spinal	Vimentin +, myogenin -, p 53 +, CD56 -, synaptophysin -, PANCK-, EMA patched +, GFAP- Loss of INI 1 expression Ki 67 index > 50%	c.592C>T(p.gln198*) (p0198*) heterozigot mutant	Microscopic total excision	36 Gy CSI/ 18 Gy posterior fossa	EU-RHAB regimen	Hematological toxicity, mucositis, febril neutropenia	24	17	DOD
4	F	5 years	Weakness	Cervical vertebra	2x 1.8x1	Yes	Loss of INI 1 expression	Unavailable	C1-C2-C3 total laminectomy and gross total mass excision	36 Gy / local RT	Vincristine, cyclophosphamide, cisplatin, doxorubicin	Hematological toxicity, mucositis, febril neutropenia	11	10	DOD
5	M	36 months	Weakness	Right frontal lobe	7.5x6.2x6.1	No	GFAP +, Ki 67 70%, vimentin +, chromogranin -, synaptophysin- p 53 -loss of INI 1 expression	Negative	Microscopic total excision	54 Gy/ local RT	EU-RHAB regimen and ASCT	Hematological toxicity, mucositis, febril neutropenia, vincristine neuropathy	25	10	DOD
6	F	18 months	Fever, cough, abdominal distantion, ptosis and upward gaze restriction	Pineal, frontal lobe, kidney, lung nodules	2x3, 2x2, 8x7, multiple > 1x1	Lung	Vimentin +, PANCK +, EMA +, Loss of INI 1 expression	Negative	Microscopic total excision of brain mass, radical nephrectomy after neoadjuvan treatment	8.4 Gy/ whole abdomen and lung / 9 Gy left flank/ total 17.4 Gy / local RT	EU-RHAB regimen after neoadjuvan (V, A,D)	Hematological toxicity, mucositis, febril neutropenia, VOD	3	2	DOD
7	F	4 months	Hematuria	Right renal mass	9x 8.7	Lymphadenopathy	Vimentin +, p 53 +, EMA +, Loss of INI 1 expression	Negative	Upfront right radical nephrectomy	10.8 Gy / right flank	EU-RHAB regimen	Hematological toxicity, mucositis, febril neutropenia	6	4	DOD
8	M	20 months	Pelvic mass	Pelvic mass adjacent to bladder	7.9X 4.8X 4.6	No	Vimentin -, EMA -,CD34 -, Loss of INI 1 expression	Negative	Total mass resection and partial cystectomy	50.4 Gy / local RT	EU-RHAB regimen and ASCT	Hematological toxicity, mucositis, febril neutropenia	41		Alive

DOD; dead of disease, CT;chemotherapy, RT; radiation therapy, ASCT; autologous stem cell transplantation, VOD; veno occlusive disease, NA; not available, (V,A,D); vincristine, actinomycin D, doxorubicine, CSI;cranio-spinal irradiation, EMA; epithelial membrane antigen, GFAP; glial fibrillary acidic protein.

A retrospective analysis of 58 patients with RTK from Austria, Switzerland, and Germany reported comparable outcomes for patients with and without autologous hematopoietic stem cell transplantation. Thirty-seven (64%) patients achieved a complete remission, 17 (29%) relapsed, 34 (59%) died of disease progression, and two (3%) died of a treatment-related complication. The mean time to the first event was 3.5 months in their study. They reported that methastatic/multifocal disease, younger age, and local stage III were associated with significantly worse survival (15). According to the SIOP study, RTK has a poor outcome especially in young patients and those with advanced disease. Neither tumur volume at diagnosis, nor pre-operative chemosensitivity are prognostic factors for survival (16). In the present study, both patients with malignant rhabdoid tumor of the kidney died. One patient who was 4 months old age relapsed at 4 months and died at6 months after initial diagnosis despite unilateral radical nephrectomy, radiotherapy and chemotherapy. Another patient with synchronous AT/RT and RTK with metastatic lung nodules relapsed after 2 months and died 3 months after diagnosis. It is difficult to exclude the possibility of metastasis from kidney to frontal lobe, pineal region and lung and/or simultaneous occurance of multiple tumors such as malignant rhabdoid kidney tumor and atypical teratoid rhabdoid tumor in this case., An infant case with synchronous malignant rhabdoid tumor in the kidney and the brain similar to our case has been reported in the literature (17). Malignant rhabdoid tumors of soft tissues can present in any part of the body. The bladder localization is rarely seen. So far, 9 patients with bladder malignant rhabdoid tumors have been reported. Malignant rhabdoid tumors of the bladder seem to be less aggressive compared to other rhabdoid tumors. Therefore, the partial cystectomy together with high-dose chemotherapy and radiotherapy could be appropriate treatment when feasible (18). In the present study, only one patient was diagnosed with malignant rhabdoid tumor of the bladder. He achieved remission with high-dose chemotherapy with autologous hematopoietic stem cell transplantation.

Although several chemotherapy-related toxicities were developed during the treatment, no toxicities were observed during or after transplantation except for grade III/IV haematologic toxicity/mucositis and febrile neutropenia. One patient experienced ifosfamide associated Wernicke-like encephalopathy. It is associated with a classic triad of symptoms consisting of ataxia, ocular motor cranial neuropathies, and altered consciousness, but not may be seen in the majority of patients. The diagnosis could be more difficult in brain tumors, because of the overlapping symptoms and the risk of encephalopathy related to both the disease and treatment. When the diagnosis is clinically suspected, treatment should be initiated immediately without waiting for laboratory confirmation. The most common magnetic resonance findings are symmetrical T2 hyperintensities in the dorsal medial thalamus, mammillary bodies, periaqueductal gray matter, and tectal plate (19,20). Therefore it is rare and under-recognized in childhood, it could be fatal without proper management. Therefore, Wernicke's encephalopathy should be considered in all children with cancer who present with acute neurologic deterioration during ifosfamide treatment, especially in brain tumors.

Microscopically, the rhabdoid tumors are characterized by diffuse proliferation of rounded or polygonal cells with eccentric nuclei, prominent nucleoli and eosinophilic cytoplasm containing hyaline-like inclusion bodies, arranged in sheets and nests together with cellular atypia and high mitotic activity. Immunohistochemically, the tumor cells are characterized by the expression of vimentin and epithelial markers such as epithelial membrane antigen, and cytokeratin, less commonly smooth muscle actin. The absence of INI1 protein expression is a distinctive feature of these tumors (21). Similarly, the common feature of patients with rhabdoid tumors of any location was loss of INI1 expression in the present study. A germline mutation of SMARCB1/B4 is observed in 25–30% of the patients with rhabdoid tumors. Under 2 years of age, tumor is usually multifocal, and affects more than one relative in patients with germline mutation (2). In the present study, genetic analysis of demonstrated a denovo germline heterozygous SMARC B1 gene mutation in one patient with AT/RT who has a localized intraventricular mass with spinal metastasis (his parents have no mutations) (No#3 patient). He died of progressive disease 24 months after diagnosis. Despite multimodal treatment approaches, the median OS of the patients is approximately 1 year or less (22). Moreover, there are studies reporting median overall survival as low as 2.5 months (23). The overall survival and event-free survival of childhood extracranial malignant rhabdoid tumors were reported 53.0%, 54.5%, respectively with a median follow-up duration of 17.8 months (range, 2.3 to 112.3 months). In addition, they reported that the OS of patients who underwent autologous hematopoietic stem cell transplantation was 66.7% and EFS was 75.0% with a median follow-up duration of 23.8 months (range, 8.1 to 42.6 months) (24). Overall survival of the rhabdoid tumors was found to be 27% at 5 years and there was no significant difference in prognosis regarding the different tumor locations (kidney 24%, soft tissue 30%, CNS 29%) in a study from Germany (25). A recent study reported that the ACNS0333 regimen dramatically improved survival rate (OS: 43%) compared to historical therapies in patients with AT/RT (26). The analysis of 130 patients with AT/RT revealed a 3-year OS of 25% in recent meta-analysis (27). In the present study, 2- year event-free and overall survival rates of all patients were

37.5% and 50%, respectively. Although the number of cases underwent autologous hematopoietic stem cell transplantation was limited, two of 3 patients are still alive. The addition of the high-dose chemotherapy with autologous hematopoietic stem cell transplantation might be have a role for prolonged survival rates in these patients. It has been suggested that aggressive therapy including early adjuvant radiotherapy and HDCT could be considered to improve the outcome of ATRT in children younger than 3 years (28). The mortality rate of rhabdoid tumors is high especially in children with germline SMARC B1 mutation, with younger age and metastasis at the time of diagnosis. Although, the present study has some limitations including retrospective nature, limited number of patients and heterogeneous group of rhabdoid tumor, it might have a role to increase the awareness of this rare disease especially in developing countries.

CONCLUSION

The most common tumor site of rhabdoid tumors is the central nervous system in children. Because of its rarity and poor prognosis, management and treatment of rhabdoid tumors is challenging and requires a multidisciplinary team. Despite intensive treatment modalities, the mortality rate is still being high. Also, the high level of awareness for rhabdoid tumor is required both definitive diagnosis at initially and chemotherapy related various toxicities during treatment. The addition of high-dose chemotherapy with autologous hematopoietic stem cell transplantation seems efficious in subset of patients who achieved complete remission. In addition, the toxicities resulting from intensive treatments could be manageable but new targeted therapies are also needed to improve survival rates of rhabdoid tumors.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Ankara Child Health and Diseases Pediatric Hematology Oncology Training and Research Hospital Ethics Committee (Date: 30.07.2019, Decision No: 2019-229).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Pediatr Pract Res 2023; 11(3): 86-91
DOI: 10.21765/pprjournal.1337536

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Obesity and Psychological Resilience in Children: Investigating the Connection

Çocuklarda Obezite ve Psikolojik Sağlamlık; Bağlantının Araştırılması

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ABSTRACT

Aim: Obesity is a critical public health issue that is increasingly prevalent among children. This study aimed to examine the psychological resilience of both obese and normal-weight children, as well as the factors influencing their resilience levels.

Material and Method: This study included obese and normal-weight children who applied to Başkent University Hospital over a period of two months. Children and their parents filled out a questionnaire consisting of parents' socio-demographic data and the "Child and Youth Resilience Measure". SPSS-23 was utilized to conduct a comparison of scale scores through Pearson's correlation coefficient test. Additionally, multiple linear regression was employed to elucidate the connections between the variables.

Results: A total of 111 adolescents were included in this study, comprising 48 (43.2%) normal weight individuals and 63 (56.8%) obese individuals. The two groups did not differ significantly in terms of age and gender distribution (p >0.05). The study revealed a negative correlation between psychological resilience and children's age (r=-0.210, p=0.027), a positive correlation with family income (r=0.247, p=0.009), and a negative correlation with obesity (r=-0.342, p <0.001). Both univariate and multivariate analyses revealed a significant negative association between obesity and the father's education level (B: -1.00, p=0.046), as well as a negative relationship between obesity and psychological resilience (B:-0.12, p=0.001).

Conclusion: Our study revealed a negative correlation between children's resilience levels and their age and obesity status, while also showing a positive correlation with family income. Further research is warranted to explore the underlying mechanisms of these associations and to develop effective interventions aimed at enhancing children's resilience.

Keywords: Child, obesity, psychological resilience

ÖZ

Amaç: Obezite, çocuklar arasında giderek yaygınlaşan kritik bir halk sağlığı sorunudur. Bu çalışmanın amacı, hem obez hem de normal kilolu çocukların psikolojik dayanıklılıklarının yanı sıra psikolojik sağlamlık düzeylerini etkileyen faktörlerin incelenmesidir.

Gereç ve Yöntem: Bu çalışmaya **iki ay boyunca** Başkent Üniversitesi Hastanesi'ne başvuran obez ve normal kilolu çocuklar dahil edilmiştir. Çocuklar ve ebeveynleri, ebeveynlere ait sosyo-demografik verilerden ve "Çocuk ve Genç Psikolojik Sağlamlık Ölçeği"nden oluşan bir anket formunu dol-durmuştur. Pearson korelasyon katsayısı testi ile ölçek puanlarının karşılaştırılması için SPSS-23 kullanılmıştır. Ek olarak, değişkenler arasındaki bağlantıları açıklamak için çoklu doğrusal regresyon kullanılmıştır.

Bulgular: Bu çalışmaya 48 (%43,2) normal kilolu, 63 (%56,8) obez olmak üzere toplam 111 adolesan dahil edilmiştir. İki grup yaş ve cinsiyet dağılımı açısından anlamlı farklılık görülmemiştir (p >0,05). Bu çalışmada; psikolojik dayanıklılık ile çocukların yaşı arasında negatif (r=-0,210, p=0,027), aile geliri ile pozitif (r=0,247, p=0.009) ve obezite ile negatif bir ilişki saptanmıştır (r=-0,342, p <0,001). Hem tek değişkenli hem de çok değişkenli analizler sonucunda obezite ile babanın eğitim düzeyi (B: -1,00, p=0,046) ve psikolojik dayanıklılık (B: -0,12, p=0,001) arasında negatif bir ilişki gözlenmiştir.

Sonuç: Çalışmamız çocukların dayanıklılık düzeyleri ile yaş ve obezite durumları arasında negatif, aile geliri ile pozitif korelasyon göstermiştir. Bu ilişkilerin altında yatan mekanizmaları keşfetmek ve çocukların dayanıklılığını artırmayı amaçlayan etkili müdahaleler geliştirmek için daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: Çocuk, obezite, psikolojik sağlamlık

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Başvuru Tarihi/Received: 03.08.2023
Kabul Tarihi/Accepted: 14.09.2023

INTRODUCTION

Childhood obesity has emerged as a pressing public health concern, posing multifaceted challenges to individuals and society at large. The complexities surrounding its etiology have led to growing concerns not only about the metabolic complications of obesity but also its profound psychological consequences (1-3). Research in this field has shown a strong association between obesity and various psychological issues, including depression, low self-confidence, impaired social communication, and body image dissatisfaction (4). As such, it is increasingly recognized that safeguarding children from obesity may also serve as a means to protect them from potential negative psychological outcomes.

Resilience refers to both the process and the outcome of successfully adapting to difficult or challenging life experiences, according to the definition from the American Psychological Association (APA) (5). It's having the mental, emotional, and behavioral flexibility and ability to adjust to both internal and external demands, per APA. Psychological resilience is a potentially protective factor against obesity (6). One possible explanation for this may be the ability of resilience to mitigate the effects of stress on eating behaviors (7). In particular, studies have shown that resilience may moderate the relationship between perceived stress and binge eating tendencies (7). Additionally, there is evidence to suggest that individuals with higher levels of psychological resilience tend to consume more fruits, vegetables, dietary fiber, and fish while consuming fewer soft drinks and fast food options (8,9). Furthermore, optimism, which is commonly observed in resilient and thriving individuals, has been associated with increased consumption of fruits, vegetables, and grains, and decreased consumption of sugar (10,11). Taken together, these findings suggest that psychological resilience may be a crucial factor in reducing the risk of obesity by promoting healthier eating habits and attitudes (6,7).

Findings from research conducted on adults have shown that resilience plays a crucial role in the psychosocial characteristics of individuals with severe obesity, particularly those who are being considered for bariatric surgery (12).

Obesity can have a significant impact on an individual's psychology, presenting itself in two distinct ways. Firstly, a high-fat diet can trigger chronic inflammation in the brain, which may potentially affect mood and behavior (2). Secondly, children with obesity may experience negative emotions due to the actions of others, resulting in issues such as poor body image and low self-esteem. Research has shown that children with a higher body mass index (BMI) are more vulnerable to discrimination, social isolation, and bullying. They may face verbal bullying, such as name-calling and teasing, physical bullying, such as hitting and pushing, and relational bullying, such as the withdrawal of friendships, within their immediate environment, such as school and home (13).

There is evidence showing that obesity and psychological resilience are mutually related (12). In this regard, psychological well-being may serve as a protective factor against childhood obesity, or the psychological resilience of an obese child may be affected. The present study aimed to compare resilience levels and explore the factors influencing those levels in both normal-weight and obese children.

MATERIAL AND METHOD

The study was carried out with the permission of Başkent University Non-invasive Clinical Researches Ethics Committee (Date: 2023, Decision No: 23/282) and was conducted according to the principles outlined in the Declaration of Helsinki. Informed consent was obtained from both the participants diagnosed with obesity and the healthy controls, as well as from their parents, before their inclusion in the study.

Measures

Body Mass Index Measure

In this research, the children were categorized as either obese or non-obese based on their BMI (Body Mass Index) percentile. The participants' BMI was calculated by dividing their weight in kilograms by the square of their height in meters. The children's height and weight were measured to determine their body mass index (BMI). BMI percentile charts, which were developed based on reference values for Turkish children, were used to categorize the children as normal weight (between the 5th and 85th percentile) or obese (above the 95th percentile) (14).

Child and Youth Resilience Measure (CYRM)

The Child and Youth Resilience Measure (CYRM) is an assessment tool designed to gather information about the psychological resilience of children and adolescents. The original scale consisted of 28 items, organized into three subscales and eight sub-dimensions (15). A short-form version of the scale was later developed, resulting in a 12-item structure (16). The factor loading values of the scale ranged from .39 to .88, indicating a good level of consistency. The internal consistency coefficient of the scale, as measured by Cronbach's alpha, was found to be .84. The scale is rated on a five-point Likert structure, with responses ranging from "Describes me completely (5)" to "Does not describe me at all (1)". In scoring the items, all positive items are reverse coded. Consequently, high scores on the CYRM indicate the presence of a negative cognitive triad, while low scores indicate a positive cognitive triad. Thus, individuals with high levels

of psychological resilience receive lower scores on the CYRM, whereas those with low levels of psychological resilience receive higher scores. The Turkish adaptation of the 12-item short form scale was conducted by Arslan (2015), specifically on children and adolescents aged 11-16, and statistical analyses were performed (17). The reliability study revealed a Cronbach alpha reliability coefficient of .76 for the entire scale.

Statistical Analysis

Descriptive statistics were used to summarize the data, with numbers and percentages reported for categorical variables and mean ± standard deviation and median (minimum-maximum) reported for continuous variables. The Chi-square test was used to analyze associations between categorical variables. Nonparametric tests were utilized due to the non-normal distribution of sample data across groups. Specifically, the Mann-Whitney U test was used to compare quantitative variables between the obese and non-obese groups.

Univariate and multivariate logistic regression analyses were performed to identify significant predictors of obesity. In the univariate analysis, variables with a significance level of p <0.25 were included in the multivariate logistic regression analysis. Statistical significance was determined by a p-value of <0.05. Data analysis was conducted using the IBM SPSS version 28.0 software for Windows (IBM Corp; Armonk, NY: 2021).

RESULTS

Our study comprised a total of 111 adolescents with a mean age of 14.0±1.9 (range: 11-16) years, among whom 43.2% (n=48) were classified as normal-weight and 56.8% (n=63) were classified as obese. There was no difference between the two groups in terms of age and gender distribution (p=0.087, p=0.386). When examining the sociodemographic data of the parents in both groups, there was only a difference in the father's educational status (p=0.021), as shown in **Table 1**. While 63.5% of fathers of obese children had a bachelor's degree or higher education level, this percentage was 83.3% for fathers of normal-weight children (p=0.021).

The mean age of the mothers was 41.5±3.9 years, and the mean age of the fathers was 45.0±6.1 years. The majority of the parents (90%) were married, and 87.4% had an income more than twice the minimum wage. Furthermore, 69.4% of the mothers and 80% of the fathers had a bachelor's degree or higher education.

The average score obtained by the children on the CYRM was 48.0±7.2 (range: 26-60). While the mean CYRM score for obese children was 50.9±7.2 (range: 35-60), it was 45.9±7.8 (range: 26-60) in the normal weight children (p<0.001).

When examining the relationship between children's psychological resilience level and sociodemographic characteristics, we found that psychological resilience was negatively correlated with child age (r= -0.210, p=0.027), positively correlated with family income (r= 0.247, p=0.009), and negatively correlated with childhood obesity (r= -0.342, p<0.001), as shown in **Table 2**.

Table 1. Comparison of the socio-demographic characteristics and resilience levels between obese and normal weight children.

	Groups of children classified by body mass index		
	Normal n (%) 48 (43.2)	**Obese n (%) 63(56.8)**	**p values**
Children's characteristics			
Age (M±SD)	13±2 (11-16)	14±2 (11-16)	0.087
Gender (n (%))			
Female	25 (52.1)	38 (60.3)	
Male	23 (47.9)	25 (39.7)	0.386
Score of the CYRM	50.9.±7.2 (35-60)	45.9±7.8 (26-60)	<0.001*
Parents' characteristics			
Age (M±SD)			
Mother	41±4 (35-48)	42±4 (36-52)	0.460
Father	45±5 (35-53	44±7 (38-56)	0.359
Marital status (n (%))			
Married	38 (79.2)	52 (82.5)	0.653
Divorced	10 (20.8)	11 (17.%)	
Income level			
Minimum wage and x2	4 (8.3)	11 (17.5)	0.078
>2x minimum wage	44 (91.7)	52 (82.5)	
Educational level (n (%))			
Mother			
Below bachelor's degree	11 (22.9)	23 (36.5)	0.073
Bachelor's degree and above	37 (77.1)	40 (63.5)	
Father			
Below bachelor's degree	8 (16.7)	23 (36.5)	0.021*
Bachelor's degree and above	40 (83.3)	40 (63.5)	

n: number, M: mean, SD: standard deviation, CYRM= Child and Youth Resilience Measure.

Table 2. Correlations Between Children's Psychological Resilience, Obesity, and Sociodemographic Variables.

		1	2	3	4	5	6	7	8	9	10
1. Psychological Resilience Level	r		-0.210	-0.342	0.022	0.104	-0.008	-0.156	0.247	0.164	0.182
	p	1	0.027*	0.000**	0.819	0.276	0.934	0.102	0.009**	0.086	0.056
2. Children's age (year)	r			0.132	0.159	0.198*	-0.084	-0.035	-0.012	-0.217	-0.136
	p		1	0.166	0.096	0.037	0.383	0.718	0.904	0.022*	0.155
3. BMI status (Obese= BMI>95p; normal= BMI 5-85p)	r				0.061	-0.115	-0.082	-0.043	-0.167	-0.146	-0.219
	p			1	0.527	0.229	0.390	0.657	0.079	0.126	0.021*
4. Maternal age (year)	r					0.189*	-0.178	-0.044	0.228	0.093	0.216
	p				1	0.047	0.062	0.650	0.016**	0.334	0.023*
5. Paternal age (year)	r						-0.230	-0.407	-0.014	-0.061	0.037
	p					1	0.015*	0.000**	0.883	0.522	0.703
6. Children's gender (year)	r							0.228	-0.161	0.146	0.016
	p						1	0.016*	0.091	0.126	0.864
7. Marital status of the parents	r								0.114	0.071	-0.007
	p							1	0.233	0.456	0.942
8. Income level of the parents	r									0.454	0.550
	p								1	0.000**	0.000**
9. Mothers's education level	r										0.806
	p									1	0.000**
10. Fathers's education level	r										
	p										1

*: p <0.005, ** p<0.01. BMI= Body mass index, p=percentile

Table 3. Factors that affect obesity in children.

	Univariate logistic regression analysis				Multivariate logistic regression analysis			
	B	Wald	OR 95% CI	p	B	Wald	OR (95% CI)	p
Children's age (year)	0.15	1.90	1.16 (0.94-1.42)	0.67				
Children's gender (Female/Male)	0.33	0.75	1.39 (0.65-3.0)	0.386				
Marital status (Married/Divorced)	0.22	0.20	1.24 (0.50-3.23)	0.653				
Income level (Minimum wage and x2, >2x minimum wage)	1.16	2.87	3.18 (0.84-12.10)	0.98				
Psychological Resilience level	-0.12	11.15	0.89 (0.83-0.95)	0.001*	-0.12	10.24	0.89 (0.82-0.95)	0.001*
Fathers's education level	-1.06	5.11	0.35 (0.14-0.87)	0.020	-1.00	3.98	2.73 (1.02-7.32)	0.046
Mothers's education level	0.66	2.33	1.93 (0.83-4.51)	0.127				

OR: odd ratio, CI=Confidence Interval.

The factors influencing obesity in children were examined using both univariate and multiple regression analyses. The results of the univariate regression analyses indicated that there were no statistically significant effects of the income level of families, the marital status of parents, the education level of the mother, as well as children's age and gender, on obesity (**Table 3**). However, the results of both univariate and multiple regression analyses revealed significant associations. Specifically, obesity was found to have a negative relationship with the father's education level (B: -1.00, odds ratio (95% CI): 2.73 (1.02-7.32), p=0.046) and psychological resilience (B: -0.12, odds ratio (95% CI): 0.89 (0.82-0.95)).

DISCUSSION

Resilience refers to the ability to maintain or promptly recover one's mental health in the face of stressful situations resulting from traumatic events. Several studies have demonstrated a decrease in psychological resilience among adolescents with obesity (18). According to the findings of this study, adolescents with obesity exhibited diminished levels of psychological resilience, and the educational attainment of their fathers emerged as a noteworthy sociodemographic variable linked to obesity.

Similar to our study, Uzun et al. (2023) showed a relationship between psychological resilience and adolescent obesity, consistent with our findings (19). The findings reveal that adolescents with higher levels of psychological resilience are more successful in dealing with obesity and receive greater social support. Additionally, it has been observed that receiving social support enhances adolescents' psychological resilience, assisting them in coping with stress and challenges associated with obesity (19). Previous research has also suggested that increasing psychological well-being can serve as a protective factor against obesity, as psychologically healthier individuals tend to have lower rates of other obesity-related disorders (20). Conversely, some studies have reported no significant relationship between obesity and psychological resilience (4). In summary, although a definitive cause-and-effect relationship has not been established, we believe that

promoting psychological resilience among adolescents may aid in preventing obesity in children and managing obesity in those who are already obese.

In our study, we examined the factors influencing obesity and found that both the education level and psychological resilience of the father had a significant negative impact on obesity. While these findings do not establish a causal relationship, they indicate that fathers of obese children tend to have lower education levels and lower psychological resilience. These results might underscore the importance of psychological resilience in obesity prevention and treatment processes. Health professionals and families should develop appropriate strategies to foster adolescents' psychological resilience and strengthen their social support systems. By doing so, more effective and sustainable outcomes in combating obesity can be achieved.

Another important finding of our study is the positive relationship between the psychological well-being of children and family income. While the income levels of families with obese children were more than twice the minimum wage, they were still lower than those of normal-weight children, although this difference was not statistically significant. This is consistent with previous research, which has also shown that the family income of obese children tends to be lower (19). Although we were not able to obtain a statistically significant difference between obese and normal-weight children due to our small sample size, there may still be a difference. A higher socioeconomic status can promote healthy eating behaviors and prevent obesity. However, some studies have also suggested that individuals with lower incomes may be less motivated to control their weight gain (21). Additionally, we found that a low-income level was associated with reduced psychological resilience, which can increase the risk of obesity by impairing adolescents' ability to cope with stress. Therefore, it is important to recognize that adolescents from low-income backgrounds may be at greater risk for obesity, and to develop preventive programs accordingly.

Psychological resilience is a proven and remediable condition in which individuals play a major role in maintaining their well-being. This study found that obese adolescents had lower psychological resilience and that their father's education level may be a significant sociodemographic factor associated with obesity. At this juncture, it can be argued that obesity may negatively impact psychological well-being, while psychological resilience may serve as a protective factor against obesity. While the causal relationship between resilience and obesity has not been fully established, it is evident that obesity might have adverse effects on mental health. These findings underscore the importance of promoting psychological resilience among obese individuals and addressing the mental health needs of those who are affected by obesity. In this regard, we firmly believe that our research significantly contributes to the literature by demonstrating the link between obesity and psychological resilience in children. Despite these findings, our study has some limitations. Firstly, the sample size is relatively small. Secondly, the evaluation of children's psychological well-being was not conducted by a child psychiatrist. We are optimistic that further research in this area will provide valuable insights and guidance.

CONCLUSION

Obesity stands as a profound public health challenge. This study has shed light on the correlation between obesity and psychological resilience in children. As such, it is appropriate to assess the psychological resilience of children with obesity and those with normal weight like the evaluation of metabolic parameters in healthy child controls. By doing so, we can implement targeted interventions to enhance the psychological well-being of children, thereby safeguarding them from adverse psychological experiences. Addressing these factors collectively may pave the way for a healthier and happier future for our younger generation.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics Committee Approval: The study was carried out with the permission of Başkent University Non-invasive Clinical Researches Ethics Committee (Date: 2023, Decision No: 23/282).

Informed Consent: Written and verbal informed consent form was obtained from participants for the 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.

Acknowledgments: We would thank all parents to participate in the study.

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Pediatr Pract Res 2023; 11(3): 92-96
DOI: 10.21765/pprjournal.1339729

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Characteristics of Anaphylactic Reactions in Children: Evaluation from a Pediatric Allergy Clinic

Çocuklarda Anafilaktik Reaksiyonların Özellikleri: Pediatrik Alerji Kliniğinde Değerlendirme

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ABSTRACT

Aims: Anaphylaxis is a severe and potentially life-threatening hypersensitivity reaction characterized by rapidly developing multisystem involvement. By systematically evaluating the clinical features of anaphylaxis patients, we can obtain valuable information about the epidemiology and clinical spectrum of this life-threatening condition in children.

Material and Method: Between January 2016 and December 2022, data regarding patients aged 0-18 years who presented to the pediatric allergy clinic with the diagnosis of 'unspecified anaphylactic shock' were retrospectively screened, and a total of 186 patients with a history of anaphylaxis were included in the study. The patients' age at diagnosis, gender, allergy history, the potential allergen-causing anaphylaxis, and clinical manifestations during anaphylactic episodes were evaluated as part of the study.

Results: Of the patients, 55.4% were male, and the median age was 5.0 years. The probable allergen triggering anaphylaxis was food in 41.9% of patients, drugs in 40.3%, bee venom in 7.5%, and idiopathic in 10.2%. Among food triggers, tree nuts were the most common (35.9%), while antibiotics were the most common probable allergens among drugs. 24.7% of the patients had a known allergy history. Respiratory system involvement was observed in 85.5% of the patients, skin-mucosa involvement was observed in 82.3%, gastrointestinal system involvement was observed in 50%, and cardiovascular system involvement was observed in 4.3%.

Conclusion: Evaluating the clinical characteristics of anaphylaxis patients is of great importance in enhancing our understanding and clinical approach to this complex hypersensitivity reaction in children. This approach aims to optimize the diagnosis, proper management, and prevention of anaphylactic reactions, ultimately leading to better health outcomes and improved quality of life for children.

Keywords: Anaphylaxis, drug allergy, adrenalin, food-induced anaphylaxis

ÖZ

Amaç: Anafilaksi, hızla gelişen çoklu sistem tutulumu ile karakterize, şiddetli ve potansiyel olarak yaşamı tehdit edici bir aşırı duyarlılık reaksiyonudur. Anafilaksi öyküsü olan hastaların klinik özellikleri sistematik olarak değerlendirilerek, çocuklarda yaşamı tehdit eden bu durumun epidemiyolojisi ve klinik spektrumu hakkında değerli bilgiler edinebiliriz.

Gereç ve Yöntem: Ocak 2016- Aralık 2022 tarihleri arasında çocuk alerji polikliniğine 'anafilaktik şok, tanımlanmamış' tanısı ile başvuran 0-18 yaş arası hastalar ile ilgili veriler geriye yönelik taranmış, anafilaksi öyküsü olan 186 hasta çalışmaya dahil edilmiştir. Hastaların tanı yaşı, cinsiyeti, alerji öyküsü, anafilaksiyi tetikleyen muhtemel alerjen öyküsü, anafilakside görülen klinik bulgular çalışma kapsamında değerlendirilmiştir.

Bulgular: Hastaların %55,4'ü erkek, medyan yaş 5,0/yıl idi. Anafilaksi tetikleyicisi muhtemel alerjenler hastaların %41,9'unda besin, %40,3'ünde ilaç, %7,5'inde arı venomu, %10,2'sinde idiopatikti. Besinlerin içerisinde en sık kuruyemiş (%35,9), ilaçların içerisinde en sık antibiyotikler muhtemel alerjenlerdi. Hastaların %24,7'sinde öncesinde bilinen alerji öyküleri vardı. Hastaların %85,5'inde solunum sistemi, %82,3'ünde deri-mukoza, %50'sinde gastrointestinal sistem ve %4,3'ünde kardiyovasküler sistem tutulumu gözlendi.

Sonuç: Anafilaksi hastalarının klinik özelliklerinin değerlendirilmesi, çocuklarda bu karmaşık aşırı duyarlılık reaksiyonuna yönelik anlayışımızı ve klinik yaklaşımımızı geliştirmede büyük önem taşımaktadır. Bu sayede anafilaktik reaksiyonların tanısını, doğru yönetimini ve önlenmesini optimize etmeyi ve sonuçta çocuklar için daha iyi sağlık sonuçları ve daha iyi yaşam kalitesi hedeflenebilir.

Anahtar Kelimeler: Anafilaksi, ilaç alerjisi, adrenalin, gıda kaynaklı anafilaksi

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Başvuru Tarihi/Received: 08.08.2023
Kabul Tarihi/Accepted: 08.09.2023

INTRODUCTION

Anaphylaxis is characterized by rapidly developing multisystem involvement and is a severe and potentially life-threatening hypersensitivity reaction (1). It represents a critical medical emergency that requires rapid diagnosis, immediate intervention, and long-term management (1). While anaphylaxis can affect individuals of all ages, its diagnosis and treatment pose greater challenges in childhood, making it even more critical in pediatric cases (2).

At present, there is no gold standard laboratory test or biomarker available for the diagnosis of anaphylaxis. The diagnosis of anaphylaxis is established worldwide using universally accepted clinical criteria, which relies on the patient's medical history and physical examination (1). The patient's medical history and clinical findings are the most crucial tools in determining whether a patient has anaphylaxis and identifying its underlying cause (3). However, none of the symptoms and signs manifested during anaphylaxis are specific to anaphylaxis alone. This situation can significantly lead to delayed or missed diagnosis in a considerable number of patients and subsequently result in delays in treatment. Therefore, the American National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) have developed clinical criteria to facilitate the diagnosis of anaphylaxis (4). Anaphylaxis typically presents with clinical manifestations involving at least two of the following systems: skin, respiratory, cardiovascular, or gastrointestinal system. Skin, mucosa, and respiratory system involvement are the most commonly observed in anaphylaxis (5). The absence of mucocutaneous symptoms, occurring in 10-20% of cases, may lead to underrecognition of anaphylaxis (6).

The incidence of anaphylaxis in children varies from country to country worldwide. In a systematic meta-analysis investigating the global incidence and prevalence of anaphylaxis in children, the reported incidence for total anaphylaxis ranged from 1 to 761 per 100,000 person-years, while for food-induced anaphylaxis (FIA), it ranged from 1 to 77 per 100,000 person-years (7). Furthermore, this meta-analysis also reported an increasing trend in the incidence of both total anaphylaxis and FIA over time (7). In a study conducted in Turkey, a screening based on diagnostic codes in patients attending hospitals in Istanbul estimated an annual incidence of 1.95 per 100,000 for anaphylaxis (8). This increase is believed to be influenced significantly by the rise in food allergies, particularly contributing to the increased frequency of anaphylaxis in children under the age of 5 (9). In another study conducted in our country, it was determined that children under the age of 2 accounted for 43% of all cases among those who experienced anaphylaxis (10). As the incidence of anaphylaxis increases worldwide and in our country, understanding the clinical characteristics and causes in children is important to improve patient care and clinical outcomes.

Our knowledge about the epidemiology of anaphylaxis is based on case series, patient records from healthcare centers and hospitals, and studies investigating the prevalence in the general population. By systematically evaluating the clinical features of anaphylaxis patients, we can gain valuable insights into the epidemiology and clinical spectrum of this life-threatening condition in children. This research article aims to investigate and analyze the clinical profiles of pediatric patients diagnosed with anaphylaxis, who presented to the pediatric allergy outpatient clinic, with the goal of understanding and improving the management of this potentially life-threatening condition.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences, Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 23/02/2023, Decision No: 33). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data on patients aged 0-18 years who presented to the University of Health Sciences, Ümraniye Training and Research Hospital Pediatric Allergy Clinic with a diagnosis of 'anaphylactic shock, undefined (International Statistical Classification of Diseases and Related Health Problems (ICD-10 code): T78.2)' between January 2016 and December 2022 were retrospectively retrieved from the hospital database. All patients with a history of anaphylaxis during the specified dates were included in the study. The patients' age at diagnosis, gender, allergy history, potential allergen history causing anaphylaxis, and clinical manifestations during anaphylactic episodes were evaluated as part of the study.

Statistics

The data were analyzed and recorded using SPSS (Statistical Package for Social Sciences for Windows 25.0) software. Descriptive statistics such as median, minimum, maximum values, as well as counts (n) and percentages (%) were utilized for presenting the data.

RESULTS

Between January 2016 and December 2022, a total of 186 patients presented to the Pediatric Allergy Clinic with a diagnosis of anaphylaxis. Among them, 55.4% (n=103) were male. The median age was 5.0 years (ranging from 0 to 18.0). In the majority of patients (74.7%, n=139), exposure to a potential allergen occurred through oral

contact. Among the probable allergens for anaphylaxis, food was responsible for 41.9% of patients (n=78), drugs for 40.3% (n=75), bee venom for 7.5% (n=14), and idiopathic/other causes for 10.2% (n=19) (**Table 1**).

Table 1. Demographic and clinical characteristics of the patients

Age (year), median (min-max)	**5,0 (0-18,0)**
Gender, n (%)	
Male	103 (55,4)
Female	83 (44,6)
Probable allergen exposure route, n (%)	
Oral	139 (74,7)
Subcutaneous	21 (11,3)
Intramuscular	14 (7,5)
Intravenous	12 (6,5)
Potential allergen, n (%)	
Food	78 (41,9)
Drug	75 (40,3)
Bee venom	14 (7,5)
Idiopathic/Others	19 (10,2)

In patients, 85.5% (n=159) had respiratory system involvement, 82.3% (n=153) had skin-mucosal involvement, 50% (n=93) had gastrointestinal system involvement, and 4.3% (n=8) had cardiovascular system involvement. All patients received adrenaline treatment upon admission to the emergency department. 24.7% (n=46) of the patients had a known allergy history. Among these patients with a history of allergies, 80.4% (n=37) had known food allergies, 17.4% (n=8) had inhalant allergies (pollen, dust mites, cat), and 2.2% (n=1) had drug allergies (**Table 2**).

Table 2. Clinical manifestations of anaphylaxis and allergy histories of the patients

Clinical findings	**n (%)**
Respiratory system involvement	159 (85,5)
Skin-mucosal involvement	153 (82,3)
Gastrointestinal system involvement	93 (50,0)
Cardiovascular system involvement	8 (4,3)
Administration of Adrenaline	186 (100)
Allergy history	46 (24,7)
Known allergens in those	
Food	37 (80,4)
Inhaled allergens (pollen, house dust mites, cat)	8 (17,4)
Drug	1 (2,2)

The most common probable allergens triggering anaphylaxis in patients who developed anaphylaxis were food items. Among food allergens, tree nuts were the most frequent probable trigger, accounting for 35.9% (n=28) of cases. Milk accounted for 16.7% (n=13) and hen's egg for 14.1% (n=11) of other probable triggers for anaphylaxis. Hazelnut (32.1%) and walnut (32.1%) were the most common triggers for anaphylaxis among the tree nuts. These were followed by peanut (21.5%), almond (7.1%), pistachio (3.6%), and cashew (3.6%). Among drugs, antibiotics were the most common triggering allergens (n=42, 56.0%). Within antibiotics, Amoxicillin/Clavulanic acid was the most frequent probable allergen (n=16, 21.3%) (**Table 3**).

Table 3. Allergens in patients (n=186)

	n (%)
1) Food (n=78)	
Tree nuts	28 (35,9)
Hazelnut	9 (32,1)
Walnut	9 (32,1)
Peanut	6 (21,5)
Cow's milk	13 (16,7)
Hen's egg	11 (14,1)
Fish	3 (3,8)
Legume	3 (3,8)
Pineapple	2 (2,6)
Others	18 (23,1)
2) Drugs (n=75)	
Antibiotic	42 (56,0)
Amoxicillin/Clavulanic acid	16 (21,3)
Clarithromycin	6 (8,0)
Ceftriaxone	6 (8,0)
Penicillin	5 (6,7)
Cefazole	5 (6,7)
Others	4 (5,3)
Non-steroidal anti-inflammatory drugs (NSAIDs)	22 (29,3)
Others	11 (14,7)
3) Bee venom (n=14)	
4) Idiopathic/Others (n=19)	

DISCUSSION

In this study, we aimed to evaluate the clinical characteristics of pediatric patients diagnosed with anaphylaxis who presented to the pediatric allergy outpatient clinic. Through the analysis of demographic data illustrating symptoms, triggers, medical history, and treatment strategies, we gained insights into the epidemiology and clinical spectrum of anaphylaxis in children.

Among the patients assessed in our study, 55.4% were male, and the median age was 5 years. Consistent with findings reported in other published studies (5,11-13), most anaphylactic reactions occur in younger children, and there is a male predominance across to all age groups. A meta-analysis compiling 54 studies investigating anaphylaxis in childhood showed that males had a higher incidence of anaphylaxis than females. However, as the older children (≥10 years), there was a tendency for a higher incidence of anaphylaxis in females compared to males, although this difference was not statistically significant (7).

Potential allergens triggering anaphylaxis were food items in 41.9% of patients, drugs in 40.3%, and bee venom

in 7.5%. Consistent with our study data, research from various countries identifies food as the most common trigger for anaphylaxis (5,11,12,14,15,16). Among food allergens, tree nuts were the most frequent allergen (35.9%), followed by milk (16.7%) and hen's egg (14.1%). The types of food triggers can vary based on age groups, different countries, and cultures. In a study conducted in China with a methodology similar to our study, milk was found to be the most common food trigger for anaphylaxis. This was followed by buckwheat, hen's egg, and fruits (15). In a study examining a multicenter anaphylaxis registry in Korea, the most common cause of FIA in children was hen's egg, followed by cow's milk, walnuts, wheat, and peanuts among 284 cases (14). In a study assessing children with a history of anaphylaxis in our country, cow's milk was identified as the most prevalent trigger for anaphylaxis among foods (16). Egg, hazelnut, lentil, and wheat were identified as the second most common triggers of anaphylaxis (16). In studies conducted in the United States, tree nuts are reported as the most common trigger for food-induced anaphylaxis (17). Dietary habits and cultural factors of the population may explain this difference between countries. The triggers of anaphylaxis can exhibit variations even among studies conducted within different regions of the same country.

In our study, respiratory system involvement was observed in 85.5% (n=159) of patients, skin-mucosa involvement in 82.3% (n=153), gastrointestinal system involvement in 50% (n=93), and cardiovascular system involvement in 4.3% (n=8). Previous studies have consistently reported that skin, mucosa, and respiratory system involvement are the most common manifestations in childhood anaphylaxis (11,18,19). In a recent study, gastrointestinal symptoms were observed to be significantly more common in infants and children with FIA (2). The distribution and severity of symptoms and signs comprising the clinical presentation of anaphylaxis can vary in each patient and even between different episodes of the same patient (1).

All of our patients received adrenaline treatment upon emergency room admission. Adrenaline is the life-saving drug in the treatment of anaphylaxis (20). The first and most crucial steps in managing all patients are ensuring airway, breathing, and circulation, followed by the prompt administration of adrenaline, the single life-saving treatment (1,6). There are also studies reporting that healthcare professionals have inadequate knowledge in diagnosing anaphylaxis and administering adrenaline (5,21-23). To increase anaphylaxis preparedness, the simplest precaution would be to conduct in-house training and develop a written anaphylaxis action plan that includes the diagnostic criteria for anaphylaxis.

In our study, the most common drug group triggering anaphylaxis was antibiotics, followed by non-steroidal anti-inflammatory drugs (NSAIDs). Among antibiotics, Amoxicillin/Clavulanic acid was the most frequently implicated drug. Antibiotics, especially those belonging to the beta-lactam group, have been consistently identified as the most common cause of drug-induced anaphylaxis in children in various studies (11,15,24). In a study conducted in the USA with one of the largest populations evaluated to date (19,836 drug-induced anaphylaxis patients), antibiotics were reported as by far the most common culprit drugs (25). Consistent with our study results, Amoxicillin/Clavulanic acid has been identified as the most commonly implicated agent among antibiotics (25). Overall, in previous studies, NSAID-induced anaphylaxis ranks second among drug triggers for anaphylaxis (15,25). Conversely, NSAIDs have been ranked first in a few studies as the leading cause of drug-induced anaphylaxis (12,14). Drug-induced anaphylaxis is more commonly observed in adults, and our knowledge regarding the role of drugs in anaphylaxis during childhood is limited (26). Beta-lactam group antibiotics and NSAIDs are likely the most commonly implicated drugs, possibly due to their high prescription rates (26).

Limitations

The fact that our study was conducted in a single hospital clinic poses a limitation to the generalizability of the research findings.

CONCLUSION

The evaluation of clinical features in anaphylaxis patients holds great significance in enhancing our understanding and clinical approach towards this complex hypersensitivity reaction in children. By systematically evaluating the clinical features and underlying triggers of anaphylaxis patients, we can gain valuable insights into the epidemiology and clinical spectrum of this life-threatening condition in children. This way, we can aim to optimize the diagnosis, proper management, and prevention of anaphylactic reactions and ultimately target better health outcomes and improved quality of life for children.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 23/02/2023, Decision No: 33).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Pediatr Pract Res 2023; 11(3): 97-100
DOI: 10.21765/pprjournal.1326593

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Effect of Ventricular Catheter Entry Point and Tip Location on Proximal End Occlusion: A Multicenter Study in Pediatric Patients

Ventriküler Kateter Giriş Noktasının ve Uç Konumunun Proksimal Uç Tıkanıklığı Üzerindeki Etkisi: Pediatrik Hastalarda Çok Merkezli Bir Çalışma

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ABSTRACT

Aim: This multicenter study investigates the effect of entry point and shunt tip location on proximal Ventriculoperitoneal (VP) shunt dysfunctions.

Material and Method: The medical records of 51 pediatric patients who were hospitalized for proximal shunt dysfunction between 2010 and 2021 were retrospectively reviewed.

Results: The study did not find statistically significant importance in terms of proximal shunt occlusion regarding the entry site of the shunt and the location of the shunt tip. There were no significant differences in the entry sites of the proximal end based on age distribution. Gender distribution did not vary significantly according to the insertion site of the proximal end.

Conclusion: It is believed that factors such as the choroid plexus and ependymal reaction play a more significant role in proximal shunt occlusion. Our findings are consistent with previous studies and emphasize the importance of the choroid plexus and ependymal reaction in shunt dysfunction. The study did not observe significant associations between the entry site of the shunt, etiology of shunt dysfunction, location of the proximal end on CT scans, and the risk of shunt failure. However, the study has limitations, including its retrospective design and limited sample size. Future prospective studies with larger sample sizes are needed. This study provides a foundation for future research aimed at improving the long-term effectiveness of VP shunt treatment and reducing complications in pediatric patients.

Keywords: Proximal shunt dysfunctions, ventricular shunting, entry site

ÖZ

Amaç: Bu çok merkezli çalışma, giriş noktasının ve şant ucu konumunun proksimal ventriküloperitoneal (VP) şant disfonksiyonları üzerindeki etkisini araştırmaktadır.

Gereç ve Yöntem: 2010 ile 2021 yılları arasında şant disfonksiyonu nedeniyle hastaneye yatırılan 51 pediatrik hastanın tıbbi kayıtları geriye dönük olarak incelendi.

Bulgular: Çalışmamızda, ventriküloperitoneal şantın giriş noktası ve şant ucu konumunun, proksimal uç tıkanıklığı açısından istatistiksel olarak anlamlı bir önemi yoktu. Yaş dağılımına göre proksimal ucun giriş yerlerinde anlamlı fark yoktu. Proksimal ucun giriş yerine göre cinsiyet dağılımı anlamlı farklılık göstermedi.

Sonuç: Proksimal şant tıkanıklığında koroid pleksus ve ependimal reaksiyon gibi faktörlerin daha önemli bir rol oynadığı düşünülmektedir. Bulgularımız, önceki çalışmalarla uyumludur ve şant disfonksiyonunda koroid pleksus ve ependimal reaksiyonun önemini vurgulamaktadır. Çalışmamız şantın giriş noktası, şant disfonksiyonunun etiyolojisi, proksimal uçların BT taramalarındaki konumu ve şant başarısızlığı riski arasında anlamlı ilişkileri gözlemlemedi. Ancak, çalışmanın geriye dönük tasarımı ve sınırlı örneklem büyüklüğü gibi sınırlamaları bulunmaktadır. Gelecekte daha büyük örneklem büyüklüğüne sahip prospektif çalışmalara ihtiyaç duyulmaktadır. Bu çalışma, pediatrik hastalarda VP şant tedavisinin uzun vadeli etkinliğini artırmayı ve komplikasyonları azaltmayı amaçlayan gelecekteki araştırmalar için temel oluşturmaktadır.

Anahtar Kelimeler: Proksimal şant disfonksiyonu, Ventriküler şant, Giriş noktası

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Başvuru Tarihi/Received: 18.07.2023
Kabul Tarihi/Accepted: 08.09.2023

INTRODUCTION

Ventriculoperitoneal (VP) shunt is a commonly utilized neurosurgical treatment method. Approximately 30,000 shunt surgeries are performed annually in the United States (1). It has been reported that VP shunt failure rates range from 10% to 50% within the first year after surgery (2-4). Numerous studies have indicated that complications are more prevalent in pediatric cases compared to adults (5, 6).

Proximal end occlusion stands as one of the most frequent complications associated with VP shunts (7, 8). Factors contributing to this complication include the type of shunt material, shunt placement and surgical techniques, as well as variables like infections and prolonged shunt use. A study exploring the theory that the proximal catheter might become occluded by brain parenchyma during insertion from the cortex to the ventricle found that protecting the catheter with a removable sheath did not reduce shunt occlusion rates(9). Another theory suggests that the proximal catheter might experience occlusion due to fragments of the choroid plexus when placed near the foramen of Monroe (10). The relationship between the location of the proximal catheter and shunt dysfunction has not been clearly established (10, 11).

The objective of this study is to investigate proximal end dysfunctions in VP shunts. The study examines the causes, symptoms, diagnosis, and treatment of proximal end occlusion. Additionally, our research assesses the potential relationship between the entry point of the shunt and the proximal catheter tip with proximal end occlusion.

MATERIAL AND METHODS

The study was carried out with the permission of Selçuk University Local Ethics Committee (Date: 01.08.2023, Decision No: 2023/374). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The medical records of pediatric patients who were hospitalized for shunt dysfunction between the years 2010 and 2021 at three medical centers, namely the Neurosurgery Departments of Bursa Uludag University, Ankara University, and Selcuk University, were reviewed. A total of 1387 pediatric patients who underwent shunt surgery were included in our study. Patients who required shunt revision due to proximal tip occlusion were included in the study, while those who underwent early surgery due to malposition or developed shunt occlusion related to slit ventricles were excluded. Demographic characteristics of the patients, etiology of the initial shunt placement, shunt type, concomitant diseases, time between the first surgery and revision, location of the proximal end observed in CT scans, detectable cause of dysfunction, and follow-up time were recorded. Patients with missing data in their medical files were excluded from the study. Informed consent forms were obtained from the parents or legal guardians of the patients.

Statistical analysis

The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilk test. Continuous variables using median (minimum: maximum) values; categorical variables were expressed as n(%). Kruskal Wallis and Mann-Whitney U tests were used for comparisons of continuous variables between study groups, in case the normal distribution was not observed according to the results of the normality test. Categorical variables were compared between groups using the Fisher Freeman Halton Test. SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.) program was used for statistical analysis, and type I error level was accepted as 5% in statistical analysis.

RESULTS

There were no significant differences in the entry sites of the proximal end based on age distribution (p=0.267). The median age at the time of surgery was 16.50 months for patients with proximal left occipital insertion, 8.50 months for those with proximal right occipital insertion, and 12 months for those with frontal insertion. Gender distribution did not vary significantly according to the insertion site of the proximal end (p=0.379) (**Table 1**).

Table 1: Comparison of proximal end entry site by demographic characteristics

	Entry point of proximal catheter			p value
	Left Occipital (n=10)	Right Occipital (n=36)	Frontal (n=5)	
Age at the time of surgery (months)	16,50 (0,10:175)	8,50 (0,40:112)	12 (4:14)	0,267[a]
Gender				
Female	5 (50%)	12 (33,30%)	3 (60%)	0,379[b]
Male	5 (50%)	24 (66,70%)	2 (40%)	

Data are expressed as median (minimum:maximum) and n(%). a: Kruskal-Wallis Test, b: Fisher Freeman Halton Test.

No significant differences were observed in the entry sites of the proximal end based on the etiology and distribution of myelomeningocele (p=0.691, p=0.347, respectively) (**Table 2**). Additionally, there were no significant differences between the groups in terms of the time to proximal end obstruction and its location on CT scans (p=0.785, p=0.673). The distribution of occlusion etiology also showed no significant differences between the entry sites of the proximal end (p=0.295). Similarly, no significant differences were found in the distribution of follow-up time based on the entry sites of the proximal end (p=0.641) (**Table 2**).

Table 2: Comparison of the proximal end's entry site and its location in the brain, and the variables indicating the non-operational status

	Entry point of proximal tip						p value
	n	Left Occipital	n	Right Occipital	n	Frontal	
Etiology							
Congenital Hydrocephalus	10	7 (70%)	35	22 (62.90%)	5	2 (40%)	0.691[b]
Meningitis, Trauma, Intracerebral Hemorrhage, MMC, Posterior Fossa Mass		2 (20%)		6 (17.10%)		2 (40%)	
Intraventicular Hematoma, Intraventricular Cystic Lesion		1 (10%)		7 (20%)		1 (20%)	
Myelomeningocele							
Yes	10	5 (50%)	36	9 (25%)	5	1 (20%)	0.347[b]
No		5 (50%)		27 (75%)		4 (80%)	
Time to proximal end obstruction (months)	10	8.50 (1:16)	36	8 (1:17)	5	9 (2:17)	0.785[a]
Location of the proximal end in CT							
Frontal	10	3 (30%)	35	6 (17.10%)	5	2 (40%)	0.673[b]
Monreo		4 (40%)		20 (57.10%)		2 (40%)	
Occipital		3 (30%)		9 (25.70%)		1 (20%)	
Obstruction Etiology							
Meningitis	10	7 (70%)	35	22 (62.90%)	5	3 (60%)	0.295[b]
Choroid Plexus		3 (30%)		8 (22.90%)		0	
Ventricular Hematoma, Malposition, Shunt Pump Failure		0		5 (14.30%)		2 (40%)	
Follow-up (months)	10	12.50 (5:16)	33	12 (3:18)	3	10 (2:13)*	0.641[c]

Data are expressed as median (minimum:maximum) and n(%). a:Kruskal-Wallis Test, b:Fisher Freeman Halton Test, c: Mann-Whitney U Test, *: In the group with frontal proximal insertion site, it was not included in the analysis due to insufficient number of data pertaining to the follow-up period (n=3)

DISCUSSION

We present the findings of a multicenter study that investigated proximal shunt malfunctions with the goal of identifying potential associations with shunt failure that could be addressed. The medical records of 51 pediatric patients who were hospitalized for shunt dysfunction between 2010 and 2021 were reviewed at three centers: Bursa Uludag University, Ankara University, and Selcuk University.

In our study, we did not observe any misplaced proximal catheters, although it is possible that some data were missing in this retrospective analysis. This finding is in line with the study by Jeremiah et al., who reported that the accuracy of ventricular catheter placement is a crucial factor in shunt failure (12).

Similarly, Dickerman et al. found no significant association between the placement of the proximal catheter away from the choroid plexus and a lower rate of shunt failure at six months in their study involving 117 shunt revisions (11). This study also did not reveal a relationship between the placement of the ventricular tip and shunt failure, in agreement with Dickerman et al. We attribute the significance of our study's findings to the importance of the choroid plexus in proximal shunt occlusion, as well as the significance of ependymal reaction. Therefore, there was no statistically significant importance in terms of proximal shunt occlusion regarding the entry site of the shunt and the location of the shunt tip.

In contrast, Farahmand et al. reported that right frontal placement of the ventricular catheter was associated with a significantly reduced risk of shunt occlusion within six months compared to occipital placement in their study involving 411 adult hydrocephalus cases (11). However, we did not find a relationship between the entry point of the shunt and the failure rate in our study.

Furthermore, Sampath et al. reported that stereotactic placement of the ventricular catheter was associated with decreased proximal malfunction rates (13). In our series, all shunts were placed using the freehand technique without the aid of ultrasound or navigation.

One of the main limitations of our study was the small sample size and retrospective design. Additionally, the evaluation of shunt valve types was not included. At times, it was not possible to determine the surgeons who performed the shunt insertions in these university clinics. Some studies have reported higher risks of shunt complications when operated on by inexperienced surgeons.

This study demonstrates that there is no relationship between etiology, the location of the proximal end in CT scans, the etiology of obstruction, and shunt failure. More detailed prospective studies with larger sample sizes are needed to further investigate and prevent shunt failure.

CONCLUSION

This multicenter study examined the proximal end dysfunctions of VP shunts in pediatric patients. We found that there was no statistically significant relationship between the entry site of the shunt and the location of the shunt tip in terms of proximal shunt occlusion. This suggests that factors such as the choroid plexus and ependymal reaction may play a more significant role in proximal shunt occlusion than the specific

placement of the shunt components. Our findings align with previous studies that have highlighted the importance of the choroid plexus and ependymal reaction in shunt malfunction. We did not observe any significant associations between the entry site of the shunt, etiology of shunt dysfunction, location of the proximal end in CT, and the risk of shunt failure. However, it is important to note that our study had limitations, including its retrospective nature and small sample size. Future prospective studies with larger sample sizes are needed to further investigate the factors influencing shunt failure.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Local Ethics Committee (Date: 01.08.2023, Decision No: 2023/374).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Pediatr Pract Res 2023; 11(3): 101-106
DOI: 10.21765/pprjournal.1341133

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Effect of Obesity on Metabolic Risk Factors in Children with Urinary Stones

Üriner Sistem Taşı Olan Çocuklarda Obezitenin Metabolik Risk Faktörlerine Etkisi

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ABSTRACT

Aim: Hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia have accepted as metabolic risk factors causing urolithiasis. There are many studies reporting that obesity increases the risk of stone formation by metabolic risk factors. The aim of this study is to evaluate the frequency of metabolic risk factors and the effect of body mass index (BMI) on them.

Material and Method: Children with urolithiasis >3 mm included in the study. Demographic information and biochemistry analyses including urine metabolic screening were recorded.

Results: Of the 155 patients (94 male/61 female) included in the study, with a mean age of 71±57 months, 98 (63%) have a family history of stones. There was at least one metabolic risk factor in 38.7% of the patients, and the most common ones were hyperoxaluria (16.8%) and hypocitraturia (16.8%), respectively. The presence of metabolic risk factors was significantly higher in patients with stone size ≥5 mm and with multiple stones, respectively (p=0.015, p=0.028). Patients with underweight and normal weight were grouped as Group 1 (n=99 patients), and those with overweight and obese as Group 2 (n=56 patients). The frequencies of hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia and cystinuria were similar between groups.

Conclusion: Family history is common in children with urinary system stones. Since the probability of metabolic risk factors is higher in patients with stone size >5 mm and multiple stones, evaluation in this regard would be appropriate, especially in these patients. There was no evidence in this study that obesity increases metabolic risk factors.

Keywords: Urolithiasis, obesity, body mass index, hyperoxaluria, hypocitraturia

ÖZ

Amaç: Hiperkalsiüri, hiperoksalüri, hiperürikozüri, hipositratüri üriner sistem taş hastalığına neden olan metabolik risk faktörleri olarak kabul edilmiştir. Obezitenin metabolik risk faktörlerine bağlı olarak taş oluşum riskini artırdığını bildiren birçok çalışma bulunmaktadır. Bu çalışmanın amacı metabolik risk faktörlerinin sıklığını ve vücut kitle indeksinin (VKİ) ile ilişkisini değerlendirmektir.

Gereç ve Yöntem: 3 mm'nin üzerinde ürolitiazisi olan çocuklar çalışmaya dahil edildi. Demografik bilgiler ve idrar metabolik taramasını da içeren ve biyokimya analizleri kaydedildi.

Bulgular: Ortalama yaşları 71±57 ay olan 155 hastanın (94 erkek/61 kadın) 98'inin (%63) ailesinde taş öyküsü vardı. Hastaların %38,7'sinde en az bir metabolik risk faktörü vardı ve en yaygın olanlar sırasıyla hiperoksalüri (%16,8) ve hipositratüriydi (%16,8). Taş boyutu ≥5 mm olan ve multipl taşı olan hastalarda metabolik risk faktörlerine daha sık rastlanmaktaydı (p=0,015, p=0,028). Hastalar, zayıf ve normal kilolu hastalar Grup 1 (n=99 hasta), fazla kilolu ve obez olanlar Grup 2 (n=56 hasta) olmak üzere gruplandırıldı. Hiperkalsiüri, hiperürikozüri, hiperoksalüri, hipositratüri ve sistinüri sıklıkları gruplar arasında benzer bulundu.

Sonuç: Aile öyküsü üriner sistem taş hastalığında önemli bir uyarıcıdır. Taş boyutu >5 mm ve birden fazla taşı olan hastalarda metabolik risk faktörlerinin görülme olasılığı daha yüksek olduğundan, özellikle bu hastalarda bu açıdan değerlendirme yapılması uygun olacaktır. Bu çalışmada obezitenin metabolik risk faktörlerini arttırdığına dair bir bulguya rastlanmadı.

Anahtar Kelimeler: Ürolitiazis, obezite, vücut kitle indeksi, hiperoksalüri, hipositratüri

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Başvuru Tarihi/Received: 11.08.2023
Kabul Tarihi/Accepted: 08.09.2023

INTRODUCTION

Urinary system stone disease occurring as a result of a process accompanied by infection as well as metabolic and anatomical factor, brings along high morbidity and mortality, causing kidney damage and chronic kidney disease in children (1). The prevalence of kidney stones in childhood is reported to be 2-3% (2). Changes in climate, socioeconomic conditions, increase in welfare level and changes in dietary habits have led to an increase in the incidence of urinary system stones in children. All these have caused changes in etiological factors, stone localization, and chemical content of the stone (3). It has been reported that more than half of the underlying cause of urinary system stone cases is metabolic disorders. Among these disorders, hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia have been accepted as metabolic risk factors that increase the risk and recurrence of urolithiasis (2). Obesity is an increasing problem both in western society and in our country. The prevalence of obesity is increasing day by day all over the world, especially in developed countries (4). As in the adult population, there is an increase in the prevalence of childhood and adolescence obesity. In studies conducted with school children in our country, it is observed that the prevalence of obesity exceeds 10% (5). Although there are many studies reporting that obesity increases the risk of stones by increasing hypercalciuria, hyperoxaluria, hyperuricosuria, which are known as metabolic risk factors, there are also studies indicating the opposite. In this study, we evaluated the demographic, clinical and laboratory characteristics of children followed up with the diagnosis of urinary system stones and the effect of body mass index on metabolic risk factors.

MATERIAL AND METHOD

The study was carried out with the permission of Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.02.2022, Decision No: 1771). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was designed as a retrospective cross-sectional study in 155 patients who were followed up with urinary system stones between 10/2019-12/2021 in the Department of Pediatric Nephrology Outpatient Clinic of Adana City Training and Research Hospital. Patients who were followed up and treated with the diagnosis of urinary system stones in the Pediatric Nephrology outpatient clinics of our hospital, between the ages of 2 months and 18 years, with stones >3 mm, and who were screened for metabolic risk factors were included in the study. Demographic information, laboratory data (hemogram, biochemistry, blood gas, urinary electrolytes, and urine metabolic screening) were recorded from patient files. BMI and BMI percentile (BMIp) of the patients were recorded and the effect of BMIp on metabolic risk factors was evaluated. Obesity was evaluated according to BMI, and obese patients were included in the study without distinction between endogenous and exogenous obesity.

Definitions:

BMI is obtained by dividing the body weight in kilograms by the square of the height in meters (BMI= kg/ m2). Patients with BMI <5p were classified as underweight, those with BMI 5–84p as normal weight, those with BMI 85–94 as overweight, and those with BMI ≥95p as obese (6).

The calcium/creatinine excretion in spot urine is >0.53 mg/mg in patients aged 1-3 years, >0.4 mg/mg in patients aged 3-5 years, >0.3 mg/mg in patients aged 5-7 years and >0.2 mg/mg in patients aged 7-18 years was defined as hypercalciuria. Uric acid/creatinine excretion in spot urine >1.9 mg/mg in children 1-3 years old, >1.5 mg/mg in children 3-5 years old, >0.9 mg/mg in children 5-10 years old mg, and >0.6 mg/mg in children aged 10-18 years was defined as hyperuricosuria. Hyperoxaluria was defined as oxalate/creatinine excretion in spot urine>80 mg/g between 2-5 years of age, >65 mg/g between 5-14 years of age and >32 mg/g between 14-18 years of age. Cystinuria was defined as urinary cystine/creatinine excretion above 98 µmol/g at the age of 3-12 years and above 81 µmol/g at the age of 13-18 years. Hypocitraturia was defined as urinary citrate/creatinine excretion ratio below 0.20 g/g between 0-5 years old and 0.14 g/g between 5-18 years old (7).

Statistical Analysis

Statistical analysis of the study was performed using the Statistical Package for Social Sciences" version 20 (IBM Corp., Armonk, NY, USA) program. Descriptive statistics of numerical data were calculated as mean ± standard deviation in parametric data and median (minimum-maximum, interquartile) in non-parametric data. Categorical data were given as percentage (%). Chi-square analysis and Fisher's exact test was used to compare categorical measures between groups. In the comparison of numerical measurements between the groups, the T test was used if the assumptions were met, and the Mann Whitney U test was used if the assumptions were not met. Mann-Whitney U test was used for continuous variables under parametric conditions and Student's t-test under nonparametric conditions. The significance level used for these tests was $p<0.05$.

RESULTS

Clinical Presentation, Family History, and Imaging

Of the 155 patients included in the study, 94 (60.6%) were male and 61 (39.4%) were female, with a mean age of 71±57 months. The mean age of the girls and boys was similar. There was a history of consanguinity in 16 (10.3%) patients. Urinary system stones were present in the family history of 98 patients (63%). Urinary tract stones were found incidentally in 62 (41.3%) patients. The most common complaint of the patients at the time of admission was abdominal pain with 44 patients (29.1 %). Hematuria, vomiting, restlessness, family history of stones and dysuria were among the other complaints of the patients. The urinary system stones of the patients were located in the left kidney in 74 (47.7%) patients, in the right kidney in 65 (41.9%) patients, in both kidneys in 11 (7.1%) patients, and in the bladder in 5 (3.2%) patients.

It was determined that 104 (68%) patients had 1 stone, 49 (32%) patients had 2 or more stones. Staghorn stones were detected in 5 (3.2%) of them. Median stone size was 5 mm (IQR 4mm, min:3mm, max:30 mm). The presence of metabolic risk factors was significantly higher in patients with stone size ≥5 mm and with multiple stones, respectively (p=0.015, p=0.028). There was a weak correlation between stone size and BMIp (p=0.029, r=0.175).

Metabolic Risk Factors

The presence of at least one of the metabolic risk factors was found in 60 patients (38.7%) included in our study. Analyzing the metabolic risk factors causing stone, hyperoxaluria was the most common risk factor in 25 patients (16.8%). This was followed by hypocitraturia in 25 (16.7%) patients, cystinuria in 12 (7.9%) patients, hypercalciuria in 9 (6.2%) patients, and hyperuricosuria in 2%. Metabolic risk factors were shown in **Table 1**.

Table 1: Metabolic risk factors in children with urinary system stone disease

	N (positive/total)	%
Hyperoxaluria	25/150	16.8%
Hypocitraturia	25/149	16.7%
Cystinuria	12 /151	7.9%
Hypercalciuria	9/145	6.2%
Hyperuricosuria	2/100	2.0%

BMI and Effect on Metabolic Risk Factors

The median BMIp of the children included in the study was calculated as 70.0 (IQR 66.0). The median BMIp for girls was 71p (IQR 64.5p), and for boys was 69.9p (IQR 68.2p), and the median BMIp was similar for both sexes. BMIp values of patients with and without positive metabolic risk factors were compared. BMIp values of patients with and without hyperoxaluria, hypocitraturia, cystinuria, hypercalciuria and hyperuricosuria were similar (**Table 2**).

Table 2: Comparison of BMIp values of patients with and without positive metabolic risk factors

		N	BMIp		p *
			Mean+ SD	Median (IQR)	
Hypercalciuria	yes	9	50.7±44.5	52.0 (85.7)	0.752
	no	136	61.0±33.6	71.0 (61.0)	
Hyperuricosuria	yes	2	15.5±0.7	15.5 (NA)	0.087
	no	98	61.5±33.6	75.0 (61.0)	
Hyperoxaluria	yes	25	66.0±36.0	77.6 (64.4)	0.082
	no	124	59.6±33.7	70.0 (61.0)	
Cystinuria	yes	12	53.0±30.8	58.0 (59.5)	0.718
	no	130	61.3±30.8	76.0 (63.5)	
Hypocitraturia	yes	25	53.6±34.9	58.8 (62.0)	0.637
	no	125	61.6±33.9	71.0 (62.0)	

*Mann Whitney-U test, NA: Not applicable

According to BMIp values, 13 (8.4%) of the patients were underweight, 86 (55.5%) were normal weight, 21 (13.5%) were overweight, 35 (22.6%) were obese. Patients with underweight and normal weight were grouped as Group 1 (n=99 patients), and those with overweight and obese were grouped as Group 2 (n=56 patients). Group 1 and Group 2 were similar in terms of age and gender (p=0.170, p=0.722). There was no difference between the two groups in terms of urine pH and serum biochemical analyzes. The frequencies of hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia and cystinuria were also similar in patients in group 1 and group 2. Comparison of underweight and normal weight patients with overweight and obese patients in terms of metabolic risk factors was shown in **Table 3**. When the patients were grouped as obese and non-obese, the groups were also similar in terms of each metabolic risk factors. Besides, the presence of any of the (at least one) metabolic risk factors was also not associated with obesity (p>0.05)

Table 3: Comparison of underweight and normal weight patients with overweight and obese patients

	Patients with Underweight and Normal weight	Patients with Overweight and Obese	p *
Laboratory analysis	**Median (IQR)**	**Median (IQR)**	
Urea (mg/dl)	21.0 (10.5)	22.0 (11.0)	0.583
Creatinine (mg/dl)	0.3 (0.2)	0.4 (0.2)	0.506
Uric acid (mg/dl)	3.6 (1.1)	3.7 (1.6)	0.958
Calcium (mg/dl)	10.0 (0.5)	10.0 (0.5)	0.880
Phosphorus (mg/dl)	5.1 (1.3)	4.9 (0.9)	0.753
Potassium (mg/dl)	4.4 (0.8)	4.4 (0.9)	0.697
Magnesium (mg/dl)	2.0 (0.2)	2.0 (0.1)	0.740
Urine pH	7.40	7.39	0.986
Metabolic risk factors	**n (%)**	**n (%)**	**p †**
Hypercalciuria	6 (6.4)	3 (5.9)	0.905
Hyperuricosuria	2 (3.1)	2 (0)	0.295
Hyperoxaluria	13 (14.0)	12 (21.4)	0.239
Cystinuria	8 (8.2)	4 (7.4)	0.741
Hypocitraturia	16 (16.8)	9 (16.4)	0.940

* Mann Whitney-U test, †Chi-square analysis

DISCUSSION

Urinary system stones may be detected between 0.2-15 years of age in childhood. In a study performed by Shahta et al. on children aged 0-18 years, the mean age was found to be 54.3 months; Sas et al. in another study found that boys were usually diagnosed between the ages of 6-11 and girls were diagnosed in adolescence (8,9). In the study of Karabacak et al. from our country, the mean patient age was found to be 9.35 years (10). The gender distribution of childhood urinary system stone disease varies according to age. The prevalence of boys was higher in the first decade of life, and the prevalence was higher in girls in the second decade of life. In the studies carried out, the male/female ratio can vary from 1.14 to 4 (11). In our study, similar to the literature, the male/female ratio was found to be 1.54.

Presence of urinary system stone disease among family members may indicate the relative risk for urinary system stone formation. The rate of those with a family history of childhood urinary system stone disease is reported between 3.15% and 78.7% in different series (1,2,12,13). In a study conducted by Erbağcı et al. in our country, a positive family history was found at a rate of 54% (14). This rate is similar to the family history rate of 63% in our study. Nowadays, there are studies pointed out monogenetic causes to be reason for stone formation in pediatric population (15). Genetic research is not recommended because of the high cost. However, the presence of nephrocalcinosis and recurrence of stone within year should be warning (16). Although the presence of a family history of urinary system stone disease is mostly associated with an underlying genetic cause, it should not be forgotten that shared environmental factors and dietary habits may also contribute to familial predisposition of idiopathic urolithiasis.

Apart from genetic factors, many epidemiological factors such as race, geographical region, climate, socioeconomic level, dietary habits play a role in the pathogenesis of urinary system stone. Regardless of epidemiological differences, the obvious situation is that the incidence of urinary system stone disease is increasing all over the world (17). Urinary system anomalies increased urinary excretion of some metabolites and ions that cause crystal formation, urinary supersaturation, urinary pH and tubular flow rate are seen as the most important risk factors (18).

Studies have shown that childhood urinary system stone disease is associated with underlying metabolic risk factors at a rate of 26-88% (2,8,19,20). In this study we detected at least one metabolic risk factor in 60 (38.7%) of the patients included in our study. Metabolic factors that have the greatest effect on the formation of calcium stones have been reported as hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia and hypomagnesemia (18). Hypercalciuria is reported as the most common metabolic disorder with a frequency of 30-50% in children with urinary system stones (2, 21).

In some studies, hypocitraturia with hypocalciuria was reported as the most common metabolic risk factors (22, 23). In our study, unlike those reported in the literature, hypercalciuria was detected less frequently (6.2%), and hypocitraturia with a frequency of 16.7%, was the second most common metabolic risk factor after hyperoxaluria. The reason for these differences may be associated with the fact that in our study, urine metabolites were studied from spot urine samples, not from collected urine for 24 hours.

The relationship between obesity and urolithiasis is well established among adult population (24,25). Ekeruo et al. reported that hypercalciuria, hyperuricosuria and hyperoxaluria were more common in obese patients compared to the non-obese patient group (25). Daudon found that the incidence of uric acid stones was 4 times higher in obese patients than in normal-weight patients, and there was an inversely proportional relationship between BMI and urine pH. (26).

Beside adult population, several studies has been conducted in pediatric population to determine the association between obesity and urolithiasis. Roddy et al. reported that both obesity and hypocitraturia, as the most common metabolic risk factor. However, there was no significant difference between obese and non-obese patients in terms of metabolic risk factors for urinary system stone formation (27). Bandari et al. showed that the incidence of hypercalciuria is increased in 110 stone forming overweight/obese children. Also, in contrast to findings in adults, no association reported between urine pH and BMI (28). Fang et al. in their study evaluated 243 pediatric stone patients retrospectively; non-overweight patients found to be more likely to have hyperoxaluria and hyperuricosuria, while overweight patients were more likely to have hypocitraturia (11). Cambareri et al. determined that stone-forming children who are overweight or obese to have low urinary volume and elevated uric acid compared to normal-weight stone-forming children (29). A systematic review from Italy evaluated studies reporting association between renal stones and obesity. In this paper, it was stated that hyperuricosuria, hypercalciuria and hyperoxaluria are more common metabolic risk factors in obese patients, respectively (30). In our study, no significant difference was found between the obese and non-obese groups in terms of hypercalciuria, hyperuricosuria and hyperoxaluria and no relationship was found between obesity and urine pH. As it is seen, although there are publications in the literature showing that obesity is a risk factor for stone formation, there are also contradictory publications.

The fact that stone formation is multifactorial and affected not only by BMI but also by the nutritional characteristics of the patient may explain these different results in the literature.

The retrospective nature of our study is one of the most important limitations. Another limitation of the study is that 24-hour urine collection in children is difficult and often not possible, so spot urinalysis is requested, and metabolic characteristics are evaluated based on these results. Another limitation of the study is the relatively low number of patients. Our patient group, which is a very good number for a single center, may be insufficient in comparing metabolic risk factors and nutritional status. In addition, no distinction was made between endogenous and exogenous obesity in the obese patients included in the study.

CONCLUSION

The important information obtained from this study; Family history is common in children with urinary system stones. Since the probability of metabolic risk factors is higher in patients with stone size >5 mm and multiple stones, evaluation in this regard would be appropriate, especially in these patients. The most common metabolic disorders were found to be hyperoxaluria and hypocitraturia. In this study, the relationship between obesity and urinary calcium, oxalate, cystine, and citrate excretion could not be demonstrated. Metabolic risk factors that increase the risk of urinary system stone formation in patients with a family history of urinary system stone disease should be investigated and treated. There is a need for more comprehensive, prospective multicenter studies that include patients' nutritional status and metabolic risk factors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.02.2022, Decision No: 1771).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Pediatr Pract Res 2023; 11(3): 107-110
DOI: 10.21765/pprjournal.1347152

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Neonatal Mortality in a Public Referral Hospital in Konya Over a Three-Year Period

Konya Şehir Hastanesinde Üç Yıllık Dönemde Yenidoğan Mortalite Oranları

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ABSTRACT

Aim: Pregnancy outcomes are important markers of a country's social and economic development, as they indicate the quality of care in the prenatal and neonatal period. The aim of this study was to determine the mortality rate and causes of mortality in the last 3 years in our Neonatal Intensive Care Unit (NICU).

Material and Method: Cases involving patients who died in our hospital between August 2020, and July 2023, were included in the study. Demographic data, length of hospitalization, prenatal risk factors, mode of delivery, causes of mortality, and mortality rate were examined.

Results: The records of a total of 4177 infants admitted between August 2020, and July 2023, were reviewed and a total of 226 patients who died during their hospitalization in the neonatal clinic between these dates were included in the study. Accordingly, the 3-year mortality rate in our NICU was calculated as 5.4%. The most common cause of mortality in infants hospitalized in the NICU was prematurity and its complications (40.7%). Other common causes were respiratory diseases, sepsis, and cardiac diseases.

Conclusion: Effective measures should be taken to reduce perinatal and neonatal mortality, such as adequate and quality antenatal care, improving child health and disease prevention actions, reducing potential complications during pregnancy, childbirth and postpartum, as well as promoting early diagnosis.

Keywords: Neonatal, neonatal mortality, mortality rate

ÖZ

Amaç: Gebeliğin sonuçları, prenatal ve neonatal dönemin kalitesini gösterdiğinden, ülkenin sosyal ve ekonomik gelişmişliğini gösteren önemli belirteçlerindendir. Bu çalışmada, yenidoğan yoğun bakım ünitemizin son üç yıllık mortalite hızının ve mortalite nedenlerinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Hastanemizde Ağustos 2020-Temmuz 2023 tarihleri arasında ölen olgular çalışmaya dâhil edilmiştir. Olguların demografik verileri, yatış süreleri, prenatal risk faktörleri, doğum şekli, mortalite nedenleri ve mortalite oranı belirlenmiştir.

Bulgular: Ağustos 2020- Temmuz 2023 tarihleri arasında yatırılan toplam 4.177 bebeğin kayıtları incelenmiş ve bu tarihler arasında yenidoğan kliniğinde yatışı sırasında vefat eden toplam 226 hasta çalışmaya dâhil edilmiştir. Bu sonuçlar ile yenidoğan yoğun bakım ünitemizde üç yıllık mortalite oranı %5.4 olarak hesaplanmıştır. Yenidoğan yoğun bakım ünitesinde yatan bebeklerin en sık mortalite nedeni prematüre ve komplikasyonları iken (%40,7), diğer sık sebepler respiratuvar hastalıklar, sepsis ve kardiyak hastalıklar olarak belirlendi.

Sonuç: Perinatal ve neonatal mortaliteyi azaltmak için yeterli ve kaliteli doğum öncesi bakım, çocuk sağlığı ve hastalıkları önlemeye yönelik eylemlerin geliştirilmesi, gebelikte, doğumda ve doğum sonrasında olası komplikasyonların azaltılmasına ek olarak erken teşhise yardımcı olmak gibi etkili önlemler alınmalıdır.

Anahtar Kelimeler: Yenidoğan, mortalite hızı, yenidoğan mortalitesi

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Başvuru Tarihi/Received: 21.08.2023
Kabul Tarihi/Accepted: 23.09.2023

INTRODUCTION

Perinatal and neonatal mortality are among the most important public health problems of a country. Pregnancy outcomes are important markers of a country's social and economic development, as they indicate the quality of care in the prenatal and neonatal period. According to the World Health Organization (WHO) statistical reports published in 2019, the number of neonatal deaths decreased to 2.3 million in 2019. According to the same data, approximately 6400 newborn deaths occur every day in the world, accounting for approximately 47% of all child deaths under the age of 5. The neonatal mortality rate of Turkey has been reduced to 0.9%(1). All measures taken to improve preventive, therapeutic, and public health in Turkey have paid off, resulting in a desired reduction in child mortality. According to the 2020 report of the UN Inter-agency Group for Child Mortality Estimation, Turkey is the 3rd fastest country to reduce infant and child mortality in the last 30 years (2,3).

The aim of this study was to investigate the 3-year neonatal mortality rate and the factors affecting this rate in our Neonatal Intensive Care Unit (NICU), which has the highest patient count in Konya Province.

MATERIAL AND METHOD

The study was carried out with the permission of Necmettin Erbakan University Non-drug and Medical Device Researches Ethics Committee (Date: 2023, Decision No: 2023/4543).

This retrospective study examined the records of 4177 infants admitted to our hospital, between August 2020, and July 2023. A total of 226 patients who died during their stay in the NICU were included in the study. Intrauterine deaths and stillbirths were excluded from the study. Demographic data (gestation week, birth weight, mode of delivery, gender), and data regarding the length of hospitalization, maternal age, comorbidities of the mother, and causes of mortality were obtained from the files of the patients. The neonatal mortality rate and the total mortality rate of the NICU were calculated. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 22.0 (SPSS, IBM Corp, Armonk, NY, USA). The conformity of numerical variables with normal distribution was checked. Non-normally distributed were presented as the median (min-max). Descriptive statistics were expressed as numbers and percentages.

RESULTS

A total of 24,228 live births occurred in our hospital between August 2020, and July 2023. And of these, 4177 infants were hospitalized in the NICU and 226 infants died in NICU care. The characteristics of the deceased patients are summarized in **Table 1**. The mean birth weight of the infants was 1465 g (370–4000) and their mean gestational age was 30 (23–42) weeks. Of these patients, 70.5% were born by cesarean section and 26.5% were resuscitated in the delivery room. In terms of pregnancy-related risk factors, 8 mothers had preterm premature rupture of membranes (PPROM), 13 had preeclampsia, 8 had maternal diabetes, and 7 had COVID-19 infection. Of the pregnant women, 12.8% did not attend routine pregnancy follow-ups (**Table 1**).

Table 1. Demographic and Clinical Characteristics

	n: 226
Gestational age* (weeks)	30 (23–42)
Birth weight* (g)	1465 (370–4000)
Gender (n/%)	
Female	103 (45.5%)
Male	123 (54.4%)
Delivery type (n/%)	
VD	66 (29.1%)
C/S	160 (70.5%)
Resuscitation (n/%)	
No	166 (73.5%)
Yes	60 (26.5%)
Maternal Age (years)	26 (15–46)
Maternal disease (n/%)	
No	156 (69%)
PPROM	8 (3.5%)
Preeclampsia	8 (5.7%)
Gestational diabetes	8 (3.5%)
COVID-19	7 (3.1%)
Unknown	29 (12.8%)
Others	5 (2.2%)
Length of hospitalization* (days)	5 (1–221)

VD: Vaginal delivery; C/S: Caesarean section; PPROM: Preterm premature rupture of membranes; Others: abruption of placenta, hypothyroidism, cancer, and traffic accident. *Median (min-max)

The most common cause of mortality in the infants hospitalized in the NICU was prematurity and its complications (40.7%). Other common causes were respiratory diseases (17.2%), sepsis (13.7%), and cardiac diseases (10.2%). The mortality rate related to asphyxia was 4.9% (**Table 2**).

Table 2. Causes of death in infants hospitalized in the NICU (n/%)

Diseases	n (%)
Prematurity	92 (40.7)
Respiratory Diseases	39 (17.2%)
Sepsis	31 (13.7%)
Congenital Heart Diseases	23 (10.2%)
Surgical Diseases	13 (5.8%)
Asphyxia	11 (4.9%)
Congenital Anomalies and Syndromes	9 (4%)
Inherited Metabolic Diseases	8 (3.5%)

It was determined that the most common reason for death was due to sepsis, respiratory diseases and CHD in term and near-term patients (**Table 3**). Patients with a gestational age of 23–25 weeks were most commonly lost. The riskiest group in terms of birth weight were infants with a birth weight of ≤1000 g (**Table 4**).

Table 3. Distribution of the Exitus patients by gestational age and birth weight.

Gestational age*, weeks	**n: 226**
23-25	61(27%)
26-28	38(16.8%)
29-32	29(12.8%)
33-34	17(7.5%)
35-37	35(15.5%)
38-40	46(20.4%)
Birth weight*, (gram)	**n: 226**
≤ 1000	90(39.8%)
1001-1500	25(11.1%)
1501-2000	29(12.8%)
2001-3000	53(23.5%)
3001-4000	28(12.4%)

*Median (min-max)

Table 4: Causes of death by gestational age

Diseases*	**23-33 (n:145) (n/%)**	**34-36 (n: 35) (n/%)**	**≥ 37 (n:46) (n/%)**
Prematurity	92 (63.4%)	-	-
Respiratory Diseases	11 (7.6%)	9 (25.7%)	11(23.9%)
Sepsis	21 (14.5%)	9 (25.7%)	9 (19.6%)
Congenital Heart Diseases	10 (6.9%)	5 (14.3%)	8 (17.4%)
Surgical Diseases	5 (3.4%)	4 (11.4%)	4 (8.7%)
Asfixia	-	4 (11.4%)	6 (13%)
Congenital Anomalies and Syndromes	1 (0.7%)	3(8.6%)	1 (2.2%)
Inherited Metabolic Diseases	2 (1.4%)	-	6 (13.8%)

*Median (min-max)

DISCUSSION

Despite all of the developments and improvements in NICUs in recent years, neonatal mortality is still an important problem in developing countries. Globally, approximately 1/3 of newborns die on the day of birth and 3/4 of them die in their first week of life (4).

Our hospital is one of the largest centers serving in its region in terms of bed capacity. This clinic accepts a large number of referrals since it has a perinatology center that performs intensive cardiac surgery, pediatric surgery, and many other surgical operations. A total of 24,228 live births occurred in our hospital between August 2020, and July 2023. The 3-year mortality rate of our clinic was determined as 5.4%. According to Turkish Neonatology Society (TNS) data of NICUs, the mean annual hospitalization-based mortality rate of Turkish centers is 4.3%–5.1%, while centers reporting a mortality rate of up to 11% also exist (5). Despite the high number of annual hospitalizations and the high-risk patient profile, our mortality rate was found to be consistent with Turkey's overall mortality rate.

The neonatal period starts from birth and ends on day 28 of life. Neonatal mortality rates are influenced by a variety of factors, such as economic and cultural factors. Neonatal mortality does not have one specific cause. It less frequently occurs due to environmental factors such as infectious diseases. Mortality during this period is mostly due to endogenous causes such as complications at birth, genetic factors, and the negative effects of maternal malnutrition on the mother and the newborn during pregnancy. Perinatal mortality rates (rate of infant deaths in the first 7 days of life and stillbirths) are an indicator of maternal health, antenatal care adequacy, and delivery quality (6,7). Although the COVID-19 pandemic was occurring during the study period, it was shown that most of the patients attended regular pregnancy follow-ups. A maternal age of <18 and >35 years is known to be a risk factor for infant mortality. Although maternal age alone does not predict a risk, it increases the risk of death when combined with other risk factors (2). Unlike the literature, maternal age was not found to be significant in our study.

Most mothers included in the present study had no prenatal risk factors. But prenatal risk factors such as preeclampsia/eclampsia, maternal diabetes, PPROM and infection increase maternal and neonatal mortality (2). It has been stated that the risk of neonatal death caused by these risk factors can be reduced with appropriate medical and obstetric care. We think that prenatal risk factors were found to be low in the mothers of the babies in our study due to the close follow-up of high-risk pregnancy

In countries with the highest infant mortality rates, half of neonatal deaths are caused by infections, while in countries with lower rates, prematurity and congenital malformations are the main causes of death (9,10). The most common cause of neonatal death was prematurity and its complications, followed by respiratory diseases, sepsis, and congenital heart diseases, respectively. It is thought that the high preterm birth rate and mortality rate of our center are due to our high annual birth rate and the fact that our center serves perinatal patients.

Congenital malformations, deformities, and chromosomal anomalies are the foremost secondary causes of neonatal mortality in developed countries. The number of deaths due to congenital anomalies/syndromes were very low in the present study. Most malformations and chromosomal abnormalities have unknown causes and are therefore not considered as preventable deaths. It is thought that mortality rates may decrease as early diagnosis of these diseases becomes possible in parallel with developments in genetic science (12).

Neonatal Resuscitation Program (NRP) trainings becoming more widespread over the years has led to a decrease in deaths due to asphyxia, which is a preventable cause of death. While the overall mortality rate due to asphyxia is 8% in Turkey, the fact that this rate was lower in our center may be due to the suitability of resuscitation conditions in the units where deliveries were performed and the high number of NRP-certified personel.

CONCLUSION

Effective measures should be taken to reduce perinatal and neonatal mortality, such as adequate and quality antenatal care, improving child health and disease prevention actions, reducing potential complications during pregnancy, childbirth and postpartum, as well as promoting early diagnosis. Besides following technological improvements to improve perinatal-antenatal care and the conditions of neonatal units, the number of trained personnel should also be increased. In addition, the number of infants requiring major surgery is increasing. Thus, it is thought that neonatal mortality rates could be further reduced with health policies and regulations such as increasing the number of surgical centers as required by regional population densities or detaching surgical centers from general purpose centers.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Necmettin Erbakan University Non-drug and Medical Device Researches Ethics Committee (Date: 2023, Decision No: 2023/4543).

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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Pediatr Pract Res 2023; 11(3): 111-115
DOI: 10.21765/pprjournal.1350527

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Effect of E148Q Variant on Disease Severity in Familial Mediterranean Fever Patients with Compound Heterozygous Mutation

Bileşik Heterozigot Mutasyonu Olan Ailevi Akdeniz Ateşi Hastalarında E148Q Varyantının Hastalık Ağırlığına Etkisi

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ABSTRACT

Aim: In this study, we aimed to evaluate the demographic and clinical findings of familial Mediterranean fever (FMF) patients carrying a compound heterozygous mutation and to investigate the effect of the E148Q variant on disease severity.

Material and Method: Patients between the ages of 0-18 years diagnosed with FMF and carrying a compound heterozygous mutation were included in the study. Disease severity was assessed using the international severity scoring for FMF (ISSF). Patients were divided into two groups according to mutation type: those with exon 10/E148Q compound heterozygous mutation (Group 1) and exon 10/exon 10 compound heterozygous mutation (Group 2).

Results: A total of 317 FMF patients with compound heterozygous mutations had a male/female ratio of: 1.07, median age at diagnosis was 6.7 (IQR:6.3) years. The most common symptom was abdominal pain (85.8%). The median age at diagnosis was 6 years in Group 2 (n=219) and 8.2 years in Group 1 (n=98) (p=0.005). Fever (75.8%) was more common in patients with two exon 10 mutations (75.8%) (p=0.001). The presence of more than two different attack types, more than two findings in an attack and an attacks lasting longer than 72 hours were more frequent in patients in Group 2 (p=0.021, p<0.001, p=0.043, respectively). The ISSF score of Group 2 was higher than the other group (p<0.001).

Conclusion: Patients with two exon 10 mutations have more severe disease than patients with other compound heterozygous mutations including the E148Q mutation. ISSF score is lower in patients with E148Q mutation in one allele.

Keywords: Familial Mediterranean fever, E148Q variant, ISSF score

ÖZ

Amaç: Bu çalışmada bileşik heterozigot mutasyon taşıyan ailevi Akdeniz ateşi (AAA) hastalarının demografik, klinik bulgularının değerlendirilmesi ve E148Q varyantının hastalık ağrılığı üzerine etkisinin araştırılması amaçlandı.

Gereç ve Yöntem: 0-18 yaşları arasında, Yalçınkaya-Özen kriterlerine göre AAA tanısı konulmuş olan ve bileşik heterozigot mutasyon saptanmış olan hastalar çalışmaya alındı. Klinik ve demografik verileri kaydedildi. Hastalık ağırlığı AAA için uluslararası şiddet skorlama sistemi (ISSF) ile değerlendirildi. Hastalar mutasyon tipine göre ekzon 10/E148Q bileşik heterozigot mutasyonu olanlar (Grup 1) ile ekzon 10/ekzon 10 bileşik heterozigot mutasyonu olanlar (Grup 2) olarak iki gruba ayrılarak değerlendirildi.

Bulgular: Toplam 317 bileşik heterozigot mutasyona sahip AAA hastalarında kadın/erkek oranı: 1.07, ortanca tanı yaşı 6.7 (IQR: 6.3) yıldı. En sık görülen semptom %85.8 oranında karın ağrısı idi. Grup 2'de (n=219) yer alan hastaların ortanca tanı yaşı 6 yıl, Grup 1'dekilerin (n=98) ise 8.2 yıldı (p=0.005). İki ekzon 10 mutasyonu olan hastalarda ateş (%75.8) diğer gruba göre daha sık görüldü (p=0.01). İkiden fazla farklı atak tipi, atakta ikiden fazla bulgu ve 72 saatten uzun süren atak varlığı Grup 2'deki hastalarda daha sıktı (sırasıyla p=0.021, p<0.001, p=0.043). Tüm hastalarda toplam ISSF skoru ortanca 2 (IQR:3) olarak bulunurken Grup 2'nin ISSF skoru diğer gruba göre daha yüksekti (p<0.001).

Sonuç: İki ekzon 10 mutasyonu olan hastalar, E148Q mutasyonunu içeren diğer bileşik heterozigot mutasyonu olan hastalara göre daha şiddetli hastalığa sahiptir. ISSF skoru bir alelinde E148Q mutasyonu olan hastalarda daha düşüktür.

Anahtar Kelimeler: Ailevi Akdeniz ateşi, E148Q varyant, ISSF skoru

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Başvuru Tarihi/Received: 26.08.2023
Kabul Tarihi/Accepted: 23.09.2023

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease that is characterized by recurrent episodes of fever and serosal inflammation (1,2). The predicted prevalence of FMF is 1/1000, the prevalence of carriage in the Turkish population is 20% (3).

A typical FMF attack lasts 12-36 hours and patients are mostly asymptomatic between attacks. The frequency of attacks ranges from once a week to several times a year (2). Approximately 96% of FMF attacks are characterized by fever. Following fever, the most common finding is abdominal pain in 90-95% of cases. Joint findings are observed in 20-75% and chest pain in 30-50% of cases (4,5).

The diagnosis is based on clinical findings, supported by family history and genetic testing. After the identification of the Mediterranean FeVer (MEFV) gene, genetic testing has been helpful in the diagnosis, especially in patients without typical clinical findings (1, 6). The MEFV gene is localized on chromosome 16p13.3 and consists of 10 exons (4). Most of the mutations associated with FMF are located in exons 2, 3, 5 and 10. The most common mutations are M694V, M680I, V726A, M694I in exon 10 and E148Q in exon 2 (5). Although studies have been reported on the genotype-phenotype relationship, the correlation has not been clearly clarified yet. Homozygous mutations in the exon 10 such as M694V, M680I, V726A are known to be associated with more severe clinical presentation. However, the potential pathologic role of the E148Q variant is still controversial (7).

The aim of this study was to evaluate the demographic and clinical findings of patients with compound heterozygous mutations and to investigate the effect of the E148Q variant on disease severity when combined with exon 10 mutations.

MATERIAL AND METHOD

This study was approved by the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 23/11/2022, Decision No: E2-22-2844). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted retrospectively in patients with a compound heterozygous mutation in the MEFV gene, aged younger than 18 years at diagnosis, who were evaluated in the Pediatric Rheumatology Department of our hospital between January 2019 and January 2023. FMF patients with MEFV mutation other than compound heterozygous mutation or FMF patients without genetic testing were excluded from the study.

Demographic data, clinical findings, attack frequency, attack duration, family history, presence of comorbidity, treatment data and MEFV mutation analysis were recorded.

The diagnosis of FMF was based on Yalçınkaya-Özen criteria with the presence of at least 3 episodes lasting 6-72 hours of fever, abdominal pain, chest pain, arthritis and the positive family history. (8). Disease severity was assessed by the international severity score for FMF (ISSF). Nine parameters were evaluated and classified as mild, moderate or severe disease with a total score of 10 (**Table 1**) (9).

Table 1: The international severity score for familial Mediterranean fever (ISSF)

1) Chronic sequela (including amyloidosis, growth retardation, anaemia, splenomegaly)	1 point
2) Organ dysfunction (nephrotic range proteinuria, FMF related)	1 point
3) Organ failure (heart, renal, etc, FMF related)	1 point
4-a) Frequency of attacks (average number of attacks between 1 and 2 per month)	1 point
4-b) Frequency of attacks (average number of attacks >2 per month)	2 points
5) Increased acute-phase reactants (any of C-reactive protein, serum amyloid A, erythrocyte sedimentation rate, fibrinogen) during the attack-free period, ≥2 weeks after the last attack (at least two times 1 months apart)	1 point
6) Involvement of more than two sites during an individual acute attack (pericarditis, pleuritis, peritonitis, synovitis, ELE, testis involvement, myalgia, and so on)	1 point
7) More than two different types of attack during the course of the disease (isolated fever, pericarditis, pleuritis, peritonitis, synovitis, ELE, testis involvement, myalgia, and so on)	1 point
8) Duration of attacks (more than 72 h in at least three attacks in a year)	1 point
9) Exertional leg pain (pain following prolonged standings and/or exercising, excluding other causes)	1 point

Severe disease ≥6, intermediate disease 3–5, mild disease ≤2.
*Criterion 4a/4b can give 0 or 1 or 2 points altogether according to the definition.
ELE, erysipelas-like erythema; FMF, familial Mediterranean fever.

At least five predominant mutations in the MEFV gene (p.M694V, p.M680I, p.M694I, p.V726A, p.E148Q) were analyzed. Patients carrying different mutations in two alleles were defined as compound heterozygotes. Patients were divided into two groups according to mutation type: Group 1 included patients with exon 10/E148Q compound heterozygous mutation and Group 2 included patients with exon 10/exon 10 compound heterozygous mutation. The two groups were compared according to clinical and demographic characteristics and ISSF score components.

Statistical Analyses

Statistical analyses were performed using the SPSS software version 25. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables, medians and interquartile range for the non-normally

distributed and ordinal variables, and frequencies for the categorical variables. In the comparisons between groups, the Mann-Whitney U test for non-normally distributed variables and the Chi-square or Fisher tests for categorical variables were used. A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

Three hundred and seventeen FMF patients with compound heterozygous mutations were included in the study. One hundred and sixty-four (51.7%) of the FMF patients were female (female/male ratio: 1.07).

The median age at onset of complaints was 4 years (IQR: 5.3), while the median age at diagnosis was 6.7 years (IQR: 6.3). During the attack, 85.8% (n=272) had abdominal pain, 70.3% (n=223) had fever, 50.5% (n=160) had arthralgia, 31.9% (n=101) had chest pain, 14.8% (n=47) had arthritis, 8.2% (n=26) had erysipelas-like erythema (ELE), and 12.6% (n=40) had diarrhea.

M694V/M680I mutation was detected in 91 (28.7%), M694V/V726A in 63 (19.9%), M694V/E148Q in 62 (19.6%), M680I/V726A in 25 (7.9%), M694V/R761H in 21 (6.6%), M680I/E148Q in 12 (3.8%) and V726A/E148Q in 11 (3.5%) patients. The most common allele was M694V in 246 (77.6%) patients.

Ninety-eight patients with exon 10/E148Q compound heterozygous mutation were classified as Group 1 and 219 patients with exon 10/exon 10 compound heterozygous mutation were classified as Group 2. Demographic, clinical, treatment characteristics and ISSF scores between the two groups are given in **Table 2**.

Table 2: Demographic, clinical, treatment characteristics and ISSF scores of patients according to the mutation type

	Group 1 Exon 10/ E148Q (n= 98)	Group 2 Exon 10/Exon 10 (n=219)	p value
Female/Male	56/42	108/111	0.20[a]
Age at onset of complaint† (n=261)	5 (6)	3.5 (5)	0.22[b]
Age at diagnosis†	8.2 (6.9)	6 (6.1)	0.005[b]
Diagnostic delay (month)	21.5 (32.4)	22.3 (28.2)	0.68[b]
Attack characteristics*			
Fever	57 (58.2)	166 (75.8)	0.001[a]
Abdominal pain	79 (80.6)	193 (88.1)	0.076[a]
Chest pain	28 (28.6)	73 (33.3)	0.40[a]
Arthralgia	44 (44.9)	116 (53)	0.18[a]
Arthritis	10 (10.2)	37 (16.9)	0.12[a]
Erysipeloid rash	7 (7.1)	19 (8.7)	0.65[a]
Exercise-related leg pain*	25 (25.5)	47 (21.5)	0.43[a]
Attack duration† (day) (n=265)	2 (2)	2 (1)	0.15[b]
Attack frequency (last 6 months) †	0 (1)	1 (2)	0.016[b]
Treatment characteristics*			0.92[a]
Colchicine	97 (99)	216 (98.6)	
Anakinra	0 (0)	1 (0,5)	
Canakinumab	1 (1)	2 (0.9)	
More than two different attack*	19 (19.4)	70 (32)	0.021[a]
More than two symptoms in an attack*	60 (61.2)	177 (80.8)	<0.001[a]
Three episodes lasting longer than 72 hours*	15 (15.3)	56 (25.6)	0.043[a]
Increased acute-phase reactants *	1 (1)	9 (4.1)	0.18[c]
Comorbidity*			0.84[a]
IgA vasculitis	2 (2)	10 (4.6)	
Sacroiliitis	2 (2)	4 (1.8)	
Juvenile idiopathic arthritis	4 (4.1)	6 (2.7)	
Inflammatory bowel disease	3 (3.1)	4 (1.8)	
Family history*, n=290	46 (49.5)	107 (54.3)	0.44[a]
ISSF score†	2 (2)	3 (2)	<0.001[b]
ISSF score, group*			<0.001[a]
Mild	67 (68.4)	94 (42.9)	
Intermediate	31 (31.6)	120 (54.8)	
Severe	0 (0)	5 (2.3)	

*n (%), †median (IQR)
aChi-Square, bMann-Whitney U, cFisher's Exact Test
ISSF: The international severity score for familial Mediterranean fever

The median age at diagnosis was 6 years in Group 2 and 8.2 years in Group 1 (p=0.005). Fever (75.8%) was more common in patients with two exon 10 mutations compared to the other group (p=0.001). The presence of more than two different attack types, more than two symptoms in an attack and an attack lasting longer than 72 hours were significantly more frequent in patients in Group 2 (p=0.021, p<0.001, p=0.043, respectively).

The median total ISSF score was 2 (IQR:3) in all patients, while the ISSF score of Group 2 was significantly higher than the other group (p<0.001). There was no organ dysfunction, organ failure, or amyloidosis in any patient in the study. Splenomegaly was detected in 16 patients (5%).

The disease was well-controlled with colchicine in 299 patients (94.3%). Four (1.3%) patients were accepted colchicine-resistant and received anakinra or canakinumab. There was no difference between the two groups in terms of treatment characteristics.

DISCUSSION

The effect of exon 10 mutation on disease severity in patients with FMF is known, however, the importance of E148Q mutation on disease severity is still controversial. In this study, compound heterozygous patients with two exon 10 mutations were found to have an earlier age at diagnosis, a longer duration of attacks and a higher rate of febrile attacks than compound heterozygous patients with the E148Q variant. In addition, ISSF score indicating disease severity was found to be higher in patients with two exon 10 mutations.

Familial Mediterranean fever begins before the age of 20 in 90% of patients (10). The average age of onset is between 3-9 years (5). In our study, the median age at onset of complaints was 4 years and the median age at diagnosis was 6.7 years (5). In 2010, Çağlayan et al. evaluated 66 patients with only compound heterozygous mutation and found that the age at diagnosis was 16 years. (11). Nowadays, increased awareness of FMF and easy availability of genetic analyses lead to earlier diagnosis. The mutation detected in the patient is the determinant of the age at diagnosis. It is known that patients with M694V homozygous mutation have an earlier age of onset (3). In this study, the number of exon 10 mutations was found to be effective on the age at diagnosis. Patients with exon 10 mutation in two alleles had a younger age at onset of symptoms and age at diagnosis than patients with exon 10 mutation in one allele and E148Q in the other allele. It suggests that patients who are compound heterozygous with the exon 10 mutation have a more severe phenotype than compound heterozygous with the E148Q variant on one allele.

The type and frequency of FMF attacks vary according to ethnic groups and the result of studies. According to studies conducted in the Turkish population, the frequency of clinical symptoms of FMF was 68.6-92.5% fever, 88.2-94.8% abdominal pain, 17.8-50.4% chest pain, 46.4-77.7% arthritis and 5.4-27.5% erysipelas-like erythema (12-14). The most common clinical findings in our patients were abdominal pain, fever and arthralgia. In addition, fever was more common in patients with exon 10 mutations in both alleles.

Several studies have reported that patients carrying the M694V/M680I and M694V/V726A compound heterozygous mutation have a relatively severe clinical course similar to the M694V homozygous mutation and pointing to non-M694V exon 10 mutations (7, 15, 16). However, suspicions about the potential pathogenic role of the E148Q variant continue to persist. Some authors consider the E148Q variant to be a benign polymorphism, while others consider it to be a mild disease-causing mutation with less penetrance and a cumulative worsening effect (7, 17, 18). In our study similarly reported that patients with two exon 10 mutations had a more severe clinical course. These patients had longer attack durations, more clinical findings and more than two attack types more frequently. This may be related to the fact that other exon 10 mutations such as M694V cause a similarly more severe clinical presentation.

Several scoring systems are used to assess disease severity in patients with FMF (19). In our study, ISSF score was higher in patients with two exon 10 mutations. In the study using the Pras disease severity score, it was found that patients whose age at diagnosis was older than 8 years had a lower disease activity score, lower frequency of attacks and lower rate of febrile attacks (10). Bilge et al. evaluated disease severity with the ISSF score and found that early-onset disease and more frequent pleuritis, ELE, arthritis and myalgia were associated with more severe disease (20). Studies comparing age at diagnosis and disease severity have shown that earlier disease onset is associated with a more severe disease outcome (21, 22).

The retrospective design of the study and the small number of patients are the mail limitations of the study. The fact that this study was conducted with FMF patients with a specific mutation allowed a more comprehensive evaluation of this group.

CONCLUSION

The clinical significance of the E148Q mutation in FMF is still controversial. In this study, patients with an exon 10 compound heterozygous mutation with E148Q in one allele were shown to have milder disease than patients carrying two exon 10 mutations. This result may be attributed to the fact that carrying two exon 10 mutations is associated with a severe phenotype rather than the

E148Q variant being associated with a mild phenotype. Detailed evaluation in FMF patient groups with different exon mutations is needed to better understand the genotype-phenotype relationship.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 23/11/2022, Decision No: E2-22-2844).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Pediatr Pract Res 2023; 11(3): 116-124
DOI: 10.21765/pprjournal.1355528

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Parental Attitudes and the Use of Physical Discipline: An Investigation into Correlates

Ebeveyn Tutumları ve Fiziksel Ceza Kullanımı: Bağıntılar Üzerine Bir Araştırma

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ABSTRACT

Aim: Parenting is the process of supporting children in their physical, emotional, social, and intellectual development. Parental violence against children is widespread throughout the world. Given the harmful effects of physical punishment, it is important to explore alternative disciplinary methods and promote positive parenting styles. The aim of this study was to investigate the attitudes of parents and their use of physical punishment.

Material and Method: This descriptive cross-sectional study was conducted at the Pediatrics Outpatient Clinic of İstanbul Medipol University Hospital between June and December 2022. The study included consenting parents who had children aged between 2 and 6 years and who applied to the clinic during this period. Participants (n:117) completed a questionnaire about socio-demographic characteristics, the 'Parental Attitude Scale' and the use of physical punishment.

Results: The study included 117 parents with children aged 2-6 years. Most participants were mothers (78,44%, n=91) with a mean age of 35.02±4.11 years. The total number of children of the participants was 117 and 59 (50.4%) of the children were male. Seventy-seven (83.7%) of the mothers were university graduates. Seventy-one (65.1%) of the participants had only one child. The main characteristic of the parents' attitudes was democracy with a score of 74.99±9.92. Only permissive attitudes were found to be statistically significantly higher among middle- and high-income parents than among low-income parents. Among the participants, 41.6% (n:47) reported using any form of punishment, 16.1% (n:18) reported using physical punishment and 74.1% (n:86) reported using verbal punishment/violence.

Conclusion: In our study, it is noteworthy that although the participant parents exhibited a democratic attitude in the foreground, physical punishment was used. Parenting and disciplinary practices should be evaluated during child health follow-up and the family should be mentored about possible damaging disciplinary methods. Appropriate parenting styles can help families develop positive parenting characteristics and promote the development of mentally healthy children. More comprehensive studies are needed on this subject.

Keywords: Parenting, parental attitudes, physical punishment, discipline

ÖZ

Amaç: Ebeveynlik, çocukların fiziksel, duygusal, sosyal ve zihinsel gelişimlerini destekleme sürecidir. Buna karşın çocuklara yönelik ebeveyn şiddeti dünya genelinde yaygındır. Fiziksel ceza gibi şiddet içeren davranışların zararlı etkileri göz önüne alındığında, alternatif disiplin yöntemlerini keşfetmek ve olumlu ebeveynlik tarzlarını teşvik etmek önemlidir. Bu çalışmanın amacı, ebeveynlerin tutumlarını ve fiziksel ceza kullanım durumlarını araştırmaktır.

Gereç ve Yöntem: Bu tanımlayıcı kesitsel çalışma, Haziran-Aralık 2022 tarihleri arasında İstanbul Medipol Üniversitesi Hastanesi Çocuk Sağlığı ve Hastalıkları Polikliniği'nde gerçekleştirildi. Çalışmaya, 2 ila 6 yaş arasında çocuğu olan ve bu süre zarfında kliniğe başvuran ebeveynler dahil edildi. Katılımcılar (n:117) sosyo-demografik özellikler, 'Ebeveyn Tutum Ölçeği' ve fiziksel ceza kullanımı hakkında sorular içeren bir anket doldurdu.

Bulgular: Çalışmaya 2-6 yaş arası çocukları olan 117 ebeveyn katıldı. Katılımcıların çoğu anneydi (%78,44, n=91) ve yaş ortalaması 35,02±4,11 yıl idi. Katılımcıların toplam çocuk sayısı 117'dir ve çocukların 59'u (%50,4) erkektir. Annelerin yetmiş yedisi (%83,7) üniversite mezunu idi. Katılımcıların yetmiş biri (%65,1) tek çocuk sahibi idi. Ebeveyn tutumlarının temel özelliği 74,99±9,92 puan ile demokrasidir. Sadece izin verici tutumlar orta ve yüksek gelirli ebeveynler arasında düşük gelirli ebeveynlere göre istatistiksel olarak anlamlı derecede daha yüksek bulundu. Katılımcıların %41,6'sı (n:47) herhangi bir ceza metodu kullandığını belirtirken, %16,1'i (n:18) fiziksel ceza kullandığını ve %74,1'i (n:86) sözel ceza/şiddet kullandığını bildirdi.

Sonuç: Çalışmamızda, katılımcı ebeveynlerin demokratik bir tutum sergilemeleri ön planda olmasına rağmen fiziksel cezanın kullanılması dikkat çekicidir. Ebeveynlik ve disiplin uygulamaları çocuk sağlığı izlemleri sırasında değerlendirilmeli ve olası zarar verici disiplin yöntemleri konusunda aileye danışmanlık verilmelidir. Uygun ebeveynlik stilleri, ailelerin olumlu ebeveynlik özellikleri geliştirmelerine yardımcı olacak ve zihinsel olarak sağlıklı çocukların gelişimini teşvik edebilir. Bu konuda daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Ebeveynlik, ebeveynlik tarzı, fiziksel ceza, disiplin

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Başvuru Tarihi/Received: 05.09.2023
Kabul Tarihi/Accepted: 28.09.2023

INTRODUCTION

Parenting is the process of supporting children in their physical, emotional, social, and intellectual development (1,2). This process involves providing guidance and discipline with compassion for the psychosocially healthy growth of children. On the other hand, parental violence against children is widespread throughout the world (3–5) Despite the existence of alternative disciplinary methods, some parents may choose to use physical punishment due to its perceived short-term effectiveness and lower effort required (5–7). Physical punishment refers to the use of physical force, such as spanking or hitting, as a means of discipline (4,5). While the effectiveness and appropriateness of physical punishment is controversial, it is clearly detrimental to the psychosocial well-being of children in the long term (8–10). Therefore, the American Academy of Pediatrics recommends that disciplinary methods should be discussed with families when the infant is 9 months old (9,11). This can help parents understand the potential risks of physical punishment and explore alternative methods to promote positive behaviors in their children (9,11).

Given the harmful effects of physical punishment, it is important to explore alternative disciplinary methods and promote positive parenting practices (8,12). In this study, we aimed to investigate the relationship between parenting styles and the use of physical punishment among parents who attended child health follow-up appointments at our hospital.

MATERIAL AND METHOD

This study was approved by the Istanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 27.04.2022, Decision No: 414). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This descriptive cross-sectional study was conducted at the Pediatrics Outpatient Clinic of İstanbul Medipol University Hospital between June and December 2022. The study included all parents who presented to the clinic during this period with a child aged between 2 and 6 years, without chronic diseases in themselves or their child, and who agreed to participate in the study. Prior to their child's participation, eligible parents were provided with detailed information about the study and signed an informed written consent. The questionnaires were self-administered by eligible parents attending a child health follow-up visit. The questionnaire included items on parents' demographic characteristics, parenting styles and disciplinary practices, including the use of physical punishment.

Measurement and Data Collection

Participants in the study were asked to complete a questionnaire consisting of three parts. The first part included questions about their socio-demographic characteristics, such as age, gender, income, job, marital status, and education level. The second part included questions from the Parenting Attitude Scale, which was validated and tested for reliability by Demir et all (13). The scale was designed to measure parenting attitudes and consists of 46 items organized into four sub-dimensions: Democratic (17 items), Authoritarian (11 items), Overprotective (9 items), and Permissive (9 items).13 High scores obtained from the dimensions indicate that the respondent supports the attitude expressed in that dimension. High scores obtained from the dimensions other than democratic attitude and equality recognition dimension indicate negative parental attitudes and define the parenting style (13).

The third part of the questionnaire included questions about whether parents had used any form of punishment with their children. Specifically, parents were asked to indicate whether they had ever used physical punishment, non-physical punishment, or a combination of both. For those who reported using physical punishment, additional questions were asked about the frequency and severity of the punishment. The questionnaire was administered to parents during their child's visit to the Pediatrics Outpatient Clinic of İstanbul Medipol University Hospital.

Statistical Analysis

The data collected in the study were entered into the statistical analysis software SPSS 22 (Statistical Package for the Social Sciences-IBM, International Business Machines Corp., United States) and analyzed using descriptive and comparative statistical methods. Descriptive statistics were presented as frequency, percentage, mean, standard deviation, median, minimum, maximum, and interquartile range (IQR) values. The normality assumption was tested using the Shapiro-Wilk test, histogram, Q-Q plot, skewness, and kurtosis values. For analyzing the differences between numerical data of two groups, the Independent Samples t-test was used when the data followed a normal distribution, while the Mann-Whitney U test was used when the data did not follow a normal distribution. The relationships between numerical data were evaluated using the Pearson correlation test when the data followed a normal distribution, and the Spearman correlation test was used when the data did not follow a normal distribution. Categorical data were analyzed using the chi-square test. The Pearson chi-square test was used when the proportion of cells with an expected value less than 5 was less than 20%, and Fisher's exact test was used when the expected value was greater than 20%.

RESULTS

The study included 117 parents with 174 (minimum:1; maximum:5) children between the ages of 2 and 6 years old who completed the questionnaire. Of the participants, %78,44 were mothers with a mean age of 35.02±4.11 years, while %21,55 (n=25) were fathers with a mean age of 39.36±5.52 years. The sociodemographic characteristics of the participants are summarized in **Table 1**.

The Parental Attitude Scale used in this study consisted of four sub-factors: Democratic, Authoritarian, Overprotective, and Permissive.13 The participants' scores on these sub-factors are presented in detail in **Table 2**.

To investigate whether there were any significant differences in the scores between mothers and fathers, the scores for each of the four sub-factors were compared using independent samples t-tests. The results, presented in **Table 3**, indicated that there were no statistically significant differences between mothers and fathers on any of the sub-factors (p>0.05). **Table 3** presents a detailed summary of the relationship between the participants' scores on the Parental Attitude Scale and their sociodemographic characteristics. Overall, when the parental attitudes of all participating parents were evaluated based on the gender of their children, it was observed that all parents exhibited overprotective attitudes toward their daughters. Among the mothers, those with daughters had significantly higher scores on both the overprotective and democratic sub-factors compared to those with sons, as shown in **Table 3**. Among the fathers, higher scores on the authoritarian sub-factor were observed for those with male children, although this difference was not statistically significant (**Table 3**).

Only permissive attitudes were found to be statistically significantly higher among middle- and high-income parents than among low-income parents (**Table 3**). Mothers with an educational level less than university level had statistically significantly higher scores only in overprotective attitude compared to mothers with higher educational level, whereas this difference was not found in any parental attitude in fathers (**Table 3**). There was no statistical difference in parental attitude scores based on the number of children. Families whose children attended nursery or kindergarten were found to have statistically higher authoritarian attitude scores than those whose children did not attend nursery or kindergarten (**Table 3**).

When the correlation relationship between the age of the participant parents and parental attitude scores was examined, it was found that the permissive attitude score increased statistically significantly as the age of the mother increased, and the democratic score increased statistically significantly as the age of the father decreased, and the results are shown in detail in **Table 4**. When the age of the child and the parental attitude scores of the mothers and fathers were examined, it was found that as the age of the child increased, the authoritarian attitude scores of the mothers increased and the permissive attitude scores of the fathers decreased and these were statistically significant (**Table 4**).

Table 1. Sociodemographic Characteristic of the Participants

Characteristics (n=number of participants answering the relevant question)	
Age (M±SD) (min-max)	
Mother (n=91)	35,02±4,11 (25-47)
Father (n=25)	39,36±5,52 (31-53)
Age groups of children (n=117)	N (%)
2 years	28 (23,9%)
3 years	15(12.8%)
4 years	28 (23,9%)
5 years	27 (23,1%)
6 years	19 (16,2%)
Gender of children (n=117)	N (%)
Girl	58 (49,6%)
Boy	59 (50,4%)
Mothers' education level (n=91)	N (%)
High school and under	15 (16,3%)
University	77 (83,7%)
Fathers' education level n(%) (n=25)	
High school and under	6 (24%)
University	19 (76%)
Siblings n(%) (n=109)	
No sibling	71 (65,1%)
At least one sibling	38 (34,9%)
Income n(%) (n=105)	
Low	76 (72,4%)
Medium or high	29 (27,6%)

n: number, M: mean, SD: standard deviation.

Table 2. Characteristics of Participants' Parental Attitude Scale Scores.

Democratic Attitude	
M±SD	74,99±9,92
Median (range)	78 (20-85)
IQR	9
Authoritarian Attitude	
M±SD	18,62±4,53
Median (range)	18 (8-32)
IQR	5
Overprotective Attitude	
M±SD	30,74±6,33
Median (range)	31 (11-45)
IQR	8
Permissive Attitude	
M±SD	21,19±5,02
Median (range)	21 (7-35)
IQR	7

Table 3. Association between Sociodemographic Characteristics and Parental Attitude Scale Scores

Sociodemographic variables		Democratic Attitude		Authoritarian Attitude		Overprotective Attitude		Permissive Attitude	
		M±SD	p-value	M±SD	p-value	M±SD	p-value	M±SD	p-value
Parent	Mother (n=91) Father (n=25)	75,13±10,12 74,48±9,32	0.773	18,33±4,05 19,68±5,96	0.293	30,60±6,51 31,28±5,74	0.635	20,83±5,05 22,52±4,77	0.136
PAS according to children's gender	Female (n=58) Male (n=59)	76,67±7,18 73,34±11,85	0.068	18,19±4,24 19,03±4,79	0.316	31,97±5,81 29,54±6,64	0.038	21,34±5,07 21,03±5,01	0.740
PAS according to children's gender of the mothers	Female (n=48) Male (n=49)	77,27±5,92 72,80±12,95	0.040	18,46±3,98 18,18±4,16	0.746	31,88±5,92 29,20±6,89	0.049	20,81±5,00 20,84±5,17	0.979
PAS according to children's gender of the fathers	Female (n=10) Male (n=15)	73,80±11,51 74,93±7,95	0.773	16,90±5,38 21,53±5,75	0.055	32,40±5,54 30,53±5,95	0.438	23,90±4,84 21,60±4,65	0.246
PAS according to income levels of the parents	Low (n=29) Medium or high (n=76)	74,86±13,92 75,33±6,84	0.869	17,52±4,86 19,04±4,40	0.127	31,14±7,41 30,16±6,00	0.486	19,21±5,24 21,38±4,76	0.045
PAS according to mothers' educational level	High school and under (n=15) University (n=77)	78,27±4,21 74,52±10,82	0.191	18,20±4,58 18,35±3,97	0.907	34,20±5,82 29,90±6,43	0.018	19,93±5,09 21,00±5,06	0.458
PAS according to fathers' educational level	High school and under (n=6) University(n=19)	72,67±16,40 75,05±6,30	0.741	21,83±8,56 19,00±5,00	0.470	30,17±5,34 31,63±5,96	0.597	26,00±6,92 21,42±3,42	0.172
PAS according to the number of children	No sibling (n=71) At least one sibling (n=46)	75,56±6,73 74,11±13,48	0.500	18,63±4,40 18,59±4,76	0.957	30,93±5,89 30,46±7,02	0.695	21,37±4,43 20,91±5,86	0.636
PAS according to preschool attendance status of the children	Yes (n=80) No (n=37)	74,39±11,08 76,30±6,69	0.335	19,26±4,79 17,22±3,59	0.023	30,61±6,33 31,03±6,43	0.744	21,00±4,69 21,59±5,72	0.554

PAS: Parenteral Attitude Score. M: mean, SD: standard deviation

Table 4. Correlation Analyses of the Relationship between Some Sociodemographic Characteristics and Parental Attitudes.

		Democratic Attitude	Authoritarian Attitude	Overprotective Attitude	Permissive Attitude
Mother's age (n=91)	r p	0.136 0.197	0.092 0.387	-0.016 0.878	0.231 0.028
Father's age (n=25)	r p	-0.434 0.030	0.112 0.593	-0.318 0.121	0.127 0.546
Parental age (n=116)	r p	-0.014 0.882	0.135 0.148	-0.066 0.479	0.235 0.011
Association between child's age and maternal attitudes (n=91)	r p	-0.040 0.702	0.254 0.014	0.041 0.695	-0.070 0.508
Association between child's age and paternal attitudes (n=25)	r p	-0.329 0.109	0.281 0.174	0.000 0.998	-0.491 0.013

Among the participants, 41.6% (n:47) reported using any form of punishment, 16.1% (n:18) reported using physical punishment and 74.1% (n:86) reported using verbal punishment/violence (intimidation, yelling, humiliation, etc.). The relationship between the sociodemographic characteristics of the participants and the frequency and variety of punishment use was examined and the findings are summarized in detail in **Table 5**. It was found that only parents whose children did not attend kindergarten/nursery school used verbal punishment/violence less frequently at a statistically significant level, while statistical significance was not found in other findings.

When the parental attitudes of those who used any punishment method and those who did not use any punishment method were analyzed among all the participating parents, it was found that the permissive attitude scores of the parents who did not use any punishment method were statistically higher. Examining mothers and fathers separately, it was found that there was no statistically significant difference between the parenting attitudes of mothers, while the overprotective and permissive attitudes of fathers were statistically higher among those who did not use any punishment method, and the results are summarized in **Table 6**.

Table 5. The Relationship between Sociodemographic Characteristics and the Frequency of Different Punishment Applications.

	Frequency of applying any punishment			Frequency of applying physical punishment			Frequency of using verbal punishment		
	n	(%)	p-values	n	(%)	p-values	n	(%)	p-values
Parent									
Mother (n:90)	35	38.9		14	15.7		67	73.6	
Father (n:23)	12	52.2	0.249	4	17.4	0.532	19	76	0.810
Total (n:113)	47	41.6		18	16.1		86	74.1	
Mothers' Educational level									
High school and under (n:15)	7	46.7		3	20		12	80	
University (n:75)	28	37.3	0.498	11	14.9	0.433	55	72.4	0.398
Total (n:90)	35	38.9		14	15.7		67	73.6	
Fathers' Educational level									
High school and under (n:6)	3	50		2	33.3		3	50	
University (n:17)	9	52.9	0.635	2	11.8	0.270	16	84.2	0.125
Total(n:23)	12	52.2		4	17.4		19	76	
Parents' Educational level									
High school and under (n:21)	10	47.6		5	23.8		15	71.4	
University (n:92)	37	40.2	0.535	13	14.6	0.223	71	74.7	0.754
Total (n:113)	47	41.6		18	16.1		86	74.1	
Income									
Low (n:28)	11	39.3		7	25		59	77.6	
Medium or high (n:74)	31	41.9	0.811	11	14.9	0.181	19	65.5	0.204
Total (n:102)	42	41.2		18	17.6		78	74.3	
Number of siblings									
No sibling (n:68)	25	36.8		8	11.8		54	76.1	
At least one sibling (n:45)	22	48.9	0.201	10	22.7	0.123	32	71.1	0.553
Total (n:113)	47	41.6		18	16.1		86	74.1	
Preschool attendance status of the children									
Yes (n:78)	37	47.4		12	15.6		63	79.7	
No (n:35)	10	28.6	0.060	6	17.1	0.835	23	62.2	0.044
Total (n:113)	47	41.6		18	16.1		86	74.1	

Table 6. The Relationship between Forms of Punishment and Parental Attitude Scores.

		Democratic Attitude		Authoritarian Attitude		Overprotective Attitude		Permissive Attitude	
		M±SD	p-values	M±SD	p-values	M±SD	p-values	M±SD	p-values
Parents' any punishment application	Yes (n:47)	76,06±6,09	0.578	19,72±4,73	0.054	30,02±6,16	0.176	20,30±5,01	0.042
	No(n:66)	75,05±11,39		18,12±3,97		31,64±6,26		22,14±4,43	
Mothers' any punishment application	Yes(n:35)	76,77±5,28	0.388	19,26±4,09	0.159	30,31±6,29	0.539	20,26±5,53	0.165
	No(n:55)	74,98±11,43		18,09±3,59		31,16±6,40		21,67±4,03	
Fathers' any punishment application	Yes(n:12)	74,00±7,93	0.745	21,08±6,24	0.275	29,17±5,93	0.049	20,42±3,23	0.047
	No(n:11)	75,36±11,72		18,27±5,72		34,00±5,07		24,45±5,69	
Parents 'physical punishment application	Yes (n:18)	74,22±9,83	0.362	21,17±5,68	0.012	29,06±5,19	0.139	19,72±5,23	0.111
	No(n:94)	76,21±8,16		18,37±3,94		31,43±6,34		21,68±4,63	
Mothers' physical punishment application	Yes (n:14)	77,07±5,16	0.669	19,57±4,41	0.295	28,79±5,46	0.167	19,43±5,52	0.147
	No(n:75)	76,05±8,59		18,40±3,70		31,33±6,40		21,43±4,53	
Fathers 'physical punishment application	Yes (n:4)	64,25±16,25	0.015	26,75±6,70	0.007	30,00±4,69	0.597	20,75±4,57	0.488
	No(n:19)	76,84±6,5		18,26±4,88		31,79±6,25		22,68±5,04	
Parents 'verbal punishment application	Yes (n:86)	74,62±7,70	0.112	19,88±4,35	0.000	30,64±6,01	0.606	20,84±4,62	0.216
	No(n:30)	77,63±11,66		15,10±2,94		31,33±7,18		22,17±6,06	
Mothers 'verbal punishment application	Yes (n:67)	75,42±7,12	0.681	19,43±3,88	0.000	30,55±6,12	0.733	20,58±4,92	0.472
	No(n:24)	76,29±12,70		15,28±2,90		31,08±7,52		21,46±5,55	
Fathers 'verbal punishment application	Yes (n:19)	71,79±9,11	0.007	21,47±5,53	0.005	30,95±5,75	0.617	21,74±3,33	0.148
	No(n:6)	83,00±1,89		14,00±3,09		32,33±6,12		25,00±7,72	

The difference between the parental attitudes of the participants who used physical punishment and those who did not use physical punishment was examined, and it was found that the authoritarian attitude score of the parents who used physical punishment was statistically higher. Analyzing mothers and fathers separately, it was found that fathers who used physical punishment had higher authoritarian attitude scores and lower democratic attitude scores, and this difference was statistically significant; there was no statistical difference between the mean parental attitude scores of mothers (**Table 6**).

When the mean parenting attitudes of the participants who used verbal punishment/violence against their children and those who did not use verbal punishment/violence against their children were analyzed, it was found that the authoritarian attitudes of those who used verbal violence were statistically higher among all participants and among both mothers and fathers when analyzed separately. It was also found that the democratic attitude scores of the fathers who perpetrated verbal violence were statistically lower than those who did not, and the findings are detailed in **Table 6**.

Regarding the frequency of use of any punishment method by the participant parents according to the age groups of the children, it was found that the frequency of use of punishment was 50, 46.4 and 65.4 per cent in the 3, 4 and 5 age groups, respectively, and these rates were statistically significantly higher than those in the 2 and 6 age groups. No statistical difference was observed in the frequency of physical and verbal punishment methods according to the age groups of the children and the findings are summarized in detail in **Table 7**.

The frequency and variety of the use of punishment and the characteristics of parents' spending time with their children were analyzed. It was found that the frequency of physical punishment was statistically lower in parents who had the habit of reading books with their children. Parents who spent time with their children through the media had a statistically significant higher frequency of verbal punishment/violence (**Table 7**).

Parental attitudes were analyzed according to parents' habits of spending time with their children, and it was found that the permissive attitude scores of parents who did not have the habit of reading books with their children were statistically higher. The findings are summarized in detail in **Table 8**.

DISCUSSION

Parenting is a reciprocal interaction process in which children are guided to adapt to the environment during their development (1,6). Parenting is a reciprocal interaction process in which children are guided to adapt to the environment during their development. It involves many psychosocial factors, especially the parents' own experiences and knowledge, which determine the parenting style (3,4). Although parents adopt different parenting styles, current studies draw attention to the fact that discipline methods for children should be positive, respectful and based on compassion (1,2,4). This study showed the relationship between parental attitudes, sociodemographic characteristics and punishment behaviors towards children. It was noteworthy that verbal punishment was widely used among parents, as well as physical punishment.

The use of punishment under the guise of disciplining children is prevalent in societies (9,14). The absence of statistical variation in the frequency and diversity of punishment by parents based on their sociodemographic characteristics in this study suggests that the punishment of children is still a widespread practice across all segments of society. We found that the frequency of

Table 7. The Relationship between Child Age Group, Parent-Child Communication, and Diversity in Punishment Use.

	Frequency of applying any punishment (n/%)			Frequency of applying physical punishment(n/%)			Frequency of using verbal punishment (n/%)		
	Yes	No	p-value	Yes	No	p-values	Yes	No	p-values
Age groups of the children (years)									
2	6 (23,1)	20 (76,9)	0.008	4 (15,4)	22 (84,6)	0.479	16 (57,1)	12 (42,9)	0.054
3	7 (50)	7 (50)		4 (28,6)	10 (71,4)		13 (86,7)	2 (13,3)	
4	13 (46,4)	15 (53,6)		2 (7,4)	25 (92,6)		18 (66,7)	9 (33,3)	
5	17 (65,4)	9 (34,6)		4 (15,4)	22 (84,6)		22 (81,5)	5 (18,5)	
6	4 (21,1)	15 (78,9)		4 (21,1)	15 (78,9)		17 (89,5)	2 (10,5)	
Total	47 (41,6)	66 (58,4)		18 (16,1)	94 (83,9)		86 (74,1)	30 (25,9)	
Reading books with children									
Yes (n:78)	34 (43,6)	44 (56,4)	0,520	9 (11,5)	69 (88,5)	0,048	60 (74,1)	21 (25,9)	0,981
No (n:35)	13 (37,1)	22 (62,9)		9 (26,5)	25 (73,5)		26 (74,3)	9 (25,7)	
Total (n:113)	47 (41,6)	66 (58,4)		18 (16,1)	94 (83,9)		86 (74,1)	30 (25,9)	
Spending time on media with children									
Yes (n:50)	23 (46)	27 (54)	0,397	8 (16,3)	41 (83,7)	0,948	44 (84,6)	8 (15,4)	0,020
No (n:63)	24 (38,1)	39 (61,9)		10 (15,9)	53 (84,1)		42 (65,6)	22 (34,4)	
Total (n:113)	47 (41,6)	66 (58,4)		18 (16,1)	94 (83,9)		86 (74,1)	30 (25,9)	
Doing homework together									
Yes (n:43)	22 (51,2)	21 (48,8)	0,106	7 (16,7)	35 (83,3)	0,894	32 (76,2)	10 (23,8)	0,704
No (n:70)	25 (35,7)	45 (64,3)		11 (15,7)	59 (84,3)		54 (73)	20 (27)	
Total (n:113)	47 (41,6)	66 (58,4)		18 (16,1)	94 (83,9)		86 (74,1)	30 (25,9)	

Table 8. Examination of the Relationship between Parents' Characteristics of Spending Time with Their Children and Parental Attitude Scores.

		Democratic Attitude		Authoritarian Attitude		Overprotective Attitude		Permissive Attitude	
		M±SD	p-values	M±SD	p-values	M±SD	p-values	M±SD	p-values
Reading books with children	Yes	75,54±9,33	0,369	18,35±4,35	0,337	30,17±6,65	0,145	20,21±4,64	0,001
	No	73,75±11,17		19,22±4,91		32,03±5,42		23,39±5,22	
Spending time on media with children	Yes	74,26±10,40	0,473	19,09±5,06	0,300	30,15±6,28	0,360	20,83±5,01	0,486
	No	75,59±9,54		18,22±4,03		31,23±6,38		21,48±5,05	
Doing homework together	Yes	75,1±10,81	0,903	19,42±4,84	0,145	30,35±6,34	0,610	20,88±4,22	0,481
	No	74,91±9,43		18,15±4,20		30,97±6,36		21,36±5,45	

verbal punishment/violence was 74.1% in this study, which is a distressing indication of the prevalence of emotional abuse that children are subjected to. Therefore, it is crucial to pay attention to the short- and long-term effects of physical and emotional abuse that children experience under the guise of disciplining and to minimize these effects (4,8,11).

Child health organizations and academics have emphasized that physical punishment violates children's rights, endangers their health and development, and stressed the importance of raising awareness among families (4,11,14). In the United States, about half of parents reported spanking their children in the past year, and a third reported spanking in the past week (14,15). In our study group, however, this rate was only 16.1%. The low rate may be due to difficulties in expressing the problem or avoiding the topic. Further extensive studies should be conducted to determine the prevalence.

Parents often use punishment to change undesired behavior in addition to stressful life events (16,17). Scientific recommendations are in the direction of reviewing parental discipline methods during child health follow-up (1,9,18). In our country, a limited number of studies in this direction draw attention to the use of punishment methods in early childhood.

It was found that fathers with male children exhibited slightly more authoritarian attitudes than fathers with female children, but this difference was not statistically significant. However, the number of participating fathers was small in our study, and we think that the results may differ with a larger sample size that includes fathers. In a meta-analysis, it was reported that compared to fathers, mothers were perceived to be more accepting, sensitive, and supportive, while also being behaviorally more controlling, demanding, and autonomy-giving (19). Similarly, in studies comparing parents on overall parenting style constructs, mothers tended to be more authoritative than fathers, while fathers tended to be more authoritarian than mothers (19). In a worldwide analysis of data from more than 15 countries, age and gender were not found to affect these differences between parents (19). In our study, fathers who used physical and verbal punishment exhibited more authoritarian and less democratic attitudes, which was statistically significant. We think that it is crucial to involve fathers in child examination processes, discuss positive parenting, learn their thoughts on this subject, and provide appropriate counseling to fathers during child health follow-ups.

Another noteworthy finding in our study is that the overprotective attitude score increased as the level of parental education decreased. Similarly, in previous studies, it was pointed out that overprotective attitude increased in parents with low education level (16,20). Overprotection reduces the child's self-confidence and prevents the child's ability to make decisions on their own (8,21).

The parents with lower income levels exhibited less permissive attitudes. There may be many social and cultural reasons why parents with lower income levels are not permissive (18,22). Generally, parents with lower income levels tend to have lower levels of education and more children (14,18,22). Considering the fact that mothers with lower education levels are more overprotective and less permissive towards their children in this study, these parents may have more limited time and opportunities for their children. At the same time, they may need more to develop their positive parenting capacities to spend more quality time with their children. In order to determine what these needs are, more comprehensive studies to be conducted in this field may be guiding.

A further remarkable finding of this study was that parents who spent time reading books with their children used less physical punishment, whereas those who spent time with media used more verbal punishment/violence. We think that efforts to increase parents' capacity to spend quality time with their children may decrease the physical and verbal punishment applied by parents. Especially considering the high frequency of screen use among parents and children today, it would be beneficial to examine the relationship between screen use and parental attitudes with new studies using a larger sample size.

Studies have shown that the punishment methods used in child rearing have negative effects on children's psychosocial development (10,12,23). However, some parents see punishment as a means of disciplining their children (4,16). As seen in our study, especially authoritarian parents may resort to physical punishment in order to set limits or make the child do what they want (7,15). Nevertheless, since physical punishment is not a socially acceptable or normalized situation, participants may give socially desirable answers to such questions, especially in studies (22,24). It may have been easier for the participants to express verbal shouting/angering/punishing the child because it is more socially acceptable.

Research has reported that many parents use verbal expressions of disapproval as a form of punishment to change unwanted behaviors (5,17). Such reprimands are temporarily effective in immediately stopping or reducing undesirable behaviors when used infrequently and targeted at specific behaviors (22,25,26). However, when used indiscriminately and frequently, verbal reprimands lose their effectiveness and may even reinforce unwanted behaviors by increasing the attention focused on the child (22,25,26). Verbal reprimands should not damage the child's self-esteem and should be directed at the

unwanted behaviors (22,25,26). Parents were more likely to use verbal correction or punishment in our study. On the other hand, it may have been easier for parents to express verbal reprimands in a social context.

As reported in the literature, we did not find any difference between physical punishment and gender disruption in our study group. Each parent has a different understanding of how to practice parenting, and not all parents practice the same way (8,21,24). They may take different directions based on their individual experiences, what they learned from their own parents, educational and cultural norms that shape their understanding and methods of parenting (1,27). Research emphasizes the importance of positive parenting for the psychosocial wellbeing of the child, even though practices may vary (3,4,8). There is a need to assess the situation in our country by carrying out extensive field studies in this area and to guide parents in monitoring their children's health.

Changing discipline practices may take time and be gradual but should be a goal for pediatricians and parents (1,11). Because opinions about discipline are formed in childhood, discussing discipline with parents can be difficult and emotionally charged. Often, parents use the pattern they learned from their own parents (17,21). However, considering that all kinds of ill-treatment against the child should be reviewed in current practices, it would be in the best interest of the child to question the disciplinary methods applied by the parents in the public eye. Discussing this issue with the family during the follow-up of the child's health by the pediatrician will enable the family to review their own patterns of behavior and find possible solutions.

CONCLUSION

In our study, it is noteworthy that although the participant parents exhibited a democratic attitude in the foreground, physical punishment was used. Parenting and disciplinary practices should be evaluated during child health follow-up and the family should be mentored about possible damaging disciplinary methods. Appropriate parenting styles can help families develop positive parenting characteristics and promote the development of mentally healthy children. More comprehensive studies are needed on this subject.

Limitations

One of the limitations of the sample is its size and further analysis with a larger sample is needed. Other limitations are that individuals abstain and give ideal answers to direct assessment questions related to physical punishment. However, what is expressed in the respondents' answers may not necessarily reflect how they would act in a real situation.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Istanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 27.04.2022, Decision No: 414).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Pediatr Pract Res 2023; 11(3): 125-129
DOI: 10.21765/pprjournal.1285808

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Çocuk Acil Servisine Levotiroksin Zehirlenmesi İle Başvuran Olgularının Değerlendirilmesi

Evaluation of Cases Presenting to the Pediatric Emergency Service with Levothyroxine Poisoning

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Öz

Amaç: Bu çalışmanın amacı, üçüncü basamak sağlık kuruluşu olan hastanemiz çocuk acil polikliniğine levotroksin zehirlemesi ile başvuran adli vakaların demografik, klinik ve laboratuar özelliklerini belirlemek, tedavi sonuçlarını incelemek, bu verileri literatür ile karşılaştırarak bu alandaki sağlık verilerine katkıda bulunmaktır.

Gereç ve Yöntem: Bu çalışmada, Selçuk Üniversitesi Tıp Fakültesi Hastanesi Çocuk Acil Polikliniğine 2016-2019 tarihleri arasında çocuk acil polikliniğine levotroksin zehirlenmesi ile başvuran adli olgu incelendi. Hastaların yaş ve cinsiyetleri, çocuk acil servise başvuru tarih ve saatleri, başvuru mevsimi, başvuru şekli, hastaneye ulaşma süreleri, adli vakaya sebep olan olay, acil servisteki takip ve tedavi yöntemleri, alım şekli, etkenin elde ediliş yolu, ilacın alınmasından sonra ilk tıbbi müdahaleye kadar geçen süre, ailelerin tutum ve davranışları, hastanın akıbeti, izlendiği yer, geliş nedenleri, istenen tetkikler ve sonuçları değerlendirildi.

Bulgular: Çalışma süresince acil servise 1743 hasta zehirlenme nedeniyle başvurmuş olup 17'si (%0,97) levotroksin zehirlenmesi idi. İlaç alımı vakaları arasında levotroksin alımının insidansı yılda %0,194 idi. Hastaların 10'u (%58,8) hastada kaza sonucu, 7 (%41,2) hasta ise intihar niyetiyle tiroksin almıştır. Bu hastaların 10'u (%58,8) kız iken 7'si (%41,2) erkek idi. En küçük hasta 20 aylık en büyük hasta ise 75 aylık iken yaş ortalaması 43,00±16,55 ay idi.

Sonuç: Levotiroksin intoksikasyonu benign bir tablo olmasına rağmen tedavi gerektiren durumlar olabilir. Bu nedenle tedavi kararı verilmesi gereken çocuk ve adölesan olgularda semptom varlığı önemli bir faktör olsa da, tedavi yaklaşımı erişkinlerden farklı olabilir. Yaş aralığına bağlı olarak vücut ağırlığı çok değişebileceği için tedaviye karar verilmesi aşamasında, semptomlar yanı sıra, kilogram başına alınan dozun da hesaplanması uygun yaklaşım gibi görülmektedir.

Anahtar Kelimeler: Levotiroksin, çocuk, intoksikasyon

Abstract

Aim: The aim of this study is to determine the demographic, clinical and laboratory characteristics of forensic cases who applied to the pediatric emergency clinic of our hospital, which is a tertiary health institution, with levotroxine poisoning, to examine the treatment results, to compare these data with the literature and to contribute to the health data in this area.

Material and Methodd: In this study, a forensic case who applied to the Pediatric Emergency Outpatient Clinic of Selçuk University Medical Faculty Hospital between 2016-2019 with levotroxine poisoning was analyzed. Age and gender of the patients, the date and time of application to the pediatric emergency department, the season of application, the method of application, the time to reach the hospital, the event that caused the forensic case, the follow-up and treatment methods in the emergency department, the method of intake, the route of obtaining the agent, the first medical intervention after taking the drug. The time elapsed, the attitudes and behaviors of the families, the fate of the patient, the place where he was followed, the reasons for his visit, the requested examinations and their results were evaluated.

Results: During the study, 1743 patients were admitted to the emergency department due to poisoning, and 17 (0.97%) were levotroxine poisoning. The incidence of levotroxine ingestion among drug intake cases was 0.194% per year. Ten (58.8%) of the patients took thyroxine as a result of accident and 7 (41.2%) patients with suicidal intention. While 10 (58.8%) of these patients were female, 7 (41.2%) were male. While the youngest patient was 20 months old and the oldest patient was 75 months old, the mean age was 43.00±16.55 months.

Conclusion: Although levothyroxine intoxication is a benign picture, there may be conditions that require treatment. For this reason, although the presence of symptoms is an important factor in children and adolescents in whom a treatment decision should be made, the treatment approach may be different from adults. Since body weight can vary greatly depending on the age range, calculating the dose per kilogram, as well as the symptoms, seems to be an appropriate approach when deciding on the treatment.

Keywords: Levothyroxine, child, intoxication

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Başvuru Tarihi/Received: 19.04.2023
Kabul Tarihi/Accepted: 25.07.2023

GİRİŞ

Çocukluk çağında, büyüme-gelişme, enerji metabolizması, SSS gelişiminde tiroid hormonları önemli bir etkiye sahiptir (1). Tiroid fonksiyon bozuklukları içerisinde en sık gözlenen hipotiroidizm olup, kazanılmış veya konjenital olabilmektedir. Hipotiroidi tedavisinde en sık kullanılan ilaç levotiroksindir ve tedavi dozu yaşa bağlı olarak değişmektedir (2).

Tiroid hormon preparatlarının çok miktarda akut olarak yutulması, Ulusal Zehir Danışma Merkezine sık olarak bildirilen zehirlenmelerdendir. Yapılan araştırmada ABD zehir kontrol merkezlerine 2014 yılında tiroid hormonu preparatları ile yaklaşık on bin zehirlenme vakası bildirilmiştir. Bunların %50'si 6 yaş altındaki küçük çocuklarda, %10'u 6-19 yaş arasındaki kişilerde ve %40'ı 19 yaşından büyüklerde meydana gelmiştir (3). Suisid amaçlı levotiroksin zehirlenmesi erişkinde fazla görülmemektir. Fakat levotiroksin tabletlerin çocuklarda kaza sebepli, akut zehirlenmeleri görülebilmektedir (4). Levotiroksinin zehirlenmesi genellikle asemptomatik seyreder. Bununla birlikte, çocuklarda nöbet, ateş yüksekliği, hipertansiyon irritabilite görüldüğü de bildirilmiştir. Erişkinlerde ise aritmi, malign hipertermi, koma gibi daha ciddi komplikasyonlar bildirilmiştir (5). Erişkinlerde 5 miligramın üzerinde olmayan, asemptomatik alımlarda herhangi bir gastrik dekontaminasyon işlemi uygulanması ve agresif tedavi başlanması önerilmemekte ise de doz ve klinik bulgular arasında doğrusal bir ilişki olmadığı da bildirilmektedir. Çocuklarda ise tedavi konusunda bir uzlaşı yoktur (6).

Bu çalışmanın amacı, üçüncü basamak sağlık kuruluşu olan hastanemiz çocuk acil polikliniğine levotroksin zehirlemesi ile başvuran adli vakaların demografik, klinik ve laboratuar özelliklerini belirlemek, tedavi sonuçlarını incelemek, bu verileri literatür ile karşılaştırarak bu alandaki sağlık verilerine katkıda bulunmaktır.

GEREÇ VE YÖNTEM

Bu çalışma, Selçuk Üniversitesi Yerel Etik Kurulundan izin alınmıştır (Tarih: 11.04.2023, Karar No: 2023/188).

Bu çalışmada, Selçuk Üniversitesi Tıp Fakültesi Hastanesi Çocuk Acil Polikliniğine 01.01.2016 ile 01.01.2019 tarihleri arasında çocuk acil polikliniğine başvuran "1 ay-18 yaş arası 17 levotroksin zehirlenmesi ile başvuran adli olgu incelendi. Adli nitelikli vakalar adli vaka defteri ve hastaların hastane kayıt sistemindeki verileri incelenerek tespit edildi. Hastaların tıbbi verileri geriye dönük olarak dosya bilgilerine göre incelenerek oluşturulan forma kaydedildi. Adli nitelik taşımayan, 18 yaş üzerine olan, travma hastaları, dosyalarına ulaşılamayan veya dosyasında verilerinde ciddi bilgi eksikliği olan hastalar çalışmaya dahil edilmedi.

Hastaların yaş ve cinsiyetleri, çocuk acil servise başvuru tarih ve saatleri, başvuru mevsimi, başvuru şekli, hastaneye ulaşma süreleri, adli vakaya sebep olan olay, acil servisteki takip ve tedavi yöntemleri, alım şekli, etkenin elde ediliş yolu, ilacın alınmasından sonra ilk tıbbi müdahaleye kadar geçen süre, ailelerin tutum ve davranışları, hastanın akıbeti, izlendiği yer, geliş nedenleri, istenen tetkikler ve sonuçları değerlendirildi.

Vakaların yaşları ay üzerinden değerlendirilip 2 gruba ayrıldı. 0-60 ay arasındakiler Grup 1, 61-120 ay arasındakiler Grup 2 olarak sınıflandırıldı. Başvuru saati olarak günün saatleri 00:00-08:00, 08:00-16:00, 16:00-00:00 olmak üzere 3 gruba ayrıldı. 00:00-08:00 zaman dilimi grup A, 08:00-16:00 zaman dilimi grup B, 16:00-00:00 zaman dilimi grup C olarak kabul edildi.

Hastalar başvuru mevsimi olarak ilkbahar, yaz, sonbahar, kış olarak 4 gruba, geliş yeri olarak il dışı, Vakaların olay ile ilgili başvurdukları ilk hastane olup olmaması kantitatif olarak, olay ile başvuru zamanı arası süre saat cinsinden değerlendirildi.

Medikal ilaç zehirlenmeleri kendi içinde tekli ilaç alımı, çoklu ilaç alımı diye iki gruba ayrıldı. Tüm vakalar intihar amacı bulunup bulunmamasına göre değerlendirildi.

Başvuru nedeni olarak tüm vakalar semptom bulunup bulunmasına göre değerlendirildi. Öncesinde bilinen hastalık epikrizde doldurulmuş olan özgeçmiş kısmına göre değerlendirildi.

Hastalar klinik bulgular, laboratuvar kan testleri (tam kan sayımı, kan şeker düzeyleri, karaciğer ve böbrek fonksiyon testleri, tiroid fonksiyon testleri ve elektrolitler) ile değerlendirildi.

Tüm vakalar, 114 Ulusal Zehir Danışma Hattına danışma durumuna göre değerlendirildi. Danışılan vakalar ayrıca mide lavajı, aktif kömür, takip süresi açısından saat cinsinden ve yoğun bakım ünitesinde takip önerisi açısından kantitatif değerlendirildi. Mide lavajı yapılan vakalar lavaj içeriğine göre ayrıca değerlendirildi.

İstatistiksel Analiz

Çalışma sonucu elde edilen veriler için Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL, USA) for Windows 23.0 programı kullanıldı. Çalışma verileri değerlendirilirken tanımlayıcı istatistiksel metodların (ortalama, standart sapma) yanısıra, niceliksel verilerin karşılaştırılmasında; bağımsız iki grubun karşılaştırmalarında "student t test" kullanıldı. Kategorik değişkenler ki-kare testi (Fisher's exact) ile karşılaştırılmıştır. Sonuçlar %95 güven aralığında ortalama±SD olarak verildi, anlamlılık $p<0.05$ düzeyinde değerlendirildi

BULGULAR

Çalışma süresince acil servise 1743 hasta zehirlenme nedeniyle başvurmuş olup 17'si (%0,97) levotroksin zehirlenmesi idi. İlaç alımı vakaları arasında levotroksin alımının insidansı yılda %0,194 idi. Hastaların 10'u (%58,8) hastada kaza sonucu, 7 (%41,2) hasta ise intihar niyetiyle tiroksin almıştır.

Bu hastaların 10'u (%58,8) kız iken 7'si (%41,2) erkek idi. En küçük hasta 20 aylık en büyük hasta ise 75 aylık iken yaş ortalaması 43,00±16,55 ay idi. Cinsiyete göre karşılaştırıldığında erkeklerin yaş ortalaması 44,71±15,91 ay iken kızların ise 41,80±17,73 ay idi. Yaş ortalaması cinsiyete göre incelendiğinde istatistiksel olarak anlamlı bir fark tespit edilmedi (p:0,733).

Yaş gruplarına göre değerlendirildiğinde hastaların 13'ünün (%76,5) 0-60 ay arasında iken 4'ünün (%23,5) 61 ayın üzerinde idi. Yaş grupları cinsiyete göre karşılaştırıldığında istatistiksel olarak anlamlı bir fark saptanmadı (p:0,559). Hastaların demografik verileri **Tablo 1**'de gösterilmiştir.

Tablo 1: Hastaların demografik verileri

	Erkek	Kız	Toplam	p
Sayı	7 (41,2)	10 (58,8)	17 (100)	
Yaş Grubu				0,559
0-60 ay	5 (38,5)	8 (61,5)	13 (76,5)	
61-120 ay	2 (50,0)	2 (50,0)	4 (23,5)	
Alım Şekli				0,514
Oyun	5 (29,4)	5 (29,4)	10 (58,8)	
Kazara	2 (11,7)	5 (29,4)	7 (41,1)	
Başvuru Saati				0,145
08:00-15:59	4 (23,5)	2 (11,7)	6 (35,2)	
16:00-23:59	3 (17,6)	8 (47,0)	11 (64,7)	
Olay saat				0,357
08:00-15:59	3 (17,6)	2 (11,7)	5 (29,4)	
16:00-23:59	1 (5,8)	3 (17,6)	4 (23,5)	
Başvurulan ilk hastane				0,686
Hayır	2 (11,7)	3 (17,6)	5 (29,4)	
Evet	5 (29,4)	7 (41,1)	12 (70,5)	
Başvuru şekli				0,516
Kendi imkanıyla	5 (29,4)	6 (35,2)	11 (64,7)	
112 ambulans ile	2 (11,7)	4 (23,5)	6 (35,2)	
Geliş Yeri				0,414
Selçuklu	6 (35,2)	6 (35,2)	12 (70,5)	
Diğer	1 (5,8)	4 (23,5)	5 (29,4)	

Hastaların yıllara göre dağılımı incelendiğinde; hastaların 2'si (%11,8) 2016, 6'sı (%35,3) 2017, 5'i (%29,4) 2018, 3'ü (%17,6) 2019 ve 1'i (%5,9) 2020 yılında zehirlenme nedeniyle hastanemize başvurduğu tespit edildi.

Hastaların başvuru mevsimi incelendiğinde en sık 6 (%35,3) hasta ile yaz mevsiminde başvurduğu tespit edildi. Beşer (%29,4) hasta ile ilkbahar ve sonbahar mevsimi iken bir (%5,9) hasta kış mevsiminde başvurduğu görüldü.

Çalışmaya alınan hastalar adli olayın gerçekleştiği zaman ile hastaneye başvurduğu zaman arasındaki geçen süre açısından incelendiğinde ortalama 79,67±81,45 olduğu tespit edildi. Adli olayın gerçekleştiği zaman ile hastaneye başvurduğu zaman arasındaki geçen süre ile cinsiyet arasında istatiksel olarak anlamlı bir fark tespit edilmedi (p:0,082).

Hastaların başvuru anındaki tam kan sayımı sonuçları cinsiyete göre karşılaştırıldığında, total lökosit sayısı, nötrofil sayısı, lenfosit sayısı, hemoglobin, hematokrit, MCV, trombosit sayısı, PDW ve sedimantasyon düzeyleri açısından istatistiksel olarak anlamlı bir fark tespit edilmedi (p>0,05). Hastaların hemogram ve biyokimyasal parametrelerinin cinsiyete göre karşılaştırılması **Tablo 2** ve **3**'de gösterilmiştir. Çalışmaya dahil edilen hastaların tiroid fonksyon testleri (TSH, fT4, fT3), cinsiyete ve yaş gruplarına göre karşılaştırıldı (**Tablo 4**). İstatiksel olarak anlamlı bir fark tespit edilmedi (p>0,05).

Zehirlenme vakaları 114 Zehir Danışma Hattına danışılma açısından incelendiğinde, tüm hastaların danışıldığı tespit edildi. Zehir Danışmaya danışılan hastaların 3'üne (%17,7) yoğun bakım şartlarında takip önerildiği, 14'ünün (%82,3) o an için servis takibi önerildi. Zehir Danışmaya danışılan zehirlenme vakaların tümüne takip önerilmekte olup önerilen takip süresine bakıldığında, en az 24 saat, en fazla 336 saat olmak üzere ortalama 74,12±86,76 saat olarak tespit edildi.

Adli vaka olarak kabul edilen tüm hastalar mide lavajı yapılma durumuna göre analiz edildiğinde, 14 (%82,3) hastaya mide lavajı yapıldığı görülürken 3 (%17,7) hastaya yapılmadığı tespit edilmiştir. Zehirlenme vakası olarak çocuk acil polikliniğine kabul edilen hastaların aktif kömür verilme açısından incelendiğinde, 16 (%94,1) hastaya aktif kömür tedavisi verildiği saptandı.

Tablo 2: Hastaların hemogram parametreleri cinsiyete göre karşılaştırılması

	Erkek		Kız		Toplam		p
	Mean±SD	Median (min-mak)	Mean±SD	Median (min-mak)	Mean±SD	Median (min-mak)	
WBC	8,76±3,55	7,9 (5,5 - 16)	10,34±1,73	10,3 (7,4 - 13,2)	9,69±2,66	9,9 (5,5 - 16)	0,088
Nötrofil	3,58±1,34	3,41 (1,8 - 5,63)	3,54±1,35	3,1 (1,94 - 6,26)	3,56±1,31	3,22 (1,8 - 6,26)	0,740
Lenfosit	4,22±2,04	4,1 (1,8 - 8,29)	5,77±1,75	6,02 (3,3 - 8,13)	5,13±1,98	4,5 (1,8 - 8,29)	0,230
Hgb	12,34±0,5	12,6 (11,6 - 12,8)	12,21±1,17	12,55 (9,8 - 13,6)	12,26±0,93	12,6 (9,8 - 13,6)	0,669
Htc	36,14±2,06	36,6 (33,2 - 39,6)	36,36±2,96	37,4 (31,5 - 39,5)	36,27±2,56	36,6 (31,5 - 39,6)	0,669
MCV	78,91±1,97	78,6 (76,8 - 82,3)	77,98±6	80,1 (65,8 - 84,6)	78,36±4,68	79,5 (65,8 - 84,6)	0,813
RDW	14,17±1,28	13,7 (13 - 16,1)	14,01±1,46	13,75 (12,3 - 17,1)	14,08±1,35	13,7 (12,3 - 17,1)	0,740
Trombosit	345,57±104,79	319 (204 - 541)	392,5±69,88	397,5 (294 - 540)	373,18±86,2	349 (204 - 541)	0,133
PDW	16,1±0,45	16 (15,7 - 17)	16,57±0,62	16,55 (15,8 - 17,9)	16,38±0,59	16,2 (15,7 - 17,9)	0,109
Sedim	6±4	6 (2 - 10)	4±2,58	2 (2 - 8)	4,6±2,99	4 (2-10)	0,517

Tablo 3: Hastaların biyokimyasal parametrelerin cinsiyete göre karşılaştırılması

	Erkek		Kız		Toplam		p
	Mean±SD	Median (min-mak)	Mean±SD	Median (min-mak)	Mean±SD	Median (min-mak)	
Glukoz	106±45,92	81 (78 - 159)	91,5±2,12	91,5 (90 - 93)	100,2±33,45	90 (78 - 159)	0,800
Üre	26,77±8,45	25 (18 - 43)	28,22±4,29	29 (21 - 36)	27,64±6,05	26 (18 - 43)	0,224
Kreatinin	0,35±0,1	0,39 (0,2 - 0,48)	0,32±0,06	0,31 (0,24 - 0,44)	0,34±0,08	0,32 (0,2 - 0,48)	0,606
Ürikasit	3,75±0,83	3,8 (2,7 - 4,7)	3,18±0,33	3,3 (2,8 - 3,6)	3,43±0,64	3,3 (2,7 - 4,7)	0,286
AST	32,14±4,34	33 (27 - 39)	35,44±7,78	34 (26 - 52)	34±6,53	33,5 (26 - 52)	0,536
ALT	13,57±2,94	14 (9 - 18)	15,6±5,64	14 (9 - 24)	14,76±4,71	14 (9 - 24)	0,740
Sodyum	137,67±2,34	138 (134 - 140)	137,7±2,06	137,5 (135 - 142)	137,69±2,09	138 (134 - 142)	0,875
Potasyum	3,96±0,44	3,93 (3,49 - 4,9)	4,05±0,33	4,07 (3,6 - 4,66)	4,01±0,37	3,95 (3,49 - 4,9)	0,364
Klor	106,07±2,56	106 (102,4 - 110)	106,48±2,36	106,5 (103 - 110)	106,31±2,38	106 (102,4 - 110)	0,813
Kalsiyum	9,61±0,21	9,6 (9,4 - 10)	10,08±0,4	10,1 (9,4 - 10,7)	9,89±0,4	9,8 (9,4 - 10,7)	0,010
Fosfor	4,59±0,84	4,2 (3,8 - 6,1)	4,84±0,64	4,85 (4,1 - 6,2)	4,74±0,71	4,4 (3,8 - 6,2)	0,315
Magnezyum	2,12±0,12	2,09 (1,98 - 2,33)	2,27±0,14	2,25 (2,01 - 2,49)	2,21±0,15	2,24 (1,98 - 2,49)	0,088
Total protein	6,85±0,51	6,95 (6,2 - 7,3)	6,7±0	6,7 (6,7 - 6,7)	6,82±0,44	6,7 (6,2 - 7,3)	0,800
Albumin	4,34±0,26	4,35 (3,95 - 4,7)	4,48±0,17	4,45 (4,24 - 4,72)	4,41±0,22	4,4 (3,95 - 4,72)	0,310
ALP	312±0	312 (312 - 312)	224,5±43,13	224,5 (194 - 255)	253,67±59,01	255 (194 - 312)	0,667

Tablo 4: Çalışmaya dahil edilen hastaların tiroid fonksyon testleri cinsiyete ve yaş gruplarına göre karşılaştırılması

	Erkek		Kız		Toplam		p
	Mean±SD	Median (min-mak)	Mean±SD	Median (min-mak)	Mean±SD	Median (min-mak)	
TSH	2,5±0,74	2,74 (1,58 - 3,33)	5,03±6,04	1,68 (0,85 - 17,87)	4,06±4,81	1,89 (0,85 - 17,87)	0,622
sT4	2,65±1,78	1,84 (1,6 - 5,78)	2,22±1,05	1,82 (1,35 - 4,28)	2,39±1,32	1,84 (1,35 - 5,78)	0,724
sT3	5,12±1,07	5,43 (3,93 - 6)	5,19±0,8	5,28 (4,19 - 5,99)	5,16±0,84	5,43 (3,93 - 6)	0,998
	0-60 ay		61-120 ay				
TSH	3,21±2,69	2,32 (0,85 - 9,93)	6,9±9,5	1,58 (1,26 - 17,87)			0,811
sT4	2,25±1,37	1,72 (1,35 - 5,78)	2,84±1,27	2,35 (1,88 - 4,28)			0,161
sT3	5,11±0,91	5,28 (3,93 - 6)	5,43±0	5,43 (5,43 - 5,43)			0,984

Çalışmaya alınan tüm vakalar, acildeki muayene sonrası sonucuna göre değerlendirildiğinde hastaların 8'i (%47,0) önerilen gözlem süresi sonrasında acil servisten taburcu edildiği, 9'unun (%53,0) çocuk sağlığı ve hastalıkları servisinde yatırılarak tedavi altına alındığı tespit edildi. Hastaların hiçbirinde çocuk yoğun bakım ünitesinde tedavisi gerekmedi. Hastanemiz çocuk acil polikliniğine getirilen zehirlenme olguların hiçbirinde exitus gözlenmedi.

TARTIŞMA

Levotiroksin, tiroid hormonunun baskın dolaşımdaki formu olan bir tiroksin (T4) analoğudur. Periferik dokularda T4, kısmen biyolojik olarak daha aktif bir tiroid hormonu olan liotironine (T3) dönüştürülür. T4 farmakolojik olarak inaktif olduğundan, T3 toksikolojik semptomların gelişmesinden sorumlu olan formdur. Semptomların alımdan geç dönemde ortaya çıkmasının nedeni T3'e dönüşüm süresidir. Yapılan farmakolojik çalışmalar ayrıca levotiroksinin Tmax'ına oral alımdan 5-6 saat sonra ulaşıldığını göstermektedir. Yaptığımız çalışmaya alınan hastalar adli olayın gerçekleştiği zaman ile hastaneye başvurduğu zaman arasındaki geçen süre açısından incelendiğinde ortalama 79,67±81,45 dk olduğu için hastaların başvuruda asemptomatik olması, klinik takip açısından hekimi yanıltmamalıdır. Eliminasyon yarı ömrü T4 için 7 gün ve T3 için 0,8 gündür (7). Yapılan bir çalışmada T3'ün tepe konsantrasyonuna alımdan 24. saatte ulaştığı gösterilmiş olup, bu da semptomların daha geç ortaya çıkmasını desteklemektedir (8). Ayrıca T3'ün eliminasyonunun sekiz güne kadar uzaması semptomların kaybolma süresinin de daha geç olacağını göstermektedir (8).

Çocukların, yetişkinlere göre yüksek dozda levotiroksine toleransı daha yüksektir. Levotiroksin toksisitesi, çoğunlukla benign bir tabloya yol açar. Amerika Birleşik Devletleri'nde 2008 yılında zehir danışma merkezine danışılan çocuk ve erişkin tüm olgular içinde, yalnızca 3 tanesinde ciddi yan etki rapor edilmiş ve hiç ölüm bildirilmemiştir (9). Çalışmamızda ise tüm vakalar, acildeki muayene sonrası sonucuna göre değerlendirildiğinde hastaların 8'i (%47,0) önerilen gözlem süresi sonrasında acil servisten taburcu edildiği, 9'unun (%53,0) çocuk sağlığı ve hastalıkları servisinde yatırılarak tedavi altına alındığı tespit edildi. Levotiroksin doz aşımı vakalarında tiroid fırtınası riskinin azaldığı gösterilmiş ve bu durumun, T4 deiyonizasyonundan türetilen bir T3 izomeri olan daha fazla revers T3 (rT3) üretimine bağlı geliştiği gösterilmiştir. rT3, yine Tiroid hormon reseptörlerine bağlanır ve böylece T3'ün etkisini bloke eder (10). Levotiroksin alımına bağlı görülen semptomlar taşikardi, ateş, sinirlilik, hiperaktivite, ishal, karın ağrısı ve hipertansiyondur (5). Çocuklarda yüksek doz tiroid hormon alımında, tedavide, antitiroid ilaçlar (propiltiyourasil, metimazol), T3 üretimini azaltıp semptomları azaltmaya yönelik olarak kullanılmaktadır.

Ayrıca steroid tedavisi, gastrointestinal emilimi azaltmak için kolestiramin veya sempatik aktiviteyi azaltmak için propranolol kullanılabileceği bildirilmektedir (2, 11). Ciddi kardiyolojik veya nörolojik semptom eşlik etmesi durumunda ise plazmaferez veya hemoperfüzyon önerilmektedir (2). Yaptığımız çalışmada plazmaferez ve hemoperfüzyon kullanımına hiçbir hastada gereklilik duyulmadı. Tedavide aktif kömür uygulaması tartışmalıdır. Çoklu ilaç intoksikasyonu ile gelen hastalarda gastrointestinal emilimi azaltacağı için önerilmekte ise de aktif kömürün levotiroksin emilimine etkisinin olmadığı, hatta duodenum ve jejunumdan emilimi artırabileceğini öne süren yayınlar da mevcuttur (12). Çalışmamızda hastalar aktif kömür verilme açısından incelendiğinde, 16 (%94,1) hastaya aktif kömür tedavisi verildiği saptandı. Çalışmamıza dahil olan hastalara diğer tedavilere gerek kalmaksızın asemptomatik taburculuğu sağlanmıştır.

Çalışmanın kısıtlılıkları olarak birincisi çalışmanın retrospektif olması idi. İkincisi çalışmanın uzun dönem sonuçlarının değerlendirilememesi olarak belirlendi. Bir diğeri hastaların intoksikasyon esnasında ilaç dozlarının hesaplanamaması idi.

SONUÇ

Sonuç olarak, Levotiroksin intoksikasyonu benign bir tablo olmasına rağmen tedavi gerektiren durumlar olabilir. Bu nedenle tedavi kararı verilmesi gereken çocuk ve adölesan olgularda semptom varlığı önemli bir faktör olsa da, tedavi yaklaşımı erişkinlerden farklı olabilir. Yaş aralığına bağlı olarak vücut ağırlığı çok değişebileceği için tedaviye karar verilmesi aşamasında, semptomlar yanı sıra, kilogram başına alınan dozun da hesaplanması uygun yaklaşım gibi görülmektedir. Ayrıca ilaç zehirlenmelerinin çocuklarda önlenebilir morbidite ve mortalite nedenleri arasında yer aldığı ve bu konuda ailelelerin çocukların ilaçlara maruziyetini önleme konusunda eğitilmesi gerektiği de unutulmamalıdır.

ETİK BEYANLAR

Etik Kurul Onayı: Bu çalışma, Selçuk Üniversitesi Yerel Etik Kurulundan izin alınmıştır (Tarih: 11.04.2023, Karar No: 2023/188).

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.

Finansal Destek: Yazarlar bu çalışmada finansal destek almadıklarını beyan etmişlerdir.

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

KAYNAKLAR

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Pediatr Pract Res 2023; 11(3): 130-135
DOI: 10.21765/pprjournal.1346814

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Comparison of the Maternal and Neonatal Outcomes for the Cesarean Section Performed During 1st and 2nd Stage of Labor

Aktif Doğum Eyleminin 1. ve 2. Evresinde Yapılan Sezaryenlerde Maternal ve Neonatal Sonuçların Karşılaştırılması

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ABSTRACT

Aim: Comparison of maternal and newborn outcomes and complications in pregnant women who have a cesarean delivery in the 2nd stage of active labor with the 1st stage cesarean deliveries.

Material and Method: In this retrospective study, 50 cases who had term, singleton, uncomplicated pregnancy and gave birth by emergency cesarean section in the second stage of labor were compared cases (n=50) who gave birth in the first stage. Demographic characteristics of the cases, indications for cesarean section, intraoperative and postoperative surgical characteristics and complications (uterine incision lengthening, arterial and/or organ injuries, hemoglobin levels, bleeding, need for blood product transfusion, relaparotomy, operation times, postoperative hospital stay) and newborn outcomes were analyzed. A p value of <0.05 was considered statistically significant.

Results: The demographic characteristics of the groups (age, number of pregnancies, body mass index, educational status) were similar (p>0.05). The rates of lengthening of the uterine incision, need for lengthening of the uterine incision, uterine artery and bladder injuries, and uterine atony were significantly higher in cesarean sections performed in the second stage (42% vs. 8%, p<0.001). Postoperative hospital stay was similar (p>0.05). Apgar scores, observation and intensive care unit needs were similar in both groups (p>0.05). No trauma or fracture occurred in newborns in either group.

Conclusion: Cesarean deliveries in the second stage of active labor cause a significant increase maternal complication, although not in newborns. Performing cesarean deliveries in the second stage by experienced obstetricians is important for the prevention and management of complications.

Keywords: Second stage cesarean, maternal, neonatal, morbidity

ÖZ

Amaç: Aktif doğum eyleminin 2. evresinde sezaryen ile doğum gerçekleştirilen gebelerde maternal, yenidoğan sonuç ve komplikasyonların 1. evrede yapılan sezaryen doğumlarla karşılaştırılmasıdır.

Gereç ve Yöntem: Retrospektif çalışmamızda gebelik komplikasyonu gelişmemiş, term, tekil gebeliği olan ve doğum eyleminin 2. evresinde acil sezaryen ile doğumu gerçekleştirilen 50 olgu çalışma grubu, 1. evrede sezaryen ile doğumu gerçekleştirilen aynı sayıda olgu (n=50) ise kontrol grubu olarak çalışmaya alındı. Olguların demografik özellikleri, sezaryen endikasyonları, intraoperatif ve postoperatif cerrahi özellikleri ve komplikasyonları (uterin insizyon uzaması, arter ve organ yaralanmaları, hemoglobin düzeyleri, kan ürünleri transfüzyonu ihtiyacı, relaparatomi, ameliyat süreleri, postoperatif hastanede kalış süresi) ile yenidoğan sonuçları incelendi. p<0.05 istatistiksel anlamlı kabul edildi.

Bulgular: Grupların yaş, gebelik sayıları, vücut kütle indeksi, eğitim durumu benzerdi (p>0.05). Uterin insizyonun uzaması, uterin insizyonun uzatılmasının gerekmesi, uterin arter ve mesane yaralanmaları ile atoni gelişimi oranları 2. evrede yapılan sezaryenlerde belirgin daha yüksekti (%42'ye karşı %8, p<0.001). Postoperatif hastanede kalış süreleri her iki grupta benzerdi (p>0.05). Apgar skorları, gözlem ve yoğun bakım ihtiyaçları her iki grupta benzerdi (p>0.05) ve hiçbir yenidoğanda travma ya da kırık meydana gelmedi.

Sonuç: Aktif doğum eyleminin 2. evresinde yapılan sezaryen doğumlar yenidoğanda olmasa da maternal komplikasyonlarda anlamlı artışa neden olur. 2. evrede sezaryen doğumların tecrübeli obstetrisyenler tarafından yapılması komplikasyonların önlenmesi ve yönetilebilmesi konusunda önemlidir.

Anahtar Kelimeler: İkinci evrede sezaryen, maternal, neonatal, morbidite

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Başvuru Tarihi/Received: 20.08.2023
Kabul Tarihi/Accepted: 20.09.2023

INTRODUCTION

The period of active labor until the baby is born is divided into 2 stages. The first stage begins with the regular and effective contractions accompanied by cervical changes (dilatation/opening and effusion/erasure) and the second stage of the labor begins with the full cervical dilation. The second stage of active labor is defined as the time from complete cervical dilatation to the complete birth of baby. Cesarean section is a preferred surgical delivery method in life-threatening situations for both the mother and the fetus. Cesarean sections performed during active labor are considered as emergency cesarean sections and found to be in relation with maternal and fetal complications (1,2). In cesarean sections performed in the 2nd stage of labor, if the head is engaged in the pelvis and is located in the deep pelvis, removal of the fetal vertex can often be compelling for the obstetrician, and this surgery is also associated with an increased risk of both maternal and fetal complications (3).

Maternal complications of emergency cesarean sections include extending of uterine incision, uterine artery injury, traumatic postpartum hemorrhage, intraoperative/postoperative increased transfusion rates, bladder injury, atony and need for hysterectomy. Neonatal complications include perinatal asphyxia, low APGAR score, admission to neonatal intensive care unit and increased neonatal mortality.

In this study, we aimed to compare maternal and newborn outcomes and complications in pregnant women who have a cesarean delivery in the 2nd stage of active labor (in the presence of full cervical dilatation) with the 1st stage cesarean deliveries. Thus, in the presence of complete cervical dilatation, a better understanding of possible maternal and fetal complications can be achieved in case of need to plan about the mode of delivery.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara Etlik City Hospital No: 1 Clinical Researches Ethics Committee (Date: 14.06.2023, Decision No: AEŞH-EK1-2023-298). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this retrospective case-control study, 50 cases who had term, singleton, uncomplicated pregnancy and gave birth by emergency cesarean section in the second stage of labor were enrolled as study group, and the same number of cases (n=50) gave birth by cesarean section in the first stage were included as the control group.

Term and singleton pregnancy with no pregnancy complications were included in the study.

Indications for cesarean sections performed in the second stage were cephalopelvic disproportion (CPD) (n=26) and fetal distress (n= 24). Indications for cesarean sections performed in the first stage were fetal distress (n=23), CPD (n=14), non-progressive labor/ unsuccessful induction (n=7), fetal macrosomia (n=2), placental abruption (n=1), malpresentation (n=2) and cord prolapse (n=1). Since high-risk pregnancies were not followed up and delivered in the delivery unit of our hospital, pregnant women with antenatal risks were excluded from the study. However, cases with diet-regulated gestational diabetes, cases with drug-regulated thyroid dysfunction, and pregnancies thought to be SGA (small for gestational age) were included in the study.

In addition to the demographic characteristics of the cases, indications for cesarean section, intraoperative and postoperative surgical characteristics and complications (extanding of uterine incision, arterial and organ injuries, hemoglobin levels, bleeding, need for transfusion and relaparatomy, duration of surgery, postoperative hospital stay) and neonatal results were analyzed statistically

SPSS (Statistical Package for Social Sciences) for Windows version 22.0 software was used for the statistical analysis of the data obtained in our study. The conformity of the data to the normal distribution was made using the Shapiro Wilk and Kolmogorov-Smirnov test. Comparisons between groups of demographic and laboratory data of all participants in those with normal distribution were made with Student's t test. Non-normally distributed data were compared between groups using the Mann-Whitney U test. Categorical data were presented as numbers and percentages and compared with the Chi-square test. Data are presented as mean±standard deviation, median (minimum-maximum) or number (percentage). The statistical significance level was accepted as $p<0.05$.

RESULTS

Demographic data of the groups (age, number of pregnancies, body mass index, education level, smoking) were found to be similar ($p>0.05$) (**Table 1**). General anesthesia was applied in 40% (n=20) of the cases who underwent cesarean section in the second stage, while general anesthesia was applied in 18% (n=9) of those who underwent cesarean section in the first stage ($p=0.015$).

In cases where cesarean section was performed in the second stage of active labor, the mean time until cesarean section was recorded as 79±70 minutes. Total operative times were similar in both groups ($p>0.05$). Active labor and cesarean section characteristics are shown in **Table 2**. Fetal head had to be pushed from the vagina in 17 of 50 cases delivered by cesarean section in the 2nd stage, and fetal foot had to be pulled in 2 cases. 21 of the emergency

cesarean sections performed in the second stage showed that at least one complication. (p<0.001) (**Table 2**, **3**) In order to remove the fetus, the uterine incision had to be extended at least 5 cm upwards (toward the uterine corpus) in an inverted T-shape in 3 cases (6%). Inverted T incision was required in only 1 case in cases where cesarean section was performed in the first stage.

Table 1. Comparison of demographic characteristics

	Cesarean section in stage 2 (n=50)	Cesarean section in stage 1 (n=50)	p
Age	27.0±6.2 (15-41)	26.6±4.3 (17-38)	0.667
BMI * (kg/m2)	29.3±5.2 (16.3-40.7)	29.9±4.5 (22.30-41.0)	0.547
Gravida (n)	1(1) (1- 5)	1(1) (1- 7)	0.981
Parity (n)	0 (1) (0-4)	0 (0) (0-5)	0.723
Abortus (n)	0 (0) (0-3)	0 (0) (0-3)	0.900
Education status			0.294
≤4 years	12 (24%)	6 (12%)	
5-12 year	22 (44%)	26 (52%)	
>12 year	16 (32%)	18 (36%)	
Smoking			0.498
None	47 (94%)	45 (90%)	
≤5	2 (4%)	one (2%)	
6-10	1 (2%)	3 (6%)	
>10	-	1 (2%)	

*BMI, body mass index

Table 2: Features of active labor and surgery

		Cesarean section in stage 2 (n=50)	Cesarean section in stage 1 (n=50)	p
Duration of active labor (hour)		5.2±2.7 (1-13)	3.5±3.0 (1-12)	0.006
Duration of oxytocin stimulation (hour)		11.8±8.7 (1-34)	9.7±8.1 (1-38)	0.379
Anesthesia	Spinal General	30 (60%) 20 (20%)	41 (82%) 9 (18%)	0.015
Interval from the start of the surgery (skin incision) to the birth of the baby (min)		5.3±4.0 (1-25)	5.4±3.9 (1-25)	0.920
Total operation time (min)		45.0±14.2 (25-80)	41.6±12.5 (20-80)	0.170
Complication * (n)		21 (42%)	4 (8%)	<0.001
Duration of hospital stay (day)		2 (0) (2-22)	2 (0) (2-21)	0.266
Duration of hospital stay (n)	>median ≤median	11 (22%) 39	6 (12%) 44	0.183

* uterine incision elongation, uterine artery injury, organ (bladder, intestine, ureter) injuries and atony

Table 3: Comparison of neonatal outcomes

	Cesarean section in stage 2 (n=50)	Cesarean section in stage 1 (n=50)	p
Birth weight (g)	3385±441 (2400- 4590)	3250±488 (2200- 4300)	0.148
Apgar score 1 min <7 (n)	6 (12%)	4 (8%)	0.505
Apgar score 5 min <7 (n)	3 (6%)	-	0.079
Observation in neonatal care service (n)	8 (16%)	4 (8%)	0.218
Follow- up in Neonatal Intensive Care Unit (n)	5 (10%)	5 (10%)	1,000

The lower segment uterine incision (Kerr incision) extended to the edges ≥2 cm from the unilateral or bilateral corners of the uterine incision in 11 (22%) cases in the 2nd stage cesarean section. In 7 cases (14%), the incision made in the lower segment was found to be torn up to the vagina. Uterine artery was injured unilaterally in 7 cases and bilaterally in 2 cases. Lateral extension of the uterine incision occurred in only 4 cases (8%) in cesarean sections performed in the first phase of active labor, and uterine artery was injured in 3 of them. There was no Kerr incision extending into the vagina.

No organ (bladder or bowel) injury occurred and no hysterectomy was required in any of the cases. While intraoperative and postpartum uterine atony developed in 3 of the deliveries by cesarean section in the 2nd stage, intraoperative atony developed in only 1 of the deliveries by cesarean section in the 1st stage. Although he need for blood product transfusion is higher in cases who underwent cesarean section in the second stage (14% vs. 4%), this difference does not show statistical significance (p=0.081) (**Table 2**).

In the first 24 hours postoperatively, erythrocyte suspension (ES) was transfused to 6 cases (12%) and fresh frozen plasma (FFP) was transfused to 3 cases (4.5%). Discrimination of intraoperative and postoperative blood product transfusions are shown in **Table 4**.

Preoperative hemoglobin levels were similar in both groups (p=0.901). In addition, postoperative 2nd hour and 6th hour values were similar between the groups (p>0.05) (**Table 5**).

While the skin incision was infected in 2 of the 2nd stage cesarean section cases, the skin incision was infected in 4 of the 1st stage cesarean section cases. Intra-abdominal abscess occurred in 1 of the patients who underwent cesarean section in the first stage. Intra-abdominal bleeding was observed in 1 of the patients who underwent cesarean section in the 2nd stage, and relaparotomy was performed in 1 of the patients who underwent cesarean section in the 1st stage due to intra-abdominal abscess.

Postoperative hospital stay was similar in both groups (p= 0.266). The need for antibiotic use in 4 cases, drain follow-up in 3 cases, relaparotomy in 2 cases, blood transfusion in 2 cases in study group. Additional interventions in those who underwent cesarean section in the 1st stage can be listed as: the need for antibiotic use in 2 cases, infected incision in 1 case and drain follow-up in 1 case. Pediatrics or neonatologists accompanied all deliveries in both groups. When newborn results were examined, Apgar scores, observation and intensive care needs were similar in both groups (p>0.05) (**Table 6**). No trauma or fracture occurred in newborns in either group.

Neonatal complications in study group (n=8, 16%) were suspicion of asphyxia (n=2), tachypnea/difficulty breathing (n=2), hypernatremia/dehydration (n=2), early-onset neonatal sepsis (n=2); asphyxia (n=2), tachypnea / respiratory distress (n=1), hypernatremia / dehydration (n=1) in the first stage cesarean section group (n=4, 8%).

Indications for the need for intensive care unit were asphyxia±intubation (n=4) (2 of these newborns died) and early-onset neonatal sepsis (n=1) in the group that underwent cesarean section in the second stage of active labor (n=5, 10%); asphyxia (n=3), early-onset neonatal sepsis (1), and bradycardia (n=1) in control goup (n=5, 10%).

DISCUSSION

Data on the incidence of cesarean section performed in the second stage of active labor, that is, when the cervix is fully dilated, is limited. While the rate of cesarean sections performed in the first stage of active labor revealed as 13-27% of all deliveries, the rate of cesarean sections performed in the second stage was noted as 1.7% of all deliveries. 2% of cesarean sections during active labor, and 2.5% of women who have reached complete dilatation (4).

When primary cesarean sections performed in active labor in low-risk nulliparous pregnancies at term were examined, it was observed that those performed in the second stage constituted 12.3% of all primary cesarean sections (5). When all pregnancies are considered, 1 out of every 4 primary cesarean sections is performed in the second stage of active labor (6).

Arrest of active labor is one of the most common indications of primary cesarean section with rates varying between 20-34% (7,8,9). World Health Organization recommended to allow up to 3 hours for nulliparous women and up to 2 hours for multiparous women (10). American Collage of Gynecologists and Obstetricians remind that the absolute maximum duration in the second stage of labor cannot be determined and allows up to 4 hours for the second stage of labor as long as the well-being of the mother and fetus allows before operative delivery is attempted (7,11). In our study, in cases where cesarean section was applied in the second stage of active labor, the average duration until cesarean section was recorded as 79±70 minutes, and there was no case in which operative delivery was attempted before cesarean section in the second stage.

There are studies showing that allowing the maximum waiting period in the second phase of labor is associated with reducing the cesarean section rate (12,13). It has also been shown that allowing the 2nd stage of labor to be prolonged to 4 hours with epidural anesthesia or to 3 hours in women without epidural anesthesia, if the mother and fetus can tolerate it, reduces the risk of cesarean section by more than 50% (14).

A relationship has been shown between the prolongation of the second stage and negative perioperative outcomes in those who delivered by cesarean section (12). However, contrary to this study, in a study (n=6273), no statistically difference was found in maternal and fetal outcomes with the increase in duration of the 2nd stage. Need for neonatal intensive care unit, low Apgar score (Apgar score <5), respiratory distress syndrome, seizure, sepsis and apnea did not increase over time. If only the second stage lasted longer than 3 hours, it was observed that the duration of hospital stay (for more than 5 days) increased approximately 2 times, regardless of the mode of delivery (15). Therefore, it would be appropriate to discuss the risks of cesarean section in the second stage with the mother before deciding on a cesarean section as the mode of delivery, since the duration of the second stage of labor exceeds the generally accepted limit of 2 hours (15).

Neonatal mortality and morbidity due to hypoxia and fetal trauma is also one of the major issues regarding cesarean sections performed in the second stage (16). It is seen that cesarean sections performed in the second stage of the labor have negative effects not only on the maternal but also on the newborn outcomes (5). Observational data suggest worse neonatal outcomes associated with prolongation of stage 2, but observational studies do not confirm absolute causality and this issue is still controversial (17). Negative neonatal outcomes may be the result of hypoxia or perinatal asphyxia in the fetus, especially if the second stage of labor is prolonged and the well-being of the fetus cannot be adequately controlled during this period (5).

While a statistically significant increase was found in neonatal morbidity (neonatal hospitalization, hypoxic-ischemic encephalopathy and subaponeurotic hemorrhage) in some studies examining neonatal morbidity in cesarean sections performed in the 2nd stage of labor (18), it was reported that there was no difference in neonatal morbidity in the 2nd stage cesarean section in larger and multicenter studies (19-21).

When the newborn results were examined, the 1st and 5th minute Apgar scores (16) and the rate of babies with a 5th minute Apgar score <4 were similar in both groups (0.6% vs. 1.1%) (5). The rate of baby followed in intensive care unit was found to be significantly higher in the group who underwent cesarean section at the 2nd stage (7.6% vs. 4.1%) (5). The median length of stay in the neonatal intensive care unit was 3-4 days (15).

In another study, neonatal intensive care unit admission rate and neonatal mortality rates were found to be

similar between the two groups (16), whereas neonatal intensive care admission rate was not different (OR: 1.63, 95% CI 0.91-2.91) in a meta-analysis, and neonatal mortality rates were similar. The rate of 5th minute Apgar score <7 was found to be significantly higher in cesarean sections performed in the second stage (OR: 5.20, OR: 2.77, respectively) (22).

Except for meconium aspiration, the need for intubation was 3 times higher in babies born by cesarean section in the second stage. It has been reported that neonatal seizures are significantly higher (OR: 2.04) in those born with stage 2 cesarean section (22).

In our study, Apgar scores and intensive care unit follow-up rates were not different between babies delivered by cesarean section at stage 2 and those delivered by cesarean section at stage 1. This can be explained by the fact that neonatologists actively accompany all deliveries in our clinic.

According to the results of our study, while organ injury was not observed in any case in emergency cesarean sections performed in the 2nd stage of the active phase of labor, the rates of other surgical complications (lengthening of the uterine incision, need for lengthening of the uterine incision, uterine artery injuries and atony development) were significantly higher than the emergency cesarean sections performed in the 1st stage. However, this increase did not have a negative effect on maternal blood transfusion need and hospital stay. In addition, newborn outcomes were similar in both groups.

As a limitation of our study, it would be appropriate to examine the maternal and neonatal morbidity and mortality results separately according to the length of the period in the second stage. Thus, predicting the risks of cesarean section according to the length of the second stage will be more valuable in patient information in cases where cesarean section is planned in the second stage. It is important to evaluate the options for cesarean section and operative vaginal delivery for the prolonged second stage of labor and to share this with the mother. Separation of groups by parity can also be recommended for future studies.

CONCLUSION

As a result, cesarean deliveries in the second stage of active labor cause a significant increase in maternal complications, although not in newborns, and require more closed care. Performing cesarean section in the 2nd stage by experienced obstetricians is important for the prevention and management of complications, similarly, it should be considered that the presence of a pediatrician or neonatologist in cases of cesarean section in the 2nd stage can improve the prognosis of the newborn.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Etlik City Hospital No: 1 Clinical Researches Ethics Committee (Date: 14.06.2023, Decision No: AEŞH-EK1-2023-298).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Pediatr Pract Res 2023; 11(3): 136-141
DOI: 10.21765/pprjournal.1351086

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Üçüncü Basamak Bir Çocuk Endokrinoloji Kliniğinde Boy Kısalığı ile İzlenen Olguların Etiyolojik Açıdan Değerlendirilmesi

Etiological Evaluation of the Cases with Short Stature in a Tertiary Pediatric Endocrinology Clinic

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Öz

Amaç: Boy kısalığı (BK) boy uzunluğunun yaşa ve cinsiyete göre iki standart sapma (SD) altında olmasıdır. Boy kısalığı etiyolojisinde en büyük grubu idiyopatik boy kısalığı (İBK) oluşturmasına karşın, patolojik boy kısalıklarının erken tanı ve tedavisi normal erişkin boy potansiyeli kaybını önlemek açısından son derece önemlidir. Bu çalışmada boy kısalığı tanısıyla izlenen olguların etiyolojik açıdan değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Trakya Üniversitesi Tıp Fakültesi Çocuk Endokrinolojisi Polikliniği'nde BK tanısıyla izlenen 536 olgu geriye dönük olarak değerlendirildi. Olguların izlem dosyalarından tanı yaşı, cinsiyeti, aile öyküsü, antropometrik ve fizik muayene bulguları, birinci ve ileri düzey laboratuvar tetkikleri, tanı ve tedavi bilgileri kaydedildi. Boy SDS'si -2 - (-2,5) SDS arası olanlar hafif BK, ≤ -2,5 olanlar ağır BK, oturma yüksekliği / boy oranı yaşa göre normal ise orantılı, bozuk ise orantısız BK olarak tanımlandı. Olguda BK hafif, doğum ağırlığı normal, fizik ve laboratuvar incelemeleri ve büyüme hızı normal olup hedef boy ile öngörülen boy uyumlu ise idiyopatik BK, büyüme plağındaki sorunlara bağlı gelişen BK ise primer BK, büyüme plağını dolaylı olarak etkileyen nedenlere bağlı ise sekonder BK olarak tanımlandı.

Bulgular: BK tanılı 536 olgunun ortalama başvuru yaşı 10,8 ±3,3 (1,3-17,7) yıl olup, 296'sı (%55,2) erkek, 240'ı (%44,8) kız ve kız/erkek oranı: 1:1,2 idi. Başvuruda olguların ortalama vücut ağırlığı SDS 2,2 ±1,1 ve ortalama boy SDS -2,8 ±0,8 idi. İdiyopatik BK gurubu %69,3 (368 olgu) ile en sık görülen BK gurubuydu. İdiyopatik BK gurubun ortalama boy SDS -2,6±0,5 ile patolojik BK gurubuna göre anlamlı yüksekti (p<0,001). İki gurup arasında puberte durumu ve cinsiyet açısından anlamlı bir fark yoktu (p=0,03, p=0,06, sırasıyla).

Sonuç: Boy kısalığı olgularının çoğu idiyopatik BK olması nedeniyle ileri tetkik yapmadan önce, ayrıntılı öykü ve fizik muayene yapılmalı ve özellikle puberte öncesi hedef boy ve öngörülen boyu benzer olan olgularda yıllık büyüme hızı izlenmelidir.

Anahtar Kelimeler: Boy kısalığı, idiyopatik boy kısalığı, etiyoloji, büyüme hormonu eksikliği

Abstract

Aim: Short stature (SS) is a stature below two standard deviations (SD) for age and gender. Although idiopathic short stature (ISS) constitutes the largest group in the etiology of short stature, early diagnosis and treatment of pathological short stature is extremely important to prevent loss of normal adult height potential. In this study, it was aimed to evaluate the cases followed with the diagnosis of short stature in terms of etiology.

Material and Method: We retrospectively evaluated 536 cases with the diagnosis of SS in Trakya University Faculty of Medicine, Pediatric Endocrinology Outpatient Clinic. Diagnostic age, gender, family history, anthropometric and physical examination findings, first and advanced laboratory tests, diagnosis and treatment information were recorded from the follow-up files of the cases. Those with a height SDS between -2 and (-2.5) SDS were defined as mild SS, those with ≤ -2.5 as severe SS, if the sitting height/height ratio was normal for age, it was defined as proportional BC, and if it was abnormal, it was defined as disproportionate SS. In the case, SS was defined as mild, birth weight was normal, physical and laboratory examinations and growth rate were normal, and if the target height was compatible with the predicted height, SS was defined as idiopathic, SS developing due to problems in the growth plate was defined as primary SS, and if it was due to causes that indirectly affected the growth plate, it was defined as secondary SS.

Results: The mean age at presentation of 536 cases diagnosed with SS was 10.8±3.3 (1.3-17.7) years, 296 (55.2%) male, 240 (44.8%) female and female/ male ratio: 1:1.2. At admission, the mean body weight SDS of the cases was 2.2 ±1.1 and the mean height SDS was -2.8 ±0.8. The idiopathic BK group was the most common SS group with 69.3% (368 cases). The mean height SDS of the idiopathic SS group was -2.6±0.5, which was significantly higher than the pathological SS group (p<0.001). There was no significant difference between the two groups in terms of puberty status and gender (p=0.03, p=0.06, respectively).

Conclusion: Since most of the short stature cases are idiopathic SS, a detailed history and physical examination should be done before further examination, and annual growth rate should be monitored especially in cases with similar prepubertal target height and predicted height.

Keywords: Short stature, idiopathic short stature, etiology, growth hormone deficiency

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Başvuru Tarihi/Received: 01.09.2023
Kabul Tarihi/Accepted: 26.09.2023

GİRİŞ

Çocukluk çağında en sık görülen endokrin sorunlardan biri olan boy kısalığı (BK) aynı zamanda üçüncü basamak hizmet sunan Çocuk Endokrinolojisi Polikliniklerine en sık başvuru nedenlerinden birini oluşturur. Boy kısalığı büyüme plağının doğrudan veya dolaylı olarak etkilenmesi sonucu ortaya çıkan bir sorun olması yanı sıra, çoğu zamanda altta bir neden olmaksızın görülen ve erişkin boyun genetik potansiyele ulaştığı ve idiyopatik olarak tanımlanan bir durumdan da kaynaklanabilir (1). Çocuklarda doğumdan itibaren erişkin boya ulaşıncaya dek büyümenin izlenmesi büyüme duraklamasının erken saptanmasını ve boy kısalığı gelişmesine yol açan kronik sorunların erken tanınıp tedavi edilmesini sağlar (2). Tanım olarak BK çocuğun ölçülen güncel boyunun aynı yaş ve cinsiyette sağlık çocuklarla karşılaştırıldığında 3 persentil altında veya -2 standart sapma (SDS) altında olması ayrıca öngörülen erişkin boyunun hedef boyundan kısa kalmasıdır (3). Boy kısalığının büyük çoğunluğu idiyopatik BK olarak tanımlanan tiptir. İdiyopatik BK'ında genelde boy hafif kısa (-2- (-2,5) SDS), öykü ve sistemik muayene ile birlikte birinci basamak laboratuvar testleri normal, hedef boy genetik ile uyumlu olup yıllık büyüme hızı (YBH) normaldir (1). İdiyopatik BK ailevi ve ailevi olmayan şeklinde 2 gruba ayrılır ve bu gruplar puberte gelişimine göre pubertesi normal veya puberte gecikmesi ile birlikte olan şeklinde iki alt grup olarak tanımlanır (1). Patolojik BK doğrudan büyüme plağındaki bozukluklara bağlı (primer) gelişebileceği gibi, büyüme plağını dolaylı olarak etkileyerek büyümeyi bozan sorunlara bağlı (sekonder) ortaya çıkabilir. Sekonder büyüme bozuklukları erken tanı alıp tedavi edilmesi durumunda çocuk genetik boy potansiyeline ulaşma şansına sahip olur (4).

Bu çalışmanın amacı üçüncü basamak hizmet veren bir Çocuk Endokrinolojisi Polikliniği'nde BK tanısıyla izlenen olguların etiyolojik açıdan değerlendirilmesi ve literatür verileri ile karşılaştırılmasıdır.

GEREÇ VE YÖNTEM

Bu çalışma için, Trakya Üniversitesi Tıp Fakültesi Girişimsel Olmayan Bilimsel Araştırmalar Etik Kurulundan izin alınmıştır (Tarih: 21.03.2022, Karar No: 06-02).

Trakya Üniversitesi Tıp Fakültesi Çocuk Endokrinolojisi Polikliniği'nde 2011-2020 tarihleri arasında boy kısalığı (BK) tanısıyla izlenen hasta dosyaları geriye dönük olarak değerlendirildi. Dosyalarında herhangi bir bölümde (anamnez, fizik muayene, tetkik sonuçları vb) eksiklik saptanan hastalar çıkarıldıktan sonra 536 olgu çalışmaya dahil edildi. Olguların izlem dosyalarından tanı yaşı, cinsiyeti, antropometrik ve fizik muayene bulguları, birinci ve ileri düzey laboratuvar tetkikleri, tanı ve tedavi bilgileri kaydedildi.

Çocukların ve ebeveynlerinin boy ölçümleri standart ölçü kurallarına göre ölçüm yapma eğitimi almış tek hemşire tarafından Harpenden stadiometer kullanılarak yapıldı. Ağırlık ölçümleri 100 grama duyarlı terazi kullanılarak yapıldı. Hastaların vücut kitle indeksleri (VKİ), hastaların ağırlıklarının boylarının (kg/m2) karesine bölünmesiyle hesaplandı. Boy, kilo ve VKİ SDS puanları Neyzi ve arkadaşları tarafından önerilen Türk standartlarına göre hesaplandı (5).

Boyu yaşa ve cinsiyete göre 3 persentil altında veya -2 standart sapma (SDS) altında olan çocuklar BK olarak tanımlandı. Tüm BK olgularına 1. basamak inceleme olarak; sol el bilek grafisi AP, tam kan sayımı, tam idrar analizi, karaciğer ve böbrek işlevleri, serum elektrolitleri ve kemik paneli (Ca, P, ALP, PTH), serum serbest (s) T4 ve TSH düzeyi, IGF1 ve IGFBP3 düzeyleri ve doku transglutamidaz IgA ve total IgA düzeyi tetkikleri yapıldı (4).

Ebeveyn boy değerleri mevcut olan hastalar için hedef boy değerleri Tanner yöntemine göre hesaplandı (6). Bu değerlerin SDS'leri Türk standartları (5) kullanılarak hesaplandı. Kemik yaşı tespiti, Greulich Pyle atlası ile çocuk endokrinoloji uzmanı tarafından sol el-el bilek grafisi kullanılarak yapıldı. Her hasta için tahmin edilen yetişkin boyu, Greulich-Pyle atlası kullanılarak Bayley-Pinneau yöntemi ile hesaplandı (7). Kemik yaşı 7'nin altında olan erkeklerde ve kemik yaşı 6'nın altında olan kadınlarda tahmin edilen yetişkin boyu hesaplanmadı. Tahmin edilen yetişkin boy değerlerinin SDS'si Türk standartlarına göre hesaplandı (4). Çocuklarda orantılı/ orantısız boy kısalığı ayrımı oturma yüksekliği/boy oranı ve kulaç-boy farkı verileri kullanılarak yapıldı (8).

Doğum ağırlığı, boy ve baş çevresinin SDS'si revize edilmiş Fenton büyüme çizelgesine göre hesaplandı (9). Doğum ağırlığı ve/veya boyu gestasyon yaşına göre -2SD'nin altında olanlar SGA olarak gruplandırıldı.

Boy SDS'si -2 – (-2,5) SDS arası olanlar hafif BK, ≤-2,5 olanlar ağır BK kabul edildi (10). Boy kısalığı sınıflamasında son ESPE sınıflaması ve Neyzi ve ark. (11) önerdiği sınıflama yöntemleri kullanıldı (12). Boy kısalığı idiyopatik BK, primer BK ve sekonder BK olarak 3 ana gruba ayrıldı. Primer ve sekonder boy kısalıkları patolojik boy kısalıkları olup, bu grupta boy kısalığına yol açan sorun doğrudan büyüme plağı bozukluklarından kaynaklanmış ise primer boy kısalığı, büyüme plağı dışında olan ve büyümeyi dolaylı olarak etkileyen bir sorundan kaynaklanıyor ise sekonder boy kısalığı olarak tanımlandı (4). Primer BK grubunda yer alan sendromların tanısı muayene bulguları ve karyotip analizi ve diğer moleküler yöntemler ile yapıldı. İskelet displazileri tanısı orantısız kısalık, radyolojik bulgular ve genetik analiz sonuçlarına dayanılarak konuldu.

Doğum ağırlığı ve / veya doğum boyu gebelik yaşına göre -2 SDS altında olan, dismorfik bulgusu ve orantısız kısalığı bulunmayan ve 3 yaşına kadar büyüme yakalaması yapamayan olgular idiyopatik intrauterin büyüme geriliğine bağlı BK olarak tanımlandı.

Sekonder boy kısalığı nedeni olarak endokrin sorunlar açısından serum sT4 düzeyi düşük veya normal olup TSH düzeyi yüksek ise edinsel primer hipotiroidi açısından olgularda tiroid otoantikorları bakıldı. Serum sT4 düşük, TSH normal veya düşük ise santral hipotiroidi tanısına yönelik olarak hipotalamo-hipofizer bölgeye manyetik rezonans görüntüleme (MRG) yapıldı ve diğer ön hipofiz hormonları denetlendi.

Sekonder BK olgularında YBH düşük, kemik yaşı geri, 1. basamak laboratuvar incelemelerinde kronik hastalıklara yönelik tetkikleri normal ve ötiroid olanlar serum IGF1 düzeyi düşük veya normal olması durumunda büyüme hormonu (BH) eksikliği açısından 2 farmakolojik (L-dopa, klonidin ya da insülin ile) büyüme hormonu uyarı testi yapılarak değerlendirildi (13,14). İki uyarı testinde doruk BH yanıtının < 10 ng/ml olması durumunda BH eksikliği tanısı konuldu ve hipotalamo - hipofizer bölgenin MR görüntülemesi yapılarak organik nedenler araştırıldı. BH uyarı testlerinde BH yanıtı normal, ancak serum IGF1 düzeyi düşük ise olguya IGF1 jenerasyon testi yapılarak biyoinaktif BH eksikliği araştırıldı (15).

Serum IgA düzeyi normal, doku transglutaminaz IgA düzeyi yüksek saptanan olgular çocuk gastroenteroloji uzmanına yönlendirildi. Olgular ince barsak biyopsi sonrası histopatolojik bulgulara dayanılarak çölyak hastalığı (ÇH) tanısı aldı.

Boyu -2- (-2,5) SDS arasında, doğum ağırlığı normal, öykü ve fizik muayene bulgularının yanı sıra 1. basamak tetkikleri normal, boy SDS ve hedef boy SDS arasındaki fark -1,5 SDS'den daha az ve YBH normal olgular idiyopatik BK olarak tanımlandı. İdiyopatik BK grubunda olgu hafif kısa, ebeveynlerden biri veya her ikisinin boyu -2- (-2,5) arasında, ağırlığı normal, KY takvim yaşı ile uyumlu ve öngörülen boy ve hedef boy birbirine yakın ise ailevi BK tanısı aldı. Boy kısalığının yanı sıra ağırlığı da etkilenmiş, pubertesi normal veya gecikmiş, öyküde gecikmiş puberteli ebeveyni olan, KY belirgin geri ancak hedef boy ve öngörülen boyu benzer olan olgu ailevi olmayan (yapısal) BK tanısı aldı (16).

İstatistiksel Değerlendirme

İstatistiksel analiz için SPSS 21.0 programı kullanıldı. Kategorik veri setlerine Pearsons ki-kare ve Fisher'in kesinlik testleri uygulandı. Karşılaştırma için Paired t-testi yapıldı ve gruplar arası karşılaştırmalar varyans analizi kullanılarak yapıldı. P değeri <0,05 olduğunda farklılıklar anlamlı kabul edildi.

BULGULAR

BK tanılı 536 olgunun ortalama başvuru yaşı 10,8 ±3.3 (1,3-17,7) yıl olup, 296'sı (%55,2) erkek, 240'ı (%44,8) kız ve kız/erkek oranı: 1:1,2 idi. Başvuruda olguların ortalama vücut ağırlığı SDS 2,2 ±1,1 ve ortalama boy SDS -2,8 ±0,8 idi. Olguların 269'u (%50,1) prepubertal, 267'si (%49,9) pubertaldi. Olguların % 57,1 'i (306) ağır BK olup, % 69,3'u (368 olgu; 213 E, 155 K) idiyopatik BK idi. İdiyopatik BK olgularının % 35,2 (185 olgu) ailevi olmayan (yapısal) BK, %34,1 (183 olgu) ailevi BK idi. İdiyopatik BK olgularının yaşlara göre dağılımı değerlendirildiğinde 1-5 yaş arasında 20 olgu (%5,4), 5-10 yaş arasında 83 olgu (%22,6) ve 10-18 yaş arasında 265 (%72) olgu vardı (**Tablo 1**).

Tablo 1 İdiyopatik BK grubunun patolojik BK nedenleri ile karşılaştırılması

	İdiyopatik BK	Patolojik BK	p
Başvuru yaşı, n (%)			
1-5 yaş	20 (5.4)	25 (14.9)	
5-10 yaş	83 (22.6)	47 (28.0)	<0.001
10-18 yaş	265 (72.0)	96 (57.1)	
Cinsiyet			
Erkek	213 (57.9)	83 (49.4)	0.06
Kız	155 (42.1)	85 (50.6)	
Puberte durumu, n (%)			
Prepubertal	173 (47.0)	96 (57.1)	0.03
Pubertal	195 (53.0)	72 (42.9)	
Vücut ağırlığı, SDS			
ortalama±SD	-2.2±0.9	-1.9±1.3	0.01
Boy, SDS			
ortalama±SD	-2.6±0.5	-3.0±1.0	<0.001
Tedavi durumu, n (%)			
Alıyor	5 (1.4)	99 (58.9)	<0.001

Boy kısalığı olgularının % 31,3 (168 olgu) patolojik (primer ve sekonder) BK idi. Yaş dağılımı açısından bakıldığında patolojik BK grubunda 1-5 yaş arasında 25 olgu (%14.9), 5-10 yaş arasında 47 olgu (%28), 10-18 yaş arasında 96 olgu (%57,1) saptandı. **Tablo 2**'de gösterildiği gibi patolojik BK grubunun %11,9 (62 olgu) primer BK, %18,8 (97 olgu) sekonder BK olup, primer BK grubunda en sık nedenler sırasıyla iskelet displazileri % 4, (25 olgu), sendromlar %4,5 (23 olgu ve %2,6 (14 olgu) ile büyümesini yakalayamamış SGA tanılı hastalardı. Sekonder BK grubunda ise en fazla %15,1 (81 olgu) ile büyüme hormonu eksiklikleri saptandı. Sekonder BK nedeni olarak hiçbir olguda kronik karaciğer hastalığı, kronik böbrek hastalığı ve tübülopati saptanmadı.

İdiyopatik BK grubu %69,3 (368 olgu) ile en sık görülen BK grubuydu. İdiyopatik BK grubunu %35,2 (185 olgu) ile ailevi olmayan (yapısal) BK ve %34,1 (183 olgu) ile ailevi BK grubu oluşturdu. İdiyopatik BK grubunun %57,9'u (213 olgu) erkeklerden, %42.1'i (155 olgu) kızlardan oluşuyordu, erkeklerin sayısı fazla olmakla birlikte istatistiksel olarak anlamlı fark saptanmadı (p=0,06). İdiyopatik BK olgularının %72'sinin (265 olgu) başvuru yaşı 10-18 yaş arasında olup patolojik BK olgularının sadece %57.1'i (96 olgu) bu yaş aralığında başvurmuştu (p<0,001). İki grup arasında puberte durumu ve cinsiyet açısından anlamlı bir fark yoktu (p=0,03, p=0,06, sırasıyla). İdiyopatik BK grubunun ortalama boy SDS'si -2.6±0.5 ile patolojik BK grubuna göre anlamlı yüksekti (p<0,001).

Tablo 2 Boy kısalığı olgularında altta yatan nedenler ve sıklığı	
Etiyolojik Nedenler n (%)	536 (%100)
Primer Boy Kısalığı Nedenleri	62 (%11.9)
Sendromlar	23 (%4.5)
-Turner Sendromu	17 (%3.2)
-Noonan Sendromu	4 (%0.7)
-Prader Willi Sendromu	1 (%0.3)
-Di George Sendromu	1 (%0.3)
İskelet Displazileri	25 (%4.8)
Büyüme Yakalaması Yapamayan SGA	14 (%2.6)
Sekonder Boy kısalığı Nedenleri	97 (%18.8)
Malnutrisyon	3 (%0.6)
Çölyak Hastalığı	7 (%1.8)
Psikososyal Nedenler	4 (%0.8)
Büyüme Hormonu Eksikliği	81 (%15.1)
-BHE (İzole+ÇHHE)	48 (%8.4)
-Biyoinaktif BH	29 (%5.4)
-BH Duyarsızlığı	1 (%0.3)
-Organik Nedenler	3 (%0.6)
Diğer Endokrin Bozukluklar	2 (%0.4)
-Hipotiroidi	2 (%0.4)
İdiyopatik Boy Kısalığı Nedenleri	368 (%69.3)
Ailevi Boy Kısalığı	183 (%34.1)
Ailevi Olmayan Boy Kısalığı	185 (%35.2)

BHE; büyüme hormonu eksikliği, SGA; small for gestasyonel age, BH; büyüme hormonu, ÇHHH; Çoklu hipofiz hormon eksikliği

TARTIŞMA

Çocukluk çağında sağlığın en önemli göstergesi olan büyüme genetik, çevresel, hormonal ve beslenme gibi etmenlerin etkisi altındadır. Özellikle beslenme süt çocukluğu döneminde büyümeyi en çok etkileyen etmen olup, bu dönemin ardından genetik ve hormonların etkisi daha belirgin olur (2). BK altta yatan bir hastalığın ilk bulgusu olabileceği gibi, büyüme hormonu- IGF1 ekseninde bozukluklara bağlı gelişen izole bir hastalık da olabilir. Bu nedenle boy kısalığının erken tanınması ve altta yatan sorunun tedavisi çocuğun hedef boy potansiyeline ulaşması açısından çok önemlidir (17).

Boy kısalığı etiyolojisine yönelik çalışmalarda en sık neden olarak İBK saptanmıştır (18, 19) Ankara ilinde 385 çocuğun geriye yönelik incelendiği bir çalışmada Demirel ve ark. (20) idiyopatik boy kısalığını %71,1 olarak bildirmişlerdir. Türkiye'de prospektif olarak yapılan 25 çocuk endokrin merkezinin katıldığı bir çalışmada 1658 kısa boylu çocuk değerlendirilmiş ve idiyopatik boy kısalığı %44,1 olarak bildirilmiştir (21). İdiyopatik boy kısalığı oranları, çalışma yöntemlerindeki farklılıklar gibi değişik sebeplerle farklı oranlarda bildirilmiş olsa da tüm çalışmalarda boy kısalığının en sık nedeni olduğu gösterilmiştir. Çalışmamızda literatür ile uyumlu olarak BK olgularının en sık nedeni % 69,3 ile idiyopatik BK (% 34,1 ailevi ve % 35,2 ailevi olmayan tip) idi.

Büyüme plağında yer alan kondrosit hücresi, ekstrasellüler matriks proteinleri ve hücre içi sinyalizasyon mekanizmalarında oluşan herhangi bir bozukluk büyümeyi doğrudan etkileyerek boy kısalığına yol açar ve primer boy kısalığı veya primer büyüme bozukluğu olarak adlandırılır (18). Bu grup içinde sendromlar, kromozom anomalileri, intrauterin büyüme geriliği ve iskelet displazileri yer alır (22). Primer BK için kesin tedavi olmamakla birlikte bu grupta yer alan hastalıkların erken tanınması ve büyüme hormonu kullanılması erişkin boy potansiyelinin artmasını sağlar. Primer BK olgularında özellikle Turner sendromu gibi kromozom anomalileri, Noonan sendromu ve Prader Willi sendromu gibi tek gen hastalıkları veya idiyopatik intrauterin büyüme geriliğinin tanınması bu olguların BH tedavisinden daha uzun süre yararlanmalarını ve erişkin boy potansiyelinin artmasını sağlar. Esen ve ark.(23) "kısa boylu olma" şikayeti ile başvurmuş 1241çocuğu değerlendirdikleri çalışmada %2,9 (28 olgu) sendromik hastalıklar, %0,7 (7 olgu) iskelet displazisi, %2 (19 olgu) IUGR olduğunu bildirmişlerdir. Uçkun ve ark. (10) ağır boy kısalığı olan 320 çocuğu değerlendirdikleri çalışmada olguların %13,1'ini (42 olgu) sendromlar, %12,8'ini (41 olgu) iskelet displazileri ve %3,75'ini (12 olgu) SGA vakalar olarak rapor etmişlerdir. İlk çalışmada boy kısalığı şikayeti ile başvurmuş tüm çocuklar çalışmaya alınmışken, ikinci çalışmada ağır boy kısalığı olanların çalışmaya alınması iki çalışma arasındaki farklı sonuçların sebebi olabilir. Biz çalışmamıza iki çalışmadan da farklı olarak boy kısalığı tanısı kesinleşmiş, hem ağır ve hem hafif BK'lı tüm vakalar dahil edildi, bu nedenle primer BK nedenleri arasında %4,5 sendromlar, %4,8 iskelet displazileri, % 2,6 SGA olgu ile farklı oranlar saptadık.

Büyüme plağı dışında ortaya çıkan sorunlar büyüme plağını dolaylı olarak etkileyerek büyümeyi olumsuz etkiler ve büyüme bozukluğuna ve boy kısalığına neden olur. Bu duruma sekonder büyüme bozuklukları veya sekonder boy kısalığı denir (22). Sekonder BK nedenleri kronik inflamatuvar hastalıklar, beslenme bozuklukları, malabsorbsiyon, psikosoyal sorunlar ve endokrin bozukluklardır (18,22). Sekonder BK yapan neden saptanır ve tedavi edilirse BK olan çocuk hızla büyüme yakalaması yaparak erişkin boy potansiyeline ulaşabilir (24). Sekonder BK yapan nedenlerin erken tanınması ve tedavisi çocuklarda büyümenin izlenmesi ile mümkün olur (25). Çalışmamızda sekonder BK sıklığı % 18,8 (97 olgu) idi, %15,5 (84 olgu) endokrin patolojiler nedeniyle gelişmişti. Sekonder boy kısalığı nedenleri arasında en sık neden endokrin sorunlar olup, bu grup içinde BH eksikliği birinci sırada yer almaktadır. Çalışmamızda sekonder BK tanısı ile izlenen olguların %15.1 'i BH eksikliği tanısı almıştır. Edinsel hipotiroidi etiyoloik nedenler arasında yalnızca %0,4 (2 olgu) idi. Edinsel hipotiroidi görülme sıklığı daha fazla olmasına karşın, büyümede duraklama ve boy kısalığı oluşumuna neden olması için daha uzun süre geçmesi gerektiğinden, olgularda boy kısalığı dışında hipotiroidi bulgularının erken ortaya çıkması daha erken tanı ve tedaviyi mümkün kılmaktadır.

Çalışmamızda da gösterdiğimiz gibi aslında , endokrin hastalıkları boy kısalığının nadir nedenleri arasındadır. Farklı çalışmalarda %5- %35 arasında geniş bir aralıkta değişen oranlar bildirilmiştir (26,27,28). Ayrıca olgularımızda BHE endokrinolojik nedenlerin %59.2'sini, boy kısalığı olan çocuk ve ergenlerin %8.4 'ünü oluşturmaktaydı. Bu bulgular, Lashari ve ark. (27) çalışmalarına benzerdi. Boy kısalığı olan çocuklarda BHE prevalansı belirgin şekilde değişkenlik göstermekte ve %2,8 ile %69 arasında değişmektedir (28, 29). Ancak bu çalışmaların çoğu, endokrin bozukluklarının sıklıkla takip edildiği endokrin polikliniklerinde yürütülmüştür. Yüksek oranların tespit edilmesinde bu durum dikkate alınmalıdır.

Çölyak hastalığı sekonder BK nedenlerinden biri olup, boy kısalığı etiyolojisine yönelik yapılan 1. basamak tetkiklerde mutlaka araştırılması önerilir (30). Çölyak hastalığı büyük çocuklarda gastrointestinal sistem bulguları olmadan yalnızca boy kısalığı ile bulgu verebilir (31). Bir çalışmada çölyak hastaları arasında BK sıklığı %54,9 saptanmıştır (30). Boy kısalığı etyolojilerinin değerlendirildiği ülkemizden yapılmış çalışmalarda %2,6- %4,9 gibi oranlar bildirilmiştir (10,23). Çalışmamızda sekonder BK nedenleri arasında literatüre uyumlu olarak %1,8 oranı ile ikinci sırada çölyak hastalığı saptanmıştır. Boy kısalığı olan çocuklarda ağırlık normal bile olsa çölyak hastalığı araştırılması gerekmektedir. Sekonder BK grubunda kronik hastalıklar arasında kronik böbrek yetmezliği, kronik karaciğer yetmezliği ve tübülopati gibi sorunlara bağlı BK sıklığı oldukça az görülür (10,23). Bununla birlikte BK olan çocukların tümünde serum elektrolitleri, kreatinin, kalsiyum, fosfor ve alkalen fosfataz düzeylerinin bakılması önerilmektedir (32). Çalışmamızda kronik böbrek hastalığı kronik karaciğer hastalığı veya tübülopatiye bağlı sekonder BK tanısı alan olgu yoktu. Bu bulguya dayanarak BK olgularında 1. basamak tetkiklerinde özellikle hastanın ayrıntılı öykü ve fizik muayenesinde kronik hastalığı düşündürecek bulgu yoksa ve ağırlığı normal ise 1. basamak tetkiklerde serum elektrolit, kemik paneli, karaciğer ve böbrek işlevlerine yönelik testlerin istenmesi gerekli olmayabilir. Bu varsayımı desteklemek açısından daha geniş serili çalışmalara ihtiyaç bulunmaktadır.

İlk 3 yaşta görülen BK nedenleri daha çok, malnütrisyon, ve Çölyak hastalığı gibi nedenlerle beslenme durumunun olumsuz etkilenmesi, nutrisyon yetersizliklerine bağlı raşitizm ve SGA doğum gibi sekonder sebepler olabilir bununla birlikte özellikle ağır boy kısalıklarında kemik displazileri gibi primer BK nedenleri de akılda tutulmalıdır (10). Bizim çalışmamızda %8,3 ile sadece 45 hasta 1-5 yaş arasındaydı. Bunların %17,7 (8olgu) orantısız BK idi.

Song ve ark. (18) yaptıkları çalışmada ailesel boy kısalığı grubunun ortalama başvuru yaşının patolojik boy kısalığı etiyoloji grubuna göre istatistiksel olarak yüksek olduğunu bulmuşlardır. Uçkun ve ark. (10) yaptığı başvuru sırasındaki yaş gruplarının dağılımının analizi, orantısız boy kısalığı (iskelet displazileri, ışınlama, raşitizm) ve büyümeyi yakalayamayan SGA vakalarının 5 yaşın altında ortaya çıktığını ortaya koydu. Öte yandan, endokrin bozukluklar 5 yaşından sonra, kronik hastalık, yetersiz beslenme ve idiyopatik boy kısalığı vakalarının 10 yaşından sonra ortaya çıktığını gösterdiler. Bütün bu çalışmaların sonuçları bizim sonuçlarımıza benzer şekilde idiyopatik boy kısalığı grubunun ortalama başvuru yaşının diğer etiyoloji gruplarına göre istatistiksel olarak daha yüksek olduğunu göstermiştir.

SONUÇ

BK olgularının büyük çoğunluğu, idiyopatik BK grubunda yer almakla birlikte, patolojik BK grubunda primer BK nedeni olarak en sık sendromlar ve kromozom anomalileri, sekonder BK nedeni ise BH eksikliği ve çölyak hastalığı saptanmıştır. Özellikle erken tanı ve tedavi bazı primer BK olgularının BH tedavisi ile erişkin boy potansiyelinin artmasını, ,sekonder BK olgularının ise erişkin potansiyeline ulaşmasını sağlayabilir. Ayrıca BK olgularında istenecek birinci basamak incelemelerin yeniden gözden geçirilerek yapılandırılmasına yönelik geniş serili çalışmalara ihtiyaç bulunmaktadır.

ETİK BEYANLAR

Etik Kurul Onayı: Bu çalışma için, Trakya Üniversitesi Tıp Fakültesi Girişimsel Olmayan Bilimsel Araştırmalar Etik Kurulundan izin alınmıştır (Tarih: 21.03.2022, Karar No: 06-02).

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.

Finansal Destek: Yazarlar bu çalışmada finansal destek almadıklarını beyan etmişlerdir.

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

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Pediatr Pract Res 2023; 11(3): 142-148
DOI: 10.21765/pprjournal.1368228

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Ultrasonography in Zellweger Syndrome: Spectrum of Early Findings

Zellweger Sendromunda Ultrasonografi: Erken Bulgular

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ABSTRACT

Aim: Zellweger syndrome (ZS), also known as cerebrohepatorenal syndrome, is a rare and severe peroxisomal biogenesis disorder that involves multiple organ systems. The affected subjects are mostly symptomatic in the neonatal or early infantile period. Bedside ultrasonography (US) is a safe and repeatable method that allows combined imaging of the abdomen and head in neonates and infants. This study aimed to investigate the spectrum of early abnormalities in bedside US examinations of the head and abdomen in a population of children with ZS.

Material and Method: US images of the head and abdomen in nine children diagnosed with ZS syndrome were analyzed retrospectively to identify the characteristics and frequencies of abnormal findings.

Results: Subependymal germinolytic cysts were the most frequent finding in head USs. Mild-to-moderate ventricular dilation, lenticulostriate vasculopathy, and thinning of the corpus callosum were among the associated findings. The kidneys showed increased cortical echogenicity and preservation of the medullar hypoechogenicity in all; 8 out of 9 patients had subcapsular cysts and 7 had small and irregular medullae. Increased periportal echogenicity, gallbladder edema, and biliary sludge were identified in 4 patients. One patient had a cystic pancreatic lesion that had not been previously reported in ZS.

Conclusion: The cerebral findings of ZS are well-defined in magnetic resonance imaging, however, combined ultrasonographic findings of the cerebrum and abdomen in this syndrome are rarely reported. As a safe, readily available, and repeatable imaging method, bedside US can be used in neonates and infants to identify the multisystem findings of ZS.

Keywords: peroxisomal disorders, ultrasonography, Zellweger syndrome

ÖZ

Amaç: Serebrohepatorenal sendrom olarak da bilinen Zellweger sendromu (ZS), çoklu organ sistemlerini etkileyen nadir ve ciddi bir peroksizomal biyogenez bozukluğudur. Etkilenen kişiler çoğunlukla yenidoğan veya erken çocukluk döneminde semptomatiktir. Yatak başı ultrasonografi (US), yenidoğan ve süt çocuklarında abdomen ve serebrumun birlikte görüntülenmesini sağlayan güvenli ve tekrarlanabilir bir yöntemdir. Bu çalışmada, ZS'li bir çocuk popülasyonunda serebrum ve abdomenin yatak başı US incelemelerindeki erken dönemdek bulgular spektrumunu araştırmayı amaçlandı.

Gereç ve Yöntem: ZS sendromu tanısı alan dokuz çocuğun serebrum ve abdomen US görüntüleri, anormal bulguların özelliklerini ve sıklığını belirlemek amacıyla retrospektif olarak analiz edildi.

Bulgular: Serebrum ultrasonlarında en sık görülen bulgu subependimal germinolitik kistler idi. Hafif- orta dereceli ventriküler genişleme, lentikülostriat vaskülopati ve korpus kallosumun incelmesi diğer ilişkili bulgular arasındaydı. Böbreklerde kortikal ekojenitenin arttığı ve tüm hastalarda medüller hipoekojenitenin korunduğu görüldü; 9 hastanın 8'inde subkapsüler kistler, 7'sinde ise küçük ve düzensiz medullalar mevcuttu. Dört hastada artmış periportal ekojenite, safra kesesi ödemi ve safra çamuru tespit edildi. Bir hastada daha önce ZS'de bildirilmemiş kistik pankreas lezyonu vardı.

Sonuç: ZS'nin serebral bulguları manyetik rezonans görüntülemede iyi tanımlanmıştır, ancak bu sendromda serebrum ve abdomenin kombine ultrasonografik bulguları nadiren bildirilmektedir. Güvenli, kolay ulaşılabilir ve tekrarlanabilir bir görüntüleme yöntemi olarak yatak başı US, yenidoğanlarda ve bebeklerde ZS'nin çoklu sistem bulgularını saptamada kullanılabilir.

Anahtar Kelimeler: Peroksizomal hastalıklar, ultrasonografi, Zellweger sendromu

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Başvuru Tarihi/Received: 29.09.2023
Kabul Tarihi/Accepted: 11.10.2023

INTRODUCTION

Zellweger syndrome (ZS), is one of the rare autosomal recessive peroxisomal biogenesis disorders caused by the mutations of PEX genes. That spectrum of disorders, also including neonatal adrenoleukodystrophy and infantile Refsum disease, is characterized by peroxisomal function loss and accumulation of very long chain fatty acids (VLCFAs) in plasma. The resultant metabolic abnormality in ZS causes severe dysfunction in multiple organ systems, mainly affecting the brain, liver, and kidneys (1-3).

Severe cerebral, hepatic, and renal involvement in ZS mostly manifests in the neonatal or early infancy period with hypotonia, seizures, failure to thrive, impaired liver function, and jaundice. Dysmorphic craniofacial features (including mid-face hypoplasia, epicanthal folds, large anterior fontanelle) and skeletal abnormalities (including brachydactyly and club foot) may be present at birth and may raise clinical suspicion for a multisystem genetic or metabolic disease (1,4). Imaging plays an important part in the diagnostic work-up for ZS and leads to biochemical and genetic testing for a definitive diagnosis (1,2,4,5).

Magnetic resonance imaging (MRI) of the brain, ultrasonography of the abdomen, and radiographs of the pelvis and knee are most commonly used to look for the specific findings of ZS which mainly include malformations of cortical development and abnormal myelination in MRI; cortical cysts and increased echogenicity of the kidneys in ultrasonography (US); and patellar and/or triradiate pelvic cartilage calcifications in radiographs (2,4-6).

Bedside US is a readily available and repeatable imaging method in neonates and infants that may allow identification of combined findings of head and abdomen in ZS (7,8). We hereby report the characteristics and frequency of the early US findings of the abdomen and cerebrum in a population of children with ZS.

MATERIAL AND METHOD

The study was carried out with the permission of Şanlıurfa Eyyübiye Training and Research Hospital Ethics Committee (Date: 20.06.2019, Decision No: 2019/20). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Cases were identified retrospectively using the electronic patient record system of the institution. Between July 2017 and April 2019, neonates or infants diagnosed as having Zellweger syndrome with clinocoradiological findings and laboratory and/or genetic results and who had at least 1 bedside ultrasonography (US) of the head and abdomen were included in the study. Gestational age, sex, and age (days) at US examination were documented from the clinical records of the patients. The presence or absence of additional computed tomography (CT) or magnetic resonance (MR) imaging studies of the head and/or abdomen and the age (days) at CT and/or MRI (if present) were noted.

The head US examinations were retrospectively evaluated for ventricular size and morphology, gray and white matter echogenicity, the presence or absence of callosal abnormalities, cystic or solid lesions, lenticulostriate vasculopathy (LSV), and ventricular or parenchymal hemorrhage. In abdominal US examinations, the liver, spleen, pancreas, and kidneys were retrospectively reviewed for any size or echogenicity abnormalities and the presence or absence of any solid or cystic lesions. The size, wall thickness, and luminal features of the gallbladder were assessed, and the intra- and extrahepatic bile ducts were reviewed for any dilation. Any additional findings were noted if present.

RESULTS

Between July 2017 and April 2019, we identified nine patients with ZS in whom the bedside US examinations of the head and abdomen were performed. Of 9 patients, 8 were neonates and 1 was an infant. Seven (7/9) were females. All examinations were performed bedside with an 8-12 MHz frequency linear probe (Shenzhen Mindray BioMedical Electronics Co., China). US was performed within the first 3 days of life in all neonates in the study and one infant was imaged on the first day of admission at 4th month of life. Of the neonates, 1 was born at the 35th week of gestation and 6 were born between the 37th to 39th gestational weeks.

Of 9 patients, 5 were also imaged with cranial magnetic resonance imaging (MRI) and/or computed tomography (CT): 4 had MRI, 1 had CT. Fetal MRI of the brain was available for 1 and MRI of the abdomen was available for 1.

In US imaging of the head, all patients had bilateral subependymal germinolytic cysts (SGCs). The cysts were tear-drop or ovoid in shape, contained hyperechoic septations, and were heterogeneous in appearance in all. In 4 out of 9 patients (44.4%), the corpus callosum was completely formed but thin for the age. 1 patient had callosal dysgenesis with agenesis of the genu, rostrum, and splenium. 8 out of 9 patients (88.8%) had mild-moderate enlargement of the lateral ventricles with mild contour abnormalities; 1 patient with callosal dysgenesis had severe enlargement of the posterior horns. Patchy hyperechoic areas were observed in the subcortical white matter areas of the frontoparietal lobes of 1 neonate; no echo abnormalities were detected in the white matter areas of the other 8 patients. Intraventricular hemorrhage was found in 1 neonate with a gestational age of 35 weeks. The patient also had hemorrhagic signal changes in the caudothalamic grooves on subsequent MRI and was presumed to have germinal matrix hemorrhage. 1 term-born infant with SEGCs on US examination also

was found to have hemorrhagic signal intensities in the caudothalamic grooves on brain MRI performed on the 9th day of life. Lenticulostriate vasculopathy (LSV) was found in 6 of the 9 patients (66.6%) (**Figure 1**). US findings of the head and their frequencies among the population are presented in **Table 1**.

Table 1. Head US Findings

	Patients; no / (%)
SEGCs	9 / (100)
Corpus Callosum	
Thin	4 / (44.4)
Dysgenetic	1 / (11.1)
Normal	4 / (44.4)
Ventricular Enlargement	
Mild to moderate	8 / (88.8)
Severe	1 / (11.1)
Hemorrhage	
Caudothalamic	2* / (22.2)
Intraventricular	1β / (11.1)
LSV	6 / (66.6)
White Matter Hyperechogenicity	1 / (11.1)

SEGS, subependymal germinolytic cysts; LSV, lenticulostriate vasculopathy;*, in 1 term and 1 preterm; β, in preterm

In US imaging of the kidneys, all patients had increased echogenicity of the renal cortex, resulting in increased corticomedullary differentiation. Multiple cortical cysts of 2-5 mm were found bilaterally in the kidneys in 8 of the 9 patients (88.8%); 1 patient had no visible anechoic cyst or millimetric hyperechoic foci to represent any micro-cysts. When present, most of the cysts were peripherally located in the cortex, however, the inner cortex also had few cysts in all patients with cortical cysts. In 7 out of 8 patients with cysts (87.5%), the cysts were surrounded by an incomplete rim of thin hyperechogenicity; 1 patient with a severe increase of cortical echogenicity had cysts with no visible peripheral hyperechogenicity. The medullary pyramids were small in 7 out of 9 patients (77.7%). One particular finding was the varying degrees of contour irregularities of the medullae; the medullae were also located more centrally than normal. The medullary pyramids preserved their hypoechogenicity in 8 of 9 patients (88.8%); 1 neonate had peripherally increased echogenicity of the medullae, resembling the transient nephrocalcinosis of the newborn. The neonate also had mild hyperechogenicity of the cortex and no cysts. Three different patterns of renal involvement observed in sonographic studies are presented in **Figure 2**.

The liver size was increased in 4 out of 9 patients (44.4%; 3 neonates and 1 infant) for the age, and the normal echogenicity of the liver parenchyma was preserved in all. 4 patients with increased liver size also had central periportal hyperechogenicity, gallbladder wall edema, and hyperechoic biliary sludge in the gallbladder (**Figure 3**). No patients had dilated intrahepatic or extrahepatic biliary ducts. No focal lesions were observed in the liver parenchyma.

One neonate in the study had a 7 mm homogeneously anechoic cyst that was located adjacent to the pancreatic tail. The central cystic part was surrounded by a 4-5 mm thick parenchyma that had the same echogenicity as the pancreas, however, a linear demarcation line was also present between the tail and the lesion. The lesion was further imaged with an MRI, however, was not biopsied due to the poor clinical condition of the patient (**Figure 4**).

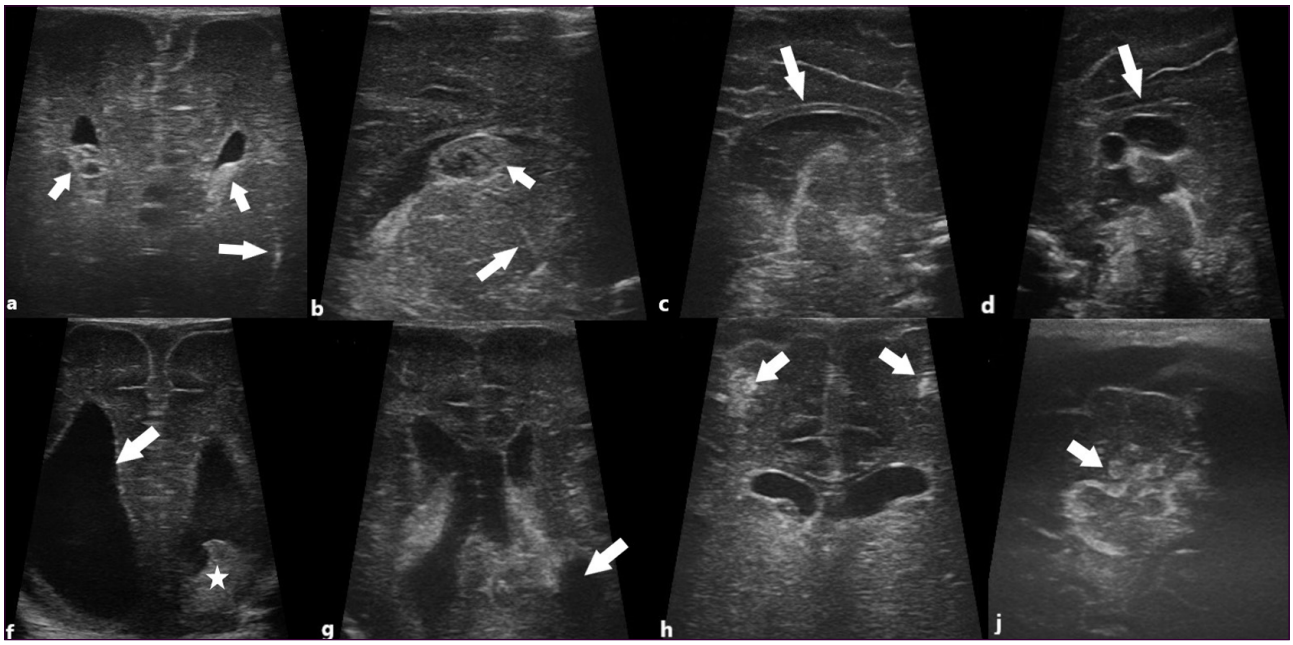

Figure 1. Coronal and sagittal plane US images of the head in two patients (a,b) show the SEGCs (short arrows) and LSV (long arrows). Midsagittal plane US images in two patients (c,d) show the corpus callosum in normal thickness and formation in one (arrow, c) and callosal dysgenesis with absent genus and rostrum in another (arrow,d). Posterior coronal US images in two patients (f,g) show severe enlargement of the lateral ventricles (arrow,f) with intraventricular hemorrhage (star,f) in one and moderate enlargement of the lateral ventricles in another (arrow,g).

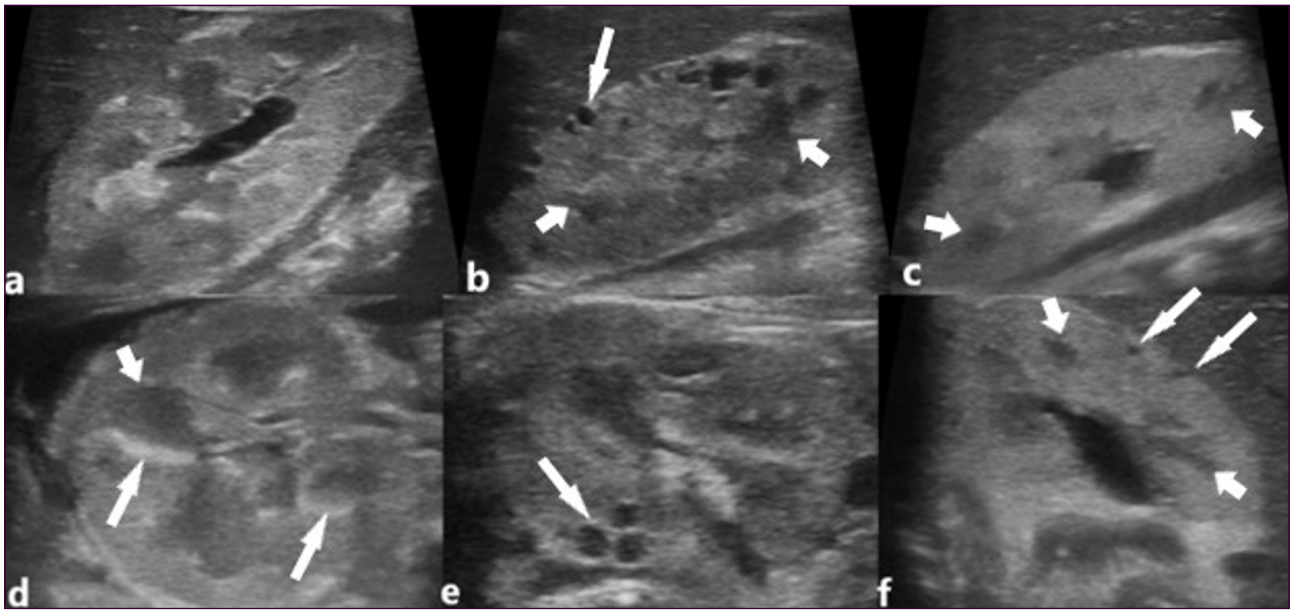

Figure 2. Coronal and transverse US images of the kidneys in three patients (a-f) show three different patterns of renal involvement in ZS. The kidneys demonstrate no cysts, and medullae preserve their volume (short arrow) but exhibit peripheral hyperechogenicity (long arrows) resembling transient nephrocalcinosis in one patient (a,d), the kidneys have multiple small subcapsular cysts with thin hyperechoic walls (short arrows), medullae are small, irregular but preserve their hypoechogenicity (short arrows) in another patient (b, e), and the kidneys show severe cortical hyperechogenicity, have fewer subcapsular cysts with no visible wall hyperechogenicity (long arrows), and the medullae are small and irregular (short arrows) in another (c,f).

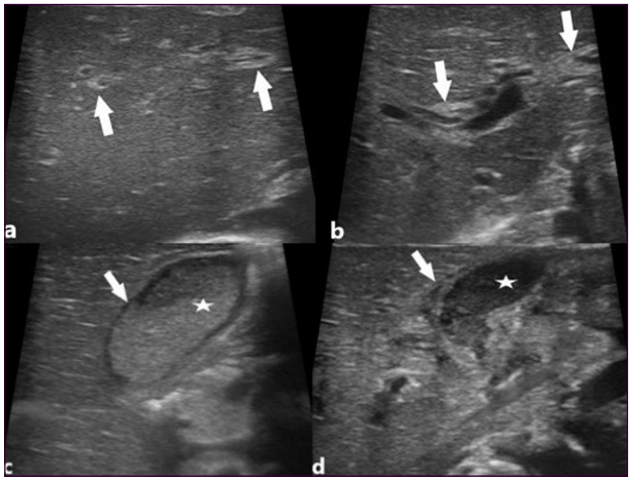

Figure 3. US images of the liver parenchyma in two patients (a,b) show increased periportal echogenicity (arrows). US images of the gallbladder in two patients (c,d) show a distended gallbladder (arrow,c) with hyperechoic biliary sludge (star,c) in one patient and a non-distended gallbladder with wall edema (arrow,d) with biliary sludge (star,d) in another.

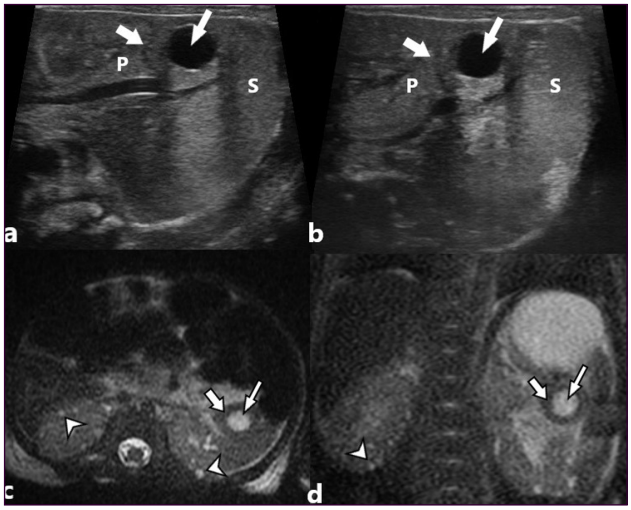

Figure 4. US images of the abdomen (a,b) in one patient show a homogeneously anechoic cyst at the pancreatic tail (long arrows), surrounded by a rim of parenchyma that is isoechoic to the pancreas and demarcated from the pancreas parenchyma with a linear hypoechogenic line (short arrows). Axial and coronal T2-weighted images of the abdomen (c,d) of the same patient show the hyperintense cyst (long arrows) surrounded by a parenchymal rim that is hypointense relative to the pancreatic parenchyma (short arrows). Note the subcapsular cysts of the kidneys (arrowheads).

DISCUSSION

The main findings on MRI of the brain in Zellweger syndrome are malformations of cortical development (typically in the form of perisylvian polymicrogyria), corpus callosum abnormalities, white matter signal abnormalities, and subependymal germinolytic cysts (SEGCs) (2,4,9).

Of the described MRI findings, SEGCs were found in all patients with ZS in the presented study. High frequency of those cysts was in accordance with an ultrasonographic study which found SEGCs in 8 out of 10 infants with ZS. Those cysts, however, are not specific to ZS or neurometabolic diseases and can also be seen in chromosomal abnormalities and congenital infections (7,8,10,11). On US examinations, most SEGCs demonstrate hyperechoic septae or peripheral hyperechogenicity, thus, their sonographic appearances can simulate heterogeneous germinal matrix hemorrhage (GMH) in

the caudothalamic grooves, as well as non-hemorrhagic germinal matrix hyperechogenicity that can be seen in intrauterine growth retardation, asphyxia or prematurity (7,8, 12,13). In two patients in the presented study (1 neonate born at the 35th week and 1 infant born at term), the MRIs of the brain demonstrated hemorrhage in those cysts, but the hemorrhagic changes were indistinguishable from the hyperechogenic components of the cysts on US images (**Figure 5**). Since the SEGCs in ZS have been reported to be non-hemorrhagic in histopathological studies (14,15), the hemorrhagic signal intensities in the presented cases may be associated with accompanying GMH. Although GMH is not a frequent finding in a neonate born at term, hemorrhage in term neonates with ZS may not be an uncommon finding as hepatic dysfunction and coagulopathy are known to cause a tendency for intracranial hemorrhage in this population and one case report also has described GMH in a term neonate with ZS (16,17).

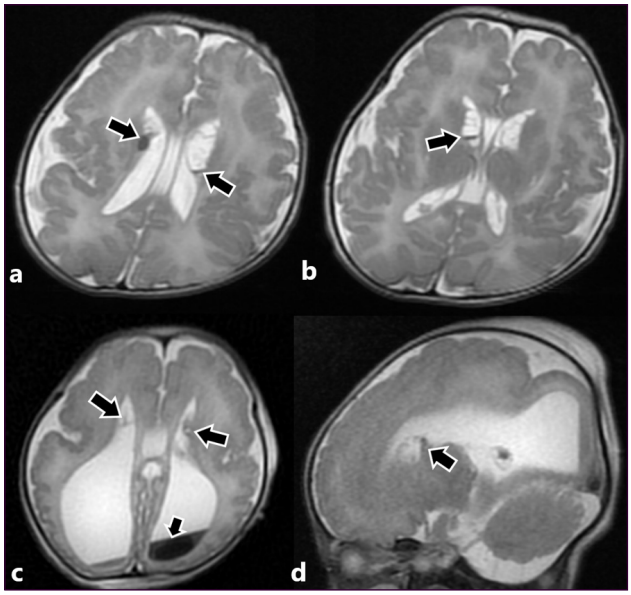

Figure 5. MRI images of the two patients with hemorrhagic signal changes in the SEGCs. Axial T2-weighted images of one patient born at term (a,b) show the low-signal areas in the SEGCs (arrows). Axial and sagittal T2-weighted images of another patient born at 35th gestational age (c,d) show the hypointense hemorrhagic signal changes in the location of the SEGCs near caudothalamic grooves (long arrows). The patient also had intraventricular hemorrhage (short arrow,c).

The white matter signal abnormalities in ZS are mostly reported as diffusely increased T2-weighted signal changes with high apparent diffusion coefficient (ADC) values on MRI and are thought to represent hypomyelination and dysmyelination rather than demyelination (18,19). In US images of the cerebrum of patients with ZS, the sonographic equivalent of the described white matter signal changes on MRI are expected to be diffuse and subtle, if detected (8). One neonate born at term with evident multifocal hyperechoic white matter areas in the frontoparietal lobes in the presented study was atypical this finding. Because the neonate was not further evaluated with MRI, it was not possible to suggest the cause of the white matter changes. Speculative explanations would be seizure activity and accompanying intramyelinic cytotoxic edema, or cytotoxic edema of the white matter areas that are not infrequently observed in other peroxisomal biogenesis disorders, such as neonatal adrenoleukodystrophy or single enzyme peroxisomal defects (19).

Lenticulostriate vasculopathy (LSV), seen on head US examinations of children as branching linear hyperechogenicity in the basal ganglia and thalami is a non-specific finding when seen alone and can also be seen in congenital infections, perinatal asphyxia, metabolic diseases, chromosomal abnormalities or as an incidental finding (7,8). The frequency of LSV in head USs of the patients with ZS in this study was high (66.6%). That was in accordance with one study that reported LSV in 70% of the ZS patients (8).

Mild to moderate ventricular enlargement and ventricular contour abnormalities are frequent features in MRIs of ZS and are present in US examinations in about 80% of the cases (2,8). On US examinations of the 9 patients in the present study, ventricular enlargement was mild to moderate in 8. Severe ventricular enlargement does not seem to be characteristic of ZS and was present in only one patient in the study who also had callosal dysgenesis. Callosal thinning is a more frequently reported feature in ZS than callosal dysgenesis and was present in 4 out of 9 patients in this study. Being less frequent than callosal thinning, partial or complete agenesis of the corpus callosum has been reported in ZS (8,20).

While hepatic dysfunction and hyperbilirubinemia are typically observed in most neonates with ZS (1,21,22), the findings of hepatomegaly, periportal inflammation, gallbladder edema or biliary sludge, and bile duct dilation were not constant on US examinations of the patients in this study and were observed in 4 out of 9 patients (44.4%). The reported frequencies of hepatomegaly and hepatic fibrosis in literature are 78% and 76% (1,22). The relatively lower liver US findings in the presented study could be due to the performance of US studies early in the neonatal period, within the first 3 days of life. Periportal hyperechogenicity observed in this group of neonates and infants most likely reflects periportal inflammation rather than periportal fibrosis since fibrosis and cirrhotic changes in the liver are not expected to develop in the early period but are commonly present with increasing age (3,21,22).

Renal involvement in ZS is seen in the form of glomerulocystic kidney disease (GCKD), which is histopathologically characterized by enlarged Bowman's spaces and tubular cystic changes (23-

25). On US examinations, GCKD is characterized by increased echogenicity of the kidneys with loss of corticomedullary differentiation. The cysts in GCKD are small, usually between 2-5 mm, and subcapsular cortical in location. Sonographic findings suggestive of GCKD are not specific to ZS and may also be seen in familial non-syndromic polycystic kidney disease, tuberous sclerosis complex, or syndromic polycystic diseases such as Bardet Biedl, Meckel Gruber, and Joubert syndromes (23-26). In renal US examinations of the patients in the presented study, a GCKD pattern with cortical hyperechogenicity and subcapsular cysts was observed in 8 out of 9 patients. As opposed to typically lost corticomedullary differentiation in GCKDs, in all patients in the presented study, corticomedullary differentiation was preserved. Renal size, as opposed to some other causes of GCKD, was within normal limits for the age of the patients. Also, in 7 out of 9 patients renal medullae was small, irregular, and centrally displaced.

1 neonate in this study had a cystic lesion in the tail of the pancreas. Although pancreatic functional impairment is one of the expected clinical features of ZS (1,3,27), the clinical records of the patient did not show any endocrinologic abnormalities at the time of the US examination. In one case report, pancreatic islet cell hyperplasia has been reported histopathologically in a patient with ZS (28). However, to our knowledge, no sonographically evident structural abnormalities or lesions of the pancreas have been described in neonates with ZS so far.

Retrospective nature and the small number of patients are the main limitations of the presented study. Due to sedation and transport risks in patients with ZS in the neonatal or infancy period, brain MRI examinations were not performed in all patients, thus, a comparative analysis of the head US and brain MRI studies were not performed. The frequent cortical migration anomalies described in MRIs of ZS patients (2,4) were not specifically sought on head US examinations and thus were not evaluated in this study.

CONCLUSION

US imaging of the head in a population of neonates and an infant with ZS in this study showed subependymal germinolytic cysts, mild to moderate ventricular dilation, thinning of the corpus callosum and lenticulostriate vasculopathy as the most common findings. Hepatomegaly, periportal hyperechogenicity, and gallbladder edema with biliary sludge was observed in US examinations of the abdomen in less than half of the cases. Bile duct dilation was not an early sonographic feature. In addition to increased cortical echogenicity and small subcapsular cortical cysts, preservation of the renal corticomedullary differentiation with small and irregular medullae was a frequent finding. In neonates and infants, bedside US may serve as a valuable tool for suggesting the diagnosis of ZS if the sonographic appearances of the common findings of ZS in different organ systems are known and sought.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Şanlıurfa Eyyübiye Training and Research Hospital Ethics Committee (Date: 20.06.2019, Decision No: 2019/20).

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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Pediatr Pract Res 2023; 11(3): 149-152
DOI: 10.21765/pprjournal.1358733

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Knowledge Levels of Individuals Living in Rural Areas about Anthrax

Kırsal Kesimde Yaşayan Bireylerin Şarbon Bilgi Düzeyi

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ABSTRACT

Aim: Anthrax, which is encountered sporadically throughout the world, is a zoonotic infectious disease especially seen in the eastern regions of our country. The spore structure maintains its vitality for a long time in the environment. This can cause epidemics among humans. In this study, we aimed to determine the knowledge levels of individuals living in rural areas and at risk of disease transmission.

Material and Method: The population of the research, which was planned in descriptive type, consisted of individuals aged 12 and over living in the A village in B. It was planned to reach the entire universe. The survey prepared by the researchers was collected by face-to-face interviews with people who agreed to participate. The data were analyzed in the SPSS package program.

Results: The median age of 201 people participating in the study was 47 (13-80). 55.7% (112 people) of them were women. Among the education levels of the participants, primary school graduates made up the largest portion with 39.3%. All participants in the study had heard of anthrax before. However, it was seen that the effect of anthrax disease on humans and animals was not known enough.

Conclusion: The fact that province B is one of the provinces where anthrax disease is most common was considered to be the reason why the participants had heard of anthrax before. However, it was understood that the effect of anthrax disease on humans and animals is not known enough. It was seen that educational activities were needed to increase society's awareness about disease protection.

Keywords: Anthrax, knowledge level, countryside, farming, contagious disease

ÖZ

Amaç: Dünya genelinde sporadik olarak karşılaşılan şarbon, özellikle ülkemizin doğu bölgelerinde görülen zoonotik bir enfeksiyon hastalığıdır. Spor yapısı ortamda uzun süre canlılığını korur. Bu da insanlar arasında salgınlara neden olabilir. Bu çalışmada kırsal kesimde yaşayan ve hastalık bulaşma riski taşıyan bireylerin bilgi düzeylerinin belirlenmesi amaçlandı.

Gereç ve Yöntem: Tanımlayıcı tipte planlanan araştırmanın evrenini B ili A köyünde yaşayan 12 yaş ve üzeri bireyler oluşturdu. Evrenin tamamına ulaşılması planlandı. Araştırmacılar tarafından hazırlanan anket, katılmayı kabul eden kişilerle yüz yüze görüşerek toplandı. Veriler SPSS paket programında analiz edildi.

Bulgular: Çalışmaya katılan 201 kişinin yaş ortancası 47 (13-80)'dir. Bu kişilerin %55,7si (112 kişi) kadındı. Katılımcıların eğitim düzeyleri arasında en büyük payı %39,3 ile ilkokul mezunları oluşturdu. Araştırmaya katılanların tamamı daha önce şarbonu duymuştu. Ancak şarbon hastalığının insan ve hayvanlar üzerindeki etkisinin yeterince bilinmediği görüldü.

Sonuç: B ilinin şarbon hastalığının en sık görüldüğü illerden biri olması, katılımcıların şarbonu daha önce duymasının nedeni olarak değerlendirildi. Ancak şarbon hastalığının insan ve hayvanlar üzerindeki etkisinin yeterince bilinmediği anlaşıldı. Toplumun şarbon hastalığından korunma konusunda farkındalığını artırmak için eğitim faaliyetlerine ihtiyaç olduğu görüldü.

Anahtar Kelimeler: Şarbon, bilgi düzeyi, kırsal kesim, hayvancılık, bulaşıcı hastalık

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Başvuru Tarihi/Received: 13.09.2023
Kabul Tarihi/Accepted: 07.10.2023

INTRODUCTION

Anthrax is a zoonotic infectious disease caused by Bacillus anthracis. The causative agent is a gram-positive bacterium that forms spores in the presence of oxygen. The spore form is highly resistant to external environments, dryness, cold, ultraviolet rays, high and low pH levels and chemical disinfectants (1). It is transmitted to animals orally through infected food and water (2,3). It can be transmitted to humans through direct contact with an infected animal as a result of injury during slaughter, consumption of infected animal meat without adequate cooking, inhalation of spores, and use of contaminated injectors in drug addicts (2,3). In general, human cases are associated with animal products. However, it is important because of its use for bioterrorism. There are national programs against anthrax, which is among the notifiable diseases (2, 4). Turkey Zoonotic Diseases Action Plan (2019-2023) includes policies to combat anthrax in Turkey (5).

In order to prevent anthrax cases, it is important to control both animal and human transmission. In this context, it is a priority to provide training to risk groups (livestock, butchers, veterinarians, etc.). In education, the main subjects are slaughtering, swimming, eating meat of infected animals, burial of carcasses, vaccination, decontamination and disinfection. In our study, it was aimed to evaluate the knowledge about anthrax disease of people living in A Village of B province.

MATERIAL AND METHOD

The study was carried out with the permission of Kafkas University Medical Faculty Ethics Committee (Date: 30.12.2022, Decision No: 13). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The population of the research, which was planned as a descriptive type, consisted of people aged 12 and over (387 people) living in A village, city B. It was planned to reach the entire universe, without making a choice for the sample of the study. The limitation of our study was the high workload of some of the villagers due to their work both in the city center and in the village. This led to the reluctance of the villagers to participate in the survey. For this reason, 201 (%51,9) people in the research universe agreed to participate in the research, while the rest did not. The data were collected through face-to-face interviews with the data collection form prepared by the researchers. The data collection form includes the sociodemographic characteristics of the individual, the transmission routes of anthrax disease, the symptoms and prevention methods.

The data were analyzed in SPSS package program. In the analyses, the descriptive criteria frequency, percentage, and median from the central concentration criteria were used.

RESULTS

The median age of 201 people participating in the study is 47 (minimum 13-maximum 80). 55.7% of these people (112 people) were women. 8.0% of the participants had not received any formal education. Considering the education levels, primary school graduates made up the largest portion with 39.3% (**Table 1**). 75.6% of the participants (152 people) were engaged in animal husbandry. 30.9% (47 people) of those who are engaged in animal husbandry and 22.4% (11 people) of those who are not engaged in animal husbandry had previously received training on anthrax. 71.1% of all participants had not received any training. To the question 'where did you get the most information about anthrax', 26.4% of the participants answered from television, radio and newspaper, 24.9% from the Ministry of Agriculture personnel, 24.9% from my neighbor, 16.9% from the internet (**Table 1**). It was known with 59.7% accuracy that unburied animal carcasses were an important source of contagion between animals. 53.8% of the participants misunderstood or did not know how the animals infected with anthrax died. 42.3% of the participants knew that it is wrong to keep the meat in the refrigerator at -40 degrees in order to prevent anthrax contamination from the meat of animals infected with anthrax (**Table 2**). 90.0% correctly stated that vaccination is necessary to protect animals from anthrax, 92.5% correctly stated that anthrax is a notifiable disease, and 85.1% correctly knew how to dispose of animals caught with anthrax (**Table 2**).

DISCUSSION

Anthrax has been brought under control in developed countries, and it is still prevalent in developing countries where agriculture is intense. It is an endemic disease in our country and it is seen that the cases originate from agriculture. The cases are mostly concentrated in Eastern Anatolia and Central Anatolia regions. Case report at most; It was built from Kars, Sivas, Ankara, Muş, Erzurum and Hakkari (1, 3).

Anthrax can be transmitted to humans by slaughtering infected animals, consuming contaminated animal products, and not burying animals properly. In order to control the disease, people need to know the methods of prevention and follow the methods (6).

In a study conducted in Eskişehir, it was found that 56.5% of 200 participants knew what anthrax

Table 1: Sociodemographic characteristics

Sociodemographic characteristics	Number	Percentage
Sex		
Woman	112	55,7
Man	89	44,3
Age		
13-22	28	13,9
23-32	23	11,4
33-42	28	13,9
43-52	54	26,9
53-62	45	22,4
63-72	18	9,0
73-80	5	2,5
Education status		
Illiterate	16	8,0
Primary school graduate	79	39,3
Secondary school graduate	52	25,9
High school graduate	38	18,9
Graduated from a Universty	16	8,0
Animal husbandry situation		
Doing animal husbandry	152	75,6
Does not farm	49	24,4
Status of receiving education about anthrax		
Educated	58	28,9
Not educated	143	71,1
Where to get the most information about anthrax		
Internet	34	16,9
TV, radio, newspaper	53	26,4
Book, magazine, article	6	3,0
Relative, neighbor, friend	50	24,9
Ministry of Agriculture and Forestry personnel	50	24,9
Ministry of Health personnel	8	4,0

TV:television

was, and in a study conducted at Erciyes University Hospital, 82.2% of 420 participants had heard of anthrax before(7, 8). In this study, all of the participants had heard of anthrax before. The fact that animal husbandry is carried out intensively in B province and that this is one of the provinces where anthrax is most common was thought to be the reason for the people involved in this study to have heard of anthrax before.

Sheep and goats infected with anthrax die in a very short time, while cattle die within a week. Bloody oozing occurs in the mouth, nose and anus of dead animals (9). Anthrax can infect the skin, intestines, or lungs in humans(4). 53.8% of the participants did not know that animals infected with anthrax could die in a very short time. Again, 34.8% of the people in this study did not correctly answer the organs that anthrax disease causes disease in humans(**Table 2**). In our study, it was understood that the effect of anthrax disease on humans and animals is not known enough.

Unburied animal carcasses are important in inter-animal contagion, as carcasses are consumed by carnivorous animals and contaminate the environment with their excrement and waste. Slaughtering of sick animals, consumption or use of products such as meat, leather and wool lead to the transmission of the disease to humans (2, 6). In the study, 59.7% of the participants knew that anthrax could be transmitted from unburied animal carcasses. It was understood that 35.3% of the participants did not know that their skin and wool could not be used after the infected animal was killed, and 57.7% did not know that they should not keep their meat in the refrigerator (**Table 2**). This situation shows the lack of information about the necessity of disposal of infected animal products.

Table 2: Distribution of people according to their answers to questions about anthrax

Questions asked	The answers given		
	True	Wrong	I don't know
	Number (%)	Number (%)	Number (%)
The most important source for the transmission of anthrax to animals is the unburied animal carcasses in the pasture.	120 (59.7)	8 (4.0)	73 (36.3)
Meat should be kept in the refrigerator at -40 degrees to prevent contamination of meat with anthrax.	54 (26.9)	85 (42.3)	62 (30.8)
Animals infected with anthrax bleed to death in less than a week.	93 (46.3)	10 (5.0)	98 (48.8)
Anthrax infects the skin, intestines and lungs in humans.	131 (65.2)	4 (2)	66 (32.8)
The most important way to protect animals from anthrax is to vaccinate all animals.	181 (90.0)	0 (0)	20 (10)
Animals caught with anthrax are killed and destroyed, their meat is not eaten, but their skin and wool can be taken to prevent loss.	42 (20.9)	130 (64.7)	29 (14.4)
Animals that have died from anthrax are buried in pits dug two meters deep by pouring quicklime on them.	171 (85.1)	6 (3)	24 (11.9)
The pastures and water sources where anthrax disease is detected are cordoned off and no animals are allowed into the pasture for 15 days.	155 (77.1)	16 (8)	155 (77.1)
It is sufficient to vaccinate the animals in the pastures with anthrax disease for one year.	103 (51.2)	32 (15.9)	66 (32.8)
Reporting of anthrax disease in both animals and humans is mandatory.	186 (92.5)	2 (1)	13 (6.5)

Animals that die from anthrax should be buried in pits at least two meters deep, with quicklime poured over them. Places where anthrax disease is seen should be cordoned off and the entry and exit of animals there should be prohibited. Anthrax is a disease that must be notified if it occurs in humans or animals (9). 85.1% of the participants knew how to bury animals that died from anthrax, 77.1% knew that pastures with anthrax should be cordoned off, and 92.5% knew that anthrax is a notifiable disease. It was seen that they knew what to do except disposal of animal products .

All animals susceptible to the disease in areas associated with communal areas such as pastures where anthrax has been observed should be vaccinated continuously for five years (9). Of the people in the study, 90% knew that vaccination is important in protecting animals against anthrax. 51.2% of the participants stated that if anthrax disease is seen in the pastures, it is sufficient to vaccinate for one year. Although most of the participants knew that vaccination is necessary to protect animals from anthrax, it was seen that they did not have enough information about the duration of vaccination.

CONCLUSION

Anthrax is a disease that continues its effects in rural areas where animal husbandry is intense. The number of studies conducted to determine the knowledge status of people living in rural areas about anthrax is limited. In the fight against this disease, it is very important to know the information status of the people in the risk group and to carry out awareness-raising activities if necessary. It has been observed that the knowledge about anthrax is not sufficient in A village of B province, whose primary livelihood is animal husbandry. Lack of information on vaccination and disposal of anthrax-infected animal products was noted. Studies should be carried out to increase public awareness about anthrax disease. Before incentive programs in the field of animal husbandry, it is necessary to attend training on zoonotic diseases..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kafkas University Medical Faculty Ethics Committee (Date: 30.12.2022, Decision No: 13).

Informed Consent: During the face-to-face interview with the participants, verbal consent was obtained and the forms were filled out.

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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Pediatr Pract Res 2023; 11(3): 153-157
DOI: 10.21765/pprjournal.1324798

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Effect of Topiramate on Ischemia-Modified Albumin and Prolidase Enzyme Levels in Nitroglycerin-Induced Adolescent Rat Brain Tissue

Topiramatın Nitrogliserinle İndüklenen Adolesan Sıçanların Beyin Dokusunda İskemi Modifiye Albümin ve Prolidaz Enzim Düzeyleri Üzerine Etkisi

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ABSTRACT

Aim: Migraine is a neurological disorder accompanied by episodic headaches that can also occur in children and adolescents. Environmental and genetic factors play a role in the pathogenesis of migraine and the possible contribution of oxidative stress (OS) is debated. Therefore, the present study focused on the possible effect of topiramate (TPM) on the oxidative stress markers ischemia-modified albumin (IMA) and prolidase enzyme activity in nitroglycerin (NTG)-induced brain tissue of adolescent rats.

Material and Method: In this study, 32 male Wistar albino rats aged 6 weeks (adolescence) were used. Rats were divided into four groups with 8 animals in each group. Rats were administered NTG intraperitoneally (i.p.) once daily and topiramate (TPM) orally (p.o.) twice daily. Groups and doses were formed as follows. Group 1: Control group; Group 2: NTG (10 mg/kg) group, Group 3: NTG (10 mg/kg) + TPM (50 mg/kg) group and Group 4: Only TPM (50 mg/kg) group. Animals were sacrificed at the end of the experiment. After the brain tissues were homogenized, IMA and prolidase enzyme activities were measured spectrophotometrically.

Result: IMA and prolidase levels increased in the NTG-treated group and this increase was found to be significant when compared with the control group ($p \leq 0.05$). The combination of NTG+TPM brought IMA and prolidase levels closer to the control group and numerically reduced them compared to the NTG group. Only the TPM group showed a significant decrease compared to the NTG group ($p \leq 0.05$). In addition, IMA and prolidase levels of TPM were close to the control group.

Conclusion: NTG increased IMA and prolidase levels, indicating that it may trigger oxidative stress. TPM partially reversed IMA and prolidase levels. These results may support the hypothesis that TPM may have an antioxidant effect that suppresses OS. Understanding the pharmacodynamic effects of TPM may enable its more effective use as a therapeutic agent.

Keywords: Topiramate, ischemia-modified albumin, prolidase, adolescent rat, oxidative stress, migraine

ÖZ

Amaç: Migren, çocuklarda ve ergenlerde görülebilen epizodik baş ağrısının eşlik ettiği nörolojik bir bozukluktur. Migrenin patogenezinde çevresel ve genetik faktörler rol oynar ve oksidatif stresin (OS) olası katkısı tartışılmaktadır. Bu yüzden sunulan çalışma, nitrogliserin (NTG) ile indüklenen adolesan ratların beyin dokusunda, topiramat'ın (TPM) oksidatif stres belirteçleri olan iskemi modifiye albümin (IMA) ve prolidaz enzim aktivitesi üzerine olası etkisine odaklanmıştır.

Gereç ve Yöntem: Bu çalışmada, Wistar albino ırkı 6 haftalık (adolesan dönem) 32 adet erkek rat kullanıldı. Sıçanlar, her grupta 8 hayvan olacak şekilde dört gruba ayrıldı. Sıçanlara, NTG intraperitoneal (i.p.) günde 1 kez ve topiramat (TPM) oral (p.o.) günde 2 kez olarak uygulandı. Gruplar ve dozlar aşağıdaki gibi oluşturuldu. Group 1: kontrol grubu; Group 2: NTG (10mg/kg) grubu, Group 3: NTG (10 mg/kg) + TPM (50 mg/kg) grubu ve Group 4: Sadece TPM (50 mg/kg) grubu. Hayvanlar deneyin sonunda sakrifiye edildi. Elde edilen beyin dokuları homojenize edildikten sonra, IMA ve prolidaz enzim aktiviteleri spektrofotometrik ölçüldü.

Bulgular: NTG ile tedavi edilen grupta IMA ve prolidaz seviyelerinde artış görülmüş ve bu artış kontrol grubuyla karşılaştırıldığında anlamlı bulunmuştur ($p \leq 0,05$). NTG+TPM kombinasyonu, IMA ve prolidaz seviyelerini kontrol grubuna yaklaştırmış ve NTG grubuna kıyasla sayısal olarak azaltmıştır. Sadece TPM uygulanan grup, NTG grubuna göre anlamlı azalış sergiledi ($p \leq 0.05$). Ayrıca, TPM'nin IMA ve prolidaz düzeyleri kontrol grubuna göre' yakın değerler aldı.

Sonuç: NTG, IMA ve prolidaz seviyelerini artırarak OS'u tetikleyebileceğini göstermiştir. TPM ise kısmende olsa IMA ve prolidaz düzeylerini tersine çevirdi. Bu sonuçlar, TPM'nin OS'u baskılayan antioksidan etkiye sahip olabileceği varsayımını destekleyebilir. TPM'nin farmakodinamik etkilerinin anlaşılması, terapötik bir ajan olarak daha etkili bir şekilde kullanılmasını sağlayabilir.

Anahtar Kelimeler: Topiramat, iskemi modifiye albümin, prolidaz, adolesan rat, oksidatif stres, migren

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Başvuru Tarihi/Received: 17.07.2023
Kabul Tarihi/Accepted: 31.07.2023

INTRODUCTION

Migraine is a neurological disorder affecting millions of children and adolescents globally (1). Migraine is a pathologic condition in which a headache triggered by optical and acoustic stimuli is accompanied by nausea and vomiting. These headaches reduce adolescents' quality of life and productivity at school (2), and they are more prone to anxiety, depression, insomnia, and behavioral disorders (3). Although migraine is common in all populations worldwide, its pathophysiology is not fully understood except for symptomatic treatments. Therefore, researchers have tried various methods to understand the etiology of migraine in experimental animal models (4). One of these methods is the administration of nitroglycerin (NTG) to induce migraine headaches. NTG is a pharmacological agent used to provide a vasodilator effect in blood vessels in cardiovascular diseases such as unstable angina and myocardial infarction (5). However, cluster headaches after NTG use are unwanted side effects. Therefore, NTG is used in in vivo research because it mimics migraine-like headaches. The vasodilating effect of NTG increases the release of exogenous and endogenous nitric oxide (NO) in the endothelium of blood vessels, causing vasodilation in the meningeal vessels of the brain, which can cause migraine headaches. Furthermore, NTG increases NO release, develops tolerance to prolonged use, and causes pro-oxidant effects (6), and NO reacts with peroxynitrite and produces superoxide, a reactive oxygen radical, leading to OS. Thus, it can cause damage to other organs, including brain tissue (6,7). Pharmacologic agents such as topiramate (TPM) and amitriptyline are used to prevent migraine attacks in children and adolescents (8). TPM is a neuromodulating antiepileptic drug and has been suggested to be effective in the prophylactic treatment of migraine by inhibiting sodium and calcium channels and reducing the release of neurotransmitters (9,10). There are studies suggesting that the use of TPM in migraine reduces headaches in adults and children. However, it was emphasized that there are limited studies in children and adolescents and possible side effects should not be ignored (9).

Migraine attacks have been linked to many factors (4). Oxidative stress (OS) is one of these factors. OS is a shift in the oxidant/antioxidant balance in the body in favor of oxidants and has been suggested to contribute to the onset of migraine attacks (11). The excess of polyunsaturated fatty acids in the nervous system and the fact that it is not rich enough in antioxidant enzymes increase the susceptibility of cells to OS (12). OS can lead to increased lipid peroxidation and damage to cell membranes, enzymes, proteins, and DNA (13). Increased oxidant products have been suggested to cause an increase in vasoconstrictors such as angiotensin and urotensin, which are thought to be involved in migraine attacks (14). Recently, ischemic-modified albumin (IMA) and prolidase enzymes have been used as OS markers (15–17). Reactive oxygen species (ROS) disrupt the oxidant/antioxidant balance in the organism during ischemia, leading to changes in the structure and function of albumin. This decreases the capacity of albumin to bind heavy metals such as nickel and cobalt to the N-terminus and leads to an increase in albumin levels. This oxidized albumin molecule is called IMA (17,18). Prolidase is a peptidase found in the cytoplasm of cells that has the unique ability to cleave proline or hydroxyproline at its C-terminal end (19). In addition to plasma, prolidase is also found in organs such as the brain, liver, and heart. Prolidase plays an important role in collagen synthesis by secreting proline, thus maintaining tissue integrity (12,18,20). It is known to affect inflammation, angiogenesis, cancer, and wound healing processes. Furthermore, proline is thought to be a neurotransmitter in the central nervous system and has been reported to be a neuromodulator in synaptic transmission. Increased proline levels affect prolidase enzyme levels and are thought to potentiate the effect of glutamine, which plays a role in the pathogenesis of migraine (18).

Migraine attacks are known to be triggered by many factors and determining the possible contribution of OS to these attacks is one of the topics of current research. To our knowledge, there is no study investigating the effect of TPM on IMA and prolidase enzyme levels, which may be markers of oxidative stress, in adolescent rats. Therefore, the present study focused on the possible effect of TPM used in the treatment of migraine in children and adolescents on IMA and prolidase enzyme activity and its relationship with oxidative stress.

MATERIAL AND METHOD

Animals

In this study, 32 male Wistar albino rats aged 6 weeks (adolescence) were used. All animals were housed under the same physiological conditions, reverse illumination was applied at 12-hour intervals, and standard rat chow and tap water were given ad-libitum in an environment with a room temperature of 20-24°C and 40-60% humidity. This study was approved by the local ethics committee and animal care guidelines were followed (Date:22/06/2023, Number:2023/08-04).

Experimental procedure

The experimental procedure was inspired and modified from previous reports (21–24) The animals were divided into 4 groups and each group consisted of 8 rats. Group 1: Healthy control group; no agent was administered. Group 2: NTG group; NTG (10mg/Kg i.p.) was administered once daily for 5 days. Group 3: NTG+TPM group; NTG (10 mg/Kg, i.p.) (1 time per day) + TPM 50 mg/kg (5 days) (administered orally twice 12 hours apart). Group 4: TPM

50 mg/kg (5 Days) only (administered orally twice 12 hours apart). All subjects were sacrificed under general anesthesia with a 10 mg/Kg dose of xylazine HCl and 75 mg/Kg Ketamine by the bloodless release method. The obtained brain tissue was stored at -80 °C until the time of the study.

Preparation of Homogenate

Samples were homogenized to 20% tissue homogenate with a glass homogenizer in ice molds using phosphate buffer (pH 7.4). Tissue homogenates were taken into pre-labeled tubes and centrifuged at 14000 g for 20 minutes at +4°C. The resulting supernatants were placed in Eppendorf tubes and stored in a deep freezer at -80°C until working (25,26).

IMA Assay

IMA levels were performed by the method reported by Bar O et al (27). Briefly, 200 µL of the supernatant sample was added to 50 µL of 0.1% cobalt chloride and vortexed. This mixture was incubated at room temperature for 10 minutes. Then, 50 µL of Dithiothreitol (DTT) was added to the mixture and incubated for 2 minutes to allow the reaction with cobalt to take place. Then 1 mL of saline solution was added and the reaction of the mixture was stopped. Blinds of the sample were prepared in the same way without the addition of DDT. The absorbance values of the samples were measured spectrophotometrically (T80+ UV-vis spectrometer, United Kingdom) at 470 nm wavelength and IMA levels were calculated.

Prolidase Assay

Prolidase activity was determined using the method proposed by Myara et al. (1982) (28). 100 µl of supernatant was mixed with 100 µl of saline. 25 µl of the mixture was taken and mixed with 75 µl of pre-incubation solution (1 mmol/L GSH, 50 mmol/L MnCl2, 1 mmol/L GSH in 50 mmol/L Tris HCl buffer at pH:7). The mixture was incubated at 37˚C for 30 min. After incubation, 100 µl of a pH 7.8 solution containing Gly-Pro was added and incubated at 37˚C for 5 min. 1 ml of glacial acetic acid was added to the mixture. To the mixture was added 300 µl of tris-HCl buffer at pH: 300 µl of tris-HCl buffer at pH: 7.8 and 1 ml of ninhydrin solution. The tube was capped and kept in a 90˚C water bath for 20 minutes. The mixture was subjected to the ice bath, cooled and absorbances were read at 515 nm without waiting.

Statistical Analysis

The results of the study are shown as Mean and Standard Deviation. One-way Analysis of Variance (ANOVA) was used to compare group means. Following the analysis of variance, the Duncan test was used to determine the different groups. The statistical significance level was taken as 5% and the SPSS (IBM SPSS for Windows, ver.26) statistical package program was used for calculations.

RESULTS

In this study, the changes in IMA and prolidase enzyme activity levels in the brain tissue of adolescent rats treated with NTG and TPM are shown in **Table 1**. When the findings were analyzed in terms of IMA levels, it was observed that the NTG group was significantly higher than the control group ($p \leq 0.05$). IMA levels approached the control with the combined application of NTG+TPM. Only the IMA values of the TPM group were similar to the control group and did not show a significant difference ($p \geq 0.05$). Brain tissue prolidase enzyme level was highest in the NTG group and this value was significant when compared with the control ($p \leq 0.05$). Prolidase levels in the NTG+TPM group decreased numerically compared to the NTG group. However, this decrease was not significant ($p \geq 0.05$). IMA and prolidase levels between the groups are also presented in detail in **Figure 1**.

Table 1: IMA and prolidase levels in NTG and TPM-treated adolescent rats.

Groups	IMA (ABSU) (Mean±SD)	PROLIDASE (U/g tissue) (Mean±SD)
Control (Sham)	0.83 ± 0.36^{b}	3.11 ± 0.38^{c}
NTG (10 mg/kg)	1.24 ± 0.29^{a}	$4.65 \pm 1,08^{a}$
NTG (10 mg/kg)+TPM (50 mg/kg)	1.03 ± 0.18^{ab}	$4.07 \pm 0,62^{ab}$
TPM (50 mg/kg)	0.93 ± 0.08^{b}	$3.45 \pm 0,65^{bc}$

IMA; Ischemic-modified albümin, NTG; Nitroglycerin, TPM; Topiramate, a,b,c p: values with different letters are significant when compared with each other. Data are presented as mean±SD ($p \leq 0.05$).

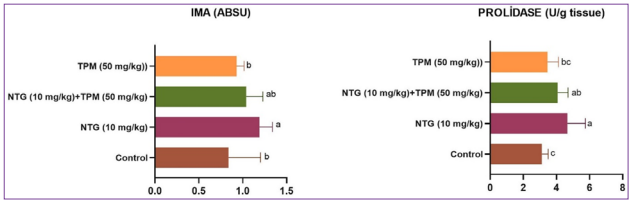

Figure 1. IMA and prolidase levels in adolescent rats. IMA; Ischemic-modified albümin, NTG; Nitroglycerin, TPM; Topiramate, a,b,c p: values with different letters are significant when compared with each other. Data are presented as mean±SD ($p \leq 0.05$).

DISCUSSION

The present study evaluated the effect of TPM on the OS markers IMA and prolidase enzyme activity in NTG-induced adolescent rats. The present study is the first study to investigate oxidative stress indicators (IMA and prolidase) in the brain tissue of adolescent rats in a migraine model based on a literature search. NTG-induced brain tissue increased IMA and prolidase activity, whereas TPM decreased the increased IMA and prolidase levels. The data presented indicated that NTG may induce OS, while TPM may exhibit antioxidant properties.

NTG administration has been reported to have the ability to induce OS (29). Indeed, in one study, NTG increased malondialdehyde, a marker of OS, and decreased

levels of antioxidant enzymes such as glutathione and glutathione peroxidase (21). NTG administration has also been shown to induce OS in rat brain tissue (30) However, there is no study showing the effect of NTG on IMA and prolidase levels, which are markers of OS. In this study, NTG administration induced OS and increased IMA and prolidase levels, consistent with the literature. These results support the hypothesis of a possible contribution of oxidative stress in migraine attacks. Increased IMA levels may cause ischemia-induced increases in reactive oxygen species, hypoxia, acidosis, and damage to cell membranes. This damage is attributed to the decreased ability of albumin to bind heavy metals (such as copper and cobalt) at its N-terminal end (31). IMA has also been reported to be a specific marker for ischemia in the circulatory system (32). However, it is elevated in neoplastic diseases, pulmonary embolism, stroke, and inflammations (31,33,34). There are studies suggesting that IMA level increases in neurological diseases such as migraine (12,18). Say et al. (2020) reported that IMA levels were high in the interictal period in their study (18). From another perspective, migraine patients may develop lesions in the white matter due to ischemia and hypoxia in small vessels in the brain and it has been suggested that this may increase IMA levels (12). In this context, IMA levels may be a marker of OS in neurological disorders. Prolidase activity is an enzyme that functions in all tissues, including the brain, and breaks down dipeptides in proline metabolism. It also plays an important role in collagen synthesis and cell growth (35). There is thought to be a linear relationship between increased prolidase and proline levels (18). Increased levels of proline in the brain have been shown to contribute to neurological disorders by triggering OS (36). N-acetyl aspartate reduction is thought to contribute to the pathophysiology of migraine. It has been reported that this decrease may be linked to OS and mitochondrial dysfunction and may trigger migraine attacks by causing intracellular migration of calcium ions, excessive production of free radicals, and oxidative phosphorylation deficiency (37). Indeed, when NTG was administered to rats, it was associated with oxidative stress as it caused mitochondrial dysfunction (2). Another study reported that NTG administration increased oxidative stress and decreased antioxidants in brain tissue (38). The findings of this study confirm the hypothesis that increased IMA and prolidase levels with NTG administration can be explained by mechanisms similar to the above literature and may be related to oxidative stress.

TPM is a monosaccharide compound. It is used in epilepsy and migraine attacks (34). In addition, TPM has neuroprotective properties with multiple mechanisms of action (39). There are a limited number of studies investigating the effect of TPM on oxidative stress. In one study, it was reported that kainite-induced increased lipid peroxidation (LPO) levels in rats decreased with TPM treatment (40). However, it was reported that TPM doses decreased NO and LPO levels and increased antioxidant enzyme activities such as catalase and superoxide dismutase in pentylenetetrazole (PTZ)-induced nephrotoxicity (41). Furthermore, TPM has been suggested to ameliorate the decreased antioxidant enzyme activity in the frontal cortex and exhibit neuroprotective properties in an experimental cocaine model in rats (42). The findings of the present study show that TPM decreases IMA and prolidase enzyme activities, which are markers of OS. The therapeutic effect of TPM suggests that it may suppress OS through various mechanisms of action such as being a glutamate receptor antagonist and intracellular blockade of calcium ions as reported in the literature. Indeed, NTG has been found to increase glutamate levels via NO and cyclic adenosine monophosphate (6). It has also been found that the increase in proline, a substrate of prolidase enzyme, increases the amount of glutamate in the synaptic pathway and increased glutamate levels may trigger cortical stimulation and cause migraine attacks (18). TPM has also been shown to improve OS parameters and exhibit antioxidant properties (39). The effect of TPM on OS could be attributed to its antagonistic effect on glutamate receptor subtypes, its antioxidant properties, or its ability to reduce IMA and prolidase levels through different mechanisms of action.

CONCLUSION

In the present study, we evaluated the effect of TPM on oxidative stress markers IMA and prolidase enzyme activity in NTG-induced adolescent rats. Results showed that NTG increased IMA and prolidase levels, while TPM restored these levels. In this context, it has been shown that IMA and prolidase enzymes may be markers of OS in neurodegenerative disorders such as migraine. However, it suggests that the antioxidant properties attributed to TPM may suppress OS or may be explained by neuroprotective mechanisms of action. Further, in vivo studies are needed to understand the antioxidant potential and mechanisms of action of TPM.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the local ethics committee and animal care guidelines were followed (Date:22/06/2023, Number:2023/08-04).

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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Pediatr Pract Res 2023; 11(3): 158-163
DOI: 10.21765/pprjournal.1351565

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Early Characteristics of Patients with Systemic Juvenile Idiopathic Arthritis and Differences with Adult-Onset Still's Disease

Sistemik Juvenil İdiyopatik Artritli Hastaların Erken Dönem Özellikleri ve Erişkin Başlangıçlı Still Hastalığı ile Farklılıkları

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Abstract

Aim: The purpose of this study was to evaluate the demographic characteristics, early clinical and laboratory findings and treatment approaches in patients with systemic juvenile idiopathic arthritis (sJIA). In addition, it was aimed to discuss the differences of patients with sJIA from adult-onset Still's disease (AOSD).

Material and Method: Patient data were collected from two tertiary hospital rheumatology centers. Pediatric patients diagnosed with sJIA according to ILAR criteria between 2015 and 2022 and adult patients diagnosed with AOSD according to Yamaguchi criteria between 2016 and 2022 were included in the study. Demographic, clinical and laboratory findings were recorded from patient files.

Results: The median age at diagnosis of 63 sJIA patients included in the study was 6.4 years. Fever (n=63, 100%), arthritis (n=53, 84.1%), skin rash (n=50, 79.4%), hepatosplenomegaly (n=42, 66.7%), and lymphadenopathy (n=24, 38.1%) were commonly observed. The monocyclic pattern was the most frequently observed disease pattern (n=39, 61.9%). The mean leukocyte count was 15830±6604/mm3, while the mean erythrocyte sedimentation rate was 75.9±27.3 mm/hour. Methotrexate (n=21, 33.3%) and cyclosporine (n=9, 14.3%) were the most frequently preferred immunosuppressive agent in combination with corticosteroids. Among biological agents, canakinumab was used in 16 patients, etanercept in 11, infliximab in 10, tocilizumab in 9 and anakinra in 9 patients. Remission was achieved in 59 (98.3%) patients within the study group. To compare with sJIA patients, 39 AOSD patients were included in the study. Arthritis and hepatosplenomegaly were more common in sJIA (p<0.001). Duration of fever, frequency of lymphadenopathy, skin rash and serositis were similar in both groups. Ferritin and CRP levels were significantly higher in AOSD (p=0.021 and p<0.001, respectively). Monocyclic pattern was more common in sJIA and chronic pattern was more common in AOSD (p=0.005). The duration of oral steroid and synthetic DMARD treatment was significantly longer in AOSD (p<0.001 and p=0.017, respectively).

Conclusion: sJIA is a complex and multifaceted autoinflammatory disease characterized by a range of symptoms including fever, rash, and arthritis. Although it has similar characteristics to AOSD, AOSD patients have longer treatment durations.

Keywords: Biological drugs, fever, juvenile idiopathic arthritis, Adult onset Still disease

Öz

Amaç: Bu çalışmanın amacı sistemik juvenil idiyopatik artrit (sJIA) hastalarının demografik özelliklerini, erken dönem klinik ve laboratuvar bulgularını ve tedavi yaklaşımlarını değerlendirmektir. Ayrıca hastalarımızın erişkin başlangıçlı Still hastalığından (EBSH) farklılıklarının tartışılması amaçlandı.

Gereç ve Yöntem: Hasta verileri iki üçüncü basamak hastane romatoloji merkezinden toplandı. Çalışmaya 2015-2022 yılları arasında ILAR kriterlerine göre sJIA tanısı alan çocuk hastalar ve 2016-2022 yılları arasında Yamaguchi kriterlerine göre erişkin başlangıçlı Still hastalığı tanısı alan erişkin hastalar dahil edildi. Demografik, klinik ve laboratuvar bulguları hasta dosyalarından kaydedildi.

Bulgular: Çalışmaya dahil edilen 63 sJIA hastasının tanı anındaki ortanca yaşı 6,4 yıldı. Ateş (n=63, %100), artrit (n=53, %84,1), deri döküntüsü (n=50, %79,4), hepatosplenomegali (n=42, %66,7) ve lenfadenopati (n=24, %38,1) yaygın olarak gözlendi. Monosiklik patern en sık gözlenen hastalık paterniydi (n=39, %61,9). Ortalama lökosit sayısı 15830±6604/mm3, ortalama eritrosit sedimentasyon hızı ise 75,9±27,3 mm/saat idi. Metotreksat (n=21, %33,3) ve siklosporin (n=9, %14,3) kortikosteroidlerle birlikte en sık tercih edilen immünsüpresif ilaçlardı. Biyolojik tedavi kapsamında hastaların 16'sında canakinumab, 11'inde etanersept, 10'unda infliximab, 9'unda tocilizumab ve 9'unda anakinra kullanıldı. Çalışma grubundaki 59 (%98,3) hastada remisyon sağlandı. sJIA hastaları ile karşılaştırmak amacıyla 39 EBSH hastası çalışmaya dahil edildi. Artrit ve hepatosplenomegali sJİA'da daha sık görüldü (p<0,001). Ateşin süresi, lenfadenopati sıklığı, deri döküntüsü ve serozit her iki grupta da benzerdi. EBSH'da ferritin ve CRP düzeyleri anlamlı derecede yüksekti (sırasıyla p=0,021 ve p<0,001). Monosiklik patern sJIA'da, kronik patern ise AOSD'da daha sıktı (p=0,005). AOSD'de oral steroid ve sentetik DMARD tedavisinin süresi anlamlı olarak daha uzundu (sırasıyla p<0,001 ve p=0,017).

Sonuç: sJIA, ateş, döküntü ve artrit gibi bir dizi semptomla karakterize karmaşık ve çok yönlü bir otoinflamatuar hastalıktır. EBSH ile benzer özelliklere sahip olsa da EBSH hastalarının daha uzun süreli tedaviye ihtiyacı vardır.

Anahtar Kelimeler: Biyolojik ilaçlar, ateş, jüvenil idiyopatik artrit, erişkin başlangıçlı Still hastalığı

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Başvuru Tarihi/Received: 28.08.2023
Kabul Tarihi/Accepted: 23.09.2023

INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA) is a rare childhood autoinflammatory disease. It differs from other juvenile arthritis subtypes with extraarticular systemic findings. Symptoms of the disease can mimic bacterial or viral infection, malignancy and other inflammatory disease. The unique combination of quotidian fevers, arthritis and salmon-colored rash serves as a defining triad (1). Additional clinical observations comprise hepatomegaly, splenomegaly, generalized lymphadenopathy, and serositis (1, 2).

All of the classic features may not be present at the onset of the disease, symptoms and signs are non-specific, overlapping with other inflammatory and non-inflammatory conditions.

Adult-onset Still's disease (AOSD) is similarly a systemic inflammatory disease, characterized by a clinical triad of high fever, arthralgia and/or arthritis and skin rash. It is proposed that AOSD and sJIA represent a continuum of the same disease (3, 4).

The purpose of this study was to evaluate the demographic characteristics, early clinical and laboratory findings and treatment approaches of sJIA patients admitted to a rheumatology referral center. It was also aimed to present the early findings of our patients and to discuss the differences from AOSD.

MATERIAL AND METHOD

This study was approved by the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 02/06/2021, Decision No: E2-21-557). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

The study was designed as a medical record review. Patient data were collected from two tertiary hospital rheumatology centers. Pediatric patients diagnosed with sJIA according to International League of Associations for Rheumatology (ILAR) criteria between 2015-2022 and adult patients diagnosed with AOSD according to the to the Yamaguchi criteria between 2016-2022 were included in the study (5). SJIA and AOSD patients with missing data were excluded.

Data Collection

Data were collected from the files of patients. Age, gender, presenting features (joint involvement, rash, fever, serositis, hepatosplenomegaly, lymphadenopathy), and all initial laboratory findings such as complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, fibrinogen, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase were recorded. Treatments, the course, frequency and number of disease attacks, treatment response, complication of disease were noted.

Definitions

The clinical course of the disease was divided into three different groups: monocyclic, polycyclic and persistent course. Monocyclic sJIA course is characterized with a single episode of systemic symptoms and arthritis, resolving within 24 months. Polycyclic course has multiple recurrences of active disease alternating with periods of remission. The persistent sJIA is characterized by ongoing active systemic features and arthritis, possibly leading to severe joint deformities (2).

Wallace criteria were used to define inactive disease. According to these criteria, there must be an absence of fever, rash, serositis, splenomegaly, lymphadenopathy, and arthritis, as well as normal levels of ESR and CRP (6).

Statistical Analyses

Data analysis was performed in IBM SPSS (Statistical Package for Social Sciences) version 25 package program. The conformity of the variables to normal distribution was examined visually and analytically. Descriptive analyses were presented as mean and standard deviation, median and interquartile range for numerical variables and frequency tables for ordinal and categorical variables. For intergroup comparisons, Student's T-Test was used for normally distributed numerical variables, Mann Whitney U test was used for non-normally distributed numerical variables, and Chi-square or Fisher's test was used for categorical variables. Results were considered statistically significant for $p<0.05$.

RESULTS

Demographic Characteristics, Clinical and Laboratory Findings and Treatments of sJIA Patients

Sixty-three sJIA patients were included in the study. The mean age at diagnosis was 6.4 years. All patients had fever at presentation. The median duration of the fever was 20 days. The most common musculoskeletal manifestation was arthritis in 53 (84.1%) patients. The other symptoms were skin rash in 50 (79.4%) patients, hepatosplenomegaly in 42 patients (66.7%), and lymphadenopathy in 24 (38.1%) patients. Sore throat, pericarditis, and pleuritis were less commonly reported symptoms (**Table 1**). The mean leukocyte

count was 158306604/mm3, while the mean ESR was 75.9±27.3 mm/hour. The median CRP and ferritin levels were 28.7 mg/dL and 1279.5 ng/ml, respectively. Disease pattern was monocyclic in 39 (61.9%) patients, polycyclic in 17 (27%) patients and chronic in 7 (11.1%) patients (**Table 1**).

Table 1. Demographic and Clinical Characteristics of sJIA Patients

	sJIA (n=63)
Age of diagnosis (years), median (IQR)	6.4 (7.7)
Fevera, n(%)	63 (100.0)
Duration of fevera (day), median (IQR)	20 (13)
Musculoskeletal features	
Artritis, n(%)	53 (84.1)
Number of the involved joints, median (IQR)	2 (3)
Arthralgia, n(%)	5 (7.9)
Organ involvementa	
Skin rash, n(%)	50 (79.4)
Hepatosplenomegaly, n(%)	42 (66.7)
Lymphadenopathy, n(%)	24 (38.1)
Sore throat, n(%)	17 (27.0)
Pericarditis, n(%)	9 (14.3)
Pleuritis, n(%)	12 (19)
Laboratory abnormalities	
Leukocyte count,±SD	15830±6604
ESR (mm/h), ±SD	75.9±27.3
CRP (mg/dl), median (IQR)	28.7 (118.4)
Ferritin (ng/ml), median (IQR)	1279.5 (4847)
ALT (U/L), median (IQR)	17.5 (30)
Disease patternsb	
Monocyclic, n(%)	39 (61.9)
Polycyclic, n(%)	17 (27.0)
Chronic, n(%)	7 (11.1)

aCollected at the time of diagnosis, bCollected at the end of the follow-up, IQR:interquartile range, SD:standart deviation, sJIA: systemic juvenile idiopathic arthritis

Corticosteroids were the most commonly used immunosuppressive agent. Thirty-eight (60.3%) of the patients had required pulse corticosteroid treatment. Among conventional immunosuppressive drugs, methotrexate (n=21, 33.3%) and cyclosporine (n=9, 14.3%) were the most frequently preferred agents. Fifty-five (87.3%) patients received biological drugs, 16 canakinumab, 11 etanercept, 10 infliximab, 9 tocilizumab and 9 anakinra. The median duration of the biological disease modifying antirheumatic drugs (DMARD) was 6 month (**Table 2**). The majority of patients (98.3%) achieved remission, and among them, 29 (49.2%) achieved drug-free remission. The median time of remission was 9 months. One (1.7%) patient died from active disease (**Table 2**).

Comparison of sJIA and AOSD patients

To compare with sJIA patients, 39 AOSD patients were included in the study. **Table 3** summarizes the demographic characteristics, clinical and laboratory findings and course of AOSD patients in comparison with sJIA patients. Arthritis and hepatosplenomegaly were more common in sJIA (p<0.001), while sore throat was more common in AOSD (p=0.041). Duration of fever, frequency of lymphadenopathy, skin rash and serositis were similar in both cases. Ferritin and CRP levels were significantly higher in AOSD (p=0.021 and p<0.001, respectively). Monocyclic pattern was more common in sJIA and chronic pattern was more common in AOSD (p=0.005). MAS developed more in sJIA patients (p=0.002) (**Table 3**). **Table 4** shows the treatments used in AOSD patients in comparison with sJIA patients. The duration of oral steroid and synthetic DMARD treatment was significantly longer in AOSD (p<0.001 and p=0.017, respectively).

Table 2. Treatment Details of sJIA Patients

	sJIA (n=63)
Pulse corticosteroid, n(%)	38 (60.3)
Duration of oral corticosteroid (month), median (IQR)	6 (5)
Synthetic DMARDs treatment	
Methetrexate, n(%)	21 (33.3)
Cyclosporine, n(%)	9 (14.3)
Biological DMARDs treatment	
Infliximab, n(%)	10 (15.9)
Etanercept, n(%)	11 (17.5)
Tocilizumab, n(%)	9 (14.3)
Anakınra, n(%)	9 (14.3)
Canakınumab, n(%)	16 (25.4)
Duration of treatment (month), median (IQR)	6 (15)
Complications	
Macrophage activation syndrome, n(%)	14 (22.2)
Last status	
Remission (drug-free) , n(%)	29 (49.2)
Remission (on medication) , n(%)	30 (50.8)
Remission, n(%)	59 (98.3)
Non-remission, n(%)	1 (1.7)
Mortality, n(%)	1 (1.7)

IQR:interquartile range, SD:standart deviation, sJIA: systemic juvenile idiopathic arthritis, DMARD: disease modifying drugs,

Table 3. Comparison of Demographic Characteristics, Clinical and Laboratory Findings and Prognosis of SJIA and AOSD Patients

	sJIA (n=63)	AOSD (n=39)	P-value
Age of diagnosis (years), median (IQR)	6.4 (7.7)	41 (32)	<0.001***
Fevera, n(%)	63 (100.0)	37 (94.9)	0.144*
Duration of fevera (day), median (IQR)	20 (13)	30 (58.3)	0.198***
Musculoskeletal features			
Artritis, n(%)	53 (84.1)	20 (51.3)	<0.001**
Number of the involved joints, median (IQR)	2 (3)	0 (2)	<0.001***
Arthralgia, n(%)	5 (7.9)	0 (0)	0.151*
Organ involvementa			
Skin rash, n(%)	50 (79.4)	26 (66.7)	0.166**
Hepatosplenomegaly, n(%)	42 (66.7)	18 (46.2)	0.041**
Lymphadenopathy, n(%)	24 (38.1)	18 (46.2)	0.422**
Sore throat, n(%)	17 (27.0)	18 (46.2)	0.024**
Pericarditis, n(%)	9 (14.3)	5 (12.8)	0.834**
Pleuritis, n(%)	12 (19)	8 (20.5)	0.856**
Laboratory abnormalities			
Leucocyte count, ±SD	15830±6604	16883±9208	0.507****
ESR (mm/h), ±SD	75.9±27.3	83.2±21.7	0.170****
CRP (mg/dl), median (IQR)	28.7 (118.4)	150 (182)	<0.001***
Ferritin (ng/ml), median (IQR)	1279.5 (4847)	3425.5 (9472.8)	0.021***
ALT (U/L), median (IQR)	17.5 (30)	40 (90)	<0.001***
Complications			
Macrophage activation syndrome, n(%)	14 (22.2)	0 (0)	0.002**
Disease patternsb			
Monocyclic, n(%)	39 (61.9)	16 (41.0)	0.005**
Polycyclic, n(%)	17 (27.0)	8 (20.5)	
Chronic, n(%)	7 (11.1)	15 (38.5)	
Last status			
Remission (drug-free) , n(%)	29 (49.2)	13 (39.4)	0.367**
Remission (on medication), n(%)	30 (50.8)	20 (60.6)	
Remission, n(%)	59 (98.3)	33 (91.7)	0.147*
Non-remission, n(%)	1 (1.7)	3 (8.3)	
Mortality, n(%)	1 (1.7)	3 (8.3)	
Comorbidities	1 (1.6)	15 (38.5)	<0.001**

aCollected at the time of diagnosis, bCollected at the end of the follow-up, *Fisher's Exact Test, **Chi-square, ***Mann-Whitney U test, ****Independent samples T test, IQR:interquartile range, SD:standart deviation, sJIA: systemic juvenile idiopathic arthritis, AOSD: adult onset still disease

Table 4. Comparison of Treatments of SJIA and AOSD Patients

	sJIA (n=63)	AOSD (n=39)	P-value
Pulse corticosteroid, n(%)	38 (60.3)	28 (71.8)	0.238**
Duration of oral corticosteroid (month), median (IQR)	6 (5)	24 (40.5)	<0.001***
Synthetic DMARDs treatment			
Methetrexate, n(%)	21 (33.3)	29 (74.4)	<0.001**
Cyclosporine, n(%)	9 (14.3)	10 (25.6)	0.152**
Leflunomide, n(%)	0 (0)	2 (5.1)	0.144*
Biological DMARDs treatment			
Infliximab, n(%)	10 (15.9)	0 (0)	0.009**
Etanercept, n(%)	11 (17.5)	1 (2.6)	0.023**
Adalimumab, n(%)	0 (0)	1 (2.6)	0.382*
Tocilizumab, n(%)	9 (14.3)	6 (15.4)	0.879**
Anakınra, n(%)	9 (14.3)	17 (43.6)	0.001**
Canakınumab, n(%)	16 (25.4)	0 (0)	0.001**
Duration of treatment (month), median (IQR)	6 (15)	5.5 (35.75)	0.521***

*Fisher's Exact Test, **Chi-square, ***Mann-Whitney U test, IQR:interquartile range, SD:standart deviation, sJIA: systemic juvenile idiopathic arthritis, AOSD: adult onset still disease, DMARD: disease modifying drugs,

DISCUSSION

Systemic juvenile idiopathic arthritis is a rare cause of fever with unknown origin in childhood and can lead to life-threatening complications if not treated. It requires high suspicion due to the nonspecific and incomplete nature of its clinical manifestations. In this study, it was shown that although fever was the most common feature in sJIA, arthritis, skin rash, hepatosplenomegaly and lymphadenopathy were also commonly observed. Acute phase reactants were shown to be elevated, reflecting systemic inflammation. Remission was achieved in 98.3% of patients with intensive treatment.

Adult-onset Still's disease is a systemic inflammatory disease that usually affects young adults (3, 4). Clinical and laboratory manifestations, complications and treatment approaches emphasize the similarities between sJIA and AOSD. Therefore, sJIA and AOSD represent a continuum of a single disease entity. We aimed to compare sJIA patients with AOSD patients. While arthritis and hepatosplenomegaly were more frequent in sJIA, duration of fever, frequency of lymphadenopathy, skin rash and serositis were similar. Monocyclic pattern was more common in sJIA and chronic pattern was more common in AOSD. Duration of oral steroid and synthetic DMARD treatment was significantly longer in AOSD.

Although sJIA can develop at any age, it tends to peak between 1 and 5 years. In our study, the age of onset was 6.4 years (7, 8). AOSD usually affects young adults; the mean age at diagnosis is approximately 38 years (3). As with sJIA, delayed diagnosis is common due to non-specific symptoms. Considering that fever is the main symptom, it is possible to make the diagnosis after excluding diseases such as infection and malignancy that cause prolonged fever. Because of the devastating complications of the disease in the early period and due to increased awareness, the delay in diagnosis is decreasing over the years. While fever was observed in all patients, other clinical findings were not present at the disease onset in all patients. Arthritis (84.1%), rash (79.1%) and hepatosplenomegaly (66.7%), the most common clinical findings. Clinical findings which specialized the diagnosis such as generalized lymphadenopathy, pericarditis, and pleuritis were lower.

The fact that fever is the only clinical finding in some patients and infections are common in early childhood, diagnosing the condition becomes challenging. In patients without accompanying arthritis, the pattern of fever (1 or 2 times a day and returning to normal) and the character of the rash (usually accompanied by fever and no residuals) may be suggestive. Kishida et al. showed that the percentage of AOSD patients with fever, arthralgia, skin rash, lymphadenopathy, splenomegaly, pericarditis, interstitial pneumonia, abdominal pain and myalgia was not different from sJIA patients (4). They also found that the incidence of disseminated intravascular coagulation and macrophage activation syndrome (MAS) in elderly-onset AOSD patients was significantly higher than in the younger-onset group (4). Although MAS did not develop in 39 AOSD patients in our study, it should be kept in mind that MAS may develop in AOSD. MAS is also a critical and life-threatening complication in sJIA and AOSD. Elevated ferritin levels are typically observed in patients with clinically established MAS. Nevertheless, elevated ferritin levels might also use as an early indicator of subclinical MAS in some cases. Early diagnosis and timely intervention have the potential to be life-saving. We found percentage of MAS 22.2% in our study. Previous studies reported MAS frequency in sJIA patients between 5-17% (9). Sağ et al reported a higher frequency of MAS (33%) (10). The high rate of MAS requires even more caution in patients with fever of unknown origin. sJIA patients are predisposed to develop MAS and this life-threatening complication can result in death due to the difficulty in diagnosis.

The cornerstone of sJIA treatment involves the use of corticosteroids and NSAIDs (1-3). These medications help control inflammation and manage symptoms, but their prolonged use can come with potential side effects. In our study median duration of corticosteroids was 6 months. We preferred MTX and cyclosporin as a NSAID. In a recent adult study, methotrexate was shown to be effective in disease control, especially in 40-70% of steroid-dependent AOSD patients (11). As the field of rheumatology has progressed, targeted therapies, such as biologic agents that inhibit specific cytokines, such as interleukin-1 and interleukin-6 inhibitors, have provided more targeted and effective treatment options for sJIA (12). In our study, biological agents were used in 87.3% of the patients and remission was achieved in 98% of the patients. Until the last few decades, the predominant treatment for patients with AOSD was corticosteroids. However, it is known that the frequency of comorbidity is high in patients with AOSD depending on the increase in age. These comorbidities caused the patient's condition to worsen easily when corticosteroids were used. Therefore, it is inevitable that elderly patients with AOSD need treatment with drugs other than corticosteroids. Methotrexate and/or biological agents are commonly used in AOSD, just as in sJIA (13). In our study, it was observed that immunosuppressive drugs other than corticosteroids and biological agents were commonly used in both sJIA and AOSD patients. However, it is noteworthy that the duration of use of oral steroids and synthetic DMARDs was also longer in AOSD.

The major limitations of our study were the retrospective design with small sample size. However, the interpretation of the data of sJIA patients with the data of AOSD patients is the strength of this study.

CONCLUSION

Early recognition, careful monitoring, and tailored treatment strategies are essential to provide the best possible outcomes for children affected by sJIA. Similar clinical findings, laboratory findings and treatment approaches of sJIA and AOSD seem to reflect the continuity of the same disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 02/06/2021, Decision No: E2-21-557).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Pediatr Pract Res 2023; 11(3): 164-170
DOI: 10.21765/pprjournal.1354171

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Effect of Two Different Virtual Reality Videos on Pain, Fear, and Anxiety During a Venous Blood Sampling in Children: A Randomized Controlled Study

Çocuklarda Venöz Kan Alma İşlemi Sırasında Kullanılan İki Farklı Sanal Gerçeklik Videosunun Ağrı, Korku ve Anksiyete Üzerine Etkisi: Randomize Kontrollü Çalışma

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Abstract

Aims: This study evaluated the effects of two different virtual reality (VR) methods on pain, fear, and anxiety during a venous blood sampling in children.

Material and Method: This randomized controlled experimental study was conducted with 153 children aged 7-12 years and their parents who applied to the pediatric blood sampling unit of a training and research hospital. Research data were collected with the Wong-Baker Faces Pain Scale, Children's Anxiety Meter-State scale, Children's Fear Scale and Information Form. The two VR methods used were VR-Water skiing and VR-Walking in nature.

Results: The children's mean pain scale score during the venous blood sampling was 1.29±1.11 with the VR-Water skiing; 1.28±1.16 with the VR-Walking in nature; and 4.34±1.41 ($p<0.001$) in the control group. The children's mean anxiety scale score during the procedure was 0.82±1.01 with the VR-Water skiing; 0.79±1.26 with the VR-Walking in nature; and 6.57±2.08 ($p<0.001$) in the control group. The children's mean fear scale score during the procedure was 0.58±0.77 with the VR-Water skiing, 0.53±0.78 with the VR-Walking in nature; and 3.17±0.92 ($p<0.001$) in the control group. The children's pain, anxiety and fear scale scores in the VR-Walking in nature and VR-Water skiing groups were similar ($p>0.05$).

Conclusion: Two different VR videos were more effective than standard care in reducing pain, fear, and anxiety during a venous blood sampling. There was no significant difference in pain, anxiety and fear levels in the two different VR groups. Therefore, the use of VR goggles is recommended to reduce pain, anxiety, and fear during blood sampling in children aged 7-12 years old.

Keywords: Virtual reality, pain, fear, anxiety, blood sampling, child

Öz

Amaç: Bu araştımanın amacı iki farklı sanal gerçeklik videosunun çocuklarda venöz kan alma işlemi sırasında oluşan ağrı, korku, anksiyete düzeyine olan etkisini değerlendirmektir.

Gereç ve Yöntem: Bu randomize kontrollü deneysel araştırma bir eğitim ve araştırma hastanesinin çocuk kan alma birimine başvuru yapan 7-12 yaş arasındaki 153 çocuk ve ebeveynleri ile yürütüldü. Araştırma verileri Wong Baker Yüzler Ağrı Ölçeği, Çocuk Korku Ölçeği ve Çocuk Anksiyete Skalası-Durumluluk Ölçeği, Bilgi Formu ile toplandı.

Bulgular: Araştırmada venöz kan örneği alma işlemi sırasında çocukların ağrı ölçeği puan ortalaması VR-Su kayağı grubunda 1.29±1.11, VR-Doğada yürüyüş 1.28±1.16, kontrol grubunda 4.34±1.41 idi. ($p<0.001$). İşlem sırasında çocukların korku ölçeği puan ortalaması VR-Su kayağı grubunda 0.58±0.77, VR-Doğada yürüyüş 0.53±0.78, kontrol grubunda 3.17±0.92 idi ($p<0.001$). İşlem sırasında çocukların anksiyete ölçeği puan ortalaması VR-Su kayağı grubunda 0.82±1.01, VR-Doğada yürüyüş 0.79±1.26, kontrol grubunda 6.57±2.08 idi ($p<0.001$). VR-Su kayağı ve VR-Doğada yürüyüş grubundaki çocukların ağrı, korku ve anksiyete ölçek toplam puan ortalamaları benzerdi ($p>0.05$).

Sonuç: Çocuklarda sanal gerçeklik gözlüğü ile izletilen iki farklı videonun, venöz kan alma işlemi sırasında çocukların yaşadığı ağrı, anksiyete ve korku düzeyini azaltmada, standard bakıma göre daha etkili olduğu belirlendi. İki farklı sanal gerçeklik grubunda ise ağrı, anksiyete, korku düzeylerinde anlamlı bir fark olmadığı belirlendi. Bu doğrultuda, 7-12 yaş çocuklarda kan alma işlemi sırasında ağrı, anksiyete ve korkuyu azaltmak amacıyla sanal gerçeklik gözlüğünün kullanılması önerilmektedir.

Anahtar Kelimeler: Sanal gerçeklik, ağrı, korku, anksiyete, kan alma, çocuk

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Başvuru Tarihi/Received: 02.09.2023
Kabul Tarihi/Accepted: 12.09.2023

INTRODUCTION

Children may experience pain, anxiety and fear during blood sampling (1,2). It is known that pain and fear that are not effectively managed can cause posttraumatic stress disorder in children and affect behavioural and physiological responses to pain later in life (3,4). There is evidence in the literature that distraction methods have been successfully used in pediatric blood sampling units to reduce children's pain, anxiety and fear levels during the blood sampling process. These methods include using virtual reality (VR) goggles (1,2,5,6), using distraction cards (7,8), viewing a kaleidoscope (4,9) and bubble-blowing (10,11). VR goggles are a safe intervention that can be used to distract children in pediatric blood sampling units to reduce their fears and increase their compliance with the procedure (12). In a recent meta-analyses of the VR intervention's effectiveness in reducing pain, anxiety and fear caused by blood sampling procedures in the pediatric population (13), some studies reported that VR technology was more effective than other distraction methods, whereas other studies reported that it was not superior to traditional distraction methods. Although the results of another meta-analyses showed that VR technology shows promise in alleviating pain, anxiety, and fear levels during medical procedures in children. However, it is essential to acknowledge that further research is necessary to explore the effectiveness of various VR methods across different age groups (14,15). In a study conducted by Ferraz-Torres et al. (2020), two types of VR methods, interactive and passive, were used to reduce pain and anxiety associated with venipuncture in children. The results demonstrated that both VR methods significantly lowered pain and anxiety levels during the procedure, with the interactive VR method proving more effective (6). Consequently, it is imperative to compare and evaluate various VR interventions and methods. Additionally, it's noteworthy that some children prefer dynamic videos, while others find relaxation videos more appealing (16). Previous studies have assessed the impact of VR goggles using a wide range of videos, including Roller Coaster (16), natural environments like hiking and nature scenes (6), Ocean Rift (16), Aquarium VR (2), popular cartoons such as Ice Age (1), video games like Mine Craft (6,17), and experiences like Spacewalker (18). In our current study, we employed 'VR-Walking in Nature' as a relaxation video and 'VR-Water Skiing' as an engaging, dynamic video. Within this context, our study aims to investigate the effects of these two distinct VR videos—relaxing and dynamic—on reducing pain, fear, and anxiety during venous blood sampling in children aged 7-12 years, thereby comparing the outcomes of the two different VR methods.

Hypothesis 1: Children in the VR groups will have lower pain scores during the blood sampling intervention than children in the control group.

Hypothesis 2: Children in the VR groups will have lower fear scores during the blood sampling intervention than children in the control group.

Hypothesis 3: Children in the VR groups will have lower anxiety scores during the blood sampling intervention than children in the control group.

Hypothesis 4: The Virtual reality-Water skiing and Virtual reality- Walking in nature methods applied during blood sampling intervention differ in their abilities to reduce children's pain, fear and anxiety.

MATERIAL AND METHOD

Design

This randomized controlled trial was conducted between June and July 2022 at the Pediatric Blood Sampling Unit of the Training Research and Hospitals. Parents and their children aged 7-12 who volunteered to participate and met the inclusion criteria were enrolled in the study. The flow diagram of the study was presented in **Figure 1** based on the CONSORT reporting criteria (**Figure 1**).

Participants

The sample size was calculated according to the study by Özalp Gerçeker et al. (2020) (16). The study's results indicated a medium effect, which aligned with the study's objective. In this context, it was determined that at least 48 children should be included in each group with d=0.60, 80% (1-β error) power, and a 95% (α error) confidence level (G*Power). Due to the dropout rate, 53 children were enrolled in each group, for 159 children. In the VR and control groups, six children were excluded from the study because they chose to terminate their participation. Therefore, the study was completed with 153 children and their parents (**Figure 1**). End of the study, post hoc analysis was performed based on the 153 children, with a large effect size and a 95% (α error) confidence level (G*Power), the power of the study was found 99%.

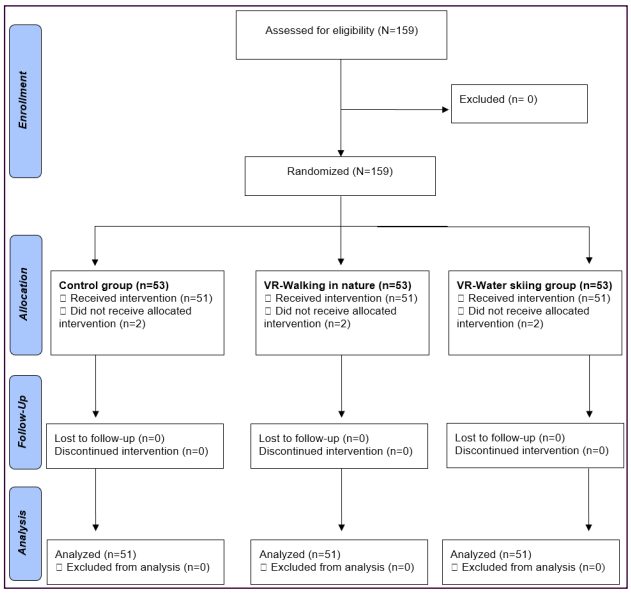

Figure 1. CONSORT flow diagram

Inclusion criteria: voluntarily agreed to participate in the research, is a child 7-12 years old, is free of chronic pain and mental health conditions, is free of hearing and visual impairments, has not used sedative or analgesic drugs within six hours before the intervention, children who do not have vertigo problems.

Exclusion criteria: refused to participate in the research, has a visual or auditory problem.

Assigning participants to the interventions and control groups employed a computer-based simple randomization (https://www.randomizer.org). A total of 153 children were randomized into the three groups, including VR-Water Skiing (n=51), VR-Walking in Nature (n=51), and the control group (n=51).

Data collection tools

Information Form: The information form was contained five questions: the child's age, gender, experience with needle procedures, the number of experiences with needle procedures, and which parent accompanied the child during the blood sampling (4,5,9,12).

Wong-Baker Faces Pain Scale (WBFPS): The WBFS allows users to rate pain by combining images and numbers. The expressions range from delighted to sad to crying. Each WBFS face is given a number rating ranging from 0 ("no harm") to 10 ("worst hurt") (19).

Children's Fear Scale (CFS): The CFS was developed by McMurtry et al. (20), translated and adapted to the Turkish language by Özalp Gerçeker et al. (2018). The CFS is used to evaluate the pain-related fear in children. This scale is a one-item self-report. The CFS is a scale from 0-4, consisting of five facial expressions ranging from a neutral expression (0=no anxiety) to a frightened face (4=severe anxiety). The content validity index value was 0.89. Test-retest reliability was found to be quite high (21).

Children's Anxiety Meter-State (CAM-S): The CAM-S was developed by Ersig et al. (22) and translated and adapted to the Turkish language by Özalp Gerçeker et al. (2018). It assesses children's anxiety in clinical settings and is used before medical procedures. The children were asked to mark how she/he felt "right now" to measure state anxiety. The children were instructed, "Put a line on the thermometer that shows how worried or angry you are". The scores varied between 0 – 10 points. The content validity index value was found to be 1.00. Test-retest reliability was found to be quite high (21).

Virtual Reality (VR): In this study, we employed Virtual Reality (VR) technology compatible with iOS mobile phones as a distraction technique. Children in the VR groups were immersed in VR 360-degree videos known as "VR-Water Skiing" and "VR-Walking in Nature". In the VR-Water Skiing group, children experienced the sensation of water skiing, complete with variable speed adjustments that simulated slowing down and speeding up. Meanwhile, in the VR-Walking in Nature group, children embarked on a virtual nature tour accompanied by calming music. To assess the suitability of these videos for children, the opinions of five experts in the field of children's health were sought, all of whom unanimously concurred that the content was suitable for child viewers. Prior to the main study, a pilot evaluation involved five children aged between 7 and 12, who watched both of these videos. Importantly, no negative feedback was received from these participants. Furthermore, VR glasses was cleaned with 70% alcohol after each use to prevent contamination.

Data collection

Before the blood sampling procedure

The subject and purpose of the study were explained to all groups before the blood sampling. The Information Form was completed. The researcher explained to the child how to use the virtual reality goggles during the blood sampling procedure. Each child was informed that the parent would be present during the procedure. Blood sampling was performed according to the relevant unit's routine practice. The scales (WBFPS, CFS, CAM-S) were introduced to the child and the parent.

During the blood sampling procedure

Virtual Reality Group (VR-Water Skiing): As soon as the child sat down in the blood sampling chair, the virtual reality goggles were put on and the 3D video was switched on. Using the VR goggles, the children in this group were shown the 3D video called "360 VR Water skiing", which began approximately three minutes before the blood sample began and continued throughout the process. After the blood sampling procedure had been completed, the video was switched off, the virtual reality goggles were removed and the child was led to the waiting area. After being allowed to rest for three minutes, the child was asked to rate the level of pain during the procedure with the WBFPS, the level of fear with the CFS, and the level of anxiety with the CAM-S scale. The parent and the researcher, who had been present during the sampling, observed the child's behaviour and rated the pain level during the procedure with the WBFPS, fear level with the CFS, and anxiety level with the CAM-S. The same steps were followed up after the blood collection procedure, in all three groups.

Virtual Reality Group (VR-Walking in Nature): As with the other group, as soon as the child sat down in the blood sampling chair, the virtual reality goggles were put on and the 3D video was switched on. Using the VR goggles, the children in this group were shown the 3D video called "360 VR Walking in nature"; as with the other group, the video began approximately three

minutes before the blood sample began and continued throughout the process. After the blood sampling procedure had been completed. The same steps were followed up as in the VR-Water skiing group.

Control Group: The children in the control group underwent blood sampling according to the clinic's routine practice. After the blood sampling procedure had been completed. The same steps were followed up as in the VR-Water skiing group.

Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences for Windows package (version 28.0). Descriptive statistic tests (numbers, percentages, minimum and maximum values, mean, standard deviations) were used to assess the socio-demographic characteristics. The normality test was used to assess homogeneous distribution. Kruskal Wallis test, Pearson Chi-Square and Mann-Whitney U tests with Bonferroni correction were used for data analysis. The intraclass correlation analysis was utilized to evaluate the agreement between different observers' measurements of the mean scores obtained from the participants' scales. Cohen categorized effect sizes into three categories: small (d=0.2), medium (d=0.5), and large (d ≥ 0.8). Cohen notably remarked that a medium effect of 0.5 is perceptible to the unaided eye of an attentive observer. To calculate effect size the Cohen effect size values were considered in this study.

Ethical Approach

This study was approved by the Haseki Training and Research Clinical Researches Ethics Committee (Date: 08.06.2022, Decision No: 69-2022) and the institution (Date: 03.03.2022, Decision No:78). Written informed consent was obtained from the parents, and verbal informed consent was obtained from the children. The study was conducted in strict adherence to the principles delineated in the Helsinki Declaration.

RESULTS

The socio-demographic characteristics of the children according to the groups are presented in **Table 1**. There was no significant difference in children's age, gender, number of the needle procedure (p>0.05).

Children's procedural pain score according to the Wong-Baker FACES was presented in **Table 2**. In the study, the mean WBFPS score of the children during the venous blood sampling was 4.34±1.41 in the control group; VR-Walking in nature was 1.28±1.16; VR-Water skiing was 1.29±1.11. There is a significant difference between the groups' mean WBFPS scores of the children (p<0.001). Children in the VR-Walking in nature and VR-Water skiing groups had lower WBFPS scores than children in the control group (p<0.001). There were no significant differences in pain scores of the VR-Walking in nature and VR-Water skiing groups (p>0.05). It was found that there was perfect agreement between the mean pain scores of the different raters, as assessed by intraclass correlation analysis (ICC) (p<0.001) (**Table 2**). The effect size of the VR-Walking in nature and VR-Water skiing was found large to reduce pain.

Children's procedural anxiety score according to the CAM-S was presented in **Table 3**. In the study, the mean CAM-S score of the children during the procedure was 6.57±2.08 in the control group; VR-Walking in nature

Table 1. The socio-demographic characteristics of the children by groups

	Control Group (n=51) M±SD		VR -Walking in Nature (n=51) M±SD		VR-Water Skiing (n=51) M±SD		Test	p
Age	9.71±1.77		9.53±1.90		9.58±2.04		0.230*	0.892
	n	(%)	n	(%)	n	(%)		
Gender								
Girl	23	(44.2)	24	(47.1)	23	(45.1)	0.087**	0.957
Boy	28	(55.8)	27	(52.9)	28	(54.9)		
Number of the needle procedure								
1 time	2	(3.8)	1	(2.0)	1	(2.0)		
2 time	12	(23.1)	11	(21.6)	9	(17.6)	1.040**	0.904
>3 time	37	(73.1)	39	(76.5)	41	(80.4)		

*: Kruskal Wallis test, **: Pearson Chi-Square, M: Mean, SD: Standard Deviation

Table 2. Distribution of pain scores during the venous blood sampling

Variables	Control Group[a]	VR-Walking in Nature[b]	VR-Water Skiing Group[c]	Z; p	Post-hoc Test*, p	95% CI		Effect size
						Lower	Upper	
Children	4.34±1.41	1.28±1.16	1.29±1.11	92.860; p<0.001	a > b =c	0.802	1.522	1.162
Parent	4.46±1.35	1.25±1.06	1.22±1.14	99.018; p<0.001	a > b =c	0.860	1.586	1.223
Researcher	4.31±1.28	1.22±0.99	1.22±1.13	100.916; p<0.001	a > b =c	0.855	1.581	1.218
ICC, p	9.111; p<0.001	72.878; p<0.001	30.162; p<0.001					

Z; Kruskal Wallis Test, ICC; Intraclass Correlation Coefficient; * Mann Whitney U test with Bonferroni correction

Table 3. Distribution of anxiety and fear scores during the venous blood sampling

Variables	Control Group[a]	VR-Walking in Nature[b]	VR-Water Skiing Group[c]	Z; p	Post-hoc Test*, p	95%CI		Effect size
						Lower	Upper	
CAM-S								
Children	6.57±2.08	0.79±1.26	0.82±1.01	104.593; p<0.001	a > b =c	0.867	1.593	1.235
Parent	6.25±2.07	0.84±1.14	0.82±1.01	104.883; p<0.001	a > b =c	0.884	1.612	1.248
Researcher	6.17±2.07	0.54±2.20	0.76±0.91	105.808; p<0.001	a > b =c	0.811	1.533	1.172
ICC, p	37.731; p<0.001	33,560; p<0.001	103.829; p<0.001					
CFS								
Children	3.17±0.92	0.53±0.78	0.58±0.77	96.311; p<0.001	a > b =c	0.795	1.516	1.155
Parent	3.13±0.84	0.59±0.73	0.61±0.75	98.999; p<0.001	a > b =c	0.830	1.554	1.192
Researcher	3.11±0.86	0.57±0.74	0.59±0.73	98.843; p<0.001	a > b =c	0.829	1.553	1.191
ICC, p	21.633; p<0.001	61.961; p<0.001	62.740; p<0.001					

Z; Kruskal Wallis Test, ICC; Intraclass Correlation Coefficient; * Mann Whitney U test with Bonferroni correction

was 0.79±1.26; VR-Water skiing was 0.82±1.01 (p<0.001). There is a significant difference between the CAM-S mean scores of the children according to the groups. Children in the VR-Walking in nature and VR-Water skiing groups had lower CAM-S scores than children in the control group (p<0.001). There were no significant differences in anxiety scores between the VR Walking in nature and VR Water skiing groups (p>0.05). There was perfect agreement between the mean anxiety scores of the different raters, as assessed by intraclass correlation analysis (ICC) (p<0.001) (**Table 3**). The effect size of the VR-Walking in nature and VR-Water skiing was found large to reduce anxiety.

Children's procedural fear score according to the CFS was presented in **Table 3**. In the study, The mean CFS score reported by the children during the procedure was 3.17±0.92 in the control group; VR-Walking in nature was 0.53±0.78; VR-Water skiing was 0.58±0.77 (p<0.001). There is a significant difference between the CFS mean scores of the children according to the groups. Children in the VR-Walking in nature and VR-Water skiing groups had lower CFS scores than children in the control group (p<0.001). There were no significant differences in fear scores between the VR-Walking in nature and VR-Water skiing groups (p>0.05). There was perfect agreement between the mean fear scores of the different raters, as assessed by intraclass correlation analysis (ICC) (p<0.001) (**Table 3**). The effect size of the VR-Walking in nature and VR-Water skiing was found large to reduce fear.

DISCUSSION

In this study, we evaluated the impact of two distinct VR methods on children aged 7-12 undergoing venous blood sampling at a pediatric blood sampling unit. Our primary focus was to assess the influence of these VR interventions on the children's levels of pain, anxiety, and fear during the procedure. While we have presented a comprehensive review of the existing literature, it is essential to delve into our interpretation of the effectiveness of these VR interventions within the context of our study. Our study results indicate that both the VR-Walking in nature and VR-Water skiing groups exhibited lower mean pain scores compared to the control group. This finding aligns with our hypothesis (H1) that VR interventions would lead to reduced pain levels during venous blood sampling. Our results concur with the findings of Ayran et al. (2023), who also reported a significant reduction in pain when using VR goggles among children aged 5-12 years during blood sampling (2). Our study's results corroborate with prior research conducted in various clinical settings. Akarsu et al. (2023) and Gerçeker et al. (2018) found that VR goggles effectively reduced pain during blood sampling in children (1,5). Notably, our study contributes to the growing body of evidence supporting the utility of VR interventions for pain management during medical procedures in pediatric populations. Additionally, numerous studies in the literature have investigated the effectiveness of VR goggles in mitigating acute procedural pain in children undergoing various medical procedures, such as vaccinations, acute burn injuries, port catheter exchanges, and dental procedures, among others (4, 23-28). These studies consistently demonstrate that the use of VR goggles can be an impactful strategy for alleviating pain and discomfort in pediatric patients. Our findings are consistent with this broader body of evidence and further emphasize the significance of incorporating VR technology into clinical practice to enhance the overall well-being of pediatric patients during painful procedures. In summary, our study supports the contention that VR interventions, specifically VR-Walking in nature and VR-Water skiing, effectively reduce pain levels, anxiety, and fear among children aged 7-12 undergoing venous blood sampling. Our findings align with previous research in this area, highlighting the potential for VR technology to serve as a valuable adjunct in pediatric pain management during various medical procedures. As the use of VR technology continues to evolve, further research and clinical integration may enhance the overall healthcare experience for pediatric patients, promoting their comfort and well-being during challenging medical procedures.

The study's findings regarding fear and anxiety scores in both the VR-Walking in nature group and VR-Water skiing group, as compared to the control group, support the acceptance of study hypotheses H2 and H3. This aligns with a body of research conducted on children aged 5-21 years, which consistently demonstrates that using VR goggles during venous blood sampling effectively reduces fear, anxiety, and pain levels (1, 12, 29-32). The mechanism behind this phenomenon lies in the immersive nature of VR technology, which isolates the child from the external environment and redirects their focus toward the visual and auditory stimuli provided by the goggles, effectively diverting their attention away from the painful procedure (31, 33). However, it's worth noting that in this study, the pain, fear, and anxiety scores did not exhibit significant differences between the VR-Walking in nature group and the VR-Water skiing group, leading to the non-acceptance of hypothesis H4. This outcome aligns with the findings of Gerçeker et al. (2020), who employed VR-Rollercoaster and VR-Ocean rift videos during blood collection and reported that both methods were equally effective in reducing pain in children aged 5-12 years (16). Moreover, Ferraz-Torres et al. (2020) investigated the application of two types of VR methods, namely interactive and passive, to alleviate pain and anxiety associated with venipuncture in children (6). The passive VR group was exposed to various natural landscape environments and animals, while the interactive VR group engaged in an interactive VR game using a controller/stick. It was reported that both VR methods, albeit effective, reduced pain and anxiety levels during the procedure, with the interactive VR method being slightly more effective (6). These findings underscore the importance of considering different VR techniques and their varying impacts on pain and anxiety reduction. Considering these results, it becomes evident that further research is warranted to comprehensively compare different VR methods across various age groups and for different painful medical interventions. This will help tailor VR interventions to the specific preferences and needs of pediatric patients. Healthcare professionals involved in the care of pediatric patients should consider the child's preferences, whether it be through video, gaming, or cartoons, and adapt the VR approach accordingly. Such personalized approaches can contribute significantly to improving the overall experience of pediatric patients during painful medical procedures, ensuring their comfort and well-being.

Limitations

This study has important limitations that warrant consideration. Firstly, the findings may not be broadly applicable as the data were collected solely from a single-center pediatric blood sampling unit, raising questions about generalizability. Secondly, despite being designed as a randomized controlled trial, blinding was not feasible for both participants and researchers, potentially introducing observer bias into the assessments of children's pain, anxiety, and fear. Thirdly, the study relied exclusively on subjective assessments for these outcomes, omitting objective measures that could have provided a more comprehensive understanding. Lastly, the study focused on children aged 7-12, limiting its applicability to a broader age range. These limitations underscore the need for cautious interpretation and call for future research to address these concerns in order to advance our understanding of VR interventions in pediatric pain management during medical procedures.

CONCLUSION

This study underscores the effectiveness of using VR goggles to display videos to children aged 7-12 years undergoing venous blood sampling at a pediatric unit. The results demonstrate that this VR intervention surpasses standard care in reducing levels of pain, anxiety, and fear associated with the procedure. Furthermore, our comparative analysis of two different VR videos revealed their similar effectiveness. Hence, it is imperative for pediatric blood sampling units to incorporate VR methods tailored to individual preferences, whether children favor dynamic or soothing video experiences. Healthcare professionals are encouraged to engage children in discussions regarding their VR method preference, be it video content, gaming, or cartoons, as this personalized approach may enhance compliance with the blood sampling process. Moving forward, we advocate for the execution of randomized controlled trials that explore diverse VR methods across various age groups, fostering a more comprehensive understanding of their applicability and effectiveness in diverse clinical scenarios.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Haseki Training and Research Clinical Researches Ethics Committee (Date: 08.06.2022, Decision No: 69-2022) and the institution (Date: 03.03.2022, Decision No:78).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgment: Authors thanks to all patients and their families.

Note: This study was presented as an oral presentation at the 3rd International Mediterranean Pediatric Nursing Congress in 2022.

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Pediatr Pract Res 2023; 11(3): 171-176
DOI: 10.21765/pprjournal.1329646

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Evaluation of Oral Food Provocation Test Results in Children Diagnosed with Food Allergy

Besin Alerjisi Tanılı Çocuklarda Oral Besin Provokasyon Testi Sonuçlarının Değerlendirilmesi

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ABSTRACT

Aims: Our study was conducted to evaluate the results of the oral food provocation tests in children with a diagnosis of food allergy and to examine the development of reactions in patients during the oral food provocation test.

Material and Method: This was a descriptive type of study. Children diagnosed with food allergy between the years 2020-2022, and who had an oral food provocation test were included in the study. The patient files were scanned retrospectively. Age, gender, allergy tests, total IgE, eosinophil values and reactions during treatment were evaluated.

Results: Oral food provocation test was applied to 40.5% (n=85) of the patients for diagnostic purposes and 59.5% (n=125) to determine the food tolerance. Of the patients who received oral provocation, 48.1% (n=101) received yoghurt, 39.0% (n=82) eggs, 5.7% (n=12) baked egg cake, 4.8% (n=10), baked yoghurt cake. Reaction was observed in 8.6% (n=18) of the patients who received oral food provocation test. Reactions were mostly urticaria. There was no statistically significant relationship between the development of the reaction and gender, the purpose of the provocation test, the age of onset of the first complaints and the age at which the provocation test was applied (p>0.05). The median specific IgE (milk) value was higher in patients who developed a reaction (p=0.034).

Conclusions: Reaction developed less than one in ten of the patients. Although the reactions are often mild such as urticaria, it is important to predict the development of the reaction in terms of the management of food allergies and the feasibility of the provocation test.

Keywords: Oral food provocation, children, food allergy

ÖZ

Amaç: Çalışmamız, besin alerjisi tanısı alan çocuklarda oral besin provokasyon testi sonuçlarını değerlendirmek ve oral besin provokasyon testi sırasında hastalarda reaksiyon gelişimini incelemek amacıyla yapılmıştır.

Gereç ve Yöntem: Çalışma tanımlayıcı tiptedir. 2020-2022 yılları arasında besin alerjisi tanısı alan ve oral besin provokasyon testi yapılan çocuklar çalışmaya dahil edildi. Hasta dosyaları retrospektif olarak tarandı. Yaş, cinsiyet, alerji testleri, total IgE, eozinofil değerleri ve tedavi sırasındaki reaksiyonlar değerlendirildi.

Bulgular: Hastaların %40,5'ine (n=85) tanı amaçlı, %59,5'ine (n=125) gıda toleransını belirlemek için oral gıda provokasyon testi uygulandı. Oral provokasyon uygulanan hastaların %48,1'ine (n=101) yoğurt, %39,0'una (n=82) yumurta, %5,7'sine (n=12) yumurtalı kek, %4,8'ine (n=10) fırınlanmış yoğurtlu kek verildi. Oral gıda provokasyon testi yapılan hastaların %8,6'sında (n=18) reaksiyon görüldü. Görülen reaksiyonlar çoğunlukla ürtikerdi. Reaksiyon gelişimi ile cinsiyet, provokasyon testinin yapılma amacı, ilk şikayetlerin başlama yaşı ve provokasyon testinin uygulanma yaşı arasında istatistiksel olarak anlamlı bir ilişki yoktu (p>0,05). Medyan spesifik IgE (süt) değeri reaksiyon gelişen hastalarda daha yüksekti (p=0,034).

Sonuç: On hastanın 1'inden daha az oranda reaksiyon gelişimi görüldü. Oral provokasyon testi sırasında gelişen reaksiyonlar genellikle ürtiker gibi hafif olsa da, gıda alerjilerinin yönetimi ve provokasyon testinin uygulanabilirliği açısından reaksiyon gelişiminin önceden tahmin edilmesi önemlidir.

Anahtar Kelimeler: Oral besin provokasyon testi, çocuklar, besin alerjisi

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Başvuru Tarihi/Received: 19.07.2023
Kabul Tarihi/Accepted: 19.09.2023

INTRODUCTION

Food allergy is an immunological response to food proteins (1). Food allergies are most commonly seen against eggs, milk, nuts such as peanut, soy, wheat, shellfish, and fish (2, 3). The frequency of food allergy has been increasing in recent years and is more common in children than adults (4). Allergic reactions triggered by food can progress with various symptoms and disorders including the skin, gastrointestinal tract, and respiratory tract. These reactions occur by Immunoglobulin E (IgE)-mediated and non-IgE-mediated (cellular) mechanisms (5).

Confirming the diagnosis of a food allergy might be essential due to the subjectivity of findings associated with food allergies and the low positive predictive values observed in the skin prick test performed with food and specific IgE levels (6). In order to confirm the diagnosis of food allergies, it may be necessary to perform oral provocation tests with the suspect food (7, 8). In the oral provocation test, the suspected allergen food is given orally to the patient in a controlled and standardized environment (9). Another use of the oral food challenge test is to evaluate the tolerability of a food in a child with a previous food allergy (10).

Although the oral food provocation test is accepted as the gold standard for the diagnosis of food allergy, some adverse reactions may be seen during the test. Although these reactions are usually in the form of mild cutaneous allergic reactions such as urticaria, it should be kept in mind that life-threatening serious reactions such as anaphylaxis may also occur after oral food provocation test (11). There are few studies in the literature on the effectiveness, applicability and reliability of oral food provocation tests. In a study in the literature, it was reported that 18.8% of patients developed a reaction during oral food provocation tests (12).

The management of food allergies is extremely important especially for the pediatric patient group, since its prevalence is increasing. Examining provocation tests, which play a crucial role in allergy management, along with the characteristics of the tested patients, is necessary. In this context, our study was conducted to retrospectively evaluate the results of the oral food provocation tests in children with a diagnosis of food allergy and to examine the development of reactions in patients during the oral food provocation test.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences, Ümraniye Training and Research Hospital Ethics Committee (Date: 22.12.2022, Decision No: 393). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This was a descriptive type of study. Children diagnosed with food allergy between the years 2020-2022, and who had an oral food provocation test were included in the study. The patient files were examined retrospectively, and all patients with a file were included in the study. The study had no exclusion criteria. Patients' age, gender, allergy tests, total IgE, eosinophil values and reactions during oral food provocation tests were evaluated within the scope of the study.

Oral Food Provocation Tests

In our clinic, oral food provocation tests were performed in the form of open oral food provocation tests, all anaphylaxis measures were taken and performed under the supervision of a physician. Consent was obtained from the parents before the test. The patients were examined before starting the oral food challenge tests and before each dose increase. Vital signs, respiratory and dermal examination findings were recorded after each dose. Adverse reactions that developed during the provocation test were also recorded. The patients were kept under observation for two hours after the last dose was given.

In open oral food provocation tests, the suspicious food is started at a low dose and dose increases are made at 15-minute intervals until the target dose is reached. The oral food provocation tests for each food are applied in accordance with the "Work Group Report: Oral Food Challenge Testing" guideline of the American Allergy and Immunology Committee (9).

Statistical Analysis

SPSS (Statistical Package for Social Sciences for Windows 25.0 program was used for the analysis and the recording of data. Descriptive data was presented wtih median, minimum, maximum values, numbers (n) and percentages (%). For the analysis of categorical data, Chi-square test was used. For the comprasion of continuous variables that non-normally distrubuted; Mann Whitney U test was used. The statistical significance level was set at $p<0.05$.

RESULTS

In the study, 43.3% (n=91) of 210 children who underwent oral food provocation test were female and 56.7% (n=119) were male. The median age of onset of the first complaint in children was 4.0 months (1.0-36.0). The median age at which the oral food provocation test was applied was 11.0 months (6.0-88.0).

When the first admission of the patients were examined, 66.2% (n=139) of the children had urticaria, 48.1% (n=101) had gastrointestinal system findings, 11.9% (n=25) had atopic dermatitis. Other accompanying clinical findings of the patients were reactive airway disease, allergic rhinitis and anaphylaxis (**Table 1**).

Table 1. Accompanying clinical findings of the patients

	n	%
Urticaria	139	66.2
Gastrointestinal system findings	101	48.1
Atopic dermatitis	25	11.9
Reactive airway disease	13	6.2
Allergic rhinitis	11	5.2
Anaphylaxis	9	4.3

Oral food provocation test was applied to 40.5% (n=85) of the patients for diagnostic purposes and 59.5% (n=125) to determine the food tolerance. Of the patients who received oral provocation, 48.1% (n=101) received yoghurt, 39.0% (n=82) eggs, 5.7% (n=12) baked egg cake, 4.8% (n=10), baked yoghurt cake. Of the patients 1.9% (n=4) had received goat yoghurt and 0.5% (n=1) had received baked goat yoghurt cake. Provocation test was performed in 52.5% (n=53) of the patients who were given yoghurt to confirm the diagnosis. In patients who were given eggs, the purpose of the provocation test was to detect the development of tolerance more frequently (n=50; 61.0%). The aim of the oral provocation test was to detect the development of tolerance in all those given goat yoghurt, baked egg, baked yoghurt, and baked goat yoghurt. In 7.9% (n=8) of the children given yoghurt, reaction development related to the provocation test was observed. Reactions developed in 8.5% (n=7) and 16.7% (n=2) of children given eggs and baked eggs, respectively. A reaction developed in 25.0% (n=1) of the children given goat yoghurt. No reaction occurred in those given baked yoghurt and baked goat yoghurt (**Table 2**).

Table 2. The foods applied in the oral provocation test, the purpose of the test and development of reaction

Foods	Total n (%)	For diagnosis (n=85) n (%)	For food tolerance (n=125) n (%)	Occurance of reaction n (%)
Yoghurt	101 (48.1)	53 (52.5)	48 (47.5)	8 (7.9)
Egg	82 (39.0)	32 (39.0)	50 (61.0)	7 (8.5)
Baked egg (cake)	12 (5.7)	0 (0)	12 (100.0)	2 (16.7)
Baked yoghurt (cake)	10 (4.8)	0 (0)	10 (100.0)	0 (0)
Goat yoghurt	4 (1.9)	0 (0)	4 (100.0)	1 (25.0)
Baked goat yoghurt (cake)	1 (0.5)	0 (0)	1 (100.0)	0 (0)

Reaction was observed in 8.6% (n=18) of the patients who received oral foodprovocation test. Of the patients 5.2% (n=11) had urticaria, 1.9% (n=4) had vomiting. Anaphylaxis was observed in 1.0% (n=2), and cough was observed in 0.5% (n=1) . The characteristics of 18 patients who had a reaction are given in **Table 3**.

Table 3. Features of patients with reactions during oral food provocation test

Patients	Gender	Age (months)	Aim of OPT	Tested food	Reaction	sIgE (kU/L) (milk)	sIgE (kU/L) (egg)
1	M	6	D	Yoghurt	Urticaria	0	-
2	M	8	D	Yoghurt	Urticaria	0	-
3	F	13	D	Yoghurt	Urticaria	0	-
4	F	26	D	Yoghurt	Urticaria	0.75	-
5	M	6	T	Yoghurt	Urticaria	0	-
6	M	8	T	Yoghurt	Vomiting	1.56	-
7	M	40	T	Yoghurt	Urticaria	4.19	-
8	M	26	T	Yoghurt	Anaphylaxis	0	-
9	F	49	T	Baked egg (cake)	Cough	-	2.57
10	F	8	D	Egg	Vomiting	-	0
11	M	8	D	Egg	Urticaria	-	0
12	M	11	T	Egg	Urticaria	-	0.32
13	F	15	T	Egg	Urticaria	-	0
14	F	14	T	Egg	Vomiting	-	0
15	F	44	T	Baked egg (cake)	Urticaria	-	0
16	M	9	T	Egg	Urticaria	-	0.11
17	F	14	T	Egg	Vomiting	-	0
18	F	45	T	Goat Yoghurt	Anaphylaxis	0.84	-

F: Female, M: Male, D:Diagnosis, T:Tolerance, OPT: Oral food provocation test, sIgE: specific Immunoglobulin E

A comparison was made between patients who exhibited a reaction and those who did not exhibit a reaction following the oral food provocation test. There was no statistically significant relationship between the development of the reaction and gender, the purpose of the provocation test, the age of onset of the first complaints and the age at which the provocation test was applied (p>0.05). For the laboratory values; the median specific IgE (milk) value was 1.56 kU/L (0.75-4.20) in patients who developed a reaction, and 0.35 kU/L (0.11-4.19) in those who did not (p=0.034). In terms of specific IgE (egg), eosinophil and total IgE values, there was no statistically significant difference between patients with and without reaction (p>0.05) (**Table 4**).

In order to prove the development of tolerance, the times between the first and last specific IgE measurements of the patients who received oral food provocation were evaluated. The median times between specific IgE first and last measurements of patients who were given eggs, yoghurt, and baked eggs in the provocation test were 4.0 months (1.0-14.0), 3.0 months (1.0-12.0), and 6.0 months (3.0-12.0), respectively. The times between two specific IgEs for patients given other foods are given in **Table 5**.

Table 4. Comparison of patients with and without reaction after oral food provocation test

	No reaction (n=192)	Reaction occured (n=18)	P value
Gender, n (%)			0.551*
Female	82 (90.1)	9 (9.9)	
Male	110 (92.4)	9 (7.6)	
Aim of the test, n (%)			0.518*
Diagnosis	79 (92.9)	6 (7.1)	
Tolerance	113 (90.4)	12 (9.6)	
Age of the onset of complaints (months) median (min-max)	4.0 (1.0-36.0)	4.5 (1.0-14.0)	0.215**
Age (months), median (min-max)	11.0 (6.0-88.0)	13.5 (6.0-49.0)	0.324**
sIgE (kU/L) (milk), median (min-max)	0.35 (0.11-4.19)	1.56 (0.75-4.20)	0.034**
sIgE (kU/L) (egg), median (min-max)	0.83 (0.10-2.98)	0.32 (0.11-2.57)	0.698**
Eosinophil (10^3/uL) (absolute), median (min-max)	280.0 (0-2220.0)	260.0 (10.0-590.0)	0.338**
Eosinophil (%), median (min-max)	3.35 (0-17.7)	3.1 (0.1-5.6)	0.564**
Total IgE (IU/mL), median (min-max)	18.0 (0-982.0)	46.5 (1.0-494.0)	0.267**

* Chi-square test, ** Mann-Whitney U test, p<0.05 is statistical significance level, sIgE: specific Immunoglobulin E

When the specific IgE first and last measurements of the patients who received oral food challenge to prove the development of tolerance were evaluated, the median value of the last measurements of specific IgE (egg), specific IgE (milk) and specific IgE (goat's milk) values was lowerin secondly measured values. The difference between the two measurements for specific IgE (egg) and sIgE (milk) was statistically significant (p<0.001 and p=0.017, respectively) (**Table 5**).

Table 5. The specific IgE first and last measurements of the patients who received oral food provocation test to prove the tolerance and the time between the two measurements

Time between sIgE measurements of each food (months)	Median	Min.	Max.
Egg (n=50)	4.0	1.0	14.0
Yoghurt (n=48)	3.0	1.0	12.0
Baked egg (cake) (n=12)	6.0	3.0	12.0
Baked yoghurt (cake) (n=10)	4.0	1.0	10.0
Goat yoghurt (n=4)	7.0	5.0	12.0
Baked goat yoghurt (cake) (n=1)	12.0	12.0	12.0
Specific IgE values (kU/L)	**Median**	**Min.**	**Max.**
sIgE (egg) first	2.78	0.00	39.40
sIgE (egg) last	0.87	0.00	2.98
P value*		<0.001	
sIgE (milk) first	0.88	0.00	6.68
sIgE (milk) last	0.46	0.00	4.19
P value*		0.017	
sIgE (goat milk) first	1.13	0.00	2.25
sIgE (goat milk) last	0.00	0.00	0.84
P value*		0.157	

* Mann-Whitney U test, p<0.05 is statistical significance level, sIgE: specific Immunoglobulin E

DISCUSSION

Food allergies are an important public health problem with an increasing frequency all over the world (13). Food allergies impair the quality of life of patients and may cause serious allergic reactions such as anaphylaxis (14). It is extremely important to diagnose food allergies and to treat patients with food allergies. In some patients with food allergies, oral food provocation tests are applied to confirm the diagnosis and detect food tolerance. For this reason, oral food provocation tests have an important place in the management of food allergies. In this context, the clinical characteristics of children who underwent oral food provocation test were evaluated in our study.

When the clinical presentations accompanying food allergy were examined in our study, urticaria, gastrointestinal system findings and atopic dermatitis were the most common ones, respectively. Other accompanying clinical findings of the patients were reactive airway disease, allergic rhinitis and anaphylaxis. In a study conducted in our country in pediatric patients with food allergy, the most common clinical diagnoses in children were reported as atopic dermatitis, gastrointestinal system diseases, and urticaria-angioedema, similar to our study (15).

In our study, oral food provocation test was applied to 40.5% of the patients for diagnosis and 59.5% to determine food tolerance. Similarly, in the literature, the oral food provocation test is most commonly used for determining the food tolerance (16). In our study, the most commonly administered foods for oral food provocation were yoghurt, eggs, and baked eggs. According to the literature, eggs were the most frequently used foods in oral food provocation tests (17).

Although it is considered the gold standard in the diagnosis of food allergiesfyo, some adverse reactions may be seen in patients during oral food provocation (18). In our study, reactions developed in 8.6% of patients who received oral food provocation. In a study conducted in our country, the frequency of reaction development after oral food provocation in children was reported as 20.6% (6). In a different study in the literature, the frequency of reaction development after oral food provocation in children was reported as 43% (19). In our study, the observed rate of reaction development was lower compared to findings in the literature. This discrepancy

may be associated with various factors, including the specific foods used in the provocation tests, the clinical characteristics of the patients, and their age. In our study, urticaria was observed most frequently in the patients with reaction, followed by vomiting. Anaphylaxis was observed in 1% of patients. Similar to the literature, the reactions seen after oral food provocation are mostly skin reactions (6, 12, 16). In another study, mild allergic reactions frequently developed during oral food provocation, and the percentage of anaphylaxis was reported as 2.4%, similar to our study (17).

In our study, we assessed the development of reactions based on food exposure during oral food provocation tests. While goat yoghurt and eggs showed the highest incidence of reactions, the reaction frequencies to different foods were relatively similar. Similarly, in a study in the literature, reaction development was observed mostly after oral food provocation with milk and eggs (19). In another study, 12.5% reaction was observed in children who were given eggs (6). This percentage is similar to the frequency of reactions developed during the oral food provocation test performed with eggs in our study (8.5%).

Factors that may be associated with reaction development during oral food provocation test were evaluated. In our study, no statistically significant relationship was found between gender, the purpose of the provocation test (diagnosis or tolerance), the age of onset of the first complaints, the age at which the provocation test was applied, total IgE and reaction development during the provocation. The specific IgE (milk) value was significantly higher in patients who developed a reaction. In a similar study conducted in pediatric patients in our country, factors associated with reaction development during oral food provocation were evaluated. Similar to our study, no relationship was found between age, gender, purpose of provocation, total IgE values and reaction development. In the same study, the induration diameter in the skin test was found to be significantly higher in those who developed a reaction (6). In future multicenter studies to be planned, there is a need to investigate the factors that may be associated with the development of the reaction during the provocation test.

When the specific IgE first and last measurements of the patients who were given oral food provocation test to prove the development of tolerance in our study, the final measurements of specific IgE (egg), specific IgE (milk) values were significantly lower than the first measurements. The decrease in the second measurements in specific IgE values suggests that tolerance to the foods has developed. Similarly, a study from the literature noted that a decline in food-specific IgE levels over time could be indicative of the emergence of clinical tolerance with regard to milk and egg allergies (20).

Limitations and Strengths

Our study was carried out on the results of the oral food provocation test performed in a tertiary hospital. The fact that the study was conducted on a single hospital database creates a limitation in terms of the generalizability of our results. On the other hand, the large number of study sample compared to similar studies in the literature is the strength of the study. In addition, presenting a wide range of data such as the clinical characteristics of the patients, laboratory values, and the change between specific IgE values is another strength of the study.

CONCLUSION

Oral food provocation test was applied to 40.5% of the patients in our study for diagnosis and 59.5% for determining the food tolerance. Reaction developed in 8.6% of the patients who received oral food provocation test. Most of the patients who developed a reaction had urticaria. Vomiting and coughing were other findings. Anaphylaxis was seen in only 2 patients. In our study, the specific IgE (milk) value was significantly higher in patients who developed a reaction than in those who did not.

As our study results show; although it has an important place in the diagnosis and management of food allergies, it is understood that it is necessary to be careful in terms of reaction development during oral food provocation tests. Although the reactions are often mild such as urticaria, it is important to predict the development of the reaction in terms of the management of food allergies and the feasibility of the provocation test. Therefore, in the light of our study findings, there is a need for further multicenter studies to evaluate the factors associated with reaction development in patients who underwent food provocation test.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Ümraniye Training and Research Hospital Ethics Committee (Date: 22.12.2022, Decision No: 393).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients for the 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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Pediatr Pract Res 2023; 11(3): 177-181
DOI: 10.21765/pprjournal.1355747

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Outcome of Maternal and Fetal Cases with Intrahepatic Cholestasis of Pregnancy

Gebelikte İntrahepatik Kolestazolan Vakaların Maternal ve Neonatal Sonuçları

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ABSTRACT

Aim: Intrahepatic cholestasis (ICP) of pregnancy is a common disorder of pregnancy manifested by pruritus and elevated bile acids.Some negative obstetric outcomes of ICP; Spontaneous preterm birth, meconium amniotic fluid, fetal asphyxia and stillbirth have been reported in the literature. Due to the lack of evidence for diagnosis, treatment, and concomitant adverse outcomes, management has two main goals: reducing troubling symptoms and perinatal morbidity and mortality.

Material and Method: Medical records of patients diagnosed and followed up with intrahepatic pregnancy cholestasis between January 2017 and June 2021 were reviewed retrospectively.

Results: The mean week of delivery of the patients was 38.1±1.4, and no fetal or neonatal death occurred during their follow-up.

Conclusion: With respect to the increased risk of adverse neonatal outcomes and stillbirth in patients with ICP, timing of birth in maternal ICP patients should be carefully evaluated. In conclusion, there is some evidence to suggest that birth at 37th weeks, especially in patients with severe bile acid level elevations, may improve outcomes. However as a result of this study in which the average gestational age at birth was 38 weeks and no fetal mortality occurred, we suggest that with close monitoring and early administration of treatment birth at 38 weeks could potentially improve outcomes in patients with low bile acid levels. Furthermore, optimal timing for birth in patients with ICP is as of yet unknown, due to the absence of randomized studies evaluating elective early induction of labor.

Keywords: Intrahepatic cholestasis, pregnancy, neonatal outcomes, bile acid, stillbirth,

ÖZ

Amaç: Gebelikte intrahepatik kolestaz (ICP), kaşıntı ve safra asitlerinin yükselmesi ile kendini gösteren, gebelikte sık görülen bir hastalıktır. ICP'nin bazı olumsuz obstetrik sonuçları; Literatürde spontan erken doğum, mekonyumlu amniyotik sıvı, fetal asfiksi ve ölü doğum bildirilmektedir. Tanı, tedavi ve eşlik eden olumsuz sonuçlara ilişkin kanıtların bulunmaması nedeniyle, tedavinin iki ana hedefi vardır: rahatsız edici semptomları ve perinatal morbidite ve mortaliteyi azaltmak.

Gereç ve Yöntem: Ocak 2017 ile Haziran 2021 tarihleri arasında intrahepatik gebelik kolestazı tanısı konularak takip edilen hastaların tıbbi kayıtları geriye dönük olarak incelendi.

Bulgular: Hastaların ortalama doğum haftası 38,1±1,4 olup, takipleri sırasında herhangi bir fetal veya neonatal ölüm yaşanmadı.

Sonuç: İCP'li hastalarda olumsuz neonatal sonuçlar ve ölü doğum riskinin artması nedeniyle, anne İCP'li hastaların doğum zamanlaması dikkatle değerlendirilmelidir. Sonuç olarak, özellikle ciddi safra asidi yüksekliği olan hastalarda 37. haftada doğumun sonuçları iyileştirebileceğini gösteren bazı kanıtlar vardır. Ancak doğumda ortalama gebelik yaşının 38 hafta olduğu ve fetal mortalitenin görülmediği bu çalışmanın sonucunda, yakın takip ve tedavinin erken uygulanmasıyla 38. haftada doğumun düşük safra asidi düzeyi olan hastalarda sonuçları potansiyel olarak iyileştirebileceğini düşünüyoruz. Ayrıca, ICP'li hastalarda doğumun optimal zamanlaması, elektif erken doğum indüksiyonunu değerlendiren randomize çalışmaların bulunmaması nedeniyle henüz bilinmemektedir.

Anahtar Kelimeler: İntrahepatik kolestaz, gebelik, yenidoğan sonuçları, safra asidi, ölü doğum,

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Başvuru Tarihi/Received: 05.09.2023
Kabul Tarihi/Accepted: 07.10.2023

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a reversible cholestasis characterized by pruritus with elevated serum bile acid concentrations and/or liver enzymes, usually beginning in the second or third trimester, without other liver diseases and chronic diseases (1). There is no agreement on diagnostic criteria for ICP. Levels of liver tests such as bile acids/salts level, AST, ALT, bilirubin, GGT can be very variable. Liver enzymes (AST-ALT) are elevated in ~60% to 85% of ICP patients. The elevation of liver enzymes (transaminases) less than twice the upper limit of normal distinguishes it from other liver diseases such as viral hepatitis and preeclampsia in pregnancy (2). The mean AST, ALT, and GGT levels in the study were 86.9±36.4, 110.5±63.6, and 55±22.9, respectively. Bile acid level for diagnosis in ICP patients South Australian Maternal and Neonatal Practice Association (SAMNCP) guideline, it was determined as 15 µmol/L, while it was determined as 10 µmol/L by the American College of Gastroenterologists (ACG). Since the limit was determined as 10 µmol/L in most studies, it was determined as 10 µmol/L in our study (3).

ICP may affect approximately 0.3-5.6% of pregnancies and may differ by ethnicity, geographic region, and seasonality (4). Although the etiology is not known exactly, increased estrogen levels during pregnancy and related changes in protein expression are possible causes. (5). In general, ICP begins in the third trimester, when circulating estrogen and progesterone levels are highest, supporting that hormone levels affect cholestasis (6,2) Most sources agree on the importance of itching and abnormal liver function (6,2). Itching usually begins 3 weeks before diagnosis and usually occurs without an increase in bile acid levels. (2) Resolution of ICP is spontaneous after birth, but women with a history of ICP have hepatobiliary and cardiovascular disease with advancing age (7,8). Some negative obstetric outcomes of ICP; Spontaneous preterm birth, meconium amniotic fluid, fetal asphyxia and stillbirth have been reported in the literature. (9-11). Despite the associated adverse outcomes, opinions regarding appropriate diagnostic criteria, maternal and fetal surveillance, treatment, and timing of delivery vary (12). The relative rarity of this condition, coupled with different guidelines, complicates management decisions for busy clinicians.

Due to the lack of evidence for diagnosis, treatment, and concomitant adverse outcomes, management has two main goals: reducing troubling symptoms and perinatal morbidity and mortality. reduce the risk (13). Ursofalk (ursodeoxycholic acid) is the most commonly used treatment for ICP. Ursodeoxycholic acid has been reported to lower bile salt levels in other tissues, including amniotic fluid and cord blood. After UDCA administration, it results in reduction in pruritus in ~60% of women and complete relief in ~40% of women (14). Symptoms typically resolve within 1-2 weeks of initiation of therapy, and a decrease in serum bile acids occurs after 2 weeks. Several studies have been conducted to evaluate the efficacy of UDCA in the treatment of pruritus, normalization of liver transaminases, and reducing the risk of poor perinatal outcome. UDCA improves pruritus, serum bile salt levels, and may reduce potential intrauterine fetal outcomes, but data on perinatal outcomes are limited (12,14-16)

The aim of this study is to examine the pregnancy results of 50 patients who developed intrahepatic cholestasis during pregnancy in the light of the literature, to discuss the current risks and how the pregnancy follow-up plan should be.

MATERIAL AND METHOD

The study was carried out with the permission of İstanbul Gelişim University Ethics Committee (Date: 10/06/20121, Decision No: 2021-21). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The medical records of patients who were followed up with the diagnosis of intrahepatic pregnancy cholestasis in a tertiary center between January 2017 and June 2021 were reviewed retrospectively. For the diagnosis of intrahepatic cholestasis of pregnancy: Having a 3rd trimester pregnancy ,widespread pruritus not due to a dermatological pathology, laboratory findings supporting ICP findings (AST-ALT > 40 U/L), ultrasonographically normal liver and gallbladder, negative serology hepatitis A, B, C, fasting bile acid level > 10 µmol/L conditions were sought. After diagnosis, Ursodeoxycholic acid 750 mg (UDCA) (Ursofalk 250 mg capsule) was started. Presence of preeclampsia or hypertension, any pre-pregnancy liver disease and a history of disease with liver involvement were considered as exclusion criteria.

Patients diagnosed with ICP were followed up in the outpatient clinic with weekly liver function tests (KFT), amniotic fluid index (ASI) evaluations and weekly non-stress tests (NST). In case of clinical progression (increased itching, jaundice), elevated LFT values and abnormal NST findings, the patient was hospitalized and NST, ASI, LFT, coagulation and bleeding profiles were monitored every other day. All of the patients were evaluated in terms of hepatic-biliary tract pathology with upper abdominal ultrasonography and hepatitis A, B and C were found to be negative in all of them. Bile acid levels were measured after fasting. Delivery was planned for patients who were hospitalized and had liver enzymes increased more than 10 times, lost variability or had a slowed NST during their follow-up. The cases were evaluated according to the criteria of time of delivery, mode of delivery, perinatal morbidity and mortality, preterm delivery and neonatal complications.

SPSS 22.0 statistical program was used for analysis in our study. Mean, standard deviation, minimum and maximum values were used from descriptive statistics.

RESULT

Fifty patients with pregnancy-related intrahepatic cholestasis were included in the study. The mean age of the patients, BMI (Body mass index), AST-ALT, GGT, T BL-D BL, ALP, GGT, fasting bile acid level, infant weight, Apgar scores, meconium contamination in amniotic fluid, cholestasis diagnosis time, method of administration and time was examined (**Table 1**). The mean age of the patients was 30.1±5.1 years, 50% of them gave birth for the first time. BMI was 24.9±3.1. Abdominal USGs of all patients were normal at the time of diagnosis. Mean AST, ALT, and GGT levels were 86.9±36.4, 110.5±63.6, and 55±22.9, respectively. When the patients were diagnosed, the mean gestational week was 30.5±3.4, and the mean delivery time was 38.1±1.4. Preeclampsia was found in 1.52% (n:3) and gestational diabetes (GDM) in 16% (n:8) of the patients. Itching was reported in 79% of patients admitted to the hospital. It was determined that the patient's complaints regressed in the 1st week postpartum.

Table 1: Patient characteristics and laboratory results

	Pregnant with cholestasis n:50/SD
Age	30.1±5.1
BMI	24.9±3.1
AST	86.9±36.4
ALT	110.5±63.6
T.BIL	0.94±0.83
D.BIL	0.50±0.70
ALP	71.9±22.1
GGT	55±22.9
Bile Acids	17.5±28.1

SD: Standard deviation

The mean week of diagnosis of the patients was 31.5±3.4, and the mean week of delivery was 38.1±1.4. (**Table 2**). The diagnosis period of 1 (in vitro fertilization patient) patient was 6. It was determined that 76% (n:38) of the patients were delivered by cesarean section, 24% (n:12) were delivered vaginally, and 16% (n:38) were delivered vaginally: 38%(n=8) of the patients gave birth before 38 weeks. When the postpartum results were examined, it was found that 8 fetuses (24%) had an Apgar score below 7 at the 1st minute at birth, and 4 fetuses (12%) had an Apgar score below 7 at the 5th minute. and no neonatal death was found. The rate of hospitalization in the neonatal intensive care unit was 10% (n=5), and the most common cause was prematurity. The rate of RDS (respiratory distress syndrome) was 6%(n=3). Meconium contamination was detected in the amniotic fluid of 18 (36%) patients. Meconium aspiration was detected in an infant hospitalized in the neonatal intensive care unit. Thirty (60%) newborns were girls and 20 (40%) were boys. There were no complications in the follow-ups. Due to the development of hepatocellular carcinoma in the follow-up of one patient, his treatment is still continuing in the medical oncology unit.

Table 2: Neonatal outcomes of ICP patients

	(Minimum-maximum)	Mean
Diagnosis time	6-34.1 weeks	31.5±3.4
Time of delivery	33.5-40.3 weeks	38.1±1.4
Birth weight	1480-3750	3126±413
Apgar 1. Bw	4-9	8.06±0.9
Apgar 5. Bw	6-10	9.76±0.7

DISCUSSION

Intrahepatic cholestasis of pregnancy, adversely affecting maternal and neonatal outcomes, is the most common gestational liver disease (1, 3, 16). This paper aims to reassess this significant cause of fetal morbidity, mortality, and negative obstetric consequences with perspective garnered in recent literature. Wikström et al. Published a study concerning patients with ICP in 2013, showing that patients with ICP were at a 2.8 fold risk of gestational diabetes (GDM), and a 2.6 fold risk of preeclampsia compared to patients without ICP (17). Throughout the study, 8 (16%) of followed up patients were diagnosed with GDM, while 3 were diagnosed with preeclampsia. Patients with ICP have a significantly increased risk of fibrosis, cholangitis, hepatitis C, gallstone disease, hepatobiliary cancer, cardiovascular disease, and immune mediated diseases (7). One patient in our study was diagnosed with hepatocellular carcinoma and is currently undergoing treatment.

Aside from effects on maternal health, ICP's impact on fetal health cannot be understated. Meconium contamination of amniotic fluid, premature births, fetal distress, and intrauterine fetal mortality are among the negative events associated with ICP. With regards to meconium contaminated amniotic fluid, gall has been shown to directly stimulate intestinal motility in animal studies (18). A meta-analysis carried out on patients with ICP complications during pregnancy showed that the incidence of meconium contamination was increased from ~11% to 19% (4). Our study found that 18 (36%) patients had confirmed meconium contamination, a figure significantly higher than in preceding literature. Neonatal hypoxia was not observed in these patients, nor was it associated with negative fetal outcomes. This increased incidence of meconium contamination could be attributed to the fact that ICP patients in the literature, in contrast to patients in our study,were brought into labor before at the 37th week. Though no clear explanation is put forward by the current literature, we hypothesize that neonatal bile acids may

have increased intestinal motility, as it did in our study. This topic requires more detailed investigation in future studies.

Another condition associated with ICP is respiratory distress syndrome (RDS). Although increased RDS incidence is likely explained at least in part by both spontaneous and iatrogenic preterm labor, animal models have demonstrated a causative association. In a rabbit model, bile acids injected directly into the trachea were shown to cause atelectasis, eosinophilic infiltration, and hyaline membrane development which was reversed through administration of surfactants.

In a swine model, bile acids were shown to cause serious chemical pneumonitis and lung edema (10). In the present study, RDS risk was found to be 6%, similar to the risk of RDS in non-complicated pregnancies in the literature. RDS was found to be especially associated with low weight births.

Fetal mortality is the most severe complication of ICP. High bile salt levels' association with stillbirth was found to possess a relative risk ratio of 2.6, consistent with current literature (8, 9). The mechanism behind fetal mortality in patients with ICP is not well understood. Negative fetal outcomes in patients with ICP have been associated with elevated levels of bile acids in amniotic fluids, cord blood, meconium, as well as elevated bile salt levels in the fetal compartments (9). Aside from the association with chronic placental insufficiency, bile acids' effects on the fetal heart are hypothesized to be directly related to fetal mortality. Clinical studies aiming to study the arrhythmogenic effect of bile acids on the fetal heart reported an increased incidence of fetal atrial flutter and supraventricular tachycardia in ICP patients. In human and animal myocytic stem cell studies, administration of bile salts was shown to decrease contractility and cause arrhythmia. In the same studies, ursodeoxycholic acid therapy was shown to prevent this effect (20). The absence of fetal mortality in the studies may be explained by close monitoring of fetal well-being and cardiac activity, as well as early administration of UDCA therapy.

In one study investigating intrauterine and postnatal outcomes, though threshold diagnostic values for bile acid vary, patients with bile acid levels above 40 µmol/L were defined as having severe cholestasis, and this was associated with adverse perinatal outcomes (11). More research assessing adverse intrauterine fetal outcomes in ICP patients showed that perinatal mortality risk in patients with bile acid levels over 100 µmol/L was 30 times higher than in patients with levels under 40 µmol/L (4). In line with findings in the literature, our threshold diagnostic value for cholestasis was defined as 10 µmol/L, and patients over this limit were diagnosed with ICP. The average bile acid level in our study was found to be 17.5±28.1. Roughly 20% of patients with ICP had bile acid levels over 40 µmol/L. Low overall bile acid levels can likely be attributed to early administration of treatment. One emergency ceasarean section was carried out in the 34th gestational week due to fetal distress in patient with high bile acid levels (211 µmol/L). We attribute the absence of fetal mortality in our study to the lack of severe cholestasis (<40 µmol/L), likely due to early treatment of patients.

Birth related perinatal mortality risk has been shown to increase from the 36th gestational week onwards; due to this, elective preterm birth is commonplace in the management of ICP patients (21). Patients followed up through the 39th week, as well as patients followed up on a weekly observation basis have been shown to have a higher risk of perinatal mortality compared to patients managed in the aforementioned way in the 36th week (21). These findings support previous studies suggesting that fetal mortality rates increased after the 36th gestational week. No fetal monitoring method has been shown to be effective in predicting negative perinatal outcomes or reducing risk of stillbirth. An explanation for this, as discussed previously, is that anoxic events may occur acutely rather than chronically. Despite a lack of evidence that antenatal testing is beneficial to fetal health, use of antenatal testing continues to be commonplace. In a study conducted among obstetric healthcare providers in the United Kingdom, 95% of maternity wards that responded to the study stated that they utilized fetal monitoring (15).

The American Congress of Obstetricians and Gynecologists recommends late preterm and preterm birth in the 36th - 37th gestational weeks. Furthermore, birth prior to the 36th week in patients with select clinical and laboratory parameters has been proposed (22,23). On the other hand, The Royal College of Obstetricians and Gynecologists has remained impartial, stating that practices developed for use at 37 weeks are not supported by evidence (5). The average gestational age at birth in our study was 38.1±1.4. In the event of adverse biochemical or clinical parameters, NST, AFI, and LFT's were carried out and births were planned with respect to the patients' health. The main limitations of this study were the absence of fetal mortality, relatively small number of patients, and a lack of understanding of bile salt levels. Despite this, early administration of treatment may account for the absence of fetal mortality. Additionally, this may be explained by (with the exception of one patient) absence of elevated serum bile acid levels.

CONCLUSION

With respect to the increased risk of adverse neonatal outcomes and stillbirth in patients with ICP, timing of birth in maternal ICP patients should be carefully evaluated. In conclusion, there is some evidence to suggest that birth at 37th weeks, especially in patients with severe bile acid level elevations, may improve

outcomes. However, as a result of this study in which the average gestational age at birth was 38 weeks and no fetal mortality occurred, we suggest that with close monitoring and early administration of treatment birth at 38 weeks could potentially improve outcomes in patients with low bile acid levels. Furthermore, optimal timing for birth in patients with ICP is as of yet unknown, due to the absence of randomized studies evaluating elective early induction of labor.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Gelişim University Ethics Committee (Date: 10/06/20121, Decision No: 2021-21).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients for the 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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Pediatr Pract Res 2023; 11(3): 182-186
DOI: 10.21765/pprjournal.1358576

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Effect of YouTube Videos on Breastfeeding Education in Mothers of Babies with Diarrhea

YouTube Videolarının İshalli Bebek Annelerinde Emzirme Eğitimine Etkisi

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ABSTRACT

Aim: YouTube videos have become influential tools for maternal education, providing novel dimensions of empowerment in breastfeeding. However, concerns exist about the quality of information in these videos. This study aims to comprehensively investigate the effects of expert-reviewed YouTube videos on mothers' attitudes towards breastfeeding and to inform mothers that breast milk protects children against diarrhea by blocking organisms that cause diarrhea.

Material and Method: The study included 42 mothers whose children sought pediatric care for diarrhea at a hospital. Participants watched three YouTube videos endorsed by pediatric specialist and filled the Iowa Infant Feeding Attitude Scale (IIFAS) questionnaire before and after watching the videos. Demographic data were recorded, and statistical analyses were conducted to assess changes in attitudes. The collected data were analyzed using SPSS Version 15.0 for Windows.

Results: Of the 42 participants, 34 completed the study. Maternal education correlated with breastfeeding knowledge. Mothers with prior education had similar IIFAS scores before watching YouTube videos, suggesting the videos were beneficial for both educated and uneducated mothers. The number of children also influenced maternal knowledge about breastfeeding ($p<0.05$). Several IIFAS items showed significant attitude shifts following the YouTube video intervention. Notably, misconceptions about nutritional benefits, iron content, formula-feeding convenience, and breastfeeding in public were effectively addressed ($p<0.05$).

Conclusion: This study underscores the potential of YouTube videos in maternal education, especially regarding breastfeeding. Expert-reviewed content enhances understanding and attitudes. While previous studies underscored breastfeeding's benefits, this study additionally emphasizes the role of maternal education. YouTube videos, when delivered by healthcare professionals, can substantially benefit breastfeeding mothers.

Keywords: Breastfeeding, YouTube videos, maternal education, attitudes, infant feeding.

ÖZ

Amaç: YouTube videoları emzirmeyi güçlendirmenin yeni boyutlarını sağlayarak anne eğitimi için etkili araçlar haline gelmiştir. Ancak bu videolardaki bilgilerin kalitesiyle ilgili endişeler mevcuttur. Bu çalışma, uzmanların incelediği YouTube videolarının annelerin emzirmeye yönelik tutumları üzerindeki etkilerini kapsamlı bir şekilde araştırmayı ve anne sütünün, ishale neden olan organizmaları bloke ederek çocukları ishale karşı koruduğu konusunda anneleri bilgilendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Çalışmaya çocukları ishal nedeniyle hastaneye başvuran 42 anne dahil edildi. Katılımcılar, pediatri uzmanı tarafından onaylanan üç YouTube videosunu izlediler ve videoları izlemeden önce ve izledikten sonra Iowa Bebek Beslenme Tutum Ölçeği anketini doldurdular. Demografik veriler kaydedildi ve tutumlardaki değişiklikleri değerlendirmek için istatistiksel analizler yapıldı. Toplanan veriler Windows SPSS 15.0 Versiyonu kullanılarak analiz edildi.

Bulgular: 42 katılımcıdan 34'ü çalışmayı tamamladı. Anne eğitimi emzirme ile ilişkilidir. Daha önce eğitim almış annelerin YouTube videolarını izlemeden önce benzer Iowa Bebek Beslenme Tutum Ölçeği puanlarına sahip olması, videoların hem eğitimli hem de eğitimsiz anneler için faydalı olduğunu ortaya koymuştur. Çocuk sayısı annelerin emzirmeye ilişkin bilgi düzeylerini de etkiledi ($p<0,05$). Birkaç Iowa Bebek Beslenme Tutum Ölçeği öğesi, YouTube video müdahalesinin ardından önemli tutum değişiklikleri gösterdi. Özellikle beslenmenin faydaları, demir içeriği, mamayla beslenmenin uygunluğu ve toplum içinde emzirmeye ilişkin yanlış kanılar etkili bir şekilde giderildi ($p<0,05$).

Sonuç: Bu çalışma, YouTube videolarının anne eğitiminde, özellikle emzirme konusundaki etkisini göstermiştir. Uzmanlar tarafından incelenen ve önerilen içerikler anlayışı ve tutumları geliştirir. Önceki çalışmalar emzirmenin faydalarını vurgularken, bu çalışma ayrıca anne eğitiminin rolünü de vurgulamaktadır. YouTube videoları sağlık uzmanları tarafından sunulduğunda emziren annelere önemli ölçüde fayda sağlayabilir.

Anahtar Kelimeler: Emzirme, YouTube videoları, anne eğitimi, tutumlar, bebek beslemesi

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Başvuru Tarihi/Received: 11.09.2023
Kabul Tarihi/Accepted: 07.10.2023

INTRODUCTION

Breastfeeding provides numerous advantages that extend beyond the properties of human milk itself (1). It is optimal nutrition for newborns, leads to a quick adaptation to extrauterine life by boosting the immune system, is more digestible, and provides a bond between the mother and baby (2,3).

The influence of YouTube videos on maternal education and breastfeeding is profound, these videos have evolved into dynamic didactic instruments, completing the process of maternal engagement with breastfeeding with novel dimensions of empowerment. The corpus of videos, often curated by seasoned healthcare practitioners, accomplished lactation consultants, and experienced maternal figures, serves as a useful tool for mothers in the education of breastfeeding. However, previous studies demonstrated less than 20% of YouTube videos on this topic were in line with the Global Quality Score (4-6). So, these videos are more likely to be useful as long as their content is determined by expert clinicians.

This study seeks to investigate the impact of three meticulously reviewed YouTube videos outlining the advantages of breast milk, as validated by the pediatric specialist, on maternal attitudes and behaviors regarding breast milk.

MATERIAL AND METHOD

In this study, mothers of 42 children aged 2 years and younger with the complaint of diarrhea were included in Şanlıurfa Training and Research Hospital Pediatrics Department. A written consent form was obtained from the participants. Mothers who were illiterate and had no access to the Internet were excluded from the study.

All mothers were asked to watch 3 YouTube videos, the content of which was previously confirmed by the pediatric specialist.

Link 1:

https://youtu.be/_JViHTNNMPo?si=-KwHYmLC1liA8n7S

Link 2:

https://www.youtube.com/watch?v=QG10-yp02tc&t=3s

Link 3:

https://www.youtube.com/watch?v=eYb8EvRtnug&t=363s

These video links were given to mothers and they were asked to watch them.

The content of these three videos was ensured to include the survey questions specified in the Iowa Infant Feeding Attitude Scale (IIFAS) (**Table 1**), while the pediatrist also delivered an education course regarding breastfeeding.

The mothers were exposed to two IIFAS, one before the education program and the second following the completion of the task of watching YouTube videos. The mothers were also questioned about their knowledge of breast milk during the training program, and they were divided into two groups educated and uneducated. Demographic features of the mothers, including the count of children and the presence of active caretaking aides for the infants, were recorded.

Table 1.The IIFAS principles

The Iowa Infant Feeding Attitude Scale

For each of the following statements, please indicate how much you agree or disagree by circling the number that most closely corresponds to your opinion (I = strong disagreement [SDI, 2 = disagreemenl 3 = neutral IN I, 4 = agreement [AI, 5 = strong agreement ISA]). You may choose any number from I to 5.

	SD	D	N	A	SA
1. The nutritional benefits of breast milk last only until the baby is weaned from breast milk.*	1	2	3	4	5
2. Formula-feeding is more convenient than breast-feeding*	1	2	3	4	5
3. Breast-feeding increases mother—infant bonding.	1	2	3	4	5
4. Breast milk is lacking in iron.*	1	2	3	4	5
5. Formula-fed babies are more likely to be overfed than are breast-fed babies	1	2	3	4	5
6. Formula-feeding is the better choice if a mother plans to work outside the home*	1	2	3	4	5
7. Mothers who formula-feed miss one of the great joys of motherhood.	1	2	3	4	5
8. Women should not breast-feed in public places such as restaurants.*	1	2	3	4	5
9. Babies fed breast milk are healthier than babies who are fed formula.	1	2	3	4	5
10. Breast-fed babies are more likely to be overfed than formula-fed babies.*	1	2	3	4	5
11. Fathers feel left out if a mother breast-feeds.*	1	2	3	4	5
12. Breast milk is the ideal food for babies.	1	2	3	4	5
13. Breast milk is more easily digested than formula	1	2	3	4	5
14. Breast milk is the ideal food for babies. *	1	2	3	4	5
15. Breast-feeding is more convenient than formula feeding	1	2	3	4	5
16. Breast milk is less expensive than formula.	1	2	3	4	5
17. A mother who occasionally drinks alcohol should not breast-feed her baby*	1	2	3	4	5

Note. Items marked with asterisks are reverse-scored and the scores for each item are then

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study protocol was approved by Harran University Clinical Research Ethics Board (Project Number: HRU/23.16.15), and written informed consent was obtained from all participants before their participation in the study.

Informational Data Form: The informational data form consists of 15 questions regarding the introduction of the child, mother, father, and family members, the child's feeding method, the status of breastfeeding, the occurrence of diarrhea, and the mother's attitude toward breastfeeding in case of diarrhea.

Iowa Infant Feeding Attitude Scale: The Infant Feeding Attitude Scale (IIFAS), developed by De La Mora and Russell in 1999, is designed to assess women's attitudes towards breastfeeding and predict the duration of breastfeeding, as well as the choice of infant feeding method (7). The validation and reliability study of the Turkish version was conducted by Ekşioğlu, Yeşil, and Turfan (8). The scale consists of 17 items on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). While 9 items in the scale affirm breastfeeding, 8 items contain positive statements about formula feeding. Formula feeding items are reverse scored (1=5, 2=4, 4=2, and 5=1). The total attitude score ranges from 17 (indicating a positive attitude towards bottle feeding) to 85 (reflecting a positive attitude towards breastfeeding).

Statistical Analysis

The collected data were analyzed using SPSS Version 15.0 for Windows. Descriptive statistics were presented as means (± standard deviations) and percentages for continuous variables, such as age and the number of children, as well as for the distribution of participants across different literacy levels and previous education. Paired Samples t-tests were used to compare the means before and after the intervention. The chi-squared test was employed to analyze the association between literacy levels and the sufficiency of knowledge regarding breastfeeding. The percentages of mothers with sufficient knowledge in different literacy groups were compared. ANOVA was used to examine the association between the number of children mothers have and their knowledge regarding breastfeeding, as well as to compare IIFAS scores among different literacy levels. Logistic regression analysis was conducted to determine if the improvement in IIFAS scores was independent of previous education regarding breastfeeding. Correlation analysis was performed to assess the relationship between age and changes in attitude scores. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

Of the 42 mothers included in the study, 34 watched the videos and participated in the second questionnaire. Demographic data of the participants are given in Table 2.The mother who had education regarding breastfeeding had 2.39±1.03 children, while mothers with no previous education had 1.63±0.67 (p=0.035). The degree of literacy had an impact on previous education. 4 of 5 mothers (80%) who graduated from university had sufficient knowledge regarding breastfeeding while 14 of 18 (77%) mothers in the high school group and 5 of 11 (45%) in the < high-school group had a sufficient education. The second important point is the number of children that mothers have. As the number of children increased, the knowledge level of mothers about breast milk became more sufficient.

Table2.The demographical features of the participants

Age, years	26.79±5.19
Literacy, N	
< High-school	11
High-school	18
University	5
How many children?	2.1±0.98
Previous Education, yes/no, n	23/11

Iowa Infant Feeding Attitude Scale score changed following breast feding education and YouTube videos (**Table 3)**. The participants' perceptions regarding the nutritional benefits of breast milk (Item 1), the presence of iron in breast milk (Item 4), the choice between formula-feeding and working outside the home (Item 6), and breastfeeding in public (Item 8) were notably impacted by the intervention of YouTube Videos ($p<0.05$). Items 10 and 14 (reverse-scored), 12, and 13 show improved attitudes towards breastfeeding's positive aspects, such as its health benefits and ease of digestion ($p<0.05$). While some items did not show statistically significant changes, the changes in attitude scores might still have practical implications and contribute to an overall shift in breastfeeding perception ($p>0.05$). Atlhough the sample sizes were small we divided participants given their literacy in three groups and found higher literacy was associated with higher IIFAS scores in ANOVA test (p=0.042).

Logistic regression analysis reveled the improvement in the IIFAS scores was independent of previous studies (p=0.256). Age had no impact on the trends of IIFAS scores changes ($p>0.05$).

Table 3. The trends in IIFAS score following the intervention by using YouTube video

	Pre-YouTube	Post- YouTube	P value
1. The nutritional benefits of breast milk last only until the baby is weaned from breast milk.*	2.3±1.23	2.97±0.99	0.028
2. Formula-feeding is more convenient than breast-feeding*	2.45±1.30	1.58±0.66	<0.001
3. Breast-feeding increases mother—infant bonding.	4.12±0.55	4.11±0.79	0.992
4. Breast milk is lacking in iron.*	3.58±1.45	2.15±0.85	0.025
5. Formula-fed babies are more likely to be overfed than are breast-fed babies	3.85±1.12	3.96±1.02	0.912
6. Formula-feeding is the better choice if a mother plans to work outside the home*	3.87±1.01	2.15±0.87	<0.001
7. Mothers who formula-feed miss one of the great joys of motherhood.	2.14±0.54	2.65±1.12	0.112
8. Women should not breast-feed in public places such as restaurants.*	3.15±0.87	2.15±0.79	0.004
9. Babies fed breast milk are healthier than babies who are fed formula.	4.12±0.67	4.55±0.23	0.088
10. Breast-fed babies are more likely to be overfed than formula-fed babies.*	2.24±1.89	1.88±0.65	<0.001
11. Fathers feel left out if a mother breast-feeds.*	2.54±0.45	2.99±1.05	0.048
12. Breast milk is the ideal food for babies.	3.95±0.96	4.55±0.24	0.045
13. Breast milk is more easily digested than formula	3.14±2.65	3.96±0.87	0.032
14. Formula is as healthy for an infant as breast*	3.78±1.01	1.75±0.87	<0.001
15. Breast-feeding is more convenient than formula feeding	3.15±1.45	3.68±1.22	0.088
16. Breast milk is less expensive than formula.	4.32±0.45	4.65±0.12	0.189
17. A mother who occasionally drinks alcohol should not breast-feed her baby*	4.05±0.68	2.18±1.59	<0.001

Note. Items marked with asterisks are reverse-scored and the scores for each item are then

DISCUSSION

YouTube videos as a means of disseminating information may provide new opportunities for maternal education, particularly in the context of breastfeeding. This study investigated the impact of carefully reviewed YouTube videos, endorsed by clinical experts, on maternal attitudes and behaviors related to breastfeeding. The findings of the study demonstrated that YouTube video-assisted education programs may improve the degree of acknowledgment and attitudes of mothers regarding breastfeeding.

Previous studies revealed numerous benefits of breastfeeding such as nutritional superiority, improvement of immune system and mother-newborn bonding (9,10). The most important step regarding breastfeeding is the education and healthcare support of mother (11). Similarly, this study demonstrated 80% of university-graduated mothers had sufficient knowledge regarding breastfeeding. Furthermore, It was observed that mothers with more than one child had sufficient knowledge about breast milk this highlights that in proportion to the number of children, the awareness of the mother about breast milk also develops. The validation of IIFAS was applied to many countries and found reliability in the assessment of breastfeeding (8,12,13). This study demonstrated substantially improvement in IIFAS scores following an intervention with YouTube videos. Attitudes related to the nutritional benefits of breast milk, the presence of iron in breast milk, the convenience of formula-feeding versus breastfeeding, and breastfeeding in public were notably impacted. These shifts highlight the influence of the intervention on addressing misconceptions and fostering a more accurate understanding of breastfeeding. Especially, the change in the knowledge regarding "Formula-feeding is more convenient than breast-feeding", "Formula-feeding is the better choice if a mother plans to work outside the home", "Breast-fed babies are more likely' to be overfed than formula-fed babies", and "A mother who occasionally drinks alcohol should not breast-feed her baby" was striking.

One of the important points of the study is that mothers have to be educated about breastfeeding during each pregnancy. Our study showed that mothers who received education during their previous pregnancies had similar IIFAS scores compared to non-educated mothers, before watching YouTube videos. Therefore, both mothers who had received education before and those who hadn't benefited from the YouTube video education. Although the content of YouTube videos is not a reliable source of medical and health-related information, the content which is delivered by healthcare professionals may provide substantial benefits to breastfeeding mothers (14,15).

However, several limitations of this study warrant consideration. The sample size was relatively small, which may impact the generalizability of the findings. Additionally, the study's scope was limited to a specific population, and cultural variations might influence the applicability of the results to broader contexts. Furthermore, the assessment of changes in attitude relied solely on self-reported survey responses, potentially introducing bias.

CONCLUSION

YouTube videos present a promising avenue for breastfeeding education, leveraging visual and dynamic content to enhance maternal understanding and empowerment. Carefully curated and expert-endorsed videos have the potential to positively

influence maternal attitudes toward breastfeeding. However, quality control and accuracy remain paramount to ensure the credibility of such videos as educational tools. Tailoring interventions to accommodate participants' educational backgrounds and demographic characteristics can further enhance the impact of breastfeeding education. Future research with larger and more diverse samples is warranted to corroborate and extend the findings of this study.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Harran University Clinical Research Ethics Committee (Date: 04/09/2023, Decision No: HRU/23.16.15).

Informed Consent: The mothers were first informed about the study and then signed written consent forms.

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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Pediatr Pract Res 2023; 11(3): 187-192
DOI: 10.21765/pprjournal.1354667

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Regional Fetal Arrhythmia Screening Results and Postnatal Follow-up Current Results In a Single Center

Tek Merkezde Yapılan Bölgesel Fetal Aritmi Tarama Sonuçları ve Postnatal Takip Güncel Sonuçları

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ABSTRACT

Aim: Fetal arrhythmias are one of the challenging diseases in pregnancies and have an important impress on fetal health. This study aims to evaluate diagnosis methods, treatment plans, and prognosis for these disorders.

Material and Method: Fetuses diagnosed with fetal arrhythmia between January 2018 and January 2021 were retrospectively screened from hospital records and 28 fetuses were identified.

Results: Fetal arrhythmia was detected in 28 fetuses out of 1254 pregnant women (2.2%). Irregular rhythm was observed in 21/28(75%) of the fetuses, supraventricular tachycardia in 4/28 fetuses (14.2%), and fetal atrioventricular (AV) block in 3/28 fetuses (10.7%). All fetuses with tachycardia were hospitalized and digoxin was started at the appropriate dose. In 1/4 of fetuses with atrial tachycardia/fibriloflutter; sotalol was added and combined treatment was started. In the other fetus with persistent tachycardia, sotalol was also added to achieve the rate control. Cardioversion was applied to the newborn who had atrial fibriloflutter at birth. In this newborn, a propafenone propranolol amiodarone triple combination was started and tachycardia was controlled. There was neither intrauterine death nor mortality in the postnatal period in patients with tachycardia. WPW syndrome was detected in one patient after birth. Prolonged medical treatment for at least two years is planned in patients with WPW syndrome and atrial fibriloflutter. 2 fetuses with complete AV block and complex congenital heart diseases had died in the intrauterine period. The other fetus with AV block had neonatal lupus and this patient also died due to heart failure in the postnatal period.

Conclusion: Fetal heart rhythm disorders can be detected prenatally with fetal echocardiography Doppler approach. Anti-arrhythmic drugs could be considered depending on the fetuses' well-being. The mother's diet, and lupus antibodies should be considered in elucidating the etiology.

Keywords: Fetal arrhythmias, fetal echocardiography, prenatal diagnosis, fetal tachycardia

ÖZ

Amaç: Fetal aritmiler gebelikte karşılaşılan önemli hastalıklardan birisidir ve fetal iyilik halini belirleyen önemli bir sağlık sorunudur. Bu çalışma bu bozuklukların tanı yöntemlerini, tedavi planlarını ve prognozunu değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmada Ocak 2018-Ocak 2021 yılları arasında fetal aritmi tanısı alan 28 fetusun kayıtları retrospektif olarak değerlendirilmiştir.

Bulgular: 1254 gebe kadının 28'inde (%2,2) fetal aritmi tespit edildi. Hastaların 21/28'inde (%75) düzensiz ritim, 4/28'inde (%14,2) supraventriküler taşikardi, 3/28'inde (%10,7) fetal av blok görüldü. Fetusta taşikardisi olan tüm gebeler hastaneye yatırılarak uygun dozda digoksin başlandı. Atriyal taşikardi/fibriloflutter olan ¼ fetusta; sotalol eklendi ve kombine tedaviye başlandı. İnatçı taşikardisi olan diğer fetüse ise hız kontrolü sağlamak amacıyla sotalol de eklendi. Atriyal fibriloflutter olan yenidoğana doğumda kardiyoversiyon uygulandı. Bu yenidoğana propafenon propranolol amiodaron üçlü kombinasyonu başlanarak taşikardi kontrol altına alındı. Taşikardisi olan hastalarda intrauterin ölüm ve postnatal dönemde mortalite görülmedi. Bir hastada doğumdan sonra WPW sendromu tespit edildi. WPW sendromu ve atriyal fibriloflutter hastaların da en az iki yıl uzun süreli medikal tedavi planlandı. AV tam bloklu ve kompleks konjenital kalp hastalığı olan 2 fetüs intrauterin dönemde kaybedildi. Diğer AV blok olan fetüsün neonatal lupusu vardı ve doğum sonrası dönemde kalp yetmezliği nedeniyle kaybedildi.

Sonuç: Fetal ekokardiyografi Doppler yaklaşımı ile fetal kalp ritim bozuklukları doğum öncesi dönemde tespit edilebilmektedir. Fetüsün sağlık durumuna göre antiaritmik ilaçlar düşünülebilir. Etiyolojinin aydınlatılmasında annenin diyeti ve lupus antikorları dikkate alınmalıdır.

Anahtar Kelimeler: Fetal aritmi, fetal ekokardiyografi, prenatal tanı, fetal taşikardi.

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Başvuru Tarihi/Received: 04.09.2023
Kabul Tarihi/Accepted: 09.10.2023

INTRODUCTION

Fetal echocardiography is important for prenatal screening in evaluating the cardiac system. It allows early intrauterine diagnosis and treatment of congenital or acquired heart diseases by estimating heart structure, function, and rhythm (1).

Fetal arrhythmias are one of the important diseases encountered in pregnancy and an important health problem that determines fetal well-being. Its incidence in all pregnancies varies between 1-2% (2-4). The conduction system in the fetal heart develops at 16 weeks of gestation and normally produces a regular rhythm and rate between 110 and 160 bpm for the remainder of pregnancy (1,5). Heart rate outside this range and/or irregular beats are defined as fetal arrhythmias. They can be categorized according to whether the rhythm is regular or irregular and heart rate (tachycardic or bradycardic).

Sinusal or supraventricular tachycardia(SVT) may be suspected if the fetal heart rate exceeds 160-180 beats/min. In this case, fetal and maternal conditions such as fetal distress, anemia, fetal thyrotoxicosis, infections, and maternal use of beta-mimetic drugs should be evaluated and considered in the differential diagnosis. If the fetal heart rate is below 100 beats/min, fetal bradycardia is mentioned and atrioventricular (AV) blocks should be considered in the differential diagnosis (5, 6).

The most common fetal arrhythmias were premature atrial complexes (PAC) (58%), followed by supraventricular tachycardias (26%) (4, 7). While the most common mechanism of SVT seen in the intrauterine period is atrioventricular reentrant tachycardia (AVRT) in approximately 70% of cases; this is followed by atrial fibriloflutters (AFL) at a rate of 20%. AFL can be seen in a structurally normal heart, as well as in cases with congenital heart disease. Fetal arrhythmias may present with non-immune hydrops during the intrauterine period; fetal death can also occur (5, 7).

Within the scope of this study, fetuses diagnosed during the fetal period and with arrhythmia were examined retrospectively in terms of diagnosis method, treatment plans, and prognosis.

MATERIAL AND METHOD

Fetuses diagnosed with fetal arrhythmia between January 2018 and January 2021 were retrospectively screened from hospital records and 28 patients were identified. The study was carried out with the permission of Hatay Mustafa Kemal University Ethics Committee (Date: 27.07.2020, Decision No: 04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

These fetuses were diagnosed with fetal echocardiography at a median week of 27 weeks (20-33 weeks of gestation) in the intrauterine period. In the postnatal period, ECG was taken for every newborn alive, and echocardiographic examination was repeated.

Fetal echocardiography was performed with the Vivid E9 Pro Ultrasound System (GE Medical Systems, Canada) with a 4C-RS convex ultrasound probe in the 1.6 to 4.6 MHz range. It was performed with 2D, M-mode, color Doppler, and pulse wave (PW) Doppler imaging methods. Four-chamber, five-chamber, three-vessel, ductal arch, and aortic arch positions were evaluated in two-dimensional imaging. M-mode and pulsed-wave Doppler were used to detect arrhythmias. M-mode ultrasonography was used to identify arrhythmias by detecting atrial and ventricular wall motion and/or movement of the semilunar and atrioventricular valves. Pulsed-wave Doppler is used to evaluate the relationship of atrial contractions to ventricular contractions. This is done by placing the Doppler cursor on the left ventricular outflow tract parallel to the aortic flow direction. When the cursor is aligned, the Doppler gate is expanded so that both left ventricular input and output can be sampled simultaneously. With this monitoring, one can measure the PR interval and evaluate the timing of atrial and ventricular contractions. The same technique can be used to collect similar timing data through simultaneous evaluation of superior vena cava and ascending aorta flow or pulmonary artery and pulmonary venous flow.

Electrocardiography (Standard 12-lead ECG) was taken at a paper speed of 25 mm/sec under similar conditions in postpartum patients. Standard speed and amplitude Nihon Kohden ECG 1250 Cardio fax S (2009, Tokyo, Japan) device was used. According to standard criteria, documented arrhythmias were classified as tachyarrhythmias (supraventricular tachycardia and atrial tachycardia) and bradyarrhythmia (AV complete block). Isolated premature complexes, sinus tachycardia, and other interval measurements were recorded. Fetuses who were first diagnosed elsewhere, had a history of drug use in the mother, and/or did not come for clinical follow-ups regularly were excluded from the study. Fetuses with arrhythmia were called for control again between 1 week and 4 weeks according to the clinical status and stability of the fetuses.

Lower-risk fetal arrhythmias were assessed as ectopic beats <3 to 5 beats per minute and fetal heart rate [FHR] <160 beats/min (4, 5). Persistent ventricular extrasystoles which were more than 3 to 5 beats/min or FHR <120 or >160 bpm were classified as high risk of morbidity (4, 6). If the fetal heart rate was less than

180 beats/min, if there was intermittent SVT (less than 50% of the whole time), if there was no ventricular dysfunction and if there was no valve failure, the patients were followed up without treatment by calling for frequent controls (4, 8). Patients were treated if hydrops or impaired systolic functions were present and/or atrial flutter was detected even if the heart rate was below 180 beats/min. Transplacental therapy is usually given if the fetal SVT heart rate is greater than 220 beats/minute, accounts for more than 50 percent of beats at a given time, and/or hydrops are present (9-15).

Digoxin is the first choice drug in fetal SVT in the approach of our center (16, 17). If the fetal status does not improve despite adequate maternal digoxin levels (1 to 2 ng/mL), other drugs (e.g. flecainide, sotalol, amiodarone) were considered in addition to or in place of digoxin, taking into account the clinical situation (11, 18).

When the FHR is slow otherwise than sinus bradycardia, patients were screened for blocked ectopic beats, long QT syndrome, second-degree heart block, or complete (third-degree) heart block (19). Umbilical cord compression was primarily evaluated in sinus bradycardia. Maternal laboratory tests for anti-Ro/SSA and anti-La/SSB antibodies were also performed. Management was planned depending on the condition of the fetus and signs of heart failure.

Pregnants with fetal arrhythmia were followed up as long as the fetuses' clinic allowed that there were no signs of hydrops and heart failure. A close-to-term birth was the targetted plan (19). Support personnel from the fields of pediatrics, neonatology, and/or cardiology were present during delivery.

Statistical Analysis

The analysis of the data collected in the study was performed using SPSS Statistics for Windows 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistical methods were used to analyze the data, which were expressed as the number and percentages.

RESULTS

Fetal arrhythmia was detected in 28 fetuses out of 1254 pregnant women (2.2%). Irregular rhythm was observed in 21/28(75%) of the fetuses, supraventricular tachycardia in 4/28 fetuses (14.2%), and complete av block in 3/28 fetuses (10.7%). 13 fetuses (46.4%) were male, 15 fetuses were female (53.5%). Median gestation week at diagnosis was 27 weeks (20 weeks to 33 weeks). All demographic and clinical features of the study is summarized in **Table 1**.

Table 1. Demographic and Clinical Features of Fetal Arrhythmia.

	Fetal Arrhythmia
Gestation week at diagnosis (median)	27 weeks (20- 33 weeks)
Gender Male number(%) Female number (%)	 13(46.4%) 15(53.5%)
Mortality Number (%)	3(10.7%) [2 cases complete AV block intrauterin death 1 case complete AV block postnatal death]
Irregular Heart rhythm PAC Number (%)	21 (75%)
Fetal tachycardia Number(%)	4 (14.2%) [3 cases SVT, 1 case AT/AF]
Fetal bradycardia Number (%)	3(10.7%) [2 cases complex congennital heart disease, 1 case neonatal lupus)

AF: Atrial fibriloflutter, AT: atrial tachycardia, AV: atrioventricular, PAC: premature atrial complex, SVT: supraventricular tachycardia.

Irregular Rhythm

Premature atrial complexes were detected in these fetuses with an irregular rhythm. Although PACs are usually isolated, 5/21 of them have bigeminy trigeminal beats. Non-conducted P wave was observed in 2/21 fetuses. These fetuses were sent with a preliminary diagnosis of bradycardia due to compensatory pause, but their heart rate was still >110 beats/min. These 21 fetuses with isolated PACs were followed up for 1 week and then at 2-week intervals. While 2 had thyroid dysfunction in the pregnancy history, caffeine, and theophylline intake was high in the diet of the remaining 10 pregnant patients (at least 2 cups of coffee and/or tea per day, chocolate intake, etc.). 5 pregnant had a history of smoking.

Follow-up and Management of Irregular Rhythm and PAC

It is known that atrial extrasystoles can trigger a reentrant tachycardia. At the same time, atrial extrasystoles with block may be confused with especially 2nd-degree AV block. Here, the patient is evaluated with whether or not there is a history of SLE in the mother, accompanying severe bradycardia, and other echocardiographic Doppler findings. It was observed that PACs disappeared in pregnant women who paid attention to their diet in the second week follow-ups of them. PACs continued until delivery in 2 fetuses, but sinus rhythm was seen in postnatal ECGs that tachycardia and/or bradycardia were not observed in these newborns.

Follow-up and Management of Fetuses with Tachycardia

Persistent tachycardia was present in 4/28 fetuses. 1/4 fetus had atrial tachycardia (atrial fibriloflutter). The other 3/4 fetuses had SVT. Structural heart examinations of these fetuses were normal. The heart rate was between

200-220 beats/min in 3 of these fetuses with SVT. The heart rate in the fetus with atrial tachycardia was between 170 and 190 beats/min. No fetus presented with hydrops. Cardiac functions were impaired in a fetus with atrial tachycardia (AT) in whom cardiomegaly and minimal pericardial effusion were also observed. All fetuses were hospitalized and digoxin was started at the appropriate dose. An additional loading dose of digoxin was given to the fetus with signs of pericardial effusion and heart failure. While there was no response to treatment in 2 fetuses, one of whom was AT; rate control was achieved in the other 2 fetuses.

In 1/4 of fetus with AT/AFL; sotalol was added and combined treatment was started. Despite the medical treatment in the same fetus, the signs of heart failure could not be controlled, so delivery was performed at the 33rd week of pregnancy. Only this fetus had a premature delivery. In the other fetus, sotalol was added and rate control was achieved. The heart rate of the other two fetuses was controlled with drugs and the rhythm was converted to sinus. Cardioversion was applied to the patient who had AT/AFL at birth. However, it was not successful. In this newborn, first propranolol and amiodarone, then propafenone propranolol amiodarone triple combination was started and tachycardia was controlled with combined triple medical therapy. There was neither intrauterine death nor mortality in the postnatal period in patients with tachycardia.

Side effects such as nausea, vomiting, and fatigue were observed in 3/4 of the pregnant women after medication. In these patients with side effects, the drug doses were reduced and the treatment was continued. In the follow-up of these four patients with tachycardia, which was a minimum of 6 months and a maximum of 2 years, their medication was continued for at least 6 more months, even though tachycardia did not continue according to their emergency applications. 24-Hour Holter monitoring, clinical follow-ups, and ECG records were evaluated regularly. WPW syndrome was detected in one patient after birth. Prolonged medical treatment for at least two years is planned in patients with WPW syndrome and atrial fibriloflutter.

Follow-up and Management of Patients with Bradycardia

Fetal bradycardia was observed in 3/28 (10.7%) fetuses. The mean heart rate in these fetuses was 45 beats/min. (44-56/min). Two fetuses were at the 20th and 22nd week of gestation and had complex structural heart disease (both with unbalanced complet atrioventricular septal defect, great vessel malposition, and left atrial isomerism in one). These fetuses, whose hydrops were evident, died in the intrauterine period. The other fetus was in the 24th week at the time of admission to our center. Anti-Ro and Anti-La antibodies were positive and the mother was diagnosed with systemic lupus erythematosus (SLE). Anti-inflammatory treatment [steroid, intravenous immunglobulin (IVIG)] was started in this fetus, who was thought to have neonatal lupus. Hydrops did not develop, but cardiomegaly and endocardial fibroelastosis were observed at level 1. The fetus was born prematurely at the 34th week, weighing 1750 g. A complete AV block was confirmed in the postnatal period. Despite the pacemaker implantation in the postnatal period, this newborn died due to heart failure at the 7th day.

DISCUSSION

In this study, the rate of arrhythmia in fetuses who underwent fetal echocardiography in three years was 2.2%, which is consistent with the literature. While PACs are especially the most common, tachycardias are observed more frequently than bradycardias (14.2% versus 10.7%, respectively). The mortality rate is significantly higher in bradycardias. [The mortality rate is 0% (0/4) in tachycardias versus 100%(3/3) in bradycardias]. The diet of pregnant women may be effective in the emergence of premature atrial complexes. There is no recent study on fetal arrhythmias in our country.

Prenatal management of fetal arrhythmias/tachycardia and bradycardia is controversial and the approach may vary from case to case. However, it is known that 8-30% of fetal and neonatal mortality can be seen in untreated severe cases. At the same time, the delivery of a preterm hydropic fetus has an unacceptably high mortality and morbidity rate. All these are conditions that make the treatment of fetal arrhythmias mandatory. The goals of antiarrhythmic therapy are to restore sinus rhythm, control rate, correct heart failure, and delay preterm labor as much as possible. There is no data providing superiority of the use of any antiarrhythmic drug over the others (18, 20-23).

Isolated premature atrial complexes generally progress well. In these fetuses, attention should be paid to the underlying disease in the mothers, and the fetuses should be followed up for the development of SVT (5, 6, 24). Irregular rhythms resulting from premature atrial beats are generally well tolerated and rarely turn into serious arrhythmias (6). Early atrial complexes are the most common cause of irregular rhythm and are usually benign. In our study, PACs constituted the largest part of fetal arrhythmias. The diety-related beverages containing caffeine and its derivatives were restricted to the mothers of these fetuses. Two mothers had hyperthyroidism. The absence of tachycardia in the course and follow-up of the patients was consistent with the literature, and it could be seen that these arrhythmias did not have significant adverse effects on fetal health.

Congestive heart failure, dilated cardiomyopathy, neurological sequelae (1.6-10%), and even death can be seen in the clinical course of fetal tachycardia. When

complicated with fetal hydrops; fetal tachycardias have a 35% higher risk of death. However, antiarrhythmic treatments can also have adverse effects such as proarrhythmia and drug-related thyroiditis. Should every case be treated? Which types of drugs and how they should be used with the duration of treatment are the subjects that are always discussed and there are no definite considerations (6, 24). In this study, cases with persistent tachycardias and/or heart failure findings such as cardiomegaly and pericardial effusion were treated with drugs. These treatment strategies lead to reduced morbidity and mortality and contributed to the fact that the patients were born as mature as possible, at least as late preterm.

Fetal tachycardia is an important clinical condition that can cause intrauterine morbidity and mortality. It is necessary to prevent complications that may occur due to low cardiac output by providing sinus rhythm or controlling tachycardia. M-mode method, Doppler study of simultaneous mitral and aortic flow or pulmonary vein and pulmonary artery or superior vena cava and descending aorta flows, tissue Doppler recordings of the mitral and tricuspid annulus all could be used in the diagnosis of fetal arrhythmia (9). In this study, the Doppler study of simultaneous mitral and aortic flow methods were preferred in diagnosis, and the M-Mode method was also evaluated. Although there are many protocols for the treatment of fetal arrhythmias, the patient's condition should be considered first. In treatment strategies, only observation can be made without medication; delivery can be performed or the mother can be started on medication (transplacental) or ways such as direct fetal therapy, such as an umbilical vein, intramuscular route, intraperitoneal, etc. can be tried. Treatment can be started even if there are no obvious signs of heart failure due to the existing risk of morbidity and mortality, as well as the difficulty in controlling the intermittent or persistent tachycardia in the follow-up of the fetuses (6, 24). Transplacental treatment was started when there are signs of heart failure, and/or the tachycardia rate is more than 50% of all beats in this study, even if the heart rate is below 180 beats/min. Digoxin treatment was preferred as the first choice. However, the efficacy of combination therapies appears in other recent studies. With this combination therapy, survival rates in the fetal period have increased significantly, and effective rate control has been achieved especially in atrial flutters. The likelihood of maternal side effects is reduced (22, 25). In our study, combination therapy was preferred in only two resistant cases. The reason for not starting combination therapy was to reduce the possibility of side effects and to provide control with a single drug, since there were no significant hydrops in the fetuses and the fetus had no signs of severe heart failure. It seems preferable to start dual therapy in pregnant women with hydrops findings. Since flecainide is not directly available in our country, sotalol treatment was preferred as the second drug in combination treatments.

In this study, the first-line drug digoxin was combined with sotalol in recurrent resistant cases. Since tachycardias may continue in the postnatal period in patients, clinical follow-ups including 24-Hour Holter monitoring were applied. Some groups argue that treatment should be continued in the first 6 months postnatally due to the risk of recurrence. Our results showed no persistent tachycardia in ¾ of these babies in the postnatal period that arrhythmia was not present at birth. In 1/4 of cases, AT/AF continued at birth. In this case with resistant AT/AF and in the other case followed up for WPW, the treatment is planned to continue for at least 2 years. No recurrence of tachycardia has been observed in these infants in their follow-up of 1 year and so far.

Currently, there is no consensus on the treatment method for fetal arrhythmia. Therefore, especially randomized control studies; should be done by taking into account ethical issues. Close monitoring is very important in terms of evaluating side effects and response to treatment in fetuses that a medication has been given.

Intrauterine mortality risk may also increase if fetal bradycardia is accompanied by complex congenital structural heart diseases. Treatment management of neonatal lupus is very difficult. Cases diagnosed late in the second trimester of pregnancy and developed heart failure might not respond to anti-inflammatory treatments well, and the rate of death due to heart failure in these patients increases in the postnatal period (19). The mortality rate due to fetal bradycardia was found to be higher in this study. Even if the mother does not have a history of lupus, antibodies should be checked in these pregnant women so that it could be the first presentation of SLE.

Limitations

Since it is a very rare clinical condition, the number of patients seems small. Randomized controlled studies should be conducted in larger numbers of patients so that different treatments can be compared.

CONCLUSION

Fetal heart rhythm disorders can be detected prenatally with fetal echocardiography Doppler approach. Anti-arrhythmic drugs could be considered depending on the fetuses' well-being. SVTs usually don't persist postnatally. Atrial tachycardias might be more resistant to treatment. By regulating the tea and coffee consumption in the mother's diet, extra beats can be reduced. Even if the mother does not have a history of lupus, sending lupus antibodies in fetal bradycardia with suspected AV block is important in elucidating the etiology.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hatay Mustafa Kemal University Ethics Committee (Date: 27.07.2020, Decision No: 04).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients for the 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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Pediatr Pract Res 2023; 11(3): 193-201
DOI: 10.21765/pprjournal.1357699

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Prehospital Care of Diabetic Ketoacidosis in a Referral Hospital Pediatric Intensive Care Unit and the Utility of Telemedicine

Bir Sevk Hastanesindeki Çocuk Yoğun Bakım Ünitesinde Diyabetik Ketoasidozun Hastane Öncesi Bakımı ve Teletıpın Faydası

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Abstract

Aim: This study aimed to investigate the effects of the type of admission (ambulance/outpatient clinic) and telemedicine use in patients admitted to the pediatric intensive care unit (PICU) with diabetic ketoacidosis (DKA).

Material and Method: A retrospective observational study was conducted at a referral PICU between January 2019 and December 2021. Telemedicine was utilized for patients admitted from other hospitals and through the emergency response system. The study recorded the type of admission (ambulance/outpatient clinic), the efficacy of telemedicine, clinical manifestations, and outcomes. The severity of the disease, complications, and length of stay in the PICU were compared between two groups: ambulance/outpatient and those with telemedicine applied/none applied.

Results: A total of 144 patients were included in the study. Of these, 51.4% were male, and the median age was 13.0 years (range: 2-18 years). About 45.1% of patients were transferred to the PICU by ambulance. Telemedicine was utilized in 56 (38.8%) patients. The usage of ambulance and telemedicine was higher in newly diagnosed and younger patients ($p < 0.001$ and $p = 0.0014$, respectively). No significant differences between the groups using and not using ambulance and telemedicine regarding the Glasgow Coma Scale, Pediatric Mortality Risk Score III, and mean HbA1c level were found. Although complications such as hypophosphatemia and acute kidney injury were more prevalent in the group that did not receive telemedicine, no statistically significant difference was observed and there was no mortality.

Conclusion: There is not enough data in the literature on the prehospital care of DKA patients admitted to PICU. Although there was no significant difference between prehospital care and outcomes in this study, we think that the low complication rate is related to telemedicine.

Keywords: Prehospital care, telemedicine, diabetic ketoacidosis, pediatric intensive care unit

Öz

Giriş: Bu çalışmada diyabetik ketoasidoz (DKA) nedeniyle çocuk yoğun bakım ünitesine (ÇYBÜ) başvuran hastalarda başvuru şeklinin (ambulans/poliklinik) ve teletıp kullanımının etkilerinin araştırılması amaçlandı.

Gereç ve Yöntem: Ocak 2019 ile Aralık 2021 tarihleri arasında retrospektif gözlemsel bir çalışma yapıldı. Başka hastanelerden kabul edilen hastalar için teletıp kullanıldı. Çalışmada, hastaların başvuru türü (ambulans/ayakta tedavi kliniği), teletıp etkinliği, klinik belirtiler ve sonuçlar kaydedildi. Hastalığın şiddeti, komplikasyonları ve ÇYBÜ'de kalış süresi iki grup arasında karşılaştırıldı: ambulans/ayakta tedavi görenler ve teletıp uygulanan/hiç uygulanmayanlar.

Bulgular: Çalışmaya 144 hasta dahil edildi. Bunların %51,4'ü erkekti ve ortanca yaş 13,0 (aralık: 2-18 yıl) yıldı. Hastaların yaklaşık %45,1'i ambulansla başvurdu. Teletıp 56 hastada (%38,8) kullanıldı. Ambulans ve teletıp kullanımı yeni tanı alan ve küçük yaş hastalarda daha yüksekti (sırasıyla $p < 0,001$ ve $p = 0,0014$). Ambulans ve teletıp kullanan ve kullanmayan gruplar arasında Glasgow Koma Skalası, Pediatrik Mortalite Risk Skoru III ve ortalama HbA1c düzeyi açısından anlamlı fark bulunamadı. Teletıp almayan grupta hipofosfatemi ve akut böbrek hasarı gibi komplikasyonlar daha sık görülmesine rağmen istatistiksel olarak anlamlı bir fark gözlenmedi. Çlışmada mortalite gözlenmedi.

Sonuç: ÇYBÜ'ye başvuran DKA'lı hastaların hastane öncesi bakımına ilişkin literatürde yeterli veri bulunmamaktadır. Bu çalışmada hastane öncesi bakım ve sonuçlar arasında anlamlı bir fark olmamasına rağmen komplikasyon oranının düşük olmasının teletıp ile ilgili olabileceğini düşünüyoruz.

Anahtar Kelimeler: Hastane öncesi bakım, teletıp, diyabetik ketoasidoz, çocuk yoğun bakım ünitesi

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Başvuru Tarihi/Received: 09.09.2023
Kabul Tarihi/Accepted: 13.10.2023

INTRODUCTION

Diabetic ketoacidosis (DKA) is the most common cause of hospitalization, morbidity, and mortality in type 1 diabetes mellitus (T1DM) in children (1). The most common cause of DKA at this age is new-onset T1DM. DKA also commonly occurs in previously diagnosed patients who use insufficient insulin or skip insulin therapy, suffer from infections, or have other comorbidities (2). DKA occurs in approximately 30-40% of children at the time of diagnosis of T1DM and a rate of 6-8% per year in children with established diabetes (2-4).

DKA is a serious complication of diabetes characterized by high blood sugar levels (hyperglycemia), ketone accumulation, and acidosis. Early diagnosis of diabetic ketoacidosis (DKA) in individuals with diabetes is of paramount importance due to the potential for severe complications and even life-threatening outcomes associated with this condition. The most common complications of DKA are cerebral damage, cognitive impairment, venous thrombosis, elevated pancreatic enzymes, acute kidney injury, cardiac arrhythmias due to electrolyte disturbances, and pulmonary disease (2-7). The mortality rate of DKA in children is 0.15-0.30% (4-6). The 2022 International Society for Pediatric and Adolescent Diabetes consensus guidelines recommend urgent screening and treatment to prevent DKA complications. In this situation, the accessibility of health centers plays an important role in determining the patient's condition at the onset of diabetes (4).

Telemedicine is defined as "the use of medical information exchanged from one location to another via electronic communication to improve a patient's clinical health status" (8). Telemedicine enables medical care to be delivered remotely through the electronic transmission of health data (9). While telemedicine has made significant advances in various areas of healthcare, its role in managing DKA is not entirely clear due to the acute and critical nature of this condition. Because DKA is a medical emergency that requires immediate and comprehensive personal medical care and monitoring. It can support pre-hospital care by guiding paramedics and emergency medical personnel on initial management steps for individuals suspected of having DKA. Teleconsultations can also aid in deciding the appropriate level of care and facilitating timely referrals to specialized facilities. Telemedicine can also be used as a tool that complements traditional in-person care, especially in critical situations like DKA. Utilizing telemedicine appropriately, especially in remote or underserved areas, can improve diabetes management, enhance patient outcomes, and contribute to preventing complications like DKA. To our knowledge, few studies in the literature examine the use of prehospital care and telemedicine in patients with DKA in the pediatric intensive care unit (PICU). In this study, we aimed to examine the impact of admission type and the benefits of telemedicine on treatment, complications, length of hospital stay, and prognosis.

MATERIAL AND METHOD

The study was carried out with the permission of Mersin University Clinical Researches Ethics Committee (Date: 15.12.2021, Decision No: 2021/755). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients admitted to the 30-bed PICU of a referral hospital with a diagnosis of DKA between January 2019 and December 2021 were retrospectively evaluated. Patient data were obtained from the hospital database. The study included newly diagnosed patients with diabetic ketoacidosis (DKA) aged between 1 month and 18 years, as well as patients with Type 1 diabetes mellitus (DM) who experienced DKA during their follow-up. Exclusion criteria comprised patients over 18 years of age, those with missing data in their medical records, and individuals admitted to intensive care through in-hospital referrals (service patients). Patient demographics, such as age, sex, anthropometric measures, age of T1DM diagnosis, type of emergency department admission (ED), and PICU (admission time, ambulance/by parent or caregiver), use of telemedicine during transport, clinical presentations, causes of DKA, laboratory parameters, biochemical changes, the severity of DKA, Glasgow Coma Scale (GCS), pediatric risk of mortality score III (PRISM III), triggers of DKA, and management, complications, prognosis, and length of stay in the PICU and hospital were recorded.

DKA is defined as a pH < 7.30 and/or a bicarbonate level < 15 mmol/L. By the criteria outlined in the most recent guidelines, the acceptable bicarbonate (HCO_3) level has been revised to 18 mmol/l. However, for our study, which predates 2022, the HCO_3 value used was 15 mmol/l. New-onset and previously diagnosed patients were included in the study. The age of the patients at the time of diagnosis and the number of DKA attacks in the last 3 years were determined. DKA was classified as mild, moderate, or severe according to severity. Mild DKA is classified by a pH of 7.20–7.30 and a serum bicarbonate level between 10-18 mEq/L; moderate DKA by a pH between 7.10–7.20 and a serum bicarbonate level of 9 to less than 5 mEq/L; and severe DKA by a pH of less than 7.10 and a bicarbonate level of less than 5 mEq/L [4]. All severe and moderate DKA patients and symptomatic [altered mental status (AMS), and Glasgow Coma Scale (GCS) < 14] mild DKA patients with a pH of < 7.25 were admitted to the pediatric intensive care unit. Pediatric risk of mortality score III (PRISM III) was used to determine disease severity and predict outcomes (10).

Mild DKA patients were admitted to the PICU because of an insufficient number of out-of-hours nurses and doctors in the inpatient service or the absence of a pediatric endocrinologist during the time they were admitted to the hospital. There was a COVID-19 pandemic at the time the study was conducted. For

this reason, some mild DKA patients were admitted to the PICU because they had symptoms consistent with COVID-19. All children with diabetes mellitus were referred to our hospital as per the policy of the provincial health directorate. All patients were referred by the emergency call center. Before admission, telemedicine consultations (via telephone or video conference, as needed) were conducted with referring physicians through the emergency department call center. For newly diagnosed patients, their diagnoses were made by the physicians at the initial center. The majority of newly diagnosed patients fell into the moderate and severe ketoacidosis category. Unfortunately, the initial diagnosis for these patients took place in locations where specialist doctors were unavailable. Consequently, the first medical professionals these patients encountered were general practitioners. These patients were referred to us due to metabolic acidosis, and through the referral system, telemedicine assistance was provided to the referring physicians. Initial treatment plans were devised in collaboration with these physicians. The treatment for both previously diagnosed and newly diagnosed patients was coordinated by the pediatric endocrinology and pediatric intensive care specialist at the referring hospital.

All patients were admitted to the PICU using a transfer form. These forms provided a detailed account of all treatments administered during prehospital care. All primary care physicians provided a summary of the patient's medical history and interventions on the transfer form, including detailed information on the treatments administered during the patient's stay. Furthermore, the medical teams transporting the patient recorded the procedures performed during the journey on the transfer and handover form. The initial team at the referral center assessed the implementation of recommended treatments via telemedicine. Telemedicine continued within the ambulance throughout transport. Transport time was approximately 40 minutes at the shortest distance and 3 hours at the longest distance in patients considered to be referred. The treatment was conducted following the DKA treatment protocol specific to our country's pediatric intensive care, as outlined in the reference (11).

Newly diagnosed patients received fluid deficit treatment at the initial center they visited. Blood gas and blood sugar levels were continuously monitored. In cases where the distance between the initial center and the PICU exceeded three hours and the patients presented with severe ketoacidosis, blood gas monitoring was conducted. In rare cases, insulin infusion was initiated in a controlled manner before the patient's departure. For patients arriving via long-distance ambulance, paramedics in the ambulance provided telemedicine assistance to ensure the safe transportation of the patient.

The insulin treatments administered at home to patients previously diagnosed with T1DM were evaluated and discussed by both their primary care doctors at the initial center and the PICU team. All of these procedures were accomplished through the utilization of telemedicine, facilitated by emergency medical dispatchers. Previously diagnosed T1DM patients who sought assistance from home did not have a prior record of self-administering extra doses of insulin. During their diabetes management education at endocrinology outpatient clinics, they were explicitly instructed not to administer additional insulin doses in cases of moderate and severe DKA. Instead, they were advised to promptly seek medical attention at the hospital.

Patients were evaluated according to the way they applied to the emergency department and PICU (ambulance/parents-caregivers and telemedicine applied/not applied). The severity of the disease, blood gas parameters, electrolyte disorders that are experienced during the treatment, complications, and length of stay in the PICU and the hospital were compared between the groups.

Statistical Analyzes

Statistics Package for the Social Sciences, version 23.0 software (IBM Inc., Chicago, IL, USA) was used for statistical analysis. Continuous data are represented by the mean and standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables are expressed by frequency and cross tables. The descriptive statistics of the variables, mean (min-max), median (min-max), frequency distribution, and percentage indicators were examined. Mean values were used in parametric tests and median values were used in non-parametric tests. The chi-square test (or Fisher's exact probability test) was used to compare demographics. Mann-Whitney U or t-test was performed for two independent groups, as appropriate. Values of $p<0.005$ were regarded as statistically significant.

RESULTS

Overall, 144 patients were enrolled and more than half of the patients (51.4%) were male. We excluded 21 patients due to missing data and four patients who were hospitalized in other services before being admitted to the PICU. While the median age of the patients was 13.0 [intequartile range (IQR) 10-15] years, the median diagnosis age of T1DM was 11.0 (IQR 6-13) years (**Table 1**). In the study, 66 (45.8%) patients were newly diagnosed with T1DM; 10 (15%) patients were under five years of age, and 24 (36.3%) patients were under 10 years old at the time of diagnosis. Of all patients, 47 (32.6%) were under the age of 10. The majority of the patients (63.2%) were admitted to the PICU in the out of working hours.

Table 1. Demographics, admission features, symptoms, etiology, and severity of Diabetic Ketoacidosis on the admission to Emergency department.

Age (year) [median (min-max, IQR)]	13.0 (2-18, 10-15)
T1DM Diagnosis Age (year) [median (min-max, IQR)]	11.0 (1-17, 9-13)
Gender (F/M)	70/74
Admission time (n, %)	
On working hours	53 (36.8)
Out-of-working hours	91 (63.2)
Admission type (n, %)	
Ambulance	65 (45.1)
Parents / Caregivers	79 (54.9)
Symptoms (n, %)	
Tachypnea	93 (64.5)
Vomiting	43 (29.9)
Weakness	37 (25.7)
Headache	14 (9.7)
AMS	8 (5.6)
Etiology (n, %)	
Skipping insulin therapy	67 (46.5)
Newly diagnosed T1DM	66 (45.8)
Infection	11 (7.6)
Severity (n, %)	
Mild	71 (49.3)
Moderate	52 (36.1)
Severe	21 (14.6)
Telemedicine (n%)	
Applied	56 (38.8%)
No applied	88 (61.1%)

AMS: altered mental status, DKA: Diabetic ketoacidosis, ED: emergency department, F: female, GCS: Glasgow Coma Scale, IQR: interquartile range, M: male, min: minimum, max: maximum, T1DM: type 1 diabetes mellitus

The most common symptoms were tachypnea (64.5%), altered mental status (AMS) (%31.9), headache (29.9%), and weakness (25.7%) (**Table 1**). The most common causes of DKA attacks were "skipping insulin therapy" (46.5%), newly diagnosed T1DM (45.8%), and infection (7.6%). Almost three-quarters of the patients had no chronic disease. While nearly half of the patients (49.3%) had moderate DKA; 36.1% had severe DKA and 14.6% had mild DKA. Among the patients previously diagnosed with T1DM, those who had their last control more than 3 months ago were more common (69.2%).

In the study, 65 patients (54.9%) were admitted to the ED by parents or caregivers; only 45.1% of patients used an ambulance (**Table 1**). Ambulance usage rates of patients diagnosed with T1DM after the first DKA attack were significantly higher than those of patients with T1DM with previous diagnoses ($p<0.001$). Ambulance usage rates of severe and mild DKA patients were similar, and there was no relationship between the DKA severities (46.2% vs. 42.9%, respectively) ($p = 0.804$). In addition, the younger DKA patients had a significantly high ambulance usage rate ($p = 0.014$). When assessing patients admitted to the PICU based on their GCS scores, there was no notable difference between the two groups (ambulance/parents or caregivers) ($p = 0.351$). However, it's important to note that the rate of ambulance utilization was noticeably greater during the initial admission to the PICU for DKA cases ($p = 0.008$), as outlined in **Table 2**.

Table 2: The comparison of transport type and T1DM diagnosis time, DKA severity, age, GCS, and PICU admission numbers

	Transport type		p
	Ambulance	Parents / Caregivers	
T1DM Diagnosis [n (%)]			
New	43 (65.2)	23 (34.8)	<0.001
Old	22 (28.2)	56 (71.8)	
DKA severity [n (%)]			
Mild	9 (42.9)	12 (57.1)	
Moderate	32 (45.1)	39 (54.9)	0.804
Severe	24 (46.2)	28 (53.8)	
Age [median (min-max, IQR)]	12 (2-17, 10-14)	14 (2-18, 11-16)	0.014
GCS [median (min-max, IQR)]	13 (10-15, 12-13)	13 (11-15, 12-13)	0.351
PICU admission number [n (%)]			
1	39 (54.2)	33 (45.8)	0.008
≥2	26 (36.1)	46 (63.9)	

DKA: Diabetic Ketoacidosis, ED: emergency department, GCS: Glasgow Coma scale, IQR: interquartile range, min: minimum, max: maximum, PICU: Pediatric Intensive Care Unit, T1DM: type 1 diabetes mellitus

Of the patients who came by ambulance, 56 (86%) were admitted by referral from other hospitals. These patients had received only isotonic IV fluids during the transport; only three patients came with the combination of IV fluid and a tightly controlled insulin infusion. The reason for giving insulin infusions to those severe DKA patients was that their hospital arrival time was longer than two hours, and they had received an upper limit of IV fluid in the primary care hospitals.

The blood gas parameters and HbA1c levels of the patients on admission are shown in **Table 3**. The median number of PICU hospitalizations for patients after the first T1DM diagnosis was 2 (min 1 - max 7, IQR 1-3). Ambulance usage rates of patients who had ≤1 PICU admission history were significantly higher than those who had ≥2 PICU admission histories ($p = 0.008$) (**Table 2**). Transport type and the utilization of telemedicine did not significantly impact the PRISM III score during the period of PICU admission ($p = 0.975$ and $p = 0.353$, respectively). The median PRISM III score of the patients in the PICU was 8 (min 4 - max 14, IQR 6-10). While complications developed in 25% (n = 36) of the patients during the intensive care follow-up, hypophosphatemia, hypoglycemia, and acute kidney injury (AKI) were the most common (**Table 4**). Cerebral edema was not seen in the PICU. Although complications such as hypophosphatemia and acute kidney injury were higher in the group that did not receive telemedicine, the study findings indicated that the implementation of telemedicine had no statistically significant effect on the incidence of complications in patients with diabetic ketoacidosis (DKA) ($p= 0.351$).

Table 3. Comparative analysis of blood gas and biochemical parameters on admission to the Emergency Department: the impact of transport types and telemedicine utilization

Parameters	Transport type		Telemedicine	
	Ambulance (n=65)	Parents / Caregivers (n=79)	Applied Telemedicine (n=56)	No Telemedicine (n=88)
Blood gas [median (IQR)]				
pH	7.1 (7.0-7.1)	7.1 (7.1-7.2)	7.1 (7.0-7.2)	7.1 (7.1-7.2)
$PaCO_2$ (mmHg)	19 (16-21)	20 (16-24)	19 (16-21)	20 (16-24)
HCO_3 (mmol/L)	5.0 (4-9)	7.5 (5.3-10.0)	5.0 (4-9)	7.0 (5.5-10.0)
BE	-21.0 (-23-(-18))	-20.0 (-23-(-17))	-21.0 (-23-(-19))	-20.0 (-23-(-17))
Lactate (mmol/L)	2.04 (1.4-2.9)	2.1 (1.5-3.0)	2.1 (1.4-2.9)	2.1 (1.4-3.0)
Biochemical [median (IQR)]				
Na (mEq/L)	132 (130-134)	132 (130-135)	132 (130-135)	132 (130-135)
K (mEq/L)	4.6 (3.9-5.1)	4.6 (4.1-5.2)	4.6 (3.9-5.0)	4.6 (4.0-5.2)
P (U/L)	3.46 (2.6-4.6)	4.18 (3.4-5.1)	3.5 (2.6-4.6)	4.1 (3.1-5.1)
Glucose (mg/dL)	521 (400-614)	525 (401-604)	524 (598-598)	523 (402-606)
Urea (mg/dL)	32 (24-38)	34 (24-44)	30 (24-38)	36 (24-44)
Kreatinin (mg/dL)	0.9 (0.8-1.3)	0.9 (0.8-1.2)	0.9 (0.8-1.2)	1.0 (0.9-1.2)
HbA1c (%)	12.1 (10.3-14.2)	12.6 (10.6-13.9)	12.3 (10.4-14.2)	12.4 (10.3-13.9)

BE: Base excess, ED: Emergency department, HbA1c: Hemoglobin A1c, HCO_3: bicarbonate, IQR: Interquartile range, K: potassium, min: minimum, max: maximum, Na: sodium, P: phosphorus, $PaCO_2$: partial pressure of carbon dioxide.

Table 4: The complications, PRISM scores, and length of stay of diabetic ketoacidosis patients in the pediatric intensive care unit

	Transport type		Telemedicine		
	Ambulance	Parents / Caregivers	Applied Telemedicine	No Telemedicine	P value
Complications n,(%)					
Hypophosphatemia	15 (10.4)	15 (10.4)	12 (8.3)	18 (12.5)	0.351
Hypoglycemia	2 (1.3)	1 (0.6)	2 (1.3)	1 (0.6)	
AKI	0	2 (1.3)	0	2 (1.3)	
Hypokalemia	0	1 (0.6)	0	1 (0.6)	
None	48 (33.3)	60 (41.6)	42 (29.1)	66 (45.8)	
PRISM score [median (min-max, IQR)]	8 (4-14, 6-10)	8 (4-14, 6-10)	9 (4-14, 7-10)	8 (4-14, 6-10)	0.456
LOS (h) [median (min-max, IQR)]	16.0 (6-280, 11-26)	16.0 (6-38, 11-20)	18.0 (6-280, 11-26)	14.5 (6-38, 11-20)	0.238

AKI: Acute kidney injury, DKA: Diabetic ketoacidosis, h: hour, IQR: Interquartile range, LOS: Length of stay, min: minimum, max: maximum, PICU: Pediatric Intensive Care Unit, PRISM: Pediatric Risk of Mortality Score

Fifty-six patients (38.9%) were treated with telemedicine. Among the patients who received telemedicine, the entirety of them were transported via ambulance, whereas 86.2% of the patients who arrived by ambulance had previously undergone telemedicine. The utilization of telemedicine was significantly higher among newly diagnosed T1DM patients compared to those with a pre-existing diagnosis, with rates of 73.2% and 28.4%, respectively (p<0.001) (**Table 5**). In comparing patients who underwent telemedicine with those who did not, it was noted that the telemedicine group comprised a significantly younger cohort (median 11.0 vs. 14.0 years, p<0.001). However, there was no statistically significant difference between the two groups regarding GCS assessment (p = 0.056) (**Table 5**).

The median length of stay of the patients in the PICU and the hospital, was 16.0 hours (min 6.0 - maximum 11.7 days, IQR 11.0 - 22.8 hours) and 5.5 days (min 1.0 - maximum 14.0 days, IQR 4.0 – 8.0 days), respectively (**Table 4**). The study revealed that the mode of transport, whether by ambulance or accompanied by parents/caregivers, did not significantly impact the length of stay in the PICU (16.0 hours for both groups, p = 0.137). However, it was determined that patients who underwent telemedicine had significantly longer durations of hospitalization and PICU admission compared to those who did not receive telemedicine (median 26.0 vs. 19.5 days, 18.0 vs. 14.5 days, respectively; p<0.001 and p = 0.017) (**Table 4**).

Table 5. The comparison of telemedicine usage and Type 1 Diabetes Mellitus diagnosis time, age, Glasgow Coma Scale, and pediatric intensive care unit admission numbers

	Telemedicine		p
	Applied Telemedicine	No Telemedicine	
Transport type [n (%)]			
Ambulance	56 (86.2)	9 (13.8)	<0.001
Parents / Caregivers	0 (0)	79 (100)	
Age [median (min-max, IQR)]	11 (2-17, 8.3-14)	14 (2-18, 11-16)	<0.001
T1DM Diagnosis [n (%)]			
New	41 (62.1)	25 (37.9)	<0.001
Old	15 (19.2)	63 (80.8)	
GCS [median (min-max, IQR)]	13 (10-15, 12-13)	13 (11-15, 12-14)	0.056
Complications [n (%)]			
+	14 (25.0)	22 (25.0)	0.351
-	42 (75.0)	66 (75.0)	

DKA: Diabetic ketoacidosis, GCS: Glasgow Coma Scale, IQR: interquartile range, min: minimum, max: maximum, T1DM: type 1 diabetes mellitus

DISCUSSION

T1DM is one of the most common chronic diseases in childhood, its rates continue to rise, and 18% of new diagnoses occur in children aged 9 years and younger (12). Its increased incidence in young children has been associated with delays in diagnosis (13). Early diagnosis and early access to health services reduce morbidity and mortality (14,15).

DKA tends to be more prevalent in young children and adolescents, with the peak incidence observed in the 10 to 14 age group (12,13,15). In our study, we found that the median age of the patients experiencing DKA was 13 years. Diabetic ketoacidosis (DKA) is not linked to a specific gender; both males and females with type 1 diabetes can experience DKA (11, 12, 14,15). In our study, we observed no gender difference in DKA occurrences. DKA is a complication of diabetes that arises from a severe lack of insulin, leading to dangerously high levels of ketones and blood sugar (1-5, 7,10). The risk of DKA is primarily associated with factors such as overall diabetes management, insulin usage, illness, infections, missed insulin doses, and individual health circumstances, rather than gender. In our study, the most common reason was skipping insulin treatment.

Treatment of DKA is teamwork and requires trained healthcare professionals (2,4,7,16). In our study, we evaluated patients with a diagnosis of DKA in a single referral center in a highly populated city. There is a limited number of studies in the literature evaluating the use of prehospital care of patients, emergency medical services (EMS), and the impact of transport-based care for children with DKA (17, 18). In our study, we observed a higher rate of admission to the PICU via ambulance compared to the study conducted by Turan et al. Additionally, within our study, there was a higher incidence of ambulance utilization among patients newly diagnosed with T1DM (17).

In our study, although the number of young, newly diagnosed, and severe DKA patients was higher in the group referred by ambulance, there was no expected significant difference between the groups in terms of complications, laboratory values at the time of admission, or length of stay in the intensive care unit. We thought that the favorable outcomes observed in the PICU for these patients could be attributed to the implementation of telemedicine during transport. However, due to the lack of homogeneity in our groups and the incompatibility of the study group with regression analysis, we were unable to provide definitive insights into this matter. Due to the long transport times of the patients, we managed the treatment via telemedicine.

Telemedicine was originally conceived as a way to reach patients in remote areas with insufficient numbers of healthcare professionals. The use of telehealth and telemedicine received a lot of attention during COVID-19. Today, this technology's use continues to become more widespread (9, 19-22). Studies on the use of telemedicine in the glycemic control of T1DM also existed before COVID-19. Shulman et al. reported that there was no apparent effect of the telemedicine interventions on hemoglobin A1c (HbA1c), severe hypoglycemia, or diabetic ketoacidosis in 2010 (23). Although telemedicine appeared to be effective in glycemic control in another meta-analysis involving adult patients, the evidence was mostly reported from small studies of relatively short duration (24). Although the number of studies reporting the use of telemedicine in the follow-up of patients with T1DM is gradually increasing in the literature, there is no study regarding the use of telemedicine during the transfer of pediatric patients to the PICU due to DKA (21-25).

In our study, we attribute fewer complications to the telemedicine group. Telemedicine allows healthcare teams to collaborate and consult remotely, especially in cases where expertise may not be readily available on-site. It can bridge geographical barriers and provide individuals in remote or underserved areas with access to specialized diabetes care and expertise in managing DKA. This can lead to improved outcomes by ensuring that individuals receive appropriate and timely care. This collaborative approach can enhance the quality of care for individuals experiencing DKA.

In our study, we found higher rates of telemedicine use in patients with new onset T1DM, at younger ages, and in patients referred by ambulance. These results were similar to the transport method (without ambulance/ambulance). Effective use of the emergency referral chain and accessibility to pediatric intensivists and pediatric endocrinologists were important. Telemedicine was administered to patients arriving by ambulance. Although most of these patients were newly diagnosed, younger, and had moderate-to-severe DKA, there was no significant difference between the two groups who received and did not receive telemedicine in terms of GCS and complications at the time of admission to the hospital. There was a similarity between the patient's admission PRISM III scores and the length of stay in the PICU. We think that the reason for this is the treatment of patients using telemedicine. In our study, we cannot evaluate whether the results would have been different if telemedicine had not been used because no control group did not use telemedicine.

Telemedicine has indeed played a significant role in improving the management of DKA by enabling more immediate intervention and closer monitoring during transport. Telemedicine allows healthcare professionals to assess and provide immediate guidance for managing DKA during transport. ın our study, emergency medical personnel communicated

with us who are remote healthcare providers discuss the patient's condition, vital signs, laboratory results, and treatment plan. Telemedicine enabled continuous monitoring of the patient's condition while in transit. This allowed for real-time assessment and adjustment of the treatment plan, ensuring that the patient is stable and receiving appropriate care during transport. In our study, no complication was observed during transport. Telemedicine provided a platform for emergency medical personnel to consult with pediatric intensivists and endocrinologists remotely. This consultation aided in confirming the diagnosis, optimizing treatment plans, and ensuring that appropriate protocols were followed during transport. We think that telemedicine is very important because it provides easy access to a limited number of specialist doctors working in reference hospitals in developing countries.

In our study, we thought that telemedicine enhances the ability to intervene promptly and monitor DKA patients closely, improving outcomes by ensuring timely and appropriate management. Our work coincided with the COVID-19 pandemic, during which telemedicine was extensively utilized. However, it's important to note that telemedicine is a complement to, not a replacement for, in-person medical care, and severe cases of DKA may still require immediate, in-person medical attention.

In the literature, the use of telemedicine has increased in patients followed by DM, especially during the COVID-19 pandemic (26, 27). Periodic consultations using telemedicine enable the care of people with diabetes while limiting the need for in-person attendance at diabetes clinics. Current literature offers limited insights into the application of telemedicine for pediatric T1DM patients. However, a local study involving 8 children with diabetes in our country shed light on its potential (28). The study highlighted that telemedicine could significantly contribute to maintaining optimal glycemic control, particularly for those newly diagnosed with T1DM, especially during exceptional situations like pandemics.

Telemedicine represents a promising avenue for enhancing care for DKA. Healthcare providers and politicians have a critical role in establishing a comprehensive program focused on leveraging telemedicine for diagnosing, monitoring, and managing pediatric DKA. Moreover, the development of standardized guidelines for telemedicine's application in evaluating and managing pediatric DKA is essential. To optimize care, teleconsultation services should be enhanced, seamlessly integrating telemedicine platforms into existing healthcare systems. This integration will facilitate remote consultations and continuous monitoring of pediatric DKA patients. Teleconsultations play a pivotal role in ensuring prompt and accurate diagnosis of DKA cases. This is especially crucial in remote or underserved areas where access to specialized care is limited, as highlighted in our study. Providing accessible teleconsultations with endocrinologists and pediatric specialists can significantly improve the quality of care for these young patients.

Another issue that should be considered in our study is the high rate of DKA in previously diagnosed patients. In the last multicenter study conducted in our country, the incidence of DKA was reported to be 49% in previously diagnosed T1DM patients (29). Risk factors for recurrent DKA were identified in one study, particularly in females, adolescents, and those from inner regional or socioeconomically disadvantaged areas (30). In other studies, it has been reported that one of the main causes of DKA in previously diagnosed patients is inadequacies and deficiencies in accessing health services (31, 32). Our study determined that almost all of the previously diagnosed patients had their last routine control examinations performed long ago. The reason for this is limited access to health services and insufficient specialist doctors compared to the number of diagnosed patients in the region. We consider that the incidence of DKA may decrease slightly with the improvement of the quality of health care that should be provided on a routine basis.

The limitations of the study: (1) Single-Center Study: Conducting the study in a single center may limit the generalizability of the findings to other settings or populations. Different healthcare facilities, regions, or patient demographics could yield different results; (2) Sample Size: The study may be limited by a small sample size, which could reduce the generalizability of the findings. A larger sample size would provide more robust results and enhance the study's external validity; (3) Retrospective Design: The study's retrospective design may introduce inherent limitations, such as reliance on medical records and potential missing or incomplete data. It is crucial to acknowledge these limitations when interpreting the study's results and drawing conclusions, as they may influence the internal and external validity of the findings. Future research should aim to address these limitations to further advance knowledge in this area.

CONCLUSION

Prehospital care of DKA patients is especially important for referral patients living in remote healthcare settings. The use of telemedicine during the transport of patients diagnosed with DKA improves outcomes. Randomized controlled trials of the use of telemedicine in the prehospital care of DKA patients are needed.

We conducted a single-center study here, and despite the good results we obtained, we could not clearly determine the effect of telemedicine on complications and outcomes. Our results about prehospital care of

patients were similar to the previous study conducted in our country (17). The important thing here was to ensure that DKA patients with intensive care indications could be managed in the best way in a reference hospital where a limited number of specialist physicians work. We believe that teleconsultation prevents undesirable consequences that may occur both during transport and during intensive care follow-up, by ensuring that patient follow-up and treatment are adjusted correctly.

Although there is information in the literature about the usability of telemedicine in the follow-up and treatment of T1DM, information on the use of telemedicine in DKA is limited. What will be the impact of telemedicine on timely diagnosis of DKA in children and initiation of treatment, and whether telemedicine-based treatment of DKA provides better results (e.g. resolution of DKA, length of hospital stay and complications) compared to face-to-face treatment, effects of telemedicine on cost, issues such as adherence to treatment plans with telemedicine, how telemedicine affects the frequency and effectiveness of follow-up and monitoring in recovering patients, and the usability of telemedicine to educate and empower caregivers of children with diabetes to recognize early signs of diabetic ketoacidosis and take prompt action may be elucidated in future randomized controlled trials.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Mersin University Clinical Researches Ethics Committee (Date: 15.12.2021, Decision No: 2021/755).

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

Acknowledgments: We thank the city's 112 emergency call center telephone officers, all PICU nurses and staff, diabetes education nurses, and the parents of our patients for permission to work.

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Pediatr Pract Res 2023; 11(3): 202-207
DOI: 10.21765/pprjournal.1369427

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Çocuklarda Güncel Sidney Sistemine Göre Gastrik İntestinal Metaplazilerin İncelenmesi: Tek Merkez Deneyimi

Investigation of Gastric Intestinal Metaplasia in Children According to the Current Sidney System: Single Centre Experience

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Öz

Amaç: Bu çalışmada, üst gastrointestinal sistem endoskopisi yapılan çocuk hastalarda gastrik intestinal metaplazi sıklığının ve kliniğe yansımasının araştırılması amaçlandı.

Gereç ve Yöntem: Ocak 2019 ile Aralık 2022 tarihleri arasında Selçuk Üniversitesi Tıp Fakültesi Hastanesi Çocuk Gastroenteroloji Kliniğinde çeşitli nedenlerle üst gastrointestinal sistem endoskopisi yapılan 1280 hastanın endoskopi ve patoloji raporları geriye dönük olarak değerlendirildi. Biyopsi örneklerinin histopatolojik incelemelerinde gastrik intestinal metaplazi tanısı konan 66 olgu çalışmaya dahil edildi.

Bulgular: Hastaların 37'si (%56,1) kadın, 29'u (%43,9) erkekti. Kadınların yaş ortalaması 12,92±4,297 yıl (1-17 yaş min/maks), erkeklerin 12,07±4,765 yıl (2-17 yaş min/maks) idi. Ortalama endoskopi sayısı 1,66/kez idi (1-5/kez min/maks). Endoskopi endikasyonları arasında karın ağrısı, büyüme geriliği ve çölyak hastalığı şüphesi ilk üç sırada yer almaktaydı. %67,1'inde *H. pylori* pozitifliği saptandı.

Sonuç: Gastrik İntestinal Metaplazi çocukluk çağında nadir görülmekle beraber riski nedeniyle göz ardı edilmemelidir. Yamalı tutulum veya submukoza ya da daha derin tabakaları tutan hastalıklarda endoskopi ile alınan biyopsilerin tanısal anlamda yeterli olamayabileceği unutulmamalıdır.

Anahtar Kelimeler: Çocuk, endoskopi, gastrik intestinal metaplazi, *Helicobacter pylori*

Abstract

Aim: The purpose of this investigation was to examine the occurrence of gastric intestinal metaplasia in pediatric patients who underwent upper gastrointestinal endoscopy and its clinical implications.

Material and Method: A retrospective evaluation was conducted on the endoscopy and pathology reports of 1280 patients who underwent upper gastrointestinal system endoscopy for various indications at the Pediatric Gastroenterology Clinic of Selçuk University Faculty of Medicine Hospital from January 2019 to December 2022. The study included 66 cases that were diagnosed with gastric intestinal metaplasia based on the histopathological examination of biopsy samples.

Results: Among the patients, 37 (56.1%) were female and 29 (43.9%) were male. The mean age for females was 12.92±4.297 years (ranging from 1 to 17 years), while for males it was 12.07±4.765 years (ranging from 2 to 17 years). The average number of endoscopies performed was 1.66 times (ranging from 1 to 5 times). The top three indications for endoscopy included abdominal pain, growth retardation, and suspicion of celiac disease. Detection of *H. pylori* positivity was observed in 67.1% of cases.

Conclusion: While Gastric Intestinal Metaplasia is uncommon in childhood, it should not be disregarded due to its associated risk. It is important to remember that endoscopic biopsies may not provide sufficient diagnostic information in cases involving patchy involvement or diseases affecting the submucosa or deeper layers.

Keywords: Child, endoscopy, gastric intestinal metaplasia, *Helicobacter pylori*

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Başvuru Tarihi/Received: 01.10.2023
Kabul Tarihi/Accepted: 13.10.2023

GİRİŞ

Metaplazi, bir hücre türünün spesifik bir dokuda bulunan diğer bir farklılaşmış olgun hücre türü ile yer değiştirmesi olarak tanımlanır (1). Gastrik intestinal metaplazi (GİM) normal mide epitelinin kolonda ve ince bağırsaktakine benzeyen kolumnar epitelle yer değiştirmesi şeklinde tanımlanmaktadır. Metaplazi *Helicobacter pylori* (*H. pylori*) ilişkili, Ph bağımlı olarak asit- baz irritasyonu ile oluşabileceği gibi hormonlar, tuz, ilaç, alkol, sigara kullanımı gibi çeşitli uyaranlar tarafından indüklenebilmektedir (2). Orijinal hücreler bir çeşit başkalaşım geçirerek çevresel uyaranlara adapte olmaktadırlar. Metaplaziye sebep olan uyaranın ortadan kalkması durumunda dokuların kendi normal özelliklerine dönüşümü halen tam olarak açıklanamamıştır. Bununla birlikte metaplaziye zemin hazırlayan zararlı uyaranların devamı durumunda ise, metaplazi önce displaziye ve ardından maligniteye ilerleyebilmektedir (3). 'GIM'nin kendisi premalign bir durum mudur yoksa mide kanseri riski artığı için bir belirteç midir?' sorusunun cevabı net değildir.

GİM çoğunlukla mide antrum bölgesinde gözlenir, nadiren aralıklarla geniş bölgelere yayılabilir. Sınıflandırılmasında Kawachi ve ark'larının paneth hücre varlığına göre ayrılan komplet-tip I ve inkomplet-tip II ve tip III tipleri en yaygın kullanılandır. İnkomplet İM kolonik epitele, komplet İM ise ince bağırsak epiteline benzemektedir (4).

Bu çalışmada, farklı nedenlerle üst gastrointestinal sistem endoskopisi (UGSE) yapılan çocuk hastalardan elde edilen endoskopik ve histopatolojik bulgular dosya kayıtlarından geriye dönük olarak araştırıldı. Hastalarda GİM sıklığı, yaş gruplarına, cinsiyete ve endoskopi endikasyonlarına göre değerlendirilip tartışıldı. *H. pylori* pozitif ve *H. pylori* negatif hastalarda özellikleri belirlenmeye çalışıldı.

GEREÇ VE YÖNTEM

Bu çalışma için, Selçuk Üniversitesi Tıp Fakültesi Yerel Etik Kurulu'ndan izin alınmıştır (Tarih: 11.04.2023, Karar No: 2023/188).

Hasta Seçimi

Çalışmaya Ocak 2019 - Aralık 2022 yılları arasında Selçuk-Üniversitesi Tıp Fakültesi Çocuk Gastroenteroloji Bilim Dalı'na farklı nedenler ile başvurarak UGSE uygulanan ve histopatolojik değerlendirmede GİM tespit edilen 1-18 yaş çocuk hastalar alınmıştır. İlk ve takip edilen endoskopik ve histopatolojik bulgular retrospektif olarak analiz edildi. Hastaların yaş, cinsiyet gibi demografik özellikleri, gastroözofageal reflü (GÖR) semptomları ve diğer şikayetleri endoskopilerinden elde, aile öyküleri, varsa eşlik eden hastalıkları kaydedildi. Endoskopi endikasyonları; dispeptik yakınmalar, karın ağrısı, büyüme geriliği, kilo alamama, sebepsiz kilo kaybı, gastrointestinal sistem (GİS) kanaması, anemi ve çölyak hastalığı seroloji pozitifliği varlığında tanı amaçlı yapılan işlemleri içermiştir. Gastrik cerrahi geçiren, daha önce *H. pylori* eradikasyon tedavisi alan, son 2 haftada antibiyotik kullanan ve/veya ilaç kullanımları ile ilgili net anamnez veremeyen hastalar çalışma dışı bırakıldıktan sonra geriye kalan 66 hasta çalışmaya dahil edilmiştir.

Endoskopik İnceleme

Endoskopik incelemeler alanında uzman pediatrik gastroenterolog tarafından Fujinon Marka Eg-530 np numaralı neonatal gastroskop cihazı ve Fujinon Marka Eg-530 fp numaralı gastroskop olmak üzere 2 adet cihazla gerçekleştirmiştir. Açlık sonrası sedo-analjezi altında tüm GİS mukozası değerlendirilmiştir. Endoskopik işlem sırasında makroskopik olarak normal dışı bulgular saptanması durumunda antrum ve korpustan mukozal biyopsi örnekleri alındı. Gerekli görülmesi halinde özofagus, bulbus ve duodenum kuşkulu lezyonlarından biyopsiler eklenmiştir. Bu ilk örneklemde histopatolojik GİM saptanması durumunda kontrol endoskopilerde tüm hastalardan Sidney protokolüne göre 2 antrum (büyük ve küçük kurvatur), 2 korpus (büyük ve küçük kurvatur) ve 1 adet incissura angularis bölgesinden olmak üzere toplam 5 biyopsi alınmıştır (5). Endoskopik bulgular sistemik olarak kaydedilmiştir. Endoskopik GİM bulguları (endoskopi ışığında gözle seçilebilen, metaplazik olabileceğinden şüphelenilen bölgeler), patoloji bulguları (histo-patolojik özellikler, kimyasal safra gastriti, *H. pylori* varlığı, displazi, atrofi ve GİM türü), kaydedilerek analiz edilmiştir.

Histolojik Değerlendirme

Doku örnekleri % 10'luk tamponlu formalinde fikse edilip rutin doku takip işlemlerinden geçirildikten sonra parafin bloklara gömülmüş ve bu bloklardan 4 µm kalınlığında örnek kesitler alınmıştır. Bu kesitlere Hematoksilen-Eozin, *H. pylori* için Giemsa ve bazen *H. pylori* antikoru ile intestinal metaplazi değerlendirmesi açısından PAS-Alcian Blue pH 2,5 boyaları uygulanmıştır. Sydney Sistemi sınıflandırmasına göre; kronik inflamasyon, nötrofil lökositler, intestinal metaplazi, atrofi ve *H. pylori* değerlendirilmiştir (5). Kronik inflamasyon plazma hücreleri, atrofi glandların yerini alan fibrozis varlığı, intestinal metaplazi ise normal şartlarda barsakta görülen; absorbtif hücreler, goblet hücreleri ve Paneth hücrelerinin midedeki varlığı ile konulmuştur. İntestinal metaplaziler; morfolojik olarak ve müsin karakterine göre komplet ve inkomplet olarak ikiye ayrılmıştır (6).

Helicobacter pylori Enfeksiyonunun Saptanması

H. pylori varlığı ve yoğunluğu; Giemsa ile boyanmayan ancak morfolojik olarak şüpheli olan dokularda immünohistokimyasal testlerle araştırılmıştır. Geriye dönük kayıtlarda varsa üre nefes testi sonuçları kaydedilmiştir.

İstatistiksel Analiz

Çalışmamızda elde edilen veriler IBM SPSS versiyon 22.0 (IBM, SPSS, Chicago, IL, ABD) programı ile analiz edilmiştir. Kategorik değişkenler için tanımlayıcı istatistik olarak frekans ve yüzde değerleri kullanıldı. Parametrelerimizin normal dağılıma uygunluğu Kolmogorov-Simirnov ve Shapiro Wilks testi ile değerlendirilmiştir. Çalışma verileri değerlendirilirken, tanımlayıcı istatistiksel yöntemlerin (ortalama, standart sapma, sayı, yüzde) yanı sıra niceliksel verilerde normal dağılım gösteren parametrelerin iki grup arasında karşılaştırılmasında Student t testi kullanılmıştır. P<0,05 değeri istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Ocak 2019-Aralık 2022 tarihleri arasında, GİS şikayetleri nedeniyle, kliniğimizde 1280 adet UGSE ve histopatolojik numune alınan işlem gerçekleştirilmiştir. Histopatolojik spesimenlerin değerlendirmesi sonucunda 66 (%5,15) hastaya gastrik intestinal metaplazi metaplazi (GİM) tanısı konuldu. GİM tespit edilen hastaların 37'si (%56,1) kadın, 29'u (%43,9) erkekti. Kadınların yaş ortalaması 12,92±4,297 yıl (median: 14,0 yıl; min-maks: 1-17 yıl) erkeklerin 12,07±4,765 yıl yıl (median: 14,0 yıl; min-maks: 2-17 yıl) idi. Kadın ve erkek arasında yaş bakımından farklılık tespit edilmedi (p:0,456).

GİM tanısı konulan hastaların başvuru şikayetleri incelendiğinde 30 (%45,4) hastada epigastrik ağrı, 10 (%15,2) hastada karın ağrısı tespit edildi. Hastaların UGSE gereksinimine neden olan başvuru şikayetleri **Tablo 1**'de gösterilmiştir.

Tablo 1: Gastrik İntestinal Metaplazi Tanılı Hastaların Başvuru Şikayetleri

Şikayet	N	%
Epigastrik Ağrı	30	45,4
Çölyak Hastalığı Seropozitifliği	11	16,7
Karın Ağrısı	10	15,2
Gastrointestinal Sistem Kanaması	10	15,2
Büyüme Geriliği-Kilo Alamama	2	3,0
Anemi	2	3,0
Sebepsiz Kilo Kaybı	1	1,5

Hastaların ek hastalık bulguları incelendiğinde; hastaların 10'unda (%15,1) çölyak hastalığı (ÇH), 2'sinde (%3,03) inflamatuar bağırsak hastalığı (İBH), 2'sinde (%3,03) otoimmün hepatit, 1'inde (%1,51) ailevi akdeniz ateşi, 1'inde (%1,51) otizm, 1'inde (%1,51) immün yetmezlik, 1'inde (%1,51) serebral palsi saptandı.

Hastaların öykülerinde GÖR hastalığını düşündürecek belirtileri olan 29 (%43,9) çocuk hasta mevcuttu. Bu belirtiler varlığında kardiyo-özofageal sfinkter (KÖS) yetmezliği en sık görülen durumdu. Hastaların 17'sinde (%25,8) ailede bir GİS hastalığı öyküsü mevcuttu. Altı (%9,1) hastanın ailesinde ise GİS malignitesi (kolon ve mide kanseri) öyküsü mevcuttu.

Çalışmaya katılan hastalara yapılan toplam endoskopi sayısı değerlendirmesinde; 42 (%63,6) hastaya bir, 14 (%21,2) hastaya iki, 6 (%9,1) hastaya üç, 1 (%1,5) hastaya dört ve 3 (%4,5) hastaya beş endoskopi yapıldığı belirlendi. Ortalama endoskopi sayısı 1,62±1,034 (median: 1,0; min-max:1-5) olarak belirlendi. Tüm hastalara, klinik düzelme varlığında, son endoskopilerinde alınan spesimenlerde metaplazi negatifliği görülmesi sonrası yeniden endoskopi yapılmadı.

En sık eşlik eden endoskopik makroskobik görünümün midede pangastrit olduğu izlendi. Ardından antral gastrit ve noduler pangastrit gelmekte idi. Duodenumda ise duodenit ve bulbitdi. Duodenogastrik reflü ilk endoskopide 5 (%7,6) hastada klinik olarak gözlenip, patolojide kimyasal gastrit şeklinde doğrulandı. Takiplerinde tedavi ile klinik iyileşme gözlenen hastaların tekrarlayan endoskopilerinde durumun azaldığı izlendi. Tüm görünümlerin tedaviye yanıtının iyi olduğu gözlendi. Gastrik İntestinal Metaplazi bulunan hastaların ayrıntılı UGSE bulguları **Tablo 2**'de verilmiştir.

Tablo 2: Gastrik İntestinal Metaplazi Bulunan Hastaların Üst Gastrointestinal Sistem Endoskopi Bulguları

	1. Endoskopi		2. Endoskopi		3. Endoskopi	
	n	%	n	%	n	%
Özofagus						
KÖS Yetmezliği	17	25,8	12	18,2	3	4,5
Özofajit	3	4,5	2	3	1	1,5
Baret özafajit	1	1,5	0	0	0	0
Mide						
Pangastrit	40	60,6	10	15,2	4	6,1
Antral gastropati	19	28,8	11	16,7	5	7,6
Duodenogastrik reflü	5	7,6	3	4,5	1	1,5
Noduler gastrit	2	3	1	1,5	0	0
Ülser	3	4,5	2	3	1	1,5
Duodenum						
Bulbit	12	18,2	5	7,6	1	1,5
Duodenit	12	18,2	3	4,5	1	1,5
Bulbus ülseri	12	18,2	2	3	0	0
Duodenal ülser	1	1,5	0	0	0	0

KÖS: Kardiyo Özofageal Sfinkter

Hastaların 40'ında (%60,6) metaplazi tipi belirtilmemiş olup 24' (%36,4) hastada inkomplet, 2 (%3) hastada komplet metaplazi tespit edilmiştir. GİM'ye en sık eşlik eden en sık üç histopatoloji bulgusu sırasıyla kronik aktif gastrit, kronik gastrit ve *H. pylori* pozitifliği idi. Displazi hiçbir hastamızda görülmezken lenfoid folikül-agregat varlığı ve atrofi nadir bulgulardandı. Gastrik İntestinal metaplaziye Eşlik Eden Histopatolojik Bulgular **Tablo 3**'de gösterilmiştir.

Tablo 3: Gastrik İntestinal metaplaziye Eşlik Eden Histopatolojik Bulgular

	1. Endoskopi		2. Endoskopi		3. Endoskopi	
	N	%	n	%	n	%
GIM	66	100	42	63,6	14	21,3
Kronik aktif gastrit	32	48,5	9	13,6	3	4,5
Kronik gastrit	25	37,9	13	19,7	6	9,1
H. pylori	23	34,8	5	7,6	2	3
Foveolar metaplazi	14	21,2	3	4,5	2	3,0
Reaktif gastropati	2	3,0	1	1,5	1	1,5
Lenfoid folikül	2	3	1	1,5	1	1,5
Gastrik eozinofili	1	1,5	0	0	0	0
Atrofi	1	1,5	1	1,5	0	0

GİM: Gastrik İntestinal Metaplazi

Tedavide 60 (%90,9) hastanın proton pompa inhibitörü (PPI), 5 (%7,5) hastanın H2 reseptör blokeri, 53 (%80,3) hastanın gastrik yüzey koruyucu tedavisini düzenli kullandığı gözlendi. Tedaviye klinik yanıt sorulduğunda 48 (%72,7) hasta tam düzelme, 15 (%22,7) hasta hafif klinik fayda gördüğünü ve 2 (%3) hasta tedaviden fayda görmediğini ifade etti.

İlk endoskopi sırasında alınan histopatoloji numunesinde 23 (%34,8) hastada *H. pylori* tespit edildi. 2. endoskopide bu sayının 5 (%7,6) hastaya, 3. endoskopide 2 (%3) hastaya düştüğü gözlendi. Kayıtlardan sadece 6 hastaya Üre Nefes Testi yapıldığı, 3'ünün (%4,5) pozitif, 3'ünün (%4,5) negatif olduğu görüldü. Toplamda 16 hasta (%24,2) *H. pylori* eradikasyon tedavisi aldı. Takip endoskopilerin sonunda tüm hastalarda histopatolojik olarak *H. pylori* negatifleşmesi gözlendi.

Tablo 4: Gastrik intestinal metaplazi vakalarında histopatolojik bulguların *H. pylori* ile ilişkisi

	1. Endoskopi		2. Endoskopi		3. Endoskopi	
	H. pylori		*H. pylori*		*H. pylori*	
	Yok n (%)	Var n (%)	Yok n (%)	Var n (%)	Yok n (%)	Var n (%)
KÖS yetersizliği	17	0	11	1	2	1
Özofajit	1	1	2	0	1	0
Barret özofagus	1	0	0	0	0	0
Antral gastrit	18	1	11	0	4	1
Pangastrit	39	1	9	1	3	1
Noduler pangastrit	2	0	0	1	0	0
Ülser	3	0	2	0	1	0
Bulbit	12	0	5	0	1	0
Duodenit	12	0	3	0	1	0
Bulbus ülser	12	1	1	1	0	0
Duodenal ülser	2	0	0	0	0	0
DGR	5	0	3	0	1	0

KÖS: Kardiyo Özofageal Sfinkter, DGR: Duodenogastrik Reflü

TARTIŞMA

Endoskopik incelemeler çocukluk çağında GİS'e ait patolojilerin tanı ve tedavisinde sık kullanılan yöntemlerdendir. Bu kullanım teknolojik gelişmeler ile her geçen gün artmaktadır. Son yıllarda narrow-band imaging, magnifying endoskopi, kromoendoskopi vs gibi ileri endoskopik sistemlere rağmen halen işlem sırasında alınan biyopsilerin histopatolojik değerlendirilmesi tanısal önemini korumaktadır.

Üçüncü basamak pediatrik bakım tesisinde 2 yıllık bir süre boyunca çocuklardan alınan 1690 ardışık antral biyopside GİM sıklığını ve klinik bağlantılarını içeren bir çalışmada, metaplazi 22 (%1,3) biyopside tespit edilmiştir. Biz çalışmamızda bu oranı %5,15 (n=66) olarak bulduk (7). Bu farklılığı klinik olarak sadece ciddi şikayet varlığında UGSE endikasyonu koymamıza bağladık.

Çocukluk çağında sıklıkla dispepsi, karın ağrısı, kusma-regürjitasyon, yutma güçlüğü vb nedenler ile UGSE yapılmaktadır (8). Çalışmamızda da dispepsi, karın ağrısı, GÖR bulguları, GİS kanaması varlığı vb gibi nedenlerle endoskopi yapıldığı gözlendi. Biz GİM tespit edilen hastaların en sık başvuru şikayetlerinin epigastrik ağrı, karın ağrısı ve çölyak seroloji pozitifliği olduğunu bulduk.

Yakın tarihli bir kılavuza göre, GİM olan hastalarda kapsamlı GIM riskini değerlendirmek için Sydney protokolü uyarınca en az beş biyopsi yapılması önerilmektedir (9). 2016 yılında GİM'nin endoskopik derecelendirilmesi (Endoscopic grading of gastric intestinal metaplasia (EGGIM)) sınıflaması geliştirilmiştir (10). EGGIM'de gastrik mukoza Narrow-Band Imaging ve yüksek rezolüsyonlu nonmagnifiye endoskop ile incelenmiştir. Toplamda 5 alan antrum (büyük ve küçük kurvatur), incisura [Operative link on gastritis assessment based on intestinal metaplasia (OLGIM)] arasında anlamlı bir korelasyon görülmüştür (9-11). Bizde şikayetleri nedeniyle endoskopik ilk örneklemde histopatolojik GİM tanısı konulan hastalarda daha sonraki incelemelerinde protokol gereğince 5 biyopsi aldık. Endoskopik işlem sırasında, makroskobik değişiklik varlığı ya da mutlak histopatolojik tanısal gereklilik dışında, pediatrik tüm hastalardan çoklu biyopsi alınması işlem ve anestezi süresini uzatma, komplikasyon riskini artırabileceği gerekçesi ile tüm hastaların ilk endoskopilerinde yapılmamıştır.

Akbulut ve ark.'nın 3081 çocuk hastanın dahil edildiği çalışmalarında, özofagusta patoloji saptananların çoğunluğunda karın ağrısı, GÖR ve dispepsi yakınmaları ön plandadır. Bizim çalışmamızda GÖR bulguları ön sırayı almaktaydı. KÖS yetmezliği en sık gözlenen endoskopi bulgusu idi (12).

Primer duodenogastrik reflü (DGR), çocuklarda histolojik olarak GİM şeklinde görülen gastrik mukozal lezyonlara neden olabilir. DGR muhtemelen bağımsız bir etiyolojik faktördür ve gastrik asit ve *H. pylori* enfeksiyonu ile birlikte

gastrik mukozal lezyonların patogenezinde sinerjik bir rol oynayabilir (13). Serimizde ilk endoskopide DGR %7,6 oranında görülmekte idi. Tedaviye yanıtın iyi olduğu gözlendi.

Geling ve ark'larının 134 çocuk hastayı içeren serilerinde en sık histopatolojik bulgu kronik gastrit ve reaktif gastropati iken bizim çalışmamızda kronik gastrit ve kronik aktif gastrit ön planda idi. Gastrik eozinofili sık patolojik bulgulardan iken bizim çalışmamızda sadece 1 hastada mevcuttu. Her iki çalışmada da displazi gözlenmedi (14). GIM ile displazi ve karsinom birlikteliği çocuklarda nadiren görülür, çünkü öncelikle bunların gelişmesi için gereken süre bireyi yetişkinliğe taşır (15).

İnsan nüfusunun yaklaşık %50'sinin *H. pylori* ile enfekte olduğu tahmin edilmektedir. Uluslararası Kanser Araştırma Ajansı tarafından birinci derecede kanserojen olarak tanımlanmış *H. pylori*, ülkemizde ve dünyada halen önemli bir halk sağlığı sorunu olmaya devam etmektedir (16). *H. pylori* ve GİM'nin her ikisinin de en sık antrumda bulunuyor olması ve GİM'nin *H. pylori* pozitif hastalarda negatif olanlardan daha yaygın olarak görülmesi aralarında bir ilişki olduğunu göstermektedir. Bu konu ile ilgili yayınlarda *H. pylori*'nin GİM morfogenezinde kolaylaştırıcı rol oynadığı, GİM'nin yaş ve duodenogastrik reflü ile arttığı ve GİM oluşumunda coğrafik ve genetik faktörlerin de etkili olduğu belirtilmektedir.(17,18). Kronik inflamasyon ve enfeksiyon, yetişkinlerde gastrik karsinogenez için önemli risk faktörleri olarak kabul edilmektedir. Meksika'da çocuklarda yapılmış bir çalışmada alınan antral biyopsiler (ortalama yaş, 8,3±4,8 yıl) gastrit aktivitesi, atrofi, GIM ve gastrik karsinogenez biyobelirteçleri kaudal tip homeobox 2'nin (CDX2) immünohistokimyasal ekspresyonu açısından incelenmiş, ephrin tip-B reseptör 4 (EphB4), matriks metalloproteinaz 3 (MMP3), makrofaj migrasyon inhibitör faktör (MIF), p53, β-katenin ve E-cadherin.molekülleri çalışılmıştır. Atrofi ve foliküler patoloji *H. pylori*+ biyopsilerde daha sık görülürken (P<,0001), GIM ve CDX2 ekspresyonu *H. pylori* durumu ile anlamlı bir korelasyon göstermemiştir (19) Çalışmamızda ilk endoskopide %34,8 oranında *H. pylori* varlığı tespit edildi. Bu oranın giderek azaldığı ve tamamen kaybolduğu gözlendi. Ciddi klinik şikayet varlığı, aile öyküsü ve ailede GİS malignitesi varlığında %24,2 hastaya eradikasyon tedavisi verildiği belirlendi. *H. pylori* sıklığı ile cinsiyet arasında anlamlı bir ilişki olmamasına rağmen, yaş büyüdükçe *H. pylori* sıklığının arttığı gözlendi. Çocuklarda *H. pylori* enfeksiyonu, gastrik antral ve korpus kronik inflamasyonu, nötrofillerin varlığı, lenfoid foliküller ve nadir mide mukozası atrofisi için daha yüksek rölatif risk ile ilişkilendirilirken, nadir görülen intestinal metaplazi antral bölgede sadece anlamlı olarak daha yüksekti (20).

Hem antrum hem de korpusu etkileyen yaygın, şiddetli GİM, displazi ve invazif kanser gelişimi açısından en yüksek risk altındaki hastaların bir tanımlayıcısıdır. Bu nedenle, GIM şu anda gastrik adenokarsinom riski taşıyan bireyleri tanımlamak için uygun klinik bir belirteçtir (21,22).

Çalışmamızın retrospektif nitelikte oluşu, çalışmaya dahil edilen hasta sayısının azlığı önemli kısıtlılıklardandır. GIM'li çocuklarda uzun vadeli doğal seyri, tedaviyi ve sürveyans protokollerini değerlendirecek çalışmalara ihtiyaç vardır.

SONUÇ

Gastrik İntestinal Metaplazi çocukluk çağında nadir görülmekle beraber riski nedeniyle gözardı edilmemelidir. Semptomu olan çocuklarda işlemin tecrübeli bir endoskopist tarafından özenle yapılması tanısal açıdan önemlidir. Yamalı tutulum veya submukoza ya da daha derin tabakaları tutan hastalıklarda endoskopi ile alınan biyopsilerin tanısal anlamda yeterli olamayabileceği unutulmamalıdır.

ETİK BEYANLAR

Etik Kurul Onayı: Bu çalışma için, Selçuk Üniversitesi Tıp Fakültesi Yerel Etik Kurulu'ndan izin alınmıştır (Tarih: 11.04.2023, Karar No: 2023/188).

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.

Finansal Destek: Yazarlar bu çalışmada finansal destek almadıklarını beyan etmişlerdir.

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

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Pediatr Pract Res 2023; 11(3): 208-213
DOI: 10.21765/pprjournal.1346343

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Single Center Experience of Magnetic Foreign Object Swallowing in Pediatric Patients

Pediatrik Hastalarda Manyetik Yabancı Cisim Yutulmasının Tek Merkezli Deneyimi

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ABSTRACT

Aim: Foreign body (FB) ingestion is a common accident in children. In recent years, the number of patients presenting with magnetic foreign body ingestion has increased due to the production of toys from magnetic foreign bodies. In this study, we investigated the treatment algorithm in patients with multiple magnetic FB ingestion, together with the literature studies conducted in recent years. We aimed to share the common result by evaluating the treatment algorithm of different studies.

Materials and Methods: Patients treated for magnetic foreign body ingestion in our clinic between January 2015 and December 2022 were retrospectively analyzed. The demographic data of the patients, the time of swallowing FB, the time of admission, the number of times they swallowed, the surgical notes, and the length of hospital stay were recorded.

Results: In seven years, 13 patients were treated for magnetic FB ingestion. There were seven male and six female patients. The mean age was 5.3±4.2 years. Five patients swallowed a single magnetic FB, one of them was removed from the esophagus by endoscopy, and four of them were spontaneously removed from the gastrointestinal tract. Three of the eight patients who ingested multiple magnetic FB had spontaneous gastrointestinal tract removal of the FB. FBs were removed by laparotomy in five patients, two of whom were emergency.

Conclusion: Ingestion of a single magnetic object occurs without the need for intervention, such as an isolated foreign body, without causing any damage to my gastrointestinal tract. Ischemia, necrosis, perforation, and even strangulation can be seen due to sandwich compression in most patients who swallow multiple magnetic foreign bodies. In rare cases, the spontaneous gastrointestinal release is possible in multiple magnetic FB ingestion. In case of multiple magnetic FB ingestion, patients who are asymptomatic can be followed. Successful results are obtained with more non-invasive treatment by applying timely and correct procedures.

Keywords: Child, buckyball, intestinal perforation, magnetic foreign body

ÖZ

Amaç: Yabancı cisim (YC) yutulması çocuklarda sık görülen bir kazadır. Son yıllarda manyetik yabancı cisimlerden oyuncak üretimine bağlı olarak manyetik yabancı cisim yutulması ile başvuran hastaların sayısı artmıştır. Bu çalışmada çoklu manyetik YC yutulması olan hastalarda tedavi algoritmasını son yıllarda yapılan literatür çalışmaları ile birlikte araştırdık. Farklı çalışmaların tedavi algoritmalarını değerlendirerek ortak sonucu paylaşmayı amaçladık.

Gereç ve Yöntem: Ocak 2015 ile Aralık 2022 tarihleri arasında kliniğimizde manyetik yabancı cisim yutulması nedeniyle tedavi gören hastalar geriye yönelik olarak incelendi. Hastaların demografik verileri, YC yutma zamanı, başvuru zamanı, kaç kez yutkundukları, ameliyat notları ve hastanede kalış süreleri kaydedildi.

Bulgular: Yedi yıl içinde 13 hasta manyetik YC alımı nedeniyle tedavi edildi. Yedi erkek ve altı kadın hasta vardı. Ortalama yaş 5,3±4,2 yıldı. Beş hasta tek manyetik YC yuttu, bunlardan biri endoskopi ile yemek borusundan çıkarıldı, dördü ise spontan olarak gastrointestinal sistemden çıktı. Çoklu manyetik YC alan sekiz hastanın üçünde, YC'in kendiliğinden gastrointestinal sistemden çıkarılması gerçekleşti. İkisi acil olmak üzere beş hastada laparotomi ile YC çıkarıldı.

Sonuç: Tek bir manyetik nesnenin yutulması, izole yabancı cisim gibi herhangi bir müdahale gerektirmeden, mide-bağırsak sistemime herhangi bir zarar vermeden gerçekleşmektedir. Çoklu manyetik yabancı cisim yutan hastaların çoğunda sandviç basısı nedeniyle iskemi, nekroz, perforasyon ve hatta boğulma görülebilmektedir. Nadir durumlarda, çoklu manyetik YC spontan gastrointestinal yolla çıkması mümkündür. Çoklu manyetik YC alımı durumunda asemptomatik hastalar takip edilebilmektedir. Zamanında ve doğru işlemler uygulanarak daha noninvaziv tedavi ile başarılı sonuçlar elde edilir.

Anahtar Kelimeler: Çocuk, buckyball, bağırsak delinmesi, manyetik yabancı cisim

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Başvuru Tarihi/Received: 19.08.2023
Kabul Tarihi/Accepted: 09.10.2023

INTRODUCTION

FB ingestion is a common accident in children. It is usually seen under the age of five (1). Studies have shown that 80% of ingestions cause no harm, with FB being expelled from the digestive tract without any damage (2). However, magnetic FBs are a special type of foreign body, as they can cause serious injury to the gastrointestinal tract and even be life-threatening. When swallowed alone, they pass through the gastrointestinal tract without any problems. However, if multiple magnetic FBs, whether metal foreign or not, are swallowed, they can attract each other in the gut and cause serious problems by causing ischemia, pressure necrosis, intestinal perforation, or volvulus. Deaths have been reported following multiple magnet ingestion (3). Magnets are widely used in daily life as gluing tools or toys used to attach documents or photos to metal products such as whiteboards and refrigerators. Especially recently, the increase in some toys made using magnets has increased the number of patients coming to the emergency services with the complaint of swallowing magnets. (4). Whether the swallowed FB is metallic or magnetic will change the clinical course considerably, so first of all, the process of questioning the witnesses should be done very carefully. Since this distinction cannot be made clearly with imaging studies, patients may need to be kept under observation (5). In this study, we present the treatment protocols of patients who ingested magnetic FB in our clinic in the last seven years, accompanied by literature information to discuss an optimized treatment strategy after magnetic FB ingestion.

MATERIAL AND METHOD

Patients treated for magnetic foreign body ingestion in our clinic between January 2015 and December 2022 were retrospectively reviewed. Demographic data of the patients, complaints on admission, examination findings, imaging tests, time of swallowing FB, time of admission, how many swallows, surgery notes, and hospitalization times were recorded. Treatment protocols for single or multiple magnetic FB ingestion were reviewed. Ethics committee approval was not required because the study was a retrospective file review.

RESULTS

It was seen that 13 patients were treated for magnetic FB ingestion in 7 years. There were seven male and six female patients. The mean age was 5.3 ±3.6 years. There were nine (69.3%) patients aged five years and younger. Among the reasons for swallowing, curiosity was in question in children aged five and under, while it was accidentally swallowed in children aged six and above. After ingestion, application times to our clinic ranged from 4 hours to 35 days. The mean hospital stay of the patients varied between those who swallowed single and multiple magnetic FBs. Individuals who swallowed single FB were generally followed up with family education. In patients who swallowed two or more magnetic FBs, the hospitalization period was 4.5±3.5 days. Five patients swallowed a single magnetic FB, one of which was removed from the esophagus by endoscopy. Four of them exited spontaneously through the gastrointestinal tract. Spontaneous gastrointestinal tract FB was detected in three of eight patients who swallowed multiple magnetic FBs. FBs were removed by laparotomy in five patients, two of whom were emergency.

Admission to hospital complaints, physical examination findings, and X-ray images of eight patients who swallowed multiple magnetic FB were carefully evaluated. Foreign bodies were evaluated in standing X-ray imaging of non-vomiting patients with normal physical examination findings, and these patients with normal intestinal gas distribution were followed up with close imaging. Early intervention was performed in patients who had abdominal tenderness and defense in their physical examination, who complained of vomiting, and who were suggestive of obstruction in standing X-ray imaging.

One of the patients who underwent laparotomy presented with the complaint of swallowing magnets 18 hours ago and later developing abdominal pain and vomiting. On examination, she had abdominal distension, diffuse tenderness, and defense. In the standing X-ray, 8 round FBs and one disc-shaped FB were seen. In addition, there was an appearance suggestive of ileus with broad-based levels (**Figure 1a**). There was acute phase elevation. In laparotomy, it was observed that there were 4 perforations in the jejunal segment due to sandwich compression, and there was ischemia-dependent necrosis in the approximately 50 cm jejunal segment due to compression of the mesentery (**Figure 1b, 1c**). The perforated areas were primarily repaired and the ischemic segment was removed, and a total of 9 magnets (**Figure1d**) in the form of 8 buckyballs and one disc, which caused the clinic, were taken out of the intestine, and an end-to-end anastomosis was performed.

Another patient who underwent laparotomy was a 16-month-old male. The patient who presented with the complaint of vomiting had widespread defense in the abdomen. He had acute phase elevation. FB, which is thought to be five spherical magnets, was seen in the X-ray graphy (**Figure 2a**). In laparotomy, there was a perforation due to sandwich compression, connecting the posterior surface of the stomach and the jejunal intestine 20 cm distal to the treitz. There were multiple perforations due to sandwich compression at 20-40-50-70 cm from the treitz (**Figure 2b, 2c**). All perforations were repaired primarily by removing the magnets from the intestine. A total of five buckyball magnets were removed (**Figure 2d**).

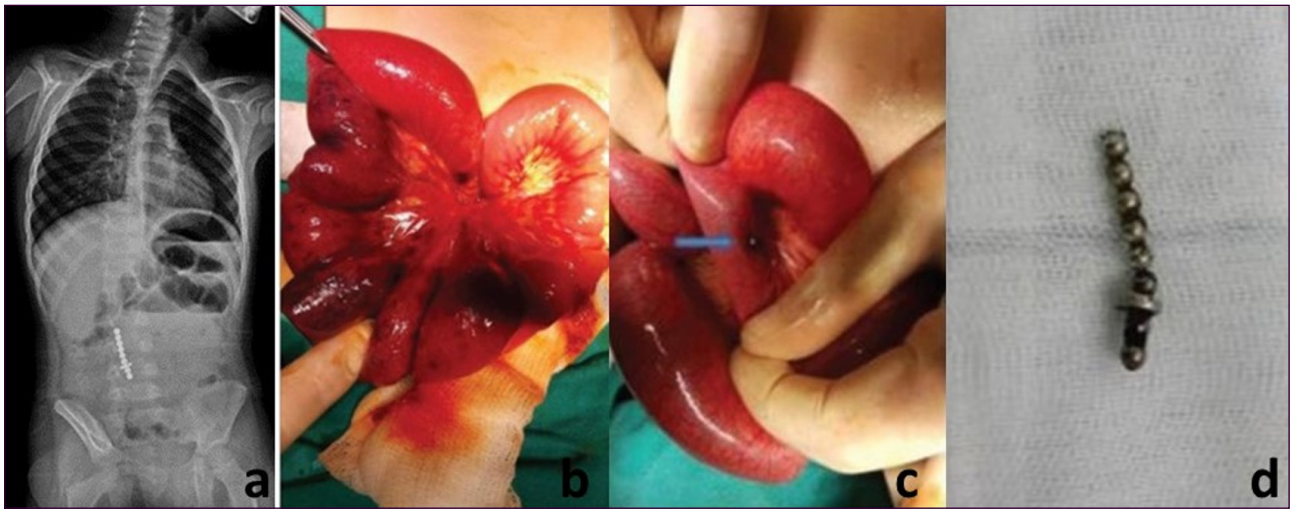

Figure 1a-1d

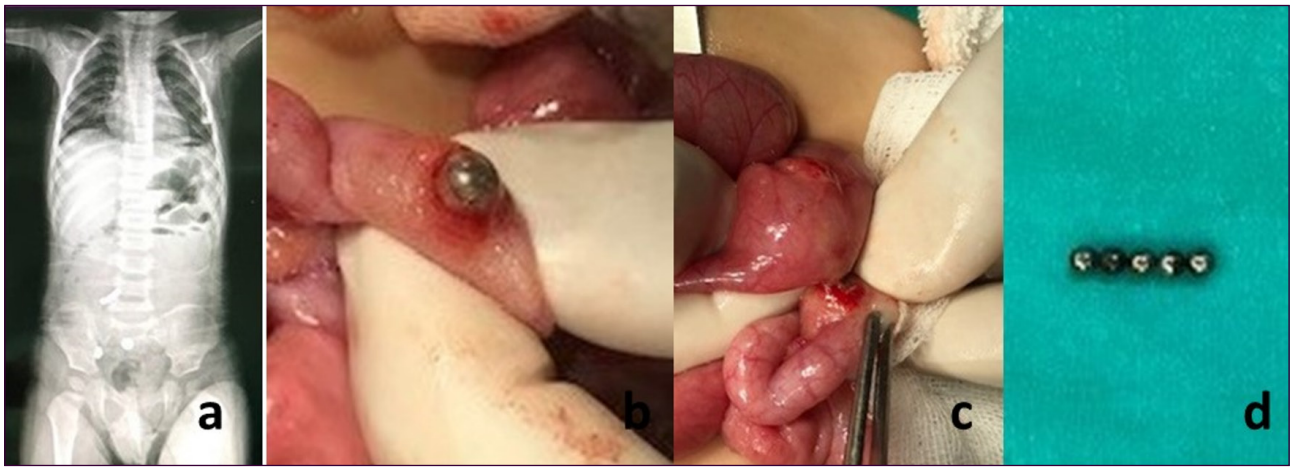

Figure 2a-2d

Esophagogastroduodenoscopy was first performed on three patients who underwent laparotomy and swallowed multiple magnetic FBs. FBs were removed by gastrotomy in a patient whose FB was found to be embedded in the gastric mucosa. In the other patient, the location of the magnets was fixed for about 1 month, when the endoscopy revealed that the stomach mucous was buried, gastrotomy was performed and it was seen that 5 of the magnetic FBs, in which a fistula was formed with the 5 cm of the jejunum, merged with the two FBs in the stomach to form a ring in the jejunum. In another patient, a gastrotomy had to be performed because removal by endoscopy was not successful.

In a patient who swallowed a single magnetic FB, esophagoscopy was performed and the esophagus was removed from the 15th cm because the FB was in the esophagus for about 4 hours and caused compression.

The clinical features of the patients who underwent surgery after magnet ingestion are summarized in **Table 1**.

DISCUSSION

In pediatric patients, swallowed FBs are typically small objects such as coins, fish bones, marbles, and drugs; A recent meta-analysis showed that batteries and sharp objects should be removed immediately, but other ingested FBs can pass through the gastrointestinal tract without intervention (5). Recently, multiple magnetic FB ingestion has become more common in children due to the increasing use of magnetic elements (4). This increase is mainly due to the increasing popularity of round ball-shaped (Buckyballs) toys, a toy with a strong neodymium magnet, and are usually sold in 125 or 216 spheres about 5mm in diameter or as part of a toy. A single magnetic FB does not cause serious morbidity because it only acts as an isolated FB. However, multiple magnetic FBs attract each other along the intestinal walls, resulting in sandwich compression, and consequently; they may lead to intestinal obstruction, fistulas, or perforation (5,6). Previous case reports have recommended endoscopic or surgical removal of ingested magnets by clinicians before FB-related symptoms develop (7, 8). Literature reviews have shown that emergency surgical intervention is required

in cases involving ingestion of multiple magnetic FBs and any symptoms suggestive of the surgical abdomen, but conservative treatment may be appropriate in cases involving ingestion of a single magnetic FB and without definitive evidence of intestinal obstruction (5). Most patients are asymptomatic or show atypical symptoms in the early stages. Most symptoms appear 1 to 7 days after ingestion. Abdominal pain gradually increases over time. However, the number of magnets ingested is not related to the severity of the disease (4). In the literature, two patients who were followed up with no other complaints other than abdominal pain at intervals of 3-6 months after swallowing multiple magnets were reported (4,9). In our study, patients with surgical abdominal symptoms were treated in accordance with the new literature. We had two patients who complained of intermittent abdominal pain and underwent laparotomy approximately 1 month later.

In another study with similar results to our study; 35 patients who swallowed multiple magnetic FB were evaluated; 6 of them were followed conservatively and it was seen that they were removed spontaneously in 3-7 days with x-ray imaging without clinical symptoms. Of the remaining 29 patients, 3 underwent laparoscopy and 2 underwent laparotomy; Laparotomy was performed in 26 of them. 22 patients who underwent laparotomy were operated under emergency conditions due to surgical abdominal findings. All patients who underwent laparotomy had multiple perforations, and primary repair was performed. It has been stated that complications can be reduced with timely diagnosis and effective treatment methods (4).

In a survey study, a total of 104 patients who swallowed magnetic FB were reached. A single magnetic body was detected in 71 of them and esophagogastroduodenoscopy was performed in 8 of them. Other patients spontaneously removed the single magnetic FB within 1-9 days. The remaining 33 patients were followed up for multiple magnetic FB swallowing. 19 patients were followed up because they were asymptomatic. Endoscopy was performed in 4 patients, but laparotomy was performed in 2 patients. Laparotomy was performed in 10 patients and multiple perforation repair was performed. According to this study, gastrointestinal injury was seen in only 11 patients out of 104 patients (10).

In another study whose findings were consistent with this study, 56 patients who swallowed magnetic FB were evaluated. Thirteen patients were followed up asymptomatically and spontaneous removal was observed between 1-6 days. The shock was seen in 2 of 26 patients who were symptomatic. 43 patients underwent surgical procedures. Laparoscopy was performed in 4 patients, and in 3 of them, they were switched to laparotomy. Laparotomy was performed on 39 patients.

Table-1 Clinical Features Of Patients Who Underwent Endoscopy And Laparotomy

	Patient -1	Patient -2	Patient-3	Patient -4	Patient -5	Patient -6
Age (year)/ gender	4,5/boy	1,5/girl	1,5/boy	5/ girl	4/ girl	4/boy
complaint	Abdominal pain-vomiting	Abdominal pain	Abdominal pain-vomiting	Fixed FBs on Xray	Abdominal pain	Difficulty swallowing
Physical examination	Abdominal tenderness, distension	Normal	Abdominal tenderness, distension	Normal	Epigastric tenderness	Difficulty swallowing
Laboratory findings	Acute phase elevation	Normal	acute phase elevation	Normal	Normal	Normal
Initial treatment plan	Laparotomy	Esophagogastroduodenoscopy	Laparotomy	Esophagogastroduodenoscopy	Esophagogastroduodenoscopy	Esophagoscopy
Reason for surgery	Physical examination findings	Physical examination findings	Physical examination findings	Fixed FBs	Epigastric tenderness	Difficulty swallowing
Surgical findings	There is perforation and strangulation	No perforation	There is perforation	There is perforation	Gastric Mucosa damage	Esophageal mucosal damage
Number of perforations	4	0	6	3	0	0
Number/ shape of magnets swallowed	8 buckyballs/1 disc	5 disc	5 buckyball	5 buckyball	5 buckyball	1 disc
Discharge time from the hospital (days)	7	4	6	6	3	2

In one patient who underwent laparotomy, end-to-end anastomosis was performed after resection due to intestinal strangulation and necrosis, while another symptomatic patient had an esophagotracheal fistula. In this study, it was stated that longer-term follow-up is required for the follow-up of possible complications, and it was stated that access to buckyball-type toys should be restricted in order to decrease the number of cases (11).

In another study, 74 patients who swallowed multiple magnetic FBs were evaluated. The treatment algorithm of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) was used in the follow-up of all patients. According to this algorithm; Gastroscopy, colonoscopy, laparoscopy, and laparotomy were performed, respectively, depending on whether the patients were symptomatic or not. According to this algorithm, 17 patients underwent endoscopy (asymptomatic patients); laparoscopy in 6 patients; Laparotomy was performed in 41 patients. Conversion to laparotomy was made in 10 patients. In this study, two peaks were observed in the patient groups between the ages of 1-3 and 6-11, and it was thought that the increase in cases in recent years was related to the increase in buckyball toys. It has been observed that the appearance of symptoms can vary between 4 hours and 40 days. In the study, it was stated that the number of cases increased each year and the NASPGHAN algorithm should be used for treatment (12). The necessity of performing an invasive procedure in asymptomatic patients is noteworthy here. Consistent with other studies, we only followed asymptomatic patients. We have seen that magnetic FBs are excreted spontaneously through the gastrointestinal tract in an average of 2-9 days.

In another study, 13 patients who swallowed magnetic FB were evaluated. While 5 patients were spontaneously removed without any intervention, endoscopy was performed in 5 patients, magnetic FBs were removed with the help of basket and grasper in 3 of them, and FBs were removed spontaneously in the other 2 patients. Laparotomy was performed on 3 patients. Deep ulcer and perforation were repaired at laparotomy. With the study, it was concluded that the number of cases increased with the increase in toys containing magnets with high neodymium additives in recent years, and the complications became more serious with the ingestion of multiple magnetic objects. It has been stated that the number of cases can be reduced by restricting access to such toys (13). In our study, gastrotomy was performed in one patient because the endoscopic removal procedure was unsuccessful.

The data of the studies conducted in recent years are summarized in **Table 2**.

CONCLUSION

The increase in the production of toys containing magnetic properties, unfortunately, causes an increase in the number of patients who apply with the complaint of magnetic FB ingestion. Restricting access to such toys and raising awareness among parents will reduce the number of patients. Serious complications can be prevented by careful evaluation of the patient's symptoms and examination findings and timely intervention in the treatment. Asymptomatic patients should be followed up with simple radiographs for at least 2-3 days. According to the symptoms, localization, and examination findings, endoscopy, laparoscopy, or laparotomy procedures can be applied.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was not required because the study was a retrospective file review.

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

Table 2. Working time and data chart of articles

Article	Working Time (year)	Patient number	Number of patients followed up asymptomatically	Endoscopy	Laparoscopy	Laparotomy	Transition to laparotomy
Huang et al. (4)	6	35	6	0	3	26	2
Miyamoto* et al (10)	2	33	19	4	0	10	2
Cai et al(11)	10	56	13		4	39	3
Wang et al (12)	10	74	0	17	6	41	10
Lai et al (13)	9	13	5	5	0	3	0
This article	7	13	7	4	0	5	3

*: is a survey study

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Pediatr Pract Res 2023; 11(3): 214-219
DOI: 10.21765/pprjournal.1354378

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Individualized Management of Subdural Effusion-Hematoma in Pediatric Shunt Patients

Pediatrik Şant Hastalarında Subdural Efüzyon-Hematoma'nın Bireyselleştirilmiş Yönetimi

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ABSTRACT

Aim: This study examines the challenges of managing subdural effusion-hematoma (SEH) following shunt procedures for treating hydrocephalus in a pediatric population. It raises questions about the effectiveness of fixed-pressure versus adjustable shunts, particularly in the management of SEH complications. While adjustable shunts have been lauded for their flexibility, neither option has fully eradicated the risk of SEH. The study aims to share clinical insights into managing these complications, given the lack of a one-size-fits-all solution.

Material And Method: This study retrospectively analyzes data from 2011 to 2022 on 496 pediatric patients who underwent ventriculoperitoneal (VP) shunt surgery for hydrocephalus at the same hospital. The study focuses on 11 patients with shunt-related subdural effusion-hematoma (SEH).

Results: This detailed study on 11 pediatric patients who developed subdural effusion-hematoma (SEH) after shunt placement reveals a diverse range of symptoms and treatments. Asymptomatic patients were closely monitored, while those with shunt infections had their shunts removed and underwent extra-ventricular drainage (EVD). In more severe cases, such as reduced consciousness, emergency interventions like shunt removal and hematoma surgery were performed. The outcomes varied, but many patients showed improvements and some were even able to continue without a shunt, based on individualized assessments and treatments.

Conclusion: The study concludes that managing SEH in pediatric patients post-shunt placement is complex and individualized, emphasizing that treatment should be symptom-based rather than solely relying on radiological findings, thereby filling a gap in the literature that mostly focuses on adults.

Keywords: Hydrocephalus, shunt, adjustable shunt, subdural effusion, subdural hematoma

ÖZ

Amaç: Bu çalışma, pediatrik bir popülasyonda hidrosefali tedavisi için şant prosedürleri sonrası subdural efüzyon-hematoma (SEH) yönetiminin zorluklarını incelemektedir. Sabit basınçlı ve ayarlanabilir şantlar arasındaki etkinliği, özellikle SEH komplikasyonlarının yönetimi açısından sorgulamaktadır. Ayarlanabilir şantlar esneklikleri için övülse de, hiçbir seçenek SEH riskini tamamen ortadan kaldırmamıştır. Çalışma, bu komplikasyonların yönetimine dair klinik içgörüler paylaşmayı amaçlamaktadır, çünkü tek tip bir çözüm yoktur.

Gereç ve Yöntem: Bu çalışma, 2011'den 2022'ye kadar aynı hastanede hidrosefali için ventriküloperitoneal (VP) şant ameliyatı geçirmiş 496 pediatrik hastanın verilerini retrospektif olarak analiz etmektedir. Çalışma, şantla ilgili subdural efüzyon-hematoma (SEH) gelişen 11 hastaya odaklanmaktadır.

Bulgular: Şant yerleştirilmesi sonrası subdural efüzyon-hematoma (SEH) gelişen 11 pediatrik hastayı detaylı olarak inceleyen bu çalışma, çeşitli belirtiler ve tedaviler ortaya koymaktadır. Asemptomatik hastalar yakından izlenmiş, şant enfeksiyonları olanlarda ise şantlar çıkarılmış ve ekstra-ventriküler drenaj (EVD) yapılmıştır. Daha ciddi vakalarda, gibi bilincin azalması gibi durumlarda, şant çıkarılması ve hematoma ameliyatı gibi acil müdahaleler yapılmıştır. Sonuçlar farklılık gösterse de, birçok hasta iyileşme göstermiş ve bazıları bile bireyselleştirilmiş değerlendirmeler ve tedaviler temelinde şantsız devam edebilmiştir.

Sonuç: Çalışma, şant yerleştirilmesi sonrası pediatrik hastalarda SEH yönetiminin karmaşık ve bireyselleştirilmiş olduğu sonucuna varmaktadır. Tedavinin belirti temelli olması gerektiğini vurgulamakta ve bu konuda çoğunlukla yetişkinlere odaklanan literatüre bir katkı sağlamaktadır.

Anahtar Kelimeler: Hidrosefali, şant, ayarlanabilir şant, subdural efüzyon, subdural hematom

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Başvuru Tarihi/Received: 02.09.2023
Kabul Tarihi/Accepted: 09.10.2023

INTRODUCTION

Shunt placement procedures for the treatment of hydrocephalus have a broad global application and continue to be a commonly utilized treatment method in today's technology (1,2). However, complications such as subdural effusion-hematoma (SEH) may occur following this type of surgical intervention. The clinical course of these complications can vary from individual to individual, ranging from mild, asymptomatic cases to states of paralysis and coma (1,2). In the literature, considerable emphasis has been placed on the positive prognostic effects of using adjustable (programmable) shunts for SEH (1-6). The inability to adjust pressure settings after the implantation of fixed-pressure shunts, coupled with the idea that cerebrospinal fluid (CSF) regulation could be influenced by individual differences, suggests that using the same shunt settings for all patients might lead to complications in some cases. On the other hand, adjustable-pressure shunts offer the flexibility to modify pressure settings post-implantation, providing particularly more controlled management in cases of SEH. It is commonly recommended in the literature that, in the presence of SEH, adjustable shunts should start at higher pressure settings and be gradually reduced (4,5). However, the course of action to be followed when SEH occurs in a patient with a fixed-pressure shunt is not clearly defined.

Our clinical experience shows that not only the application of shunts but also patients' responses to shunt complications are highly individualistic. Therefore, applying a standardized approach to every patient is not very likely, both in the treatment of hydrocephalus and in the management of shunt complications. When evaluating different types of shunts, although the most advantageous seems to be the adjustable shunt, even its use has not completely eliminated the risk of SEH. It has merely facilitated the management of complications (4-6).

In our study, we aim to discuss the characteristics of pediatric patients who developed SEH following shunt application, our follow-up and treatment approaches, and our outcomes. While we may not have the chance to prepare a one-size-fits-all guideline for these situations, we would like to share our experiences in the management of post-shunt SEH cases based on our clinical observations.

MATERIAL AND METHOD

The study was carried out with the permission of Selçuk University Local Ethics Committee (Date: 26.09.2023, Decision No: 2023/436). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data from our hospital's information system was retrospectively analyzed, covering the period from 2011 to 2022 and involving 496 patients under the age of 18 who had undergone ventriculoperitoneal (VP) shunt surgery and were still under our follow-up. Of these patients, 11 who had shunt-related SEH and whose diagnosis, radiological imaging and treatment were entirely carried out at our hospital were included in the study.

Inclusion criteria for the study were as follows:

- Patients being under the age of 18 at the time of the operation
- Having been diagnosed with hydrocephalus via brain computed tomography (CT) or magnetic resonance imaging (MRI) prior to the first shunt operation
- All surgical procedures, treatments, and follow-ups related to the patient's shunt having been carried out by departments at our hospital, and data being accessible within our hospital's information system
- Complete post-operative radiological imaging having been conducted and this data being accessible within the system
- Patients having at least a 6-month period of stable well-being following the diagnosis and treatment of SEH.

Patients who had a history of head trauma or anticoagulant medication use—factors that could potentially cause SEH—were excluded from the study. This exclusion was implemented to ensure a more predictable assessment of SEH solely related to shunt placement, eliminating the influence of other contributing factors like head trauma or anticoagulant use.

RESULTS

Of the 11 patients included in the study, 63.6% (n: 7) were male. The average age was 72.3 months (min. 12 - max. 132), and the average follow-up period was 72.9 months (8-120). The etiology of the shunts in these patients were as follows: congenital hydrocephalus accounted for 54.5% (n: 6), post-meningitis hydrocephalus was 18.2% (n: 2), and hydrocephalus developing after premature birth-intraventricular hemorrhage was 27.3% (n: 3). All the initial shunt types applied upon diagnosing hydrocephalus were of fixed pressure. Of these, 54.5% (n: 6) were medium-pressure burr-hole type shunts, 36.6% (n: 4) were medium-pressure flat abdomen type shunts, and 9% (n: 1) was a medium-pressure mini burr-hole type shunt.

The presenting complaints of the patients when SEH was initially diagnosed through imaging were as follows: 36.3% (n: 4) were asymptomatic, 36.3% (n: 4) were preliminarily diagnosed with shunt infection (nausea, vomiting, and restlessness (n: 2), nuchal rigidity (n:1), and fever of unknown origin (n: 1)), 9% (n: 1) presented with

altered consciousness and a drop in the Glasgow Coma Scale (GCS: 8), 9% (n: 1) exhibited reduced cooperation with his mother and a tendency to sleep, and 9% (n: 1) oral feeding was reduced.

In the initial stage of treatment management for patients diagnosed with SEH, either asymptomatically or symptomatically, decisions were made based on their neurological examinations and symptoms;

The average follow-up duration for the 36.3% (n: 4) of patients in the asymptomatic group was 78 months (range 12-120). The cortical pressures of their SEH were minimal. The initial approach for these patients involved close neurological examination and follow-up of radiological images. Despite an increase in SEH volume in two patients during follow-up, monitoring continued because they remained asymptomatic. At the end of the 12th month, routine follow-up was resumed in the asymptomatic patient group, which included one patient whose SEH had stabilized since diagnosis (n: 1), one whose SEH had ceased to progress in the images (n: 1), and two whose SEH had regressed (n: 2).

In the 36.3% (n: 4) of patients preliminarily diagnosed with shunt infection (experiencing symptoms such as nausea, vomiting, restlessness [n: 2], neck stiffness [n: 1], and unlocalized fever [n: 1]), all had their shunts removed, sent for culture, and had an extra-ventricular drainage (EVD) system installed. Normally, cerebrospinal fluid (CSF) is drained from the EVD at rates of 3-5-7 cc/hour based on CSF pressure conditions; however, in these patients, CSF was drained at 1 cc/hour, and their tolerance was evaluated. In patients with no regression upon neurological examination, EVD was kept closed for monitoring. If their well-being continued, the EVD was removed (75%, n: 3). Patients who completed their infection treatments continued their follow-ups without a shunt. Control brain CT scans showed that the brain parenchyma had expanded, and the subdural hygroma (SEH) had either regressed or completely disappeared. For one patient who could not tolerate the closed monitoring of the EVD, an adjustable (programmable) shunt was implanted after the infection treatment was completed.

One patient (9%, n: 1) presented to the hospital with altered consciousness and a moderate-to-low Glasgow Coma Scale (GCS) score of 8. Due to the patient's decreased neurological exam, emergency shunt removal and bilateral subdural hematoma surgery were performed. In the immediate postoperative period, the patient's GCS improved to 13-14. Follow-up examinations showed that the brain parenchyma had expanded, there was some ventricular enlargement, but there was no extraventricular cerebrospinal fluid (CSF) passage. The patient has been followed up for 52 months without a shunt and with a GCS of 15.

In patients with decreased cooperation with their mother and increased sleepiness (9%, n: 1) (Image 1), as well as in patients with reduced oral intake (9%, n: 1), the shunt was ligated at the neck. This procedure is done under local anesthesia and involves making a 1 cm incision perpendicularly over the palpable shunt tract in the neck area, after which the shunt is located, looped, and tied off with a free silk suture. The aim of the procedure is to intentionally disrupt the continuity of the shunt tract and render the shunt nonfunctional. This allowed for controlled monitoring without the shunt. Early follow-up without the shunt was tolerated and improvements in symptoms were observed, leading to the removal of the shunts and the discharge of the patients. Patients were then closely monitored in outpatient clinics. Despite the expansion of the brain parenchyma seen in brain CT scans, the absence of periventricular CSF passage led to the continuation of shunt-free follow-up for the patients (**Figure 1**).

DISCUSSION

Shunt-related Subdural Effusion/Hematoma (SEH) is a frequently encountered complication following hydrocephalus surgery, although there is insufficient information in the literature regarding its management (7-9). It is generally believed that the primary cause is the tearing of the cortical bridging veins due to the altered fluid dynamics following the placement of a ventricular shunt (4). In the literature, most cases of SEH are likely interpreted as a postoperative complication related to the shunt and have been noted to occur within the first 6 months following the initial shunt operation (10-12). In our series, this time span is 66 months (min.3 - max.100 months). The values that led us to find an average time above that reported in the literature are generally attributable to groups that were diagnosed as asymptomatic and/or due to shunt infection. Nevertheless, it is evident that SEH complications can also develop years after the initial shunt surgery (**Figure 1**). Can this etiology be entirely explained by CSF (Cerebrospinal Fluid) balance, or are there other overlooked factors at play? This could be the subject of another study.

In the literature, the almost singular recommendation for preventing SEH is the installation of an adjustable shunt in each patient, starting with the drainage of cerebrospinal fluid (CSF) at high pressure (7-9). Due to our healthcare policy, an adjustable shunt system is obtained for specific cases only when the patient's unique situation is indicated. Indeed, in a 10-year follow-up, only 11 out of 496 pediatric shunt patients were identified as candidates for an adjustable shunt, and of those, only two had the system implemented. While there have certainly been other indications for which we have applied adjustable shunts, considering that only 0.4% of adjustable shunt usage is attributed to SEH pathology, it is clear that it is not an absolute necessity for all patients.

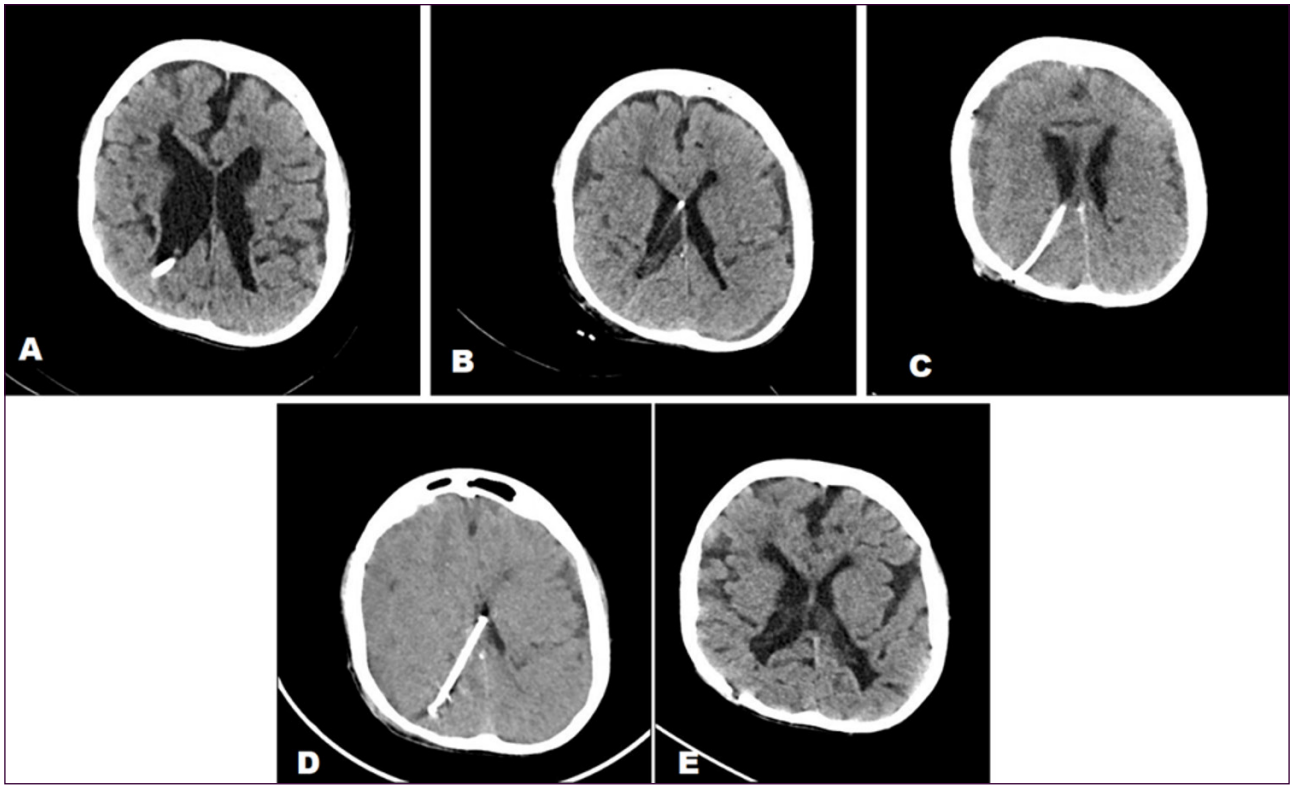

Figure 1- Six-year-old patient, diagnosed with congenital hydrocephalus during the newborn period, has been followed up at our hospital after the implementation of a 'Burr Hole Type Medium Pressure, Fixed Pressure Setting' shunt.
1A - During the two-year follow-ups of the patient, brain computed tomography (CT) scans appeared normal.
1B - In the third year following shunt placement, control brain CT scans revealed the presence of bilateral subdural effusion/hematoma (SEH). The patient, whose neurological examination was stable, was closely monitored.
1C - During the patient's outpatient check-up three months later, it was observed that the effusion had increased and the ventricles were becoming less distinct. The patient was in good general condition and had no active complaints. It was decided to continue monitoring as long as the neurological examination remained stable. The family was informed about the situation and follow-up outpatient examinations continued.
1D - The patient presented with symptoms of reduced cooperation with his mother and increased sleepiness at the sixth month of SEH detection. Brain CT scans showed an increase in the size of the SEH and less distinct ventricles. The neurological examination revealed a Glasgow Coma Scale (GCS) score of 14. The patient's shunt was ligated at the neck, disabling it, and the patient was admitted for general condition monitoring. During the 4 days of hospital stay, it was observed that the patient's general condition improved and complaints regressed. A shunt removal operation was performed.
1E - An average of 2 years of shunt-free follow-ups revealed a GCS of 15 for the patient, and he had no active complaints. Control brain CT scans showed the ventricular structure was similar to the period when the patient was followed up with a shunt (Figure 1A), there was no extraventricular cerebrospinal fluid (CSF) passage, and the sulci appeared relaxed

Indeed, there are multiple publications emphasizing that the development of SEH can still occur despite the presence of an adjustable shunt, underscoring that it is not an unequivocal solution (3-5, 12-14).

The clinical manifestation of SEH is highly variable and individualized, often not aligning with radiological findings (10,11). In addition to 36.3% of the patients being asymptomatic, another 36.3% were diagnosed while being investigated for shunt infection. Even for those with shunt infections, their presentation involved symptoms like general malaise, fever, and neck stiffness rather than noticeable changes in neurological examinations. After treatment for the shunt infection, these patients reverted to their previous general state. All of these patients underwent shunt removal therapy, and only one could not tolerate follow-up without a shunt, leading to the implementation of an adjustable shunt. None underwent "burr hole surgery for hematoma drainage" specifically for SEH. From this perspective, one might speculate that if the patients diagnosed with SEH while being investigated for suspected shunt infection had not exhibited symptoms due to the infection, perhaps they would also have fallen into the asymptomatic group. However, this remains an unprovable hypothesis.

In the literature, cases of SEH that are noted to require emergency surgery are usually those with severe clinical symptoms, significant blood accumulation, and serious intracranial pressure (10-12). In our series, we have had only one such case, who underwent both shunt removal and bilateral burr hole drainage of the subdural hematoma in the same session. This patient showed marked improvement in neurological examination during the early postoperative period. Although closely monitored for potential shunt requirement, subsequent follow-ups revealed no such need.

In the literature, the incidence of shunt-related SEH in patients is reported to range from 5% to 35%. None of these rates are specifically pediatric-focused (6-8,12,13). In our study, the incidence of SEH among the included patients is 2.2%. One of our inclusion criteria, which likely contributed to this lower incidence rate, was that all follow-up and treatments related to the shunt must have been conducted at our hospital. Given that shunt patients require long-term follow-up, fulfilling this criterion of receiving treatment and follow-up at a single center is a challenging requirement.

At the time of initial shunt implantation in our hospital, if the patient has no specific individual conditions, whichever type of shunt is available is used. Should specific conditions arise for the patient (such as the occurrence of SEH, presence of slit ventricles, skin issues, etc.), the most suitable alternative shunt type is determined, and it is procured by our hospital, indicating the patient's special condition. Therefore, our initial choice of shunt type is solely determined by what is available at our hospital at the time of the procedure. While there are publications stating that adjustable shunts may be preventative for SEH but are not a definitive solution, none of these literature findings are specific to the pediatric age group. In fact, much of the data comes from studies that focus on adult populations dealing with conditions like normal-pressure hydrocephalus (6,8,12-14). For pediatric patients who continue to fare well during a shunt-free period, especially prior to the trial of an adjustable shunt, complete shunt removal should also be considered as a viable option. In our study, only 2 patients who could not tolerate being shunt-free received an adjustable shunt, and their average follow-up duration after this operation has been 28 months. During this period, imaging and neurological examinations for these patients remained stable. Additionally, in our study, 45.4% (n: 5) of patients benefited from the removal of the shunt, and the average follow-up duration for these patients has been 69.6 months.

Limitations

Due to the small sample size, statistical evaluations are not meaningful. Therefore, we have shared our clinical experiences with the patients, but no statistical assessments have been made. Future studies may be planned with larger patient populations, and perhaps including adult populations for a more comprehensive analysis.

CONCLUSION

Managing the follow-up and treatment of patients with SEH due to shunt placement presents a perplexing and challenging task, given the inherent variability in clinical courses and radiological images across individual cases.

Our study findings underscore that, despite not performing any surgical interventions on asymptomatic patients, their SEH remained stable or even regressed. This emphasizes that treatment planning should always be tailored to the patient's symptoms, rather than focusing solely on correcting radiological findings.

While most existing data on SEH are related to adult populations, our study contributes to the literature by specifically examining the pediatric period.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Local Ethics Committee (Date: 26.09.2023, Decision No: 2023/436).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients for the 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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Pediatr Pract Res 2023; 11(3): 220-223
DOI: 10.21765/pprjournal.1361428

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Çocuk Acil Servisten Çocuk Yoğun Bakım Ünitesine Yatırılan veya Dış Merkeze Sevk Edilen Kritik Hastaların İncelenmesi: 5 Yıllık Tek Merkez Deneyimi

Investigation of Critical Patients Admitted to the Pediatric Intensive Care Unit or Referred to an External Center from the Pediatric Emergency Department: A 5-Year Single Center Experience

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Öz

Amaç: Çocuk acil servisimizden çocuk yoğun bakım ünitelerine yatışı sağlanarak tedavisinin devamı temin edilen hastaların epidemiyolojik, demografik özellikleri, tanısal ve mevsimsel dağılımları irdelenmiştir. Bunun neticesinde yoğun bakım ihtiyacı kararının verilmesi ve uygun yoğun bakım ünitesi karar süreçlerinin doğru ve hızlı ilerlemesini sağlamak amaçlanmıştır.

Gereç ve Yöntem: Ocak 2018- Aralık 2022 tarihleri arasında Ümraniye Eğitim ve Araştırma Hastanesi çocuk acil servisine başvuran ve çocuk acil servisinden herhangi bir çocuk yoğun bakım ünitesine yatışı sağlanmış 0-18 yaş arasındaki hastalar ile ilgili veriler, hastane veri tabanından geriye dönük olarak tarandı. Çalışmaya alınan hastaların tanısı, yaşı, cinsiyeti, acil servise başvuru tarihleri, dış merkez sevklerinin nitelikleri çalışma kapsamında geriye dönük olarak incelendi.

Bulgular: Çalışmaya 400'ü kız (%47.6), 440'i erkek (%52.4) toplam 840 hasta dahil edildi. Ortalama çocuk acil servisinde kalış süresi 236.7445 dk (3.9457 saat) idi. Hastalar en sık solunum sistemi (%37.14), nörolojik sistem (%20.35) ve zehirlenme (%12.5) kaynaklı tanılar ile yoğun bakıma yatırıldı. Kasım (n=90, %10.7) ve Ocak (n=89, %10.6) dönemlerinde daha fazla yatış görülürken, en az yatış Temmuz (n=60, %7.14) ve Ağustos (n=60, %7.14) aylarında gözlendi. Çocuk yoğun bakım yatışı yapılan hastaların %70.35'i kendi hastanemizde yoğun bakıma, %29.64'ü dış merkez çocuk yoğun bakım ünitelerine sevk edilerek yatırılmıştır.

Sonuç: Acil serviste kritik hastaların tanınması, demografik ve zamansal olarak irdelenmesi, yoğun bakım ünitesi karar sürecini, uygun sağlık hizmetine zamanında erişimi ve sağlık hizmeti planlamasını kolaylaştıracaktır.

Anahtar Kelimeler: Çocuk acil, çocuk yoğun bakım, kritik hasta

Abstract

Aim: The epidemiological, demographic characteristics, diagnostic and seasonal distributions of the patients who were admitted to pediatric intensive care units from our pediatric emergency department were examined. As a result, it is aimed to make the decision on the need for intensive care and to ensure that the appropriate intensive care unit decision processes proceed accurately and quickly.

Material and Method: Data regarding patients aged 0-18 years who were admitted to the Ümraniye Training and Research Hospital Pediatric Emergency Service between January 2018 and December 2022 and who were admitted to any pediatric intensive care unit from the pediatric emergency department were retrospectively scanned from the hospital database. The diagnosis, age, gender, date of admission to the emergency department, and qualifications of external center referrals of the patients included in the study were examined retrospectively within the scope of the study.

Results: A total of 840 patients, including 400 girls (47.6%) and 440 boys (52.4%), were included in the study. mean length of stay in the pediatric emergency department was 236.7445 min (3.9457 h). Patients were admitted to the intensive care unit with the most common diagnoses of respiratory system (37.14%), surgical system (20.35%) and intoxication (12.5%). More hospitalizations were observed in November (n=90, 10.7%) and January (n=89, 10.6%), while the least hospitalizations were observed in July (n=60, 7.14%) and August (n=60, 7.14%). Of the patients hospitalized in pediatric intensive care, 70.35% were transferred to intensive care units in our own hospital and 29.64% were transferred to pediatric intensive care units in an external center.

Conclusion: Recognizing critically ill patients in the emergency department and examining them demographically and temporally will facilitate the intensive care unit decision process, timely access to appropriate healthcare, and healthcare planning.

Keywords: pediatric emergency, pediatric intensive care, critically patients

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Başvuru Tarihi/Received: 16.09.2023
Kabul Tarihi/Accepted: 11.10.2023

GİRİŞ

Pediatrik acil tıp ve pediatrik yoğun bakım tıbbı gelişmiş ülkelerde köklü ve olgun disiplinlerdir. Bu nedenle, akut hasta veya yaralı çocukların bakımında önemli bir rol oynayarak klinik sonuçlar üzerinde olumlu etkiler göstermişlerdir. Çocuk acil servisin önemli bir işlevi kritik hastalığı olan pediyatrik hastaların uygun şekilde tedavi edilmesini sağlamaktır. Acil serviste çocuk yoğun bakım ekibinin erken katılımı ve ekiplerin birden fazla alt uzmanlıkla koordineli çalışması, daha iyi klinik sonuçlara yol açmaktadır (1, 2). Son yirmi yılda acil servise başvuran kritik hastaların sayısında bir artış olmuş ve bu durum modern çağda sağlık hizmeti sunumunun gidişatını değiştirmiştir (3). Epidemiyolojik analiz, klinisyenlerin çeşitli yaş gruplarının farklı etiyolojilerine dayalı başvuru oranlarındaki önemli farklılıkları belirlemesini sağlayabilir. Ayrıca, acil servise başvuran kritik durumdaki çocukların epidemiyolojik verilerinin anlaşılması, doğru klinik değerlendirmeyi ve yoğun bakım ünitesine (YBÜ) yatışla ilgili karar vermeyi hızlandırmaya yardımcı olabilir. Pediatrik hastaların acil servisten yoğun bakıma kabulü, kritik bakım gerektiren acil bir klinik duruma işaret eder ve bu kritik durum hastalığın ciddiyetine ve ölüm riskine bağlıdır. Yoğun bakım tedavisinin sonucu, ilk acil servis yönetiminin yeterliliği ve yoğun bakım imkanlarına uygun yöntem ve uygun zamanda erişimi ile de ilişkilidir (4). Bazı araştırmalar, YBÜ kabulünün faydalarının, YBÜ'ne yatırılan ve YBÜ'ne alınmayan benzer hastalar karşılaştırılarak belirlenebileceğini iddia etmektedir; bu durum, YBÜ ihtiyacı olan hastalardan ivedilikle YBÜ bakım imkanlarına kavuşan hastaların hayatta kalma şanslarına yararını doğrulamaktadır (5).

Çalışmamızın sonuçlarını yayınlayarak; çocuk acil servisimizden çocuk yoğun bakım ünitelerine yatışı sağlanarak tedavisinin devamı temin edilen hastaların epidemiyolojik, demografik özelliklerinin yanı sıra, tanısal ve mevsimsel dağılımlarının irdelenmesi neticesinde yoğun bakım ihtiyacı kararının verilmesi ve uygun yoğun bakım ünitesi karar süreçlerinin doğru ve hızlı ilerlemesini sağlamak amaçlanmıştır.

GEREÇ VE YÖNTEM

Bu çalışma, İstanbul Sağlık Bilimleri Üniversitesi Ümraniye Eğitim ve Araştırma Hastanesi Klinik Araştırmalar ve Etik Kurulundan (Tarih: 23.02.2023, Sayı: B.10.1.THK.4.34.H.GP.0.01/48) izin alındıktan sonra Helsinki Bildirgesi ilkelerine uygun bir şekilde yapıldı. Retrospektif bir çalışma olduğu için hasta ya da hasta yakınlarından onam alınmadı.

Ocak 2018- Aralık 2022 tarihleri arasında Ümraniye Eğitim ve Araştırma Hastanesi Çocuk Acil Servisine başvuran ve çocuk acil servisinden herhangi bir çocuk yoğun bakım ünitesine yatışı sağlanmış 0-18 yaş arasındaki hastalar ile ilgili veriler hastane veri tabanından geriye yönelik tarandı. Çalışmaya alınan hastaların tanısı, yaşı, cinsiyeti, acil servise başvuru tarihleri, dış merkez sevklerinin nitelikleri çalışma kapsamında geriye dönük olarak incelendi.

İstatistiksel Değerlendirme

İstatistiksel analiz için IBM SPSS 23.0 programı kullanıldı. Verilerin analizinde sayı, yüzde, ortalama ve standart sapma değerlerini içeren tanımlayıcı istatistikler kullanılmıştır.

BULGULAR

Ocak 2018- Aralık 2022 tarihleri arasında Ümraniye Eğitim ve Araştırma Hastanesi Çocuk Acil Servisine başvuran ve çocuk acil servisinden herhangi bir çocuk yoğun bakım ünitesine yatışı sağlanmış 0-18 yaş arasındaki 400'ü kız (%47.6), 440'i erkek (%52.4) toplam 840 hasta dahil edildi (**Tablo 1**). Ortalama yaş 53.4 (1–254) ay, ortalama çocuk acil servisinde kalış süresi 236.7445 dk (3.9457 saat) idi. Hastaların dış merkez çocuk yoğun bakım ünitelerine sevklerinde çocuk acil servisimizde kalış süresi ortalama 296.14 dk (4.93 saat), hastanemiz çocuk yoğun bakım ünitesine yatırdığımız hastalarda ise bu süre 211.72 dk (3.528 saat) idi (**Tablo 1**).

Tablo 1. Hastaların cinsiyet dağılımları ve acilde kalış süreleri

		Ümraniye ÇYBÜ yatanlar (n, %)	Dış merkez sevk (n, %)	Toplam
Cinsiyet	Kız	279 (69.75)	121(30.25)	400
	Erkek	312 (70.9)	128 (29.1)	440
Acilde kalış süresi		211.72dk (3.528 saat)	296.14 dk (4.93 saat)	236.7445 dk (3.9457 saat)

ÇYBÜ: çocuk yoğun bakım ünitesi

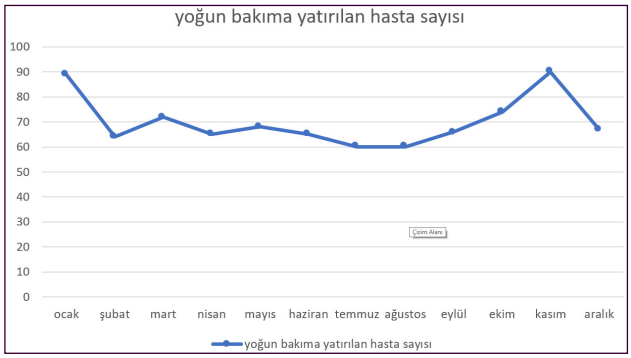
Çalışmanın planlandığı tarihler arasında çocuk acilimize herhangi bir şikayetle başvuran toplam hasta sayısı 924293 olarak tespit edildi. Çocuk yoğun bakıma yatırılan hasta sayısının toplam çocuk acil başvuru sayısına oranı %0.09088 olarak tespit edildi. Çalışmanın yapıldığı dönem aralığında hastanemiz çocuk yoğun bakım ünitesine gerçekleştirdiğimiz hasta yatışı aynı dönemde çocuk yoğun bakım ünitemize yatan toplam hastanın %28.17'si (591/2098) idi. Hastaların yoğun bakıma yatış nedenleri incelendi. Hastaların 312'si (%37.14) solunum sistemi, 171'i (%20.35) nörolojik sistem, 105'i (%12.5) zehirlenme, 85'i (%10.11) sepsis ve enfeksiyon hastalıkları, 61'i (%7.26) kardiyovasküler sistem, 41'i (%4.88) gastrointestinal sistem, 26'sı (%3.09) endokrin sistem, 21'i (%2.5) travma ve çevresel etkenler, 18'i (%2.14) hematoloji-onkoloji kaynaklı tanılar ile yatırılmıştı (**Tablo 2**).

Kasım (n=90, %10.7) ve Ocak (n=89, %10.6) aylarında daha fazla yatış görülürken, en az yatış Temmuz (n=60, %7.14) ve Ağustos (n=60, %7.14) aylarında gözlendi (**Şekil 1**).

Tablo 2. Hastaların çocuk yoğun bakım ünitesine yatış nedenleri

	Ümraniye ÇYBÜ Yatanlar (n, %)	Dış Merkez Sevk (n, %)	Toplam (n, %)
Çocuk Yoğun bakım yatış nedenleri			
Solunum sistemi hastalıkları	202 (24.05)	110 (13.09)	312 (37.14)
Nörolojik sistem hastalıkları	118 (14.05)	53 (6.31)	171 (20.35)
Zehirlenmeler	78 (9.28)	27 (3.22)	105 (12.5)
Sepsis ve enfeksiyon hastalıkları	62 (7.38)	23 (2.73)	85 (10.11)
Kardiyovasküler sistem hastalıkları	53 (6.31)	8 (0.95)	61 (7.26)
Gastrointestinal sistem hastalıkları	34 (4.05)	7 (0.83)	41 (4.88)
Endokrin sistem hastalıkları	16 (1.9)	10 (1.18)	26 (3.09)
Travma ve çevresel etkenler	14 (1.66)	7 (0.83)	21 (2.5)
Hematoloji-onkoloji hastalıkları	14 (1.66)	4 (0.47)	18 (2.14)
Toplam	591 (70.35)	249 (29.65)	840 (100)

ÇYBÜ: çocuk yoğun bakım ünitesi



Şekil 1. Yoğun bakıma yatırılan hasta sayısının aylara göre dağılımı

Çocuk yoğun bakım yatışı yapılan hastaların %70.35'i (591/840) kendi hastanemiz yoğun bakımına, %29.64'ü (249/840) dış merkez çocuk yoğun bakım ünitelerine transfer edilerek yatırıldı. Dış merkez sevki yapılan hastaların %47.39'u (118/249) devlet eğitim araştırma ve üniversite hastanelerine, %52.61'i (131/249) ise özel hastanelere sevk edildi.

TARTIŞMA

Çocuk acil serviste takip edilen en kritik hasta gruplarından biri de çocuk yoğun bakıma yatışı yapılacak olan hastalardır. Bu hasta grubunun özelliklerinin bilinmesi hastaların bu kritik süreçlerini yönetimini olumlu yönde etkileyecektir. Literatür incelendiğinde çocuk yoğun bakıma gelen hastaların geliş şekillerine bakıldığında hastaların çoğunun çocuk acil servisten geldiği görülmektedir (6-9). Bu durum hastanın değerlendirilmesi ve yoğun bakıma gelene kadar sürenin önemini arttırmaktır. Kritik hasta çocukta ilk acil müdahale, uygun hasta yönetimi ve uygun zaman ve yöntemle hastanın çocuk yoğun bakım imkanlarına ulaştırması, yoğun bakım tedavi sürecini ve sonucunu da etkilemektedir. Çalışmamızın bulgularına göre çocuk acil servisinde kalış süresi 236.7445 dk (3.9457 saat) idi. Hastaların dış merkez çocuk yoğun bakım ünitelerine sevklerinde çocuk acil servisimizde kalış süresi ortalama 296.14 dk (4.93 saat), hastanemiz çocuk yoğun bakım ünitesine yatırdığımız hastalarda ise bu süre 211.72 dk (3.528 saat) idi. Hastalar çocuk acilde geçirdikleri süreler açısından literatür ile kıyaslandığında, çocuk acil servisimizden çocuk yoğun bakım ünitesine yatışına kadar geçen bekleme süreleri kliniğimizde daha kısadır (10).

Literatürde çocuk acil birimi tarafından yapılmış kritik hastaların çocuk yoğun bakımlara sevkini irdeleyen bir çalışmaya rastlanmamıştır. Çocuk yoğun bakımda yatmakta olan hastaların yatış tanılarını inceleyen çalışmalarda en sık yatış endikasyonlarının sırasıyla solunum sistemi hastalıkları, nörolojik hastalıklar ve zehirlenmeler olduğu görülmektedir (6, 8, 11, 12). Bizim çalışmamızda da yoğun bakım yatış nedenleri bu çalışmalarla paralellik göstermektedir. Havan ve arkadaşlarının yaptığı bir çalışmada (7) en çok yatış endikasyonu kardiyak hastalıklar olarak tespit edilmiştir. Bu durum çocuk kalp ve damar cerrahisi hastalarının hepsinin ameliyat sonrası dönemde yoğun bakımlarında izlenmesi ve hastanelerinin organ nakli merkezi olmasından kaynaklanmaktadır. Çalışmamızda ilk üç yatış sebebini takiben sırayla, sepsis ve enfeksiyon hastalıkları, kardiyovasküler sistem hastalıkları, gastrointestinal sistem hastalıkları, endokrin sistem hastalıkları, travma ve çevresel etkenler ve hematoloji-onkoloji kaynaklı tanılar yatışta rol oynamışlardır.

Dış merkez yoğun bakım ünitelerine yaptığımız hasta sevklerinde özel hastane (%52.61) ile devlet ve üniversite hastanelerine (%47.39) gerçekleştirilen yatışların oransal olarak çok yakın olması bulunduğumuz şehirde nitelikli özel çocuk yoğun bakım ünitelerinin en az devlet ve üniversite hastaneleri kadar aktif olarak hizmet verdiğinin bir göstergesi olabilir.

Çalışma döneminde acil serviste 924293 vaka görüldü. Bunlardan yalnızca 840 (%0.09088) hastanın çocuk yoğun bakıma yatışı gerçekleştirildi. Literatürde benzer bir çalışmada (10) bu oran %1.74 olarak bulunmuştur. Oranlar arasındaki 20 kat farkın, çocuk acil polikliniklerinin aciliyeti olmayan poliklinik hastalarıyla fazlasıyla meşgul olmalarından kaynaklandığını düşünmekteyiz.

SONUÇ

Sonuç olarak, literatürde acil seviste takip edilip yoğun bakıma yatırılan hastalar hakkında yapılan çalışmalar kısıtlıdır. Bu hastaların çocuk acil servisinde geçirdiği süreçler irdelenerek, kritik hastaların yoğun bakım ihtiyaçlarının zamanında tespiti, uygun yoğun bakım hizmetine erişiminin sağlanmasını kolaylaştıracaktır.

ETİK BEYANLAR

Etik Kurul Onayı: Bu çalışma, İstanbul Sağlık Bilimleri Üniversitesi Ümraniye Eğitim ve Araştırma Hastanesi Klinik Araştırmalar ve Etik Kurulundan (Tarih: 23.02.2023, Sayı: B.10.1.THK.4.34.H.GP.0.01/48)

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.

Finansal Destek: Yazarlar bu çalışmada finansal destek almadıklarını beyan etmişlerdir.

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

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