Turkish Journal of Pediatric Disease / *Türkiye Çocuk Hastalıkları Dergisi*

ANKARA BİLKENT ŞEHİR HASTANESİ ÇOCUK HASTANESİ

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Turkish Journal of Pediatic Disease
Türkiye Çocuk Hastalıkları Dergisi

ANKARA BİLKENT ŞEHİR HASTANESİ
ÇOCUK HASTANESİ

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Turkish Journal of Pediatric Disease has been a member of the DOI® system since March 2013.
Türkiye Çocuk Hastalıkları Dergisi Mart 2013 tarihinden itibaren DOI® sistemi üyesidir.

Turkish Journal of Pediatric Disease is indexed in Turkish Medical Index of TUBITAK/ULAKBIM, EBSCOhost Research Databases, CINAHL and Turkey Citation Index.
Türkiye Çocuk Hastalıkları Dergisi TÜBİTAK/ULAKBİM Türk Tıp Dizini, EBSCOhost Research Databases, ve Türkiye Atıf Dizini tarafından indekslenmektedir.

The paper used to print this journal conforms to ISO 9706: 1994 standard (Requirements for Permanence).
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Bu dergi geri dönüştürülebilir, imha etmek istediğinizde lütfen geri dönüşüm kutularına atınız.

AIMS and SCOPE / AMAÇ ve KAPSAM

The Turkish Journal of Pediatric Disease is an open access and a scientific publication journal of the Ankara Bilkent City Hospital, Children's Hospital. The journal is published in accordance with independent, unbiased, and double-blind peer review principles. The journal is published bimonthly (January, March, May, July, September, November).

In the Turkish Journal of Pediatric Disease original articles, reviews, case reports, editorials, short reports, book reviews, biographies and letters to the editor are also published in the journal. Besides if related with pediatrics, articles on aspects of pedatric surgery, dentistry, public health, genetics, pshyciatrics and nursery could be published. The publication language of Turkish Journal of Pediatric Disease is English.

Manuscripts submitted to the Turkish Journal of Pediatric Disease will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in the field, in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

Turkish Journal of Pediatric Disease is indexed in Turkish Medical Index of Tübitak / Ulakbim, EBSCOhost Research Databases and Turkey Citation Index.

Journal is published on acid free paper.

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Scientific and ethical responsibility

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Türkiye Çocuk Hastalıkları Dergisi, Ankara Bilkent Şehir Hastanesi Çocuk Hastanesi'nin açık erişimli bilimsel yayındır. Dergi bağımsız, tarafsız ve çift-kör hakemlik ilkelerine uygun olarak yayınlanır. Dergi iki ayda bir yayınlanmaktadır (Ocak Mart, Mayıs, Temmuz, Eylül, Kasım).

Türkiye Çocuk Hastalıkları Dergisi'nde orijinal makale, derleme, olgu sunumu, editöryal, çalışma yöntemi, kısa rapor, kitap incelemeleri, biyografiler ve editöre mektup yayınlanmaktadır. Ayrıca pedatrik cerrahi, diş hekimliği, halk sağlığı, genetik, çocuk ve ergen psikiyatrisi ve hemşirelik konularında makaleler yayınlanabilir. Türkiye Çocuk Hastalıkları Dergisi'nin yayın dili İngilizcedir.

Türkiye Çocuk Hastalıkları Dergisi'ne gönderilen yazılar çift kör hakemlik sürecinden geçecektir. Her bir yazı tarafsız bir değerlendirme süreci sağlamak için alanda uzman en az iki harici, bağımsız hakem tarafından incelenecektir. Baş editör, tüm başvurular için karar alma sürecindeki nihai otoritedir.

Türkiye Çocuk Sağlığı ve Hastalıkları Dergisi Tübitak/Ulakbim Türk Tıp Dizini, EBSCOhost Research Databases ve Türkiye Atıf Dizini tarafından indekslenmektedir.

Dergimiz asitsiz kâğıda basılmaktadır.

Abonelik İşlemleri

Türkiye Çocuk Hastalıkları Dergisi Tıp Fakültesi olan Üniversite Kütüphanelerine, Çocuk Sağlığı ve Hastalıkları AD Başkanlıkları'na, Sağlık Bakanlığı'na bağlı Eğitim ve Araştırma Hastanelerinin Başhekimlikleri'ne ve konu ile ilgilenen bilim insanlarına ücretsiz olarak ulaştırılmaktadır. Yayınlanan makalelerin tam metinlerine https://dergipark.org.tr/tr/pub/tchd adresinden ücretsiz olarak ulaşılabilir. Abonelik işlemleri için lütfen https://dergipark.org.tr/tr/pub/tchd adresini ziyaret ediniz.

Yazarların Bilimsel ve Hukuki Sorumluluğu

Yazarlar Türkiye Çocuk Hastalıkları Dergisi'ne bir yazı gönderirken, yazıların telif haklarını Türkiye Çocuk Hastalıkları Dergisi'ne devretmiş olmayı kabul ederler. Yayınlanmamak üzere reddedilirse veya herhangi bir sebepten yazı geri çekilirse telif hakkı yazarlara geri verilir. Türk Türkiye Çocuk Hastalıkları Dergisi'ne ait Telif Hakkı Devri ve Yazarlık Formları (https://dergipark.org.tr/tr/pub/tchd adresinden indirilebilir). Şekiller, tablolar veya diğer basılı materyaller de dahil olmak üzere basılı ve elektronik formatta daha önce yayınlanmış içerik kullanılıyorsa yazarlar telif hakları sahiplerinden gerekli izinleri almalıdır. Bu konudaki hukuki, finansal ve cezai yükümlülükler yazarlara aittir.

INSTRUCTIONS FOR AUTHORS

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The editorial and the publication processes of the journal are shaped in accordance with the guidelines of the World Association of Medical Editors (WAME), the Committee on Publication Ethics (COPE), the International Council of Medical Journal Editors (ICMJE), the Council of Science Editors (CSE), the European Association of Science Editors (EASE) and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

The originality, high scientific quality, and the citation potential are the most important criterias for a manuscript to be accepted for the publication. Manuscripts submitted for the evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed if manuscript have been submitted to another journal for the evaluation and have been rejected for the publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with a detailed information of the organization, including the name, date, and location of the organization.

Manuscripts submitted to the Turkish Journal of Pediatric Disease will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in the field, in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions. Articles accepted for publication in the Turkish Journal of Pediatrics are put in the order of publication, with at least 10 original articles in each issue, taking into account the acceptance dates. If the articles sent to reviwers for evaluation are assessed as senior for publication by the reviewers, the section editor and the editor considering all aspects (originality, high scientific quality and citation potential), it receives publication priority in addition to the articles assigned for the next issue.

An approval of the research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for the experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts that are concerning experimental researchs on humans, a statement should be informed included that shows a written informed consent of the patients and the volunteers who were given a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information of the patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity carefully. For the photographs that may reveal the identities of the patients, releases signed by the patient or their legal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

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3. Final approval of the version to be published; AND

4. Agreement to be accountable of all aspects of the work in ensuring that questions related to the accuracy or the integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she had done, an author should be able to identify which co-authors are responsible for the specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all of the four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all of the four criteria should be acknowledged in the title page of the manuscript.

The Turkish Journal of Pediatric Disease requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through https://dergipark.org.tr/en/pub/tchd) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without a further review. As a part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all of the responsibility for the authorship during the submission and review stages of the manuscript.

The Turkish Journal of Pediatric Disease requires and encourages the authors and the individuals who involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to the potential bias or a conflict of interest. Any financial grants or other supports received for the submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all of the contributing authors. Cases of the potential conflict of interest of the editors, authors, or reviewers are being resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

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MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with the ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in May 2022 - http://www.icmje.org/recommendations).

CONSORT	Randomised controlled trials
STROBE	Observational epidemiological research
STARD	Diagnostic accuracy
PRISMA	Systematic reviews and meta-analysis
ARRIVE	Experimental animal studies
TREND	Non-randomized public behavior

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www.dergipark.org.tr/en/journal/2846/submission/step/manuscript/new. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will go firstly through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions not conforming to the journal's guidelines will be returned to the submitting author with the technical correction requests.

Authors are required to submit the following:

Copyright Transfer and Acknowledgement of Authorship Form and

ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all of the contributing authors) during the initial submission. These forms are available for downloading at www.dergipark.org.tr/en/pub/tchd.

Manuscripts should be written using Microsoft Word™ (2010 and higher) software, in Times New Roman, 12 point size and double line spacing. There should be 2 cm margins on all sides on the pages. "System International" (SI) units should be used in manuscripts. Tables and graphics should be cited in the text. Abbreviations can be used provided that they are written openly at the first place they appear in the abstract and text, and the abbreviation is given in parentheses.

In the article, when giving the mean and percentile, 2 digits should be used after the decimal point (such as 231.69 or 231.70, instead of 231.7). In the representations other than integers, two digits should be written after the dot, and in the representation of statistical values (such as p, r, t, z values), three digits should be written after the dot. In the presentation of p values, instead of $p<0.05$ or $p>0.05$, the full p value should be given with three digits after the dot (eg $p=0.029$) with the test statistic. If this value is less than one thousandth, it should be displayed as $p<0.001$.

Preparation of the Manuscript Title page:

Title page should be submitted for all of the submissions and this page should include:

Title page of the manuscript should include the English title of the article. The title page should include the authors' names, degrees, ORCID number and the institutional/professional affiliations, a short title (max 50 character), abbreviations, financial disclosure statement, and the conflict of interest statement. For manuscripts sent by the authors in Turkey, a title in Turkish is also required. If a manuscript includes authors from more than one institution, each author's name should be followed by a superscript number that corresponds to this/her institution, which is listed separately. Please provide a contact information for the corresponding author, including name, e-mail address, and telephone and fax numbers.

Important Notice: The title page should be submitted separately.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html). For manuscripts sent by the authors in Turkey, key words in Turkish are also required.

MANUSCRIPT TYPES

Original Articles:

Word count: up to 3,500 (Introduction, Methods, Results, Discussion)

Title: maximum of 20 words

Structured abstract: up to 250 (Objective, Materials and Methods, Results and Conclusion)

Keywords: 3-6 word, listed in alphabetical order.

Figures and tables: are not limited, but must be justified thoroughly

References: up to 40

Original articles should include; English title, English structured abstract (structured as, English key words. If the article is in Turkish, Turkish title and English title, Turkish structured summary and English summary (structured as Purpose, Material and Method, Conclusion and Discussion), Turkish and English keywords are required.

for most readers, reading the abstract first, is critically important. Moreover, various electronic databases integrate only abstracts into their index, so important findings should be presented in the abstract.

The other sections of the manuscript should include Introduction, Materials and Methods, Results, Discussion, Acknowledgement (if required) and References. All sections of the manuscripts should start on a new page.

Review Articles:

Word count: up to 5000

Abstract: up to 500 (Objective, Materials and Methods, Results and Conclusion)

Keywords: 3-6 word, listed in alphabetical order.

Figures and tables: are not limited, but must be justified thoroughly

References: up to 80

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Review articles should include; English title, English abstract and English key words. For manuscripts sent by authors in Turkey, a Turkish title, Turkish abstract and Turkish key words are also required.

Case Reports:

Word count: up to 2000

Abstract: up to 200

Keywords: 3-6 word, listed in alphabetical order.

Figures and tables: total 5

References: up to 15

There is a limited space for the case reports in the journal and reports on rare cases or conditions that constitute challenges in the diagnosis and the treatment, those offering new therapies or revealing knowledge that are not included in the literature, and interesting and educative case reports are being/ will be accepted for publication. The text should include Introduction, Case Presentation and Discussion.

Case reports should include; English title, English abstract and English key words. For manuscripts sent by authors in Turkey, a Turkish title, Turkish abstract and Turkish key words are also required.

Letters to the Editor:

Word count: up to 1500

Figures and tables: total 3

References: up to 15

This type of manuscript discusses about the important parts, overlooked aspects, or lacking parts of the previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a Letter to the Editor. Readers can also present their comments on published manuscripts in the form of a Letter to the Editor. An abstract and Keywords should not be included. Tables, Figures, Images, and other media can be included. The text should not include subheadings. The manuscript that is being commented on, must be properly cited in this manuscript.

Letters to the Editor should include; English title. For the letter to the editor sent by authors in Turkey, a Turkish title also required.

Study Protocols:

The Turkish Journal of Pediatric Disease welcomes study protocols to improve the transparency of research and inform the scholarly community about the trials that are being underway. Publication decision of study protocols will be by editorial decision. Study protocols for the pilot or feasibility studies are not generally taken into consideration.

Study protocol articles should follow the SPIRIT guidelines that provides a detailed account of the hypothesis, rationale, and methodology of the study. All study protocols must provide an Ethics Committee Approval. All protocols for the clinical trials require a trial registration number and the date of registration.

Tables

Tables should be included in the main document, presenting after the reference list, and they should be numbered consecutively in the order they are referred in the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by the footnotes (even if they were defined within the main text). Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text. The following symbols should be used for abbreviations in sequence: *, †, ‡, §, ||, ¶, **, ††, ‡‡.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or in the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures should also be blind. Any information within the images that may indicate an individual or an institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses as in the following format: The skin prick tests were performed using a multi-prick test device (Quantitest, Panatrex Inc, Placentia, California, USA).

All references, tables, and figures should be referred in the main text, and they should be numbered consecutively in the order that they are referred in the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

REFERENCES

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If the reference is a journal;

Author(s)' surname and initial(s) of the first name (all authors if the number of authors are 6 or less, first 6 authors if the number of authors of an article is more than 6 followed by "ve ark." in Turkish references and "et al." in international references). Title of the article, title of the manuscript abbreviated according to Index Medicus

(http://www.ncbi.nlm.nih.gov/sites/entrez/query.fcgi?db=nlmcatalog). Year;Volume:First and last page number.

Example: Benson M, Reinholdt J, Cardell LO. Allergen-reactive antibodies are found in nasal fluids from patients with birch polen-induced intermittent allergic rhinitis, but not in healthy controls. Allergy 2003;58:386-93.

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Author(s)' surname and initial(s) of the first name. Title of the article. Title of the manuscript abbreviated according to Index Medicus (http://www.ncbi.nlm.nih.gov/sites/entrez/query. fcgi?db =nlmcatalog). Year;Volume (Suppl. Supplement number): First and last page number.

Example: Queen F. Risk assessment of nickel carcinogenicity and occupational lung cancer. Envirol Health Perspect 1994;102 (Suppl. 1):S2755-S2782.

If the reference is a book;

Author(s)' surname and initial(s) of the first name. Title of the book. Edition number. City of publication; Publisher, Year of Publication.

Example: Ringsven MK, Bond N. Gerontology and leadership skills for nurses. 2nd ed. Albany, NY: Delmar Publishers, 1996.

If the reference is a book chapter;

Surname and initial(s) of the first name of the author(s) of the chapter. Title of the chapter. In: Surname and initial(s) of the first name(s) of the editor(s) (ed) or (eds). Title of the book. Edition number. City of

publication: Publisher, Year of publication: First and last page numbers of the chapter.

Example: Phillips SJ, Whistant JP. Hypertension and stroke. In: Laragh JH, Brenner BM (eds). Hypertension: Pathophysiology, Diagnosis and Management. 2nd ed. New York: Raven P, 1995:466-78.

If the reference is a conference paper presented in a meeting;

Author(s)' surname and initial(s) of the first name (all authors if the number of authors are 6 or less, first 6 authors if the number of authors of a conference paper is more than 6 followed by "et al.". Title of the conference paper, If applicable In: Surname and initial(s) of the first name(s) of the editor(s) (ed) or (eds). Title of the abstract book. Title of the meeting; Date; City of the meeting; Country. Publisher; Year: Page numbers.

Example: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O (eds). MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. North-Holland; 1992: 1561-5.

If the reference is an online journal:

Author(s)' surname and initial(s) of the first name (all authors if the number of authors are 6 or less, first 6 authors if the number of authors of an article is more than 6 followed by "ve ark." in Turkish references and "et al." in international references).Title of the article, title of the manuscript abbreviated according to Index Medicus Year; Volume (Number). Available from:URL address. Accessed date:day.month. year.

Example: Arrami M, Garner H. A tale of two citations. Nature 2008;451(7177): 397-9. Available from: URL:www.nature.com/nature/journal/v451/n7177/full/451397a.html. Aaccessed 20 January 2008.

If the reference is a website:

Name of the web site. Access date. Available from: address of the web site.

Example: Centers for Disease Control and Prevention (CDC). Acsess date: 12 March 2013. Available from: http://www.cdc.gov/

If the reference is a thesis:

Author's surname and initial of the first name. Title of the thesis (thesis). City; Name of the university (if it is a university); Year.

Example: Özdemir O. Fibrillin-1 gene polymorhism and risk of mitral valve disorders. (Thesis). *Ankara*: Gazi University, 2006.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue were raised by the reviewers, and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be cancelled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for the grammar, the punctuation, and the format. Once the publication process of a manuscript is completed, it will be published online on the journal's webpage as an ahead-of-print publication before being included in it's scheduled issue. A PDF proof of the accepted manuscript will be sent to the corresponding author and their publication approval will be requested within 2 days of their receipt of the proof.

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Any request to change the author list after submission, such as a change in the order of the authors or the deletion or the addition of author names, is subject to the Editorial Board's approval. To obtain this approval, please find and complete the change of authorship form on the Journal's website and send it to the Journal's office. This form should include the following information: The reason for the change of authorship signatures of all authors (including the new and/or removed author)

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In a case where a manuscript has taken more than six months' time for the review process, that this allows the author for withdrawing the manuscript.

YAZARLAR İÇİN BİLGİ

Türkiye Çocuk Hastalıkları Dergisi, Ankara Şehir Hastanesi Çocuk Hastanesi'nin açık erişimli bilimsel yayındır. Dergi bağımsız, tarafsız ve çift-kör hakemlik ilkelerine uygun olarak yayınlanır. Dergi iki ayda bir yayınlanmaktadır (Ocak Mart, Mayıs, Temmuz, Eylül, Kasım)

Türkiye Çocuk Hastalıkları Dergisi'nde orijinal makale, derleme, olgu sunumu, editöryal, çalışma yöntemi, kısa rapor, kitap incelemeleri, biyografiler ve editöre mektup yayınlanmaktadır. Ayrıca pedatrik cerrahi, diş hekimliği, halk sağlığı, genetik, çocuk ve ergen psikiyatrisi ve hemşirelik konularında makaleler yayınlanabilir. Türkiye Çocuk Hastalıkları Dergisi'nin yayın dili İngilizcedir.

Derginin yayın ve yayın süreçleri, Dünya Tıbbi Editörler Derneği (World Association of Medical Editors (WAME)), Yayın Etiği Komitesi (Committee on Publication Ethics (COPE)), Uluslararası Tıbbi Dergi Editörleri Konseyi (International Council of Medical Journal Editors (ICMJE)), Bilim Editörleri Konseyi (Council of Science Editors (CSE)), Avrupa Bilim Editörleri Birliği (EASE) ve Ulusal Bilgi Standartları Organizasyonu (National Information Standards Organization (NISO) (NISO)) kurallarına uygun olarak şekillendirilmiştir. Dergi, Bilimsel Yayıncılıkta Şeffaflık ve En İyi Uygulama İlkeleri'ne (Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice)) uygundur.

Yazıların yayına kabulü için en önemli kriterler özgünlük, yüksek bilimsel kalite ve atıf potansiyelidir. Değerlendirme için gönderilen yazılar daha önce elektronik veya basılı bir ortamda yayınlanmamış

olmalıdır. Dergi, değerlendirilmek üzere başka bir dergiye gönderilen ve reddedilen yazılar hakkında bilgilendirilmelidir. Önceki inceleme raporlarının sunulması değerlendirme sürecini hızlandıracaktır. Kongre ve toplantılarda sunulan yazılarda yazının sunulduğu toplantının kongrenin adı, tarihi ve yeri de dahil olmak üzere ayrıntılı bilgi ile birlikte sunulmalıdır.

Türkiye Çocuk Hastalıkları Dergisi'ne gönderilen yazılar çift kör hakemlik sürecinden geçecektir. Her bir yazı tarafsız bir değerlendirme süreci sağlamak için alanda uzman en az iki harici, bağımsız hakem tarafından incelenecektir. Baş editör, tüm başvurular için karar alma sürecindeki nihai otoritedir. Türkiye Çocuk Hastalıkları Dergisi'nde yayınlanmak üzere kabul edilmiş makaleler kabul tarihleri dikkate alınarak her sayıda en az 10 orijinal makale olacak şekilde yayın sırasına alınır. Değerlendirilmek üzere hakemlere gönderilen makaleler tüm yönleri (özgünlük, yüksek bilimsel kalite ve atıf potansiyeli) dikkate alınarak hakemler, alan editörü ve editör tarafından öncelikli olarak yayınlanmaya aday bir makale olarak değerlendirilir ise bir sonraki sayıda o sayı için atanmış makalelere ek olarak yayınlanma önceliği alır.

Yazarlardan deneysel, klinik ve ilaç çalışmaları ve bazı vaka raporları için gerekirse, etik kurul raporları veya eşdeğer bir resmi belge istenecektir. İnsanlar üzerinde yapılan deneysel araştırmalarla ilgili yazılar için, hasta ve gönüllülerin yazılı bilgilendirilmiş olurlarının alınabileceği prosedürlerin ayrıntılı bir açıklamasının ardından elde edildiğini gösteren bir ifade eklenmelidir. Hayvanlar üzerinde yapılan çalışmalarda, hayvanların acı ve ıstıraplarını önlemek için alınan önlemler açıkça belirtilmelidir. Hasta onamı, etik komite adı ve etik komite onay numarası hakkında bilgi de makalenin Materyal-Metod bölümünde belirtilmelidir. Hastaların anonimliklerini dikkatlice korumak yazarların sorumluluğundadır. Hastaların kimliğini ortaya çıkarabilecek fotoğraflar için, hasta veya yasal temsilcisi tarafından imzalanan bültenler eklenmelidir.

Tüm başvurular intihal araştırılması için yazılımsal olarak (iThenticate by CrossCheck) taranır.

İntihal, atıf manipülasyonu ve gerçek olmayan verilerden şüphelenilmesi veya araştırmaların kötüye kullanılması durumunda, yayın kurulu COPE yönergelerine uygun olarak hareket eder.

Yazar olarak listelenen her bireyin Uluslararası Tıp Dergisi Editörleri Komitesi (ICMJE - www.icmje.org) tarafından önerilen yazarlık kriterlerini karşılaması gerekir. ICMJE yazarlığın aşağıdaki 4 kritere dayanmasını önerir:

1. Çalışmanın tasarımı, verilerin elde edilmesi, analizi veya yorumlanması

2. Dergiye gönderilecek kopyanın hazırlanması veya bu kopyayının içeriğini bilimsel olarak etkileyecek ve ileriye götürecek şekilde katkı sağlanması

3. Yayınlanacak kopyanın son onayı.

4. Çalışmanın tüm bölümleri hakkında bilgi sahibi olma ve tüm bölümleri hakkında sorumluluğu alma

Bir yazar, yaptığı çalışmanın bölümlerinden sorumlu olmanın yanı sıra, çalışmanın diğer belirli bölümlerinden hangi ortak yazarların sorumlu olduğunu bilmeli ayrıca yazarlar, ortak yazarlarının katkılarının bütünlüğüne güvenmelidir.

Yazar olarak atananların tümü yazarlık için dört kriteri de karşılamalı ve dört kriteri karşılayanlar yazar olarak tanımlanmalıdır. Dört kriterin tümünü karşılamayanlara makalenin başlık sayfasında teşekkür edilmelidir.

Yazı gönderim aşamasında ilgili yazarların, yazarlık katkı formunun imzalı ve taranmış bir versiyonunu (https://dergipark.org.tr/en/pub/tchd adresinden indirilebilir) Türkiye Çocuk Hastalıkları Dergisi'ne göndermesini gerektirir. Yayın kurulu yazarlık şartarını karşılamayan bir kişinin yazar olarak eklendiğinden şüphe ederse yazı daha fazla incelenmeksizin reddedilecektir. Makalenin gönderilmesi aşamasında bir yazar makalenin gönderilmesi ve gözden geçirilmesi aşamalarında tüm sorumluluğu üstlenmeyi kabul ettiğini bildiren kısa bir açıklama göndermelidir.

Türkiye Çocuk Hastalıkları Dergisi'ne gönderilen bir çalışma için bireylerden veya kurumlardan alınan mali hibeler veya diğer destekler Yayın Kuruluna bildirilmelidir. Potansiyel bir çıkar çatışmasını bildirmek için, ICMJE Potansiyel Çıkar Çatışması Bildirim Formu, katkıda bulunan tüm yazarlar tarafından imzalanmalı ve gönderilmelidir. Editörlerin, yazarların veya hakemlerin çıkar çatışması olasılığı, derginin Yayın Kurulu tarafından COPE ve ICMJE yönergeleri kapsamında çözümlenecektir.

Derginin Yayın Kurulu, tüm itiraz durumlarını COPE kılavuzları kapsamında ele almaktadır. Bu gibi durumlarda, yazarların itirazları ile ilgili olarak yazı işleri bürosu ile doğrudan temasa geçmeleri gerekmektedir. Gerektiğinde, dergi içinde çözülemeyen olayları çözmek için bir kamu denetçisi atanabilir. Baş editör itiraz durumlarında karar alma sürecinde alınacak kararlarla ilgili nihai otoritedir.

Yazarlar Türkiye Çocuk Hastalıkları Dergisi'ne bir yazı gönderirken, yazıların telif haklarını Türkiye Çocuk Hastalıkları Dergisi'ne devretmiş olmayı kabul ederler. Yayınlanmamak üzere reddedilirse veya herhangi bir sebepten yazı geri çekilirse telif hakkı yazarlara geri verilir. Türk Türkiye Çocuk Hastalıkları Dergisi'ne ait Telif Hakkı Devri ve Yazarlık Formları (https://dergipark.org.tr/tr/pub/tchd adresinden indirilebilir). Şekiller, tablolar veya diğer basılı materyaller de dahil olmak üzere basılı ve elektronik formatta daha önce yayınlanmış içerik kullanılıyorsa yazarlar telif hakları sahiplerinden gerekli izinleri almalıdır. Bu konudaki hukuki, finansal ve cezai yükümlülükler yazarlara aittir.

Yazıların sonuçlarının rapor edilemesi sırasında genellikle istatistiksel analizler gereklidir. İstatistiksel analizler uluslararası istatistik raporlama standartlarına uygun olarak yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Tıp dergilerine katkıda bulunanlar için istatistiksel yönergeler. Br Med J 1983: 7; 1489-93). İstatistiksel analizler hakkında bilgi, Materyal ve Metot bölümünde ayrı bir alt başlık ile açıklanmalı ve bu süreçte kullanılan istatistiksel yazılımlar mutlaka belirtilmelidir.

Türkiye Çocuk Hastalıkları Dergisi'nde yayınlanan yazılarda belitilen ifade veya görüşler, editörlerin, yayın kurulunun veya yayıncının görüşlerini yansıtmaz; editörler, yayın kurulu ve yayıncı bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmez. Yayınlanan içerikle ilgili nihai sorumluluk yazarlara aittir.

YAZININ HAZIRLANMASI

Yazılar, Tıbbi Çalışmalarda Bilimsel Çalışmanın Yürütülmesi, Raporlanması, Düzenlenmesi ve Yayınlanması için Uluslararası Tıbbi Dergi Editörleri Konseyi (International Council of Medical Journal Editors (ICMJE)) Önerileri'ne uygun olarak hazırlanmalıdır (Aralık 2019'da güncellenmiştir - http://www.icmje.org/icmje-recommendations). Bu liste aşağıda görülebilir.

Yazılar yalnızca derginin çevrimiçi (online) makale gönderme ve değerlendirme sistemi aracılığıyla gönderilebilir.

https://dergipark.org.tr/tr/journal/2846/submission/step/manuscript/new Başka herhangi bir araç aracılığıyla gönderilen yazılar değerlendirmeye alınmayacaktır.

CONSORT	Randominize kontrollü çalışma
STROBE	Gözlemsel epidemiyolojik çalışmalar
STARD	Tanı yöntemleri
PRISMA	Sistemetik derleme ve metaanaliz
ARRIVE	Deneysel hayvan çalışmaları
TREND	Randomize olmayan tutum ve davranış çalışmaları

Dergiye gönderilen yazılar öncelikle sekreterlik tarafından yazının derginin kurallarına uygun olarak hazırlanıp hazırlanmadığı yönünden teknik bir değerlendirme sürecinden geçecektir. Derginin yazım kurallarına uymayan yazılar, düzeltme talepleriyle birlikte gönderen yazara iade edilecektir.

Yazarların yazıları hazırlarken ve sisteme yüklerken aşağıdaki konulara dikkat etmesi gerekmektedir:

Telif Hakkı Devri ve Yazarlık Formunun Kabulü ve ICMJE tyarafından önerilen Potansiyel Çıkar Çatışması Bildirim Formu İlk başvuru sırasında (katkıda bulunan tüm yazarlar tarafından doldurulmalıdır) sisteme yüklenmelidir. Bu formları www.dergipark.org.tr/tr/pub/tchd adresinden indirebilirsiniz.

Yazılar, Microsoft Word™ (2010 ve üstü) yazılım programı kullanılarak, Times New Roman karakterinde, 12 punto büyüklüğünde ve çift satır aralığı ile yazılmalıdır. Sayfalarda her yönden 2 cm boşluk bırakılmalıdır. Yazılarda "System International" (SI) birimleri kullanılmalıdır. Tablo ve grafiklere metin içinde atıf yapılmalıdır. Kısaltmalar öz ve metinde ilk geçtikleri yerde açık yazılıp, parantez içinde kısaltma verilmek kaydıyla kullanılabilirler.

Makale içinde, ortalama ve yüzdelik verilirken, ondalıklı hanelerin gösteriminde noktadan sonra 2 basamak kullanılması gerekmektedir (231.7 yerine; 231.69 veya 231.70 gibi). Tam sayı dışındaki gösterimlerde noktadan sonra iki hane, istatistiksel değerlerin gösteriminde ise (p, r, t, z değerleri gibi) noktadan sonra üç hane yazılması gerekir. p değerlerinin sunumunda $p<0.05$ veya $p>0.05$ yerine test istatistiği ile birlikte tam p değerinin noktadan sonra üç hane içerek şekilde verilmesi (ör: $p=0.029$) gerekmektedir. Bu değerin binde birden küçük olması durumunda $p<0.001$ şeklinde gösterim yapılmalıdır.

Kapak sayfasının hazırlanması:

Kapak sayfası tüm yazılarla birlikte gönderilmeli ve bu sayfa şunları içermelidir:

Yazının kapak sayfasında yazının İngilizce başlığı bulunmalıdır. Kapak sayfası yazarların adlarını, akademik ünvanlarının, ORCID numaralarını, kurumsal/mesleki bağlantılarını, yazının kısa başlığını (en fazla 50 karakter), kısaltmaları, finansal açıklama bildirimini ve çıkar çatışması bildirimini içermelidir. Yazı Türkiye'de bulunan bir merkez tarafından gönderilmişse yazılar için Türkçe bir başlık da gereklidir. Bir yazı birden fazla kurumdan yazar içeriyorsa, her yazarın adını, ayrı olarak listelenen kurumlarına karşılık gelen bir üst simge numarası izlemelidir. Tüm yazarlar için için isim soy isim, e-posta adresi, telefon ve faks numaraları dahili iletişim bilgileri verilmelidir. Ayrıca yazı ile ilgili olrak iletişim kurulacak sorumlu sorumlu yazarın kim olduğu belirtilmelidir.

Önemli Uyarı: Kapak sayfası ayrı bir belge olarak yüklenmelidir.

Anahtar kelimeler:
Özetin sonunda konu indeksleme için her gönderime en az üç en fazla altı anahtar kelime eklenmelidir. Anahtar kelimeler kısaltma olmadan tam olarak listelenmelidir. Anahtar kelimeler "National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html)" veritabanından seçilmelidir. Yazı Türkiye'de bulunan bir merkez tarafından gönderilmişse Türkçe anahtar kelimeler de gereklidir.

Yazı türleri:

Orijinal araştırma makalesi

Kelime sayısı: En çok 3500 kelime (Başlık, özet, anahtar kelimeler, kaynaklar, tablo ve figür yazıları hariç).

Ana metnin içereceği bölümler: Giriş, Yöntemler, Sonuçlar, Tartışma

Başlık: En çok 20 kelime

Yapısal özet: En çok 250 kelime. Bölümler: Amaç, Gereç ve Yöntem, Sonuçlar ve Tartışma

Anahtar kelimeler: En az 3 en fazla altı kelime, alfabetik olarak sıralanmıştır.

Şekiller ve tablolar: Sayı sınırı yok ancak tam olarak gerekçelendirilmeli ve açıklayıcı olmalıdır.

Referanslar: En çok 40.

Orijinal makaleler; İngilizce başlık, İngilizce yapılandırılmış özet (yapılandırılmış, İngilizce anahtar kelimeler. Yazı Türkiye'de bulunan bir merkez tarafından gönderilmişse Türkçe başlık, Türkçe yapılandırılmış özet (Amaç, Gereç ve Yöntem, Sonuç ve Tartışma olarak yapılandırılmıştır) ve Türkçe anahtar kelimeler de gereklidir.

Çoğu okuyucu ilk olarak başlık ve özeti okuduğu için bu bölümler kritik öneme sahiptir. Ayrıca, çeşitli elektronik veritabanları yazıların sadece özetlerini indeksledikleri için özette önemli bulgular sunulmalıdır.

Makalenin diğer bölümleri Giriş, Gereç ve Yöntemler, Sonuçlar, Tartışma, Teşekkür (gerekirse) ve Kaynaklar'dan oluşmalıdır. Makalelerin tüm bölümleri yeni bir sayfada başlamalıdır.

Derleme:

Kelime sayısı: En fazla 5000

Özet: En fazla 500 kelime

Anahtar kelimeler: En az üç en fazla altı kelime, alfabetik olarak sıralanmıştır.

Şekiller ve tablolar: Sayı sınır yok ancak tam olarak gerekçelendirilmeli ve açıklayıcı olmalıdır.

Referanslar: 80'e kadar

Derleme makaleleri, tıptaki belirli konuların kapsamlı olarak gözden geçirildiği, konunun tarihsel gelişimini, mevcut bilinenleri, araştırıma ihtiyacı olan alanları içeren yazılarır. Konu hakkında orijinal araştırmaları yazarlar tarafından yazılmalıdır. Tüm derleme yazıları kabulden önce diğer yazılara eşdeğer değerlendirme süreçlerine tabi tutulacaktır.

Derleme makaleleri şunları içermelidir; İngilizce başlık, İngilizce özet ve İngilizce anahtar kelimeler. Derleme Türkiye'de bulunan bir merkez tarafından gönderilmişse Türkçe başlık, Türkçe özet ve Türkçe anahtar kelimeler de gerekmektedir.

Olgu Sunumu:

Kelime Sayısı: En fazla 2000 kelime

Özet: En fazla 200 kelime

Anahtar Kelime: En az üç en fazla altı kelime

Tablo ve Şekil: Toplamda en fazla beş ile sınırlandırılmıştır.

Referans: En fazla 15

Dergiye sınırlı sayıda olgu sunumu kabul edilmektedir. Olgu sunumlarının tanı ve tedavide zorluk oluşturan, nadir, literatürde yer almayan yeni tedaviler sunan ilginç ve eğitici olguların seçilmesine dikkat edilmektedir. Olgu sunumu giriş, olgu sunumu ve tartışma içermelidir.

Olgu sunumları şunları içermelidir; İngilizce başlık, İngilizce özet ve İngilizce anahtar kelimeler. Türkiye'de bulunan bir merkez tarafından gönderilmişse Türkçe başlık, Türkçe özet ve Türkçe anahtar kelimeler de gereklidir.

Editöre mektup:

Kelime sayısı: En fazla 1500 kelime

Şekil ve tablolar: En fazla 3

References: En fazla 15

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(http://www.ncbi.nlm.nih.gov/sites/entrez/query.fcgi?db=nlmcatalog) Yıl;Cilt:İlk ve son sayfa numarası.

Örnek: Benson M, Reinholdt J, Cardell LO. Allergen-reactive antibodies are found in nasal fluids from patients with birch polen-induced intermittent allergic rhinitis, but not in healthy controls. Allergy 2003;58:386-93.

Kaynak dergi eki ise;

Yazar(lar)ın soyadı adının başharf(ler)i. Makalenin başlığı. Derginin Index Medicus'a uygun kısaltılmış ismi (http://www.ncbi.nlm.nih.gov/sites/entrez/query.fcgi?db=nlmcatalog) Yıl;Cilt

(Suppl. Ek sayısı):İlk sayfa numarası-Son sayfa numarası.

Örnek: Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect 1994; (102 Suppl 1):275–82.

Kaynak kitap ise;

Yazar(lar)ın soyadı, adının başharf(ler)i. Kitabın adı. Kaçıncı baskı olduğu. Basım yeri: Basımevi, Basım Yılı.

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Örnek: Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM (eds). Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York: Raven P, 1995:466–78.

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Örnek: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O (eds). MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. North-Holland; 1992. p. 1561-5.

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Örnek: Arrami M, Garner H. A tale of two citations. Nature 2008;451(7177): 397-9. Available from: URL:www.nature.com/nature/journal/v451/n7177/full/451397a.html. Aaccessed 20 January 2008.

Kaynak web sitesi ise:

Web sitesinin adı. Erişim tarihi. Available from: Web sitesinin adresi.

Örnek: Centers for Disease Control and Prevention (CDC). Erişim tarihi: 12 Mart 2013.

Available from: http://www.cdc.gov/

Kaynak tez ise:

Yazarın soyadı adının baş harfi. Tezin başlığı (tez). Tezin yapıldığı şehir adı: Üniversite adı (üniversite ise); Yılı.

Örnek: Özdemir O. Fibrillin-1 gen polimorfizmi ve mitral kapak hastalığı riski. (Tez). Ankara: Gazi Üniversitesi, 2006."

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Bir makalenin inceleme süreci altı aydan uzun bir zaman almış ve yazarlara karar bildirilmemişse yazının geri çekilme talebi olumlu karşılanır.

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Original Articles / *Özgün Araştırmalar*

Case Reports / *Olgu Sunumları*

Review / *Derleme*

Can Platelet Mass Index Be Used as a Prognostic Marker in Children Diagnosed with Multisystem Inflammatory Syndrome Associated with Coronavirus?

Koronavirus ile İlişkili Multisistem İnflamatuar Sendrom Tanılı Çocuklarda Trombosit Kitle İndeksi Prognostik Bir Belirteç Olarak Kullanılabilir mi?

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ABSTRACT

Objective: We've aimed at evaluating whether the platelet mass index (PMI) can be a prognostic marker for children diagnosed with MIS-C.

Material and Methods: 31 children diagnosed with MIS-C and treated at our university hospital between March 2020 and November 2021 were included. Demographic data, clinical findings and laboratory values at the time of hospitalization, admission to the intensive care unit and duration of hospitalization were evaluated retrospectively. PMI of each patient at the time of hospitalization was calculated and recorded.

Results: There was a statistically significant negative correlation between PMI and ferritin (r= -0.635, moderate, p<0.001), CRP (r= -0.377, weak, p= 0.036), and procalcitonin (r= -0.481, weak, p=0.006) levels. There was a statistically significant positive relationship between PMI and leukocyte count (r=0.367, weak, p=0.042) and lymphocyte count (r=0.384, weak, p=0.033). Median PMI values of the patients requiring intensive care (1701.35 fl/nl) were lower, compared to the median PMI values of the patients not requiring intensive care (2523.94 fl/nl), however, statistical results could not be reached due to the low (4 of 31) number of patients requiring intensive care. Median PMI values of the patients whose ferritin level was >400 ng/ml (1415.2; 533.4 – 3600.5) were statistically lower compared to the median PMI values of the patients whose ferritin level was ≤400 ng/ml (2705.7; 1395.2 – 9167.6).

0000-0002-1880-546X : EKER İ
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Conclusion: The findings in our study demonstrate that low PMI levels identified in children with MIS-C at the time of diagnosis may be with more severe clinical courses

Key Words: Child, Coronavirus Disease, Mass Index, Multisystem Inflammatory Syndrome, Platelet, Prognosis

ÖZ

Amaç: Trombosit kitle indeksinin (TKİ) MIS-C tanısı alan çocuklarda prognostik bir belirteç olup olmadığının değerlendirilmesi.

Gereç ve Yöntemler: Mart 2020 ile Kasım 2021 tarihleri arasında üniversite hastanemizde MIS-C tanısı konan ve tedavi gören 31 çocuk çalışmaya dahil edildi. Hastaneye yatış anındaki, yoğun bakıma yatış anındaki ve hastanedeki yatış süresince demografik veriler, klinik bulgular ve laboratuvar değerleri retrospektif olarak değerlendirildi. Her hastanın yatış anındaki TKİ değerleri hesaplandı ve kaydedildi.

Bulgular: TKİ ile ferritin (r= -0.635, orta, p<0.001), CRP (r= -0.377, zayıf, p= 0.036) ve prokalsitonin (r= -0.481, zayıf, p= 0.006) düzeyleri arasında istatistiksel olarak anlamlı negatif korelasyon bulundu. TKİ ile lökosit sayısı (r= 0.367, zayıf, p= 0.042) ve lenfosit sayısı (r= 0.384, zayıf, p= 0.033) arasında istatistiksel olarak anlamlı pozitif ilişki bulundu. Yoğun bakım gerektiren hastaların ortanca TKİ değerlerinin (1701.35 fl/nl), yoğun bakım gerektirmeyen hastaların ortanca TKİ değerlerinden (2523.94 fl/nl) istatistiksel olarak daha düşük olduğu saptandı (p= 0.005). Ferritin düzeyi >400 ng/ml olan hastaların ortanca TKİ değerlerinin (1415.2; 533.4 – 3600.5), ferritin düzeyi ≤400 ng/ml olan hastaların ortalama TKİ değerlerinden (2705.7; 1395.2 – 9167.6) istatistiksel olarak daha düşük olduğu saptandı (p= 0.005).

Sonuç: Çalışmamızdaki bulgular, MIS-C'li çocuklarda tanı anında tespit edilen düşük TKİ düzeylerinin, daha şiddetli klinik seyire yol açabileceğini ortaya koymaktadır.

Anahtar Sözcükler: Çocuk, Koronavirüs Hastalığı, Kitle İndeksi, Multisistem İnflamatuar Sendrom, Trombosit, Prognoz

INTRODUCTION

Upon understanding that the outbreak of the pneumonia epidemic in China in December 2019 was caused by a novel coronavirus type known as severe acute respiratory syndrome coronavirus (SARS-CoV-2), this disease was named "Coronavirus Disease 2019" (COVID-19). The epidemic was rapidly spread worldwide in a short time causing a pandemic (1). In April 2020, a severe disease presenting with findings of multiple organ involvement, rash, high fever, and high acute phase reactants, particularly in the gastrointestinal and cardiovascular systems was identified in children with previous COVID-19 infection. This presentation was named multisystem inflammatory syndrome associated with COVID-19 (MIS-C) by US Center for Disease Control and Prevention (2). While the etiology of MIS-C is similar to cytokine storm syndrome, macrophage activation syndrome, and Kawasaki disease, it is believed to be caused by an abnormal immune response to the virus. Covid-19 (SARS-CoV-2) Reverse Transcriptase PCR tests of most children diagnosed with MIS-C are negative and have positive serology. This suggests that MIS-C may be developed due to postviral immunologic responses, especially in cases with previous asymptomatic SARS-CoV-2 infection (3, 4).

There is a wide spectrum of the clinical picture in MIS-C due to its effect on multiple systems. Findings manifest weeks after the SARS-CoV-2 infection. Most cases are healthy and have no accompanying disease. It is generally prevalent in obese children. While fever is the most frequently identified finding, it is persistent and prolonged. It may be accompanied by gastrointestinal findings accompanied by vomiting, severe stomach aches and/or diarrhea, cardiac dysfunction, dehydration, mucocutaneous symptoms mimicking Kawasaki disease including conjunctivitis and rash, headache, neurological findings such as irritability and encephalopathy, and acute respiratory distress syndrome (ARDS). Some cases require intensive care due to hypotension and cardiac dysfunction requiring inotrope support. Moreover, there are reported cases with severe clinical conditions requiring extracorporeal membrane oxygenation (4).

Further tests must be done to confirm the MIS-C diagnosis in cases with the clinically suspected multisystem inflammatory syndrome in the presence of persistent high fever, history of encountering SARS-CoV, at least two of the following findings. These findings include rash (maculopapular), complaints of gastrointestinal systems (diarrhea, vomiting, stomach ache), changes in the oral mucosa (chapped and/or red lips, strawberry tongue or oropharyngeal mucosa erythema) bilateral nonexudative conjunctivitis, lymphadenopathy, meningism, papilledema, encephalopathy, changes in mental perception or focal neurological findings (2-4).

It is reported that approximately 60% of the children diagnosed with MIS-C need to be admitted to the intensive care unit, and unfortunately 2% result in mortality (5). It is determined that platelet counts and mean platelet volumes (MPV) of the patients can be used as a prognostic marker in COVID-19 infection just like in sepsis and severe diseases (6-9). It is demonstrated that the platelet mass index (PMI) calculated by using MPV, and platelet counts manifest the platelet functions much better compared to the platelet counts and MPV (10). Based on this, we aimed to evaluate whether PMI can be used or not as a prognostic marker in children diagnosed with MIS-C.

MATERIALS and METHODS

The statistical power analysis made for the study hypothesis identified that at least 19 patients with MIS-C needed to be included in the study to test the hypothesis with 80% power and 0.05 error. Required permits were obtained for the study from the Republic of Turkey Ministry of Health Directorate General of Health Services COVID-19 Scientific Research Evaluation

Committee (decision dated 17.11.2021 and numbered 2021-01-17T17_09_20), Afyonkarahisar University of Health Sciences (AFSÜ) Health Application and Research Center, and AFSÜ Clinical Researches Ethics Committee (decision dated 03.12.2021 and numbered 2021/13). 31 pediatric patients, diagnosed with MIS-C in accordance with the diagnostic criteria in the Republic of Turkey Ministry of Health COVID-19 Pediatric Patient Management and Treatment Guideline, and treated at AFSÜ Faculty of Medicine Department of Pediatric Health and Diseases between the dates of March 2020 and November 2021 were included in the study and hospital records of these patients were examined retrospectively (Table I) (11).

Demographic data of the patients, findings at the time of initial hospitalization, sedimentation rate, D-dimer, CRP, fibrinogen, LDH, ferritin, procalcitonin, albumin, troponin-T, pro-BNP levels, hemogram parameters, need for admission to the intensive care unit, intubation requirement, and duration of hospitalization were recorded. Platelet mass index (PMI) of each patient at the time of hospitalization was calculated and recorded using the formula [Platelet count] × [MPV / 1000] fl/nl (for example, platelet mass index of a patient with platelet count: 200 x 109/L and MPV: 9 fl is 1800 fl/nl) (10).

Statistical Package for the Social Science (SPSS 18.0 for Windows; SPSS Inc) was used for statistical analysis. The normal distribution test of continuous variables was performed by using the Shapiro-Wilk test. The Mann–Whitney U-test was used to test the difference between not normally distributed quantitative data, among the studied groups. Spearman correlation analysis was performed to detect correlational relations between variables where the assumption of the normal distribution is not provided. Correlation strength (positive or negative) was classified as 0.3–0.5 = weak, 0.5–0.69 = moderate, and 0.7–0.9 = strong correlation. The nonnormally distributed continuous data were reported as median (minimum-maximum). Categorical data are presented as numbers (n) and percentages (%). Statistical significance was defined as a two-tailed p value of<0.050.

Table I: Republic of Turkey Ministry of Health Guideline MIS-C Diagnostic Criteria

Multisystem Inflammatory Syndrome (Mis-C) Diagnostic Criteria
Being 0-21 of age
Fever measured >38.0 C persisting over 24 hours or presence of fever notified by the family
Evidence of inflammation in laboratory tests (presence of minimum 2 or more evidence)
High CRP
High sedimentation
High fibrinogen
High procalcitonin
High D-dimer
High ferritin
High LDH
High IL-6 level
Increased neutrophil count
Lymphopenia
Hypoalbuminemia
Severe disease setting requiring hospitalization
Multiple organ system involvements (presence of minimum 2 or more)
Cardiovascular (shock, high troponin, high BNP, abnormal ECHO findings, arrhythmia)
Respiratory (pneumonia, ARDS, pulmonary embolism)
Renal (Renal failure)
Neurologic (convulsion, stroke, aseptic meningitis)
Hematologic (coagulopathy, high D-dimer)
Gastrointestinal (high liver enzymes, diarrhea, ileus)
Dermatologic (erythroderma, mucositis, other rashes)
Absence of other alternative diagnoses (bacterial sepsis, infections associated with myocarditis such as enterovirus infection, staphylococcic, or streptococcal toxic shock syndromes)
Evidence of previous or current SARS-COV-2 infection (presence of at least one of the following)
SARS-COV-2 RT-PCR positive result
SARS-COV-2 serology positive result
SARS-COV-2 antigen-positive result
SARS-COV-2 positive case exposure within 4 weeks before onset of symptoms

CRP: *C-Reactive Protein,* ***LDH:*** *Lactate Dehydrogenase,* ***IL-6:*** *Interleukin-6,* ***BNP:*** *Brain natriuretic peptide,* ***ECHO:*** *Echocardiography,* ***ARDS:*** *Acute respiratory distress syndrome,* ***SARS-COV-2:*** *Severe acute respiratory syndrome coronavirus 2,* ***RT-PCR:*** *Real-time polymerase chain reaction.*

RESULTS

54.8% of the children (n=14) were male, and 45.2% (n=17) were female. The median age was 5.19 years, the youngest patient was three months of age, and the oldest patient was 18 years of age. While the median duration of hospitalization was 10 days, the shortest duration of hospitalization was 5 days, and the longest duration of hospitalization was 25 days. 12.9% of the children (n=4) required admission to the intensive care unit. While the median duration of the patients receiving treatment in the intensive care unit was 4.5 days, the shortest duration in the intensive care unit was 2 days, and the longest duration in the intensive care unit was 8 days. Laboratory values of the patients at the time of hospitalization are given in Table II.

Median platelet mass index of the patients at the time of hospitalization was 2172.6 (533.4-9167.6) fl/nl, median D-dimer level was 2.4 (0.0-32.9) ng/ml, median ferritin level was 424.1 (33.8-2466.0) ng/ml, median CRP level was 14.8 (0.1-273.5) mg/l, median procalcitonin level was 1.4 (0.1-56.7) ng/ml, median lymphocyte count was 1.5 (0.1-188.0) x 103/mm^3, and median sedimentation rate was 53.0 (11.0-142.0) mm/h.

It was identified that there was a statistically significant negative relationship between the platelet mass index and ferritin (r= -0.635, p<0.001, moderate), CRP (r= -0.377, p= 0.036, weak) and procalcitonin levels (r= -0.481, p= 0.006, weak) (Table III). In

Table II: Laboratory values of the patients at the time of hospitalization.

Laboratory Parameters	Values (n=31)
Platelet mass index (fl/nl)	2172.6 (533.4-9167.6)
D-dimer (ng/ml)	2.4 (0.0-32.9)
Ferritin (ng/ml)	424.1 (33.8-2466.0)
CRP (mg/l)	14.8 (0.1-273.5)
Sedimentation rate (mm/h)	53.0 (11.0-142.0)
Fibrinogen (mg/dL)	479.1 (149.8-739.0)
LDH (U/L)	319.0 (176.0-1101.0)
MPV (fl)	10.6 (8.2-12.8)
Platelet count (x10^3/mm^3)	204.0 (42.0-1118.0)
Erythrocyte count (x10^6/mm^3)	4.2 (3.2-5.3)
Leukocyte count (x10^3/mm^3)	9.7 (2.1-24.4)
Lymphocyte count (x10^3/mm^3)	1.5 (0.1-188.0)
Procalcitonin (ng/ml)	1.4 (0.1-56.7)
Albumin (g/dL)	3.4 (2.3-4.9)
Troponin-T (ng/ml)	0.0 (0.0-0.1)
proBNP (pg/ml)	1001.0 (11.9-35000.0)

Values are presented as median (minimum-maximum)

Table III: Relationship of platelet mass index with laboratory values.

	Platelet Mass Index (fl/nl)	
	r	p
Ferritin(ng/ml)	-0.635	<0.001
CRP (mg/l)	-0.377	0.036
Procalcitonin (ng/ml)	-0.481	0.006
Leukocyte count (x10^3/mm^3)	0.367	0.042
Lymphocyte count (x10^3/mm^3)	0.384	0.033

Table IV: Comparison of PMI and D-Dimer values based on admission to the intensive care unit

	Admission to Intensive Care	
	No (n:27)	Yes (n:4)
D-dimer level (ng/ml)	2.0 (0.0-8.9)	17.4 (4.9-32.9)
Platelet mass index (fl/nl)	2175.6 (750.0-9167.6)	1396.5 (533.4-3479.0)

Values are presented as median (minimum-maximum)

other words, it was identified that ferritin, CRP, and procalcitonin levels were increasing while PMI were decreasing and this was statistically significant (Figure 1).

It was identified that there was a statistically significant positive relationship between the platelet mass index and leukocyte count (r=0.367, p=0.042, weak) and lymphocyte count (r=0.384, p=0.033, weak) (Table III). In other words, it was identified that leukocyte count and lymphocyte count were decreasing while PMI of the patients were decreasing and this was statistically

Table V: Comparison of PMI values of the patients divided into two groups based on ferritin levels.

	Ferritin value(ng/ml) ≤400 (n:15)	Ferritin value(ng/ml) >400 (n: 16)	p
Platelet mass index values (fl/nl)	2705.7 (1395.29167.6)	1415.2 (533.4-3600.5)	0.002

Values are presented as median (minimum-maximum)

significant (Figure 2). No statistically significant relationship was identified between platelet mass index and D-dimer, fibrinogen, LDH, troponin-T, proBNP, albumin levels, sedimentation rate, and duration of hospitalization.

It was identified that the platelet mass index of the patients requiring admission to the intensive care unit was lower than the platelet mass index of the patients not requiring admission to the intensive care unit. And the D-dimer of the patients requiring admission to the intensive care unit was higher than the D-dimer of the patients not requiring admission to the intensive care unit. However, statistical results could not be reached due to the low number of patients requiring intensive care (Table IV).

When the patients were divided into two groups as ≤400 ng/ml (n:15) and >400 ng/ml (n:16) based on their ferritin levels, it was identified that the median platelet mass index (1415.2; 533.4 – 3600.5) of the group with ferritin level of >400 ng/ml was statistically lower than the median platelet mass index (2705.7; 1395.2 – 9167.6) of the group having ferritin level of ≤400 ng/ml (Table V). These results supported our findings that showed increasing ferritin levels of patients were accompanied by statistically significantly decreasing platelet mass index levels.

DISCUSSION

It is known that the MIS-C patients are asymptomatic during the active phase of COVID-19 or have mild respiratory symptoms, however, they develop multiorgan dysfunction within three to four weeks after the exposure to the virus, and this is caused by strongly activated T lymphocytes. A cytokine storm and cytotoxicity are developed as a result of such excessive activity of T lymphocytes. In addition, excessively activated T lymphocytes cause increased reactive oxygen radicals and oxidative stress along with monocyte and macrophages. Increased oxidative stress leads to changes and degradation in macromolecules such as DNA, proteins, and lipids. Furthermore, the presence of autoantibodies developed against the endothelial cells and leading to even more increased multisystem inflammation by causing endothelial dysfunction are among the important factors in the pathophysiology of MIS-C (12). Therefore, initial treatments involving intravenous immunoglobin (IVIG) and low-moderate dose steroid administration are recommended for most of the patients hospitalized due to MIS-C (13). Our findings

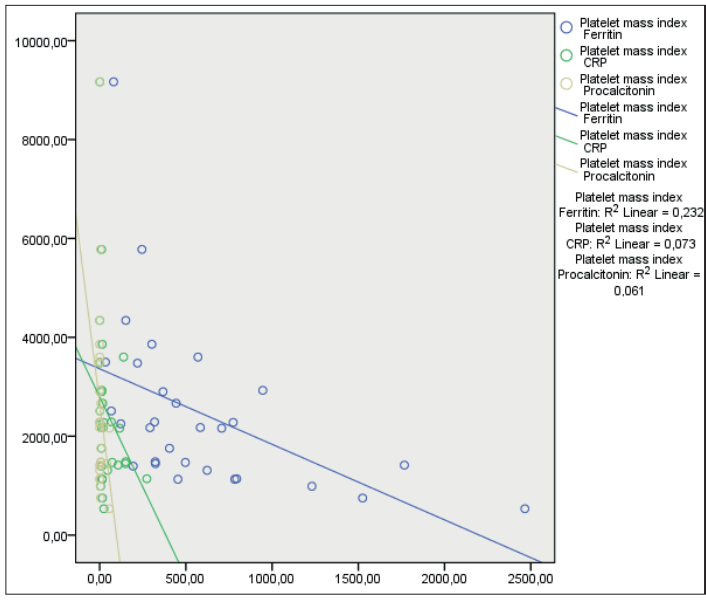

Figure 1: Platelet mass index and ferritin, CRP and procalcitonin level scatter plot.

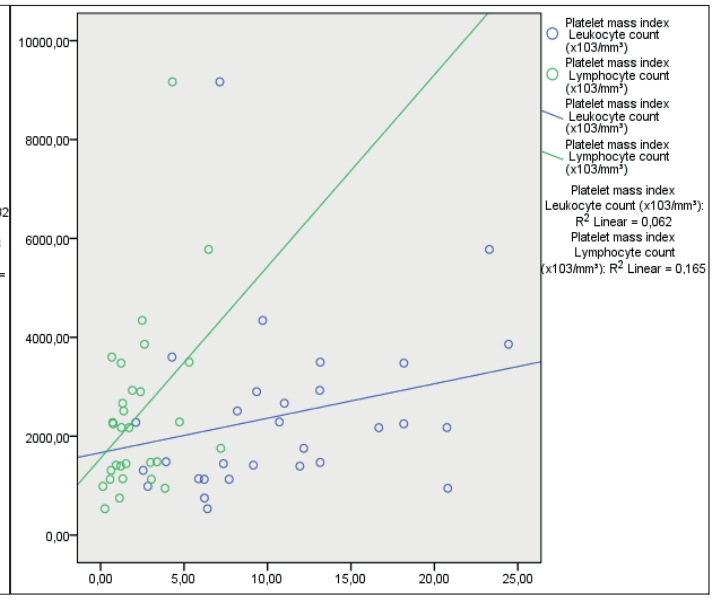

Figure 2: Platelet mass index and leukocyte count and lymphocyte count scatter plot.

in our study indicate that starting intravenous immunoglobulin and steroid treatment at an early stage in patients with low platelet mass index who are potential to be diagnosed with MIS-C may lead to a less severe course of the disease.

It is known that overproduction of pro-inflammatory cytokines and acute-phase reactants negatively affect the megakaryopoiesis leading to smaller and lesser platelet release from the bone marrow than normal (14). In the light of this information, we believe that hyperinflammation, the main factor of MIS-C pathophysiology, may cause smaller and lesser platelet release from the bone marrow of the patients, and decreased platelet volume and platelet count and platelet mass index which is calculated using these two parameters. In our study, we aimed to investigate the presence of such a condition in MIS-C and its relationship with the inflammation parameters. As a result, we have identified that the leukocyte counts, lymphocyte counts, and PMI of the patients statistically decrease as the ferritin, CRP, and procalcitonin levels increase. Our findings suggest that hyperinflammation in MIS-C and suppressed megakaryopoiesis through immune-mediated mechanisms, and thus the peripheral release of smaller and lesser platelets from the bone marrow may probably be the cause of low platelet mass index associated with MIS-C. Furthermore, our hypothesis is supported by the fact that the median platelet mass index (1415.2; 533.4 – 3600.5) of the group with ferritin level of >400 ng/ml is statistically lower than the median platelet mass index (2705.7; 1395.2 – 9167.6) of the group with ferritin level of ≤400 ng/ml.

Gu, et al. (15) reported that increased D-Dimer levels (fibrin degradation products indicating increased coagulation) and mild thrombocytopenia are observed in most patients requiring hospitalization due to COVID-19 infection, and the presence of high levels of D-Dimer along with severe thrombocytopenia is related to a more severe course of disease that leads to increase in the need for admission to the intensive care unit and mortality. Differently from the patients hospitalized due to COVID-19, most children diagnosed with MIS-C had negative COVID-19 PCR test while they had positive serological findings indicating that they had the infection. These findings indicate that hyperinflammation and secondary suppressing of megakaryopoiesis as a consequence are the prominent pathophysiologies in MIS-C in contrast with COVID-19 infection, in which the prominently common pathophysiologies are in coagulation. Furthermore, this demonstrates that lower platelet mass index values are accompanied by higher hyperinflammation levels and this may cause higher probability for the patients' with MIS-C to have worse outcomes.

Godfred, et al. (16) reported that the admission to the intensive care unit in children with MIS-C is 63.9%, and the mortality rate is 1.8%. Abrams, et al. (5) reported that the admission to the intensive care unit in children with MIS-C is 60%, and the mortality rate is 2%. In our study, the percentage of patients requiring admission to the intensive care unit is 12.9%, which is lower than what is reported in the literature. This can be explained by making an early diagnosis based on MIS-C suspicion and starting steroid and IVIG treatment in the early stage thus preventing the inflammatory storm stage and stabilizing the clinical course in the early stage. Likewise, we have seen that the duration of hospitalization had no relation with the platelet mass indexes of children diagnosed with MIS-C, and we have evaluated that this was based on two factors; i) starting the same treatment protocol in patients diagnosed with MIS-C in the clinic where this study was conducted, and ii) continuing their hospitalizations in the clinic until the end of this protocol schedule.

CONCLUSION

The findings in our study are valuable in demonstrating that, children with MIS-C who have lower PMI levels at the time of diagnosis have higher ferritin, CRP and procalcitonin levels. We can suggest that children with MIS-C who have lower PMI levels at the time of diagnosis have higher inflammatory status. This may lead to a more severe clinical course. Only 4 of 31 children in our cohort required admission to the intensive care unit. Because of this, it is impossible to evaluate statistically, but we identified that the median platelet mass index (1396.5 fl/nl) of the patients requiring admission to the intensive care unit was lower than the platelet mass index (2175.6 fl/nl) of the patients not requiring admission to the intensive care unit. These findings may support our suggestion. Thus, we believe that it will be useful if the physicians, who will be observing the children diagnosed with MIS-C, plan the treatment by taking into account the platelet mass index of the patients as well. Starting intravenous immunoglobulin and steroid treatment at an early stage in patients with low platelet mass index who are potential to be diagnosed with MIS-C may lead to a less severe course of the disease and may reduce the need for admission to the intensive care unit. Investigating the platelet mass index cut-off values in a broader population of cases that can anticipate the intensive care needs of the patients will greatly contribute to the literature on this subject.

REFERENCES

1. Liu YC, Kuo RL, Shih SR. COVID-19: The first documented coronavirus pandemic in history. Biomed J 2020;43:328-33.
2. Centers for Disease Control and Prevention. MIS-C and COVID-19. Available at: https://www.cdc.gov/mis-c/ (Accessed March 29, 2021).
3. Perez-Toledo M, Faustini SE, Jossi SE, Shields AM, Kanthimathinathan HK, Allen JD, et al. Serology confirms SARSCoV-2 infection in PCR-negative children presenting with Paediatric Inflammatory Multi-System Syndrome. MedRxiv 2020. doi: 10.1101/2020.06.05.20123117
4. Ekemen Keles Y, Yilmaz Ciftdogan D. Multisystem Inflammatory Syndrome in Children. Journal of Child 2021;21:74-82.
5. Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health 2021;5:323-1.
6. Yardımcı AC, Yıldız S, Ergen E, Ballı H, Ergene E, Guner YS, et al. Association between platelet indices and the severity of the disease and mortality in patients with COVID-19. Eur Rev Med Pharmacol Sci 2021;25:6731-40.
7. Zhong Q, Peng J. Mean platelet volume/platelet count ratio predicts severe pneumonia of COVID-19. J Clin Lab Anal 2021; 35: e23607.
8. Guclu E, Kocayigit H, Okan HD, Erkorkmaz U,Yurumez Y, Yaylaci S, et al. Effect of COVID-19 on platelet count and its indices. Rev Assoc Med Bras 2020; 66: 1122-7.
9. Liu Y, Sun W, Guo Y, Chen L, Zhang L, Zhao S, et al. Association between platelet parameters and mortality in coronavirus disease 2019: retrospective cohort study. Platelet 2020; 31:490-6.
10. Ilhan O, Bor M. Platelet mass index and prediction of severity of transient tachypnea of the newborn. Pediatr Int 2019;61:697-705.
11. T.C. Sağlık Bakanlığı COVID-19 (SARS-CoV-2 enfeksiyonu) çocuk hasta yönetimi ve tedavi rehberi. Bilimsel Danışma Kurulu Çalışması, T.C Sağlık Bakanlığı, 06 Ocak 2022.
12. Graciano-Machuca O, Villegas-Rivera G, López-Pérez I, Macías-Barragán J, Sifuentes-Franco S. Multisystem Inflammatory Syndrome in Children (MIS-C) Following SARS-CoV-2 Infection: Role of Oxidative Stress. Front Immunol 2021;12:723654.
13. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 2. Arthritis Rheumatol 2021;73:e13-e29.
14. Eldessouki Ibrahim S, Morad CS, Farouk N, Louis A. Platelet indices as markers of inflammation in systemic sclerosis patients: Relation to vascular endothelial growth factor and flow mediated dilatation. The Egyptian Rheumatologist 2018;40:239-42.
15. Gu SX, Tyagi T, Jain K, Gu VW, Lee SH, Hwa JM, et al. Thrombocytopathy and endotheliopathy: crucial contributors to COVID-19 thromboinflammation. Nat Rev Cardiol 2021;18:194-209.
16. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. California MIS-C Response Team. COVID-19-Associated Multisystem Inflammatory Syndrome in Children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep 2020;69:1074-80.

The Relationship Between Feeding Pattern and Measurements of Refraction in Preschool Children

Okul Öncesi Çocuklarda Beslenme Şekli ile Kırma Kusurları Arasındaki İlişki

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ABSTRACT

Objective: To compare the effect of feeding human milk as opposed to formula and human milk on refractive error in preschool children aged 3 to 6 years.

Material and Methods: One hundred and seventy six eyes of 88 children were evaluated. According to the feeding pattern, the patients who fed only breast-fed were classified as Group I, and the patients who fed with combination of breast-fed and formula were classified as Group II. Results were retrospectively compared between groups.

Results: A total of 88 children undergone detailed ophthalmological examinations, of which 40 (45.5 %) were males and 48 (54.5 %) were females. Maternal birth age of 27.3% (n=24) of the children included in the study was over 30 years and birth weight of 96.6% (n=85) was over 2500 grams.

The mean ± standard deviation of the spherical, cylindrical and spherical equivalent (SE) values were 1.61±1.46 D; -0.98 ± 0.69 D and 1.12±1.43 D in group I and 1.00±2.57 D; -0.90 ± 0.81 D and 0.55 ± 2.72 D in group II, respectively (p=0.507 for spherical; p=0.299 for cylindrical and p=0.799 for SE). Although myopic refraction was less common in the breastfed group, there was no significant difference in myopic refraction between the groups (p= 0.507).

Conclusion: In conclusion, mean refractive error were different according to feeding pattern, but this study did not show significant differences between groups (p<0.050). There is a need to confirm this finding by performing more studies with a larger sample sizes.

Key Words: Breastfeeding, Human milk, Preschooler, Refractive errors

ÖZ

Amaç: 3-6 yaş arası okul öncesi çocuklarda sadece anne sütü alımı ile anne sütü ve formula mamanın birlikte alımının kırma kusurları üzerine etkisini karşılaştırmak.

Gereç ve Yöntemler: 88 çocuğun yüz yetmiş altı gözü değerlendirildi. Beslenme şekline göre sadece anne sütü ile beslenenler Grup 1, anne sütü ve formula mama ile beslenenler Grup 2 olarak sınıflandırıldı. Sonuçlar geriye dönük olarak gruplar arasında karşılaştırıldı.

Bulgular: Çalışmaya 40'ı (%45.5) erkek, 48'i (%54.5) kız olmak üzere toplam 88 çocuğun 176 gözü dâhil edildi. Çalışmaya dâhil edilen çocukların %27.3'ünün (n=24) anne doğum yaşı 30 yaşın üzerinde ve %96.6'sının (n=85) doğum ağırlığı 2500 gramın üzerindeydi.

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Etlik Zübeyde Hanım Maternity and Women's Health Teaching and Research Hospital and numbered 2022/80.

Contribution of the Authors / Yazarların katkısı: KIRAN YENİCE E: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, , Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***KARA C:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/ study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar.

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Sferik, silendirik ve sferik eşdeğer (SE) değerlerinin ortalama ± standart sapması sırasıyla grup I'de 1.61±1.46 D; -0.98 ±0.69 D, 1.12±1.43 D ve grup II'de 1.00±2.57 D; -0.90±0.81 D ve 0.55 ±2.72 D'di (Sferik için p=0.507; silendirik için p=0.299 ve SE için p=0.799). Anne sütü alan grupta miyopik kırılma daha az olmasına rağmen, gruplar arasında miyop kırma kusuru açısından anlamlı bir fark yoktu.

Sonuç: Sonuç olarak, ortalama kırma kusurları beslenme şekline göre farklıydı, ancak bu çalışmada gruplar arasında anlamlı fark saptanmadı (p<0.050). Daha büyük örneklem büyüklükleri ile daha fazla çalışma yaparak bu bulguyu doğrulamaya ihtiyaç vardır.

Anahtar Sözcükler: Emzirme, Anne Sütü, Kırma Kusurları, Okul Öncesi

INTRODUCTION

Refractive errors, especially myopia, are one of the most common causes of visual impairment. Although the prevalence of refractive errors varies among countries, the reasons for these differences remain unclear. Studies have indicated that in addition to genetic factors, gene-environment interaction may also be effective in the occurrence of refractive errors (1-6). Also, nutrition intake, particularly breastfeeding during infancy, is thought to affect retinal and visual development, which may have a vital role in eye development.

Breast milk intake is very important in the growth and development of the newborn and especially in protecting it from diseases. The intake of DHA (docosahexaneoic acid) and arachidonic acid (ARA) especially in the early stages of life in term newborns is very effective in terms of eye and neural development, because DHA is accumulated in the membrane lipids of the retina and brain (7-10). Inadequate infant nutrition can affect vision development and especially retinal development, leading to myopia (11).

Some studies have suggested that the probability of refractive errors, especially myopia, is lower in those who are initially breastfed, and that they have better vision levels than those who are formula-fed. In other words, breastfed children have a higher sferik equivalent (SE) than formula-fed children (12-14).

In our current study, we aim to evaluate the association between feeding pattern and refraction errors in preschool children.

MATERIAL and METHODS

This retrospective study following the Helsinki Declaration standards was reviewed and approved by the Ethics Review Committee of Etlik Zübeyde Hanım Maternity and Women's Health Teaching and Research Hospital and numbered 2022/80. Informed consent was obtained from all patients.

Children born between 37-42 weeks postmenstrual age admitted to Etlik Zübeyde Hanım Maternity and Women's Health Teaching and Research Hospital ophthalmology clinic were accepted in the study. Children born prematurely and without cycloplegic examination results were excluded from the study. Questions were directed to the families of the children, and their gestational birth weight (BW), age, gender, feeding pattern during the initial 6 months of life (only breastfeed, breastfeed and formula together) and information on the mothers' pregnancy and delivery type and maternal birth age were recorded. Children were evaluated into two subgroups according to feeding pattern during the initial 6 months of life; only breastfed children (Group I, n= 52) and children fed with combination of breast and formula milk (Group II, n= 36). In the group fed with a combination of breast and formula milk, the frequency of feeding with formula was less than half of the daily feeding amount. All of the participants underwent a complete ophthalmic examination and cycloplegic refraction. Refraction examination was performed with cycloplegic retinoscopy, automated refractometry (Welch Allyn SureSight Autorefractor, USA) and autokeratorefractometer (Zeiss Autoref keratometer, Germany). Two drops of 1% cyclopentolate hydrochloride (Sikloplejin, Abdi İbrahim, Turkey) were performed for dilatation before the examination. The cycloplegic examination values of all patients were recorded as diopters (D). Also, according to results, significant myopia is -3.00 D or less; significant hyperopia is +3.00 D or more; significant astigmatism is -2.00 D or less and anisometropia was 1.00 D or more were recorded.

SPSS 25.0 program was used for statistical analysis. Categorical data were presented as n (numbers) and % and descriptive data as mean ± standard deviation (SD). Chi-square test was used in the analysis of categorical data. Normal distribution fit was checked with the Kolmogorov-Smirnov test. The differences were evaluated by using the t-test for normally distributed data, and the Mann-Whitney U test for non-normally distributed data. p-values of 0.050 or less were noted statistically significant.

RESULTS

A total of 88 children undergone detailed ophthalmological examinations retrospectively, of which 40 (45.5 %) were males and 48 (54.5 %) were females. The mean age of the children was 4.6 ± 1.1 (3 to 6 years) in group I and 4.7 ± 1.1 (3 to 6 years) in group II, respectively. The gestational BW of 96.6 % (n=85) of the children participating in the study was over 2500 grams and the maternal birth age of 72.7 % (n=64) of the children participating in the study was less than 30 years. Moreover, 49 (55.7%) children were delivered vaginally, and 39 (44.3%) were delivered via Caesarian section. Of the 88 children included in the study, 59.1% (n=52) had a history of breastfeeding, and 40.9% (n=36) had a history of breastfeeding and formula. There were no significant difference between the groups for age (A), BW, gender distribution, type of birth (The p values for A, BW, gender and type of birth were 0.485, 0.786, 0.060 and 0.197 respectively) (Table I).

The spherical, cylindrical and spherical equivalent (SE) values were 1.61 ± 1.46 D; -0.98 ± 0.69 D and 1.12 ±1.43 D in

Table I: Demographic data of children.

	Group 1 (n=52)	Group 2 (n=36)	p
Gender			
Female*	24 (46.1)	24 (66.7)	0.060ǂ
Male*	28 (53.9)	12 (33.3)	
Age at examination (years)†	4.6 ± 1.1 (3-6)	4.7 ± 1.1 (3-6)	0.485§
Birth weight*			
<2500 g	2 (4)	1 (2.8)	0.786ǂ
>2500 g	50 (96)	35 (97.2)	
Maternal age*			
<20 years	38 (73)	26 (72.2)	0.929ǂ
>20 years	14 (27)	10 (27.8)	
Type of birth*			
NSVD	26 (50)	23(63.9)	0.197ǂ
C/S	26 (50)	13 (36.1)	

***:** *n(%),* **†:** *Mean ± SD (Range),* **ǂ:** *Chi-square test,* **§:** *Student-t test,* ***SD:** Standart deviation*

Table II: Refraction values of groups.

	Group 1 (n=52)	Group 2 (n=36)	p
Spherical (D)*	1.61 ± 1.46 (-3.50 to 4.50)	1.00 ± 2.57 (-6.25 to 4.50)	0.507‡
Cylindrical (D)*	-0.98 ± 0.69 (-3.25 to 0.00)	-0.90 ± 0.81 (-4.00 to 0.00)	0.299‡
SE (D)*	1.12 ± 1.43 (-4.50 to 4.25)	0.55 ± 2.72 (-7.13 to 4.00)	0.799‡
Significant myopia (<-3.00 D)	1 (1.9)	3 (8.3)	0.275§
Significant astigmatism † (<-2.00 Dn	3 (5.8)	2 (5.5)	1.000§
Significant hyperopia † (>3.00 D)	6 (11.5)	6 (16.7)	0.411§
Anisometropia † (>1.00 D)	6 (11.5)	2 (5.5)	0.463§

:** *Mean ± SD (Range),* **†:** *n(%),* **ǂ:Student-t test,* **§:** *Chi-square test,* ***SE:** Spherical equivalent,* ***SD:** Standard deviation,* ***D:** Diopter*

group I and 1.00 ± 2.57 D; -0.90 ± 0.81 D and 0.55 ± 2.72 D in group II, respectively (p=0.507 for spherical; p=0.299 for cylindrical and p=0.799 for SE). Although myopic refraction was less common in the breastfed group, there was no significant difference in myopic refraction between the groups (p= 0.507). Also, significant myopia was found in 1.9 % (n=1) and 8.3 % (n=3) of group I and group II patients, respectively. There was no statistically significant difference between groups (p=0.275). On the other hand, significant astigmatism was seen in 5.8 % (n=3) of the patients in Group I and 5.5 % (n=2) of patients in Group II, and there was no significant difference between the groups (p= 1.000).

In addition, no significant difference was observed between the groups in terms of anisometropia (p=0.463) and the significant hyperopia (p=0.411). Feeding types and refractive errors of children are presented in Table II.

DISCUSSION

This study is one of the rare publication in the literature comparing feeding pattern and refraction errors in preschool children. In present study, although the SE values were higher in the breast-fed group, no significant difference was observed between feeding pattern and refractive errors.

In the study of Chong et al. (13) including 797 Singaporean children aged 10-12 years, the association between breastfeeding and myopia was evaluated. Myopia was detected in 521 children (65.4%), and 8.5% of them had a history of breastfeeding. The prevalence of myopia in breastfed children was found to be lower than in children who were not breastfed (p = 0.040) (13).

In the study performed by Sham et al. (14) with 3009 children aged between 6-72 months, 29.4% of the children had a history of breastfeeding. The prevalence of myopia was found to be 11.3%, and this rate was found to be lower in the breast-fed group (11.2%) than in the non-breastfed group (11.9%). However, this difference was not found to be significant.

In the study of Shirzadeh et al. (15) 367 children aged 1-5 years were evaluated and refractive measurement was performed with retinoscopy without cycloplegic agents. The frequency of myopia (SE at least -0.5 D) was determined as 5.2%, and it was suggested that myopia was less common in breastfed children compared to other feeding groups. Although the SE values differed between the groups, there was no statistically significant difference. It has been stated that age, ethnicity and refraction examination without the use of cycloplegic agents may play an important role in the emergence of these results.

Studies in the literature have found differences in astigmatism rates. In the study of Shirzadeh et al. (15) astigmatism (cylinder of -0.50 D or higher) was 11.2% in the right eye and 10.2% in the left eye, while this rate was 28.9% (cylinder of 0.75 D or higher) in the study of Tajbakhsh et al. (16). In present study, astigmatism (cylinder of -1.00 D or higher) was 32.7% in breast-fed group and 16.7% in group who fed with combination of breast-fed and formula. Also, significant astigmatism (cylinder -2.00 D and higher) was 5.8% and 5.6 % in group I and group II, respectively. An important reason for the difference between studies may be the different age groups included in the study.

Chong et al. (13) found that breastfed children (SE -1.61 D) were more hyperopic than non-breast-fed children (SE -2.1D). Similarly, Sham et al. (14) reported that hyperopia was more important in the breastfed group and breastfeeding status was independently associated with SE. In their study examining the relationship between breastfeeding and SE, Liu et al. (17) found that breastfeeding for less than 6 months was positively associated with increased hyperopia. In our study, although hyperopia (38.9%) was less common in the non-breast-fed group, no significant difference was found between the groups.

In the early stages of life, which is a critical period of growth and development, it has shown that breast milk is affect eye development and also retinal and nerve development (18). Although there is a progression from neonatal hyperopia to emmetropia in this period, it has been reported that age has a significant impact on the development of myopia (16,19). It has been stated that breast milk intake at an early age affects retinal development, which may be effective in the development of juvenile-onset myopia (12). However, since eye development continues in early childhood, the effect of breastfeeding can be masked by eye development. Limitations of the study include its design, sample size, lack of ocular biometry, and family history.

On the other hand, the number of patients fed only with formula was not included in the study because the number of patients was very small. This may have affected the comparison of refraction between groups.

CONCLUSION

In conclusion, this study supports that myopia is seen less frequently in breastfed children in preschool age. Considering the emmetropization process, there is a need for larger, longer-term studies with a wider age range to shed light on this issue in the future.

REFERENCES

1. Sandfeld L, Weihrauch H, Tubaek G, Mortzos P. Ophthalmological data on 4.5- to 7-year-old Danish children. Acta Ophthalmol 2018; 96:379-83.
2. Cui J, Fu J, Li L, Chen W, Meng Z, Su H, et al. Prevalence and pattern of refractive error and visual impairment among schoolchildren: the Lhasa childhood eye study. BMC Ophthalmol 2021; 21:363.
3. Grzybowski A, Kanclerz P, Tsubota K, Lanca C, Saw SM. A review on the epidemiology of myopia in school children worldwide. BMC Ophthalmol 2020; 20:27.
4. Cai XB, Shen SR, Chen DF, Zhang Q, Jin ZB. An overview of myopia genetics. Exp Eye Res 2019;188:107778.
5. Xiong S, Sankaridurg P, Naduvilath T, Zang J, Zou H, Zhu J, et al. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. Acta Ophthalmol 2017;95:551-66.
6. Jiang D, Shi B, Gao H, Guo Y, Zhou S, Zhang Y. Associations between reading and writing postures and myopia among school students in Ningbo, China. Front Public Health 2022;10:713377.
7. Ramiro-Cortijo D, Singh P, Liu Y, Medina-Morales E, Yakah W, Freedman SD, et al. Breast Milk Lipids and Fatty Acids in Regulating Neonatal Intestinal Development and Protecting against Intestinal Injury. Nutrients 2020;12:534.
8. Nguyen MTT, Kim J, Seo N, Lee AH, Kim YK, Jung JA, et al. Comprehensive analysis of fatty acids in human milk of four Asian countries. J Dairy Sci 2021;104:6496-507.
9. Hoffman DR, Boettcher JA, Diersen-Schade DA. Toward optimizing vision and cognition in term infants by dietary docosahexaenoic and arachidonic acid supplementation: a review of randomized controlled trials. Prostaglandins Leukot Essent Fatty Acids 2009; 81:151-8.
10. Normia J, Niinivirta-Joutsa K, Isolauri E, Jääskeläinen SK, Laitinen K. Perinatal nutrition impacts on the functional development of the visual tract in infants. Pediatr Res 2019; 85:72-8.
11. Wu RK, Liang JH, Zhong H, Li J, Pan CW. The Lack of Association of Breastfeeding and Myopia in Children and Adolescents: Finding from a School-Based Study and a Meta-Analysis of the Literature. Breastfeed Med 2019;14:580-6.
12. Bozkurt E, Bozkurt HB, Üçer MB. Comparative Effect of Feeding Human Milk as Opposed to Formula on Visual Function and Ocular Anatomy. Breastfeed Med 2019; 14:493-8.
13. Chong YS, Liang Y, Tan D, Gazzard G, Stone RA, Saw SM. Association between breastfeeding and likelihood of myopia in children. JAMA 2009;293:3001–2.
14. Sham WK, Dirani M, Chong YS, Hornbeak DM, Gazzard G, Li J, et al. Breastfeeding and association with refractive error in young Singapore Chinese children. Eye 2010; 24: 875-80.
15. Shirzadeh E, Kooshki A, Mohammadi M. The relationship between breastfeeding and measurements of refraction and visual acuity in primary school children. Breastfeed Med 2016;11:235-8.
16. Tajbakhsh Z, Talebnejad MR, Khalili MR, Masoumpour MS, Mahdaviazad H, Mohammadi E, et al. The prevalence of refractive error in schoolchildren. Clin Exp Optom 2022;105:860-4.
17. Liu S, Ye S, Wang Q, Cao Y, Zhang X. Breastfeeding and myopia: A cross-sectional study of children aged 6-12 years in Tianjin, China. Sci Rep 2018;8:10025.
18. Shoji H, Shimizu T. Effect of human breast milk on biological metabolism in infants. Pediatr Int 2019;61:6-15.
19. Huo L, Qi Y, Zhao S. Refractive errors and risk factors for myopia in infants aged 1-18 months in Tianjin, China. BMC Ophthalmol 2021;21:403.

Evaluation of Eye Consultations Requested From the Pediatric Emergency Service: Experience of A Tertiary Center

Pediatrik Acil Servisten İstenen Göz Konsültasyonlarının Değerlendirilmesi: Üçüncü Basamak Merkez Deneyimi

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ABSTRACT

Objective: In this study, it was aimed to evaluate the reasons for visits, demographic and clinical characteristics of patients, the methods of approach to these patients who visited the pediatric emergency service and were consulted to ophthalmology.

Material and Methods: The files of patients consulted to the Ophthalmology Clinic from Pediatric Emergency Department were analyzed retrospectively. Age and gender distribution of patients, complaints at the time of visits, clinical characteristics, diagnoses, diagnostic examinations and treatment methods were recorded.

Results: Of the 241 patients, 164 (68.0%) were male and 77 (32.0%) were female. The median age was 11.0 (3.0-15.0) years. According to age groups, the highest number of patients was in the 12-17 age group with 117 (48.5%) patients. The most common complaints were foreign body in eye with 30.3% (n=73), eye redness with 10.8% (n=26), sticky eye with 8.3% (n=20) and eyelid swelling with 8.3% (n=20). The most common diagnoses were foreign body (31.1%, n=75), conjunctivitis (26.1%, n=63) and corneal epithelial defect (10.0%, n=24). Considering the distribution of diagnoses by age groups, conjunctivitis was the most common in the 0-5 and 6-11 age groups, foreign body in the 12-17 age group. While medical treatment was given to 59.3% (n=143) of the patients, intervention under local anesthesia was performed for 29.5% (n=71) of the patients. Of the seven patients that were hospitalized, five of them were treated under general anesthesia and two of them received surgical operations.

Conclusion: Pediatric emergency visits with eye complaints in children were most common between 12-17 years of age and the most common cause was foreign bodies in the eye. All hospitalized patients were 0-5 years old and the most common reason for hospitalization was foreign bodies. Clinicians' awareness should be increased on common pediatric eye emergencies accordingly.

Key Words: Consultation, Eye, Foreign body, Pediatric emergency

ÖZ

Amaç: Bu çalışmada, çocuk acil servisine başvuran ve göz hastalıklarına konsülte edilen hastaların başvuru nedenleri, demografik ve klinik özellikleri, bu hastalara yaklaşım yöntemlerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çocuk Acil Servisi'nden Göz Hastalıkları Kliniği'ne konsülte edilen hastaların dosyaları geriye dönük olarak incelendi. Hastaların yaş ve cinsiyet dağılımı, başvuru anındaki şikayetleri, klinik özellikleri, tanıları, tanı muayeneleri ve tedavi yöntemleri kaydedildi.

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by the local Health Sciences University, Hamidiye Scientific Research ethics committee with the date 27.07.2022 and number 22/390.

Contribution of the Authors / Yazarların katkısı: SAYIN O: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***UGUR C:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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Bulgular: Toplam 241 hastanın 164'ü (%68.0) erkek, 77'si (%32.0) kadındı. Ortanca yaş 11.0 (3.0-15.0) yıldı. Yaş gruplarına göre en fazla hasta sayısı 117 (%48.5) hasta ile 12-17 yaş grubundaydı. En sık başvuru şikayeti %30.3 (n=73) ile gözde yabancı cisim, %10.8 (n=26) ile gözde kızarıklık, %8.3 (n=20) ile gözde çapaklanma, %8.3 (n=20) ile göz kapağında şişlikti. En sık konulan tanılar yabancı cisim (%31.1, n=75), konjonktivit (%26.1, n=63) ve kornea epitel defekti (%10.0, n=24)'dü. Tanıların yaş gruplarına göre dağılımına bakıldığında konjonktivit en sık 0-5 ve 6-11 yaş gruplarında, yabancı cisim ise 12-17 yaş grubunda görüldü. Hastaların %59.3'üne (n=143) medikal tedavi uygulandı ve %29.5'ine (n=71) lokal anestezi altında müdahale yapıldı. Hastanede yatan 7 hastanın 5'i genel anestezi altında müdahale ile tedavi edilirken, 2'si cerrahi olarak tedavi edildi.

Sonuç: Çocuklarda göz şikayeti ile acil servise başvurular en sık 12-17 yaş arası olup, en sık neden gözdeki yabancı cisimlerdi. Hastaneye yatırılan hastaların tamamı 0-5 yaş aralığında olup en sık yatış nedeni yabancı cisimlerdi. Klinisyenlerin sık görülen pediatrik göz acilleri konusunda farkındalığı artırılmalıdır.

Anahtar Sözcükler: Konsültasyon, Göz, Yabancı cisim, Pediatrik acil

INTRODUCTION

Pediatric ocular emergencies occupy an important place among the patients who visited the emergency department (1). Eye injuries constitute about 8-14% of all injuries in childhood (2). Annually, more than quarter million children sustain eye injuries that require hospitalization (3). Pediatric population groups are at increased risk because of greater exposure to hazards, decreased ability to avoid or detect hazards, immature motor skills, limited common sense and a lower likelihood of functional recovery following eye injury (4). Ocular injuries are among the leading causes of deprivation amblyopia, bilateral low vision, non-congenital monocular blindness, and long-term acquired visual disability (4,5).

Children typically depend on someone else for personal hygiene and self-care. They may have difficulty recognizing eye symptoms and expressing discomfort such as watering of the eye, infection or foreign body. Most of these eye emergencies can be treated on an outpatient basis with simple medical intervention. Ocular trauma is one of the most common causes of acquired blindness in children (6). Some of them require surgical intervention. Examination of pediatric patients is more specific than adult patients. It requires more careful examination and treatment due to both the difficulty of examination and the inability of pediatric patients to express themselves correctly.

In this study, it was aimed to evaluate the reasons for visits, demographic and clinical characteristics of patients who were presented to the pediatric emergency service and consulted to an ophthalmologist, and the methods of approach to these patients. With this study, we think that we will contribute to informing parents about this issue by identifying common eye emergencies in children. In addition, we think that we will contribute to the determination of early diagnosis and appropriate treatment approach by increasing the awareness of physicians working in the emergency department about common eye emergencies.

MATERIALS and METHODS

The files of patients under the age of 18 who were consulted to the Ophthalmology Clinic from the Pediatric Emergency Department of the Konya City Hospital between January 2021 and June 2021 were retrospectively analyzed from the medical records. Patients who visited to the Pediatric Emergency Department with eye complaints and were treated by a pediatric emergency doctor were not included in the study. All of the 241 patients who were consulted to the Ophthalmology Clinic from the Pediatric Emergency Department were included in this study. Age and gender distribution of 241 patients, complaints at the time of visits, clinical characteristics, diagnoses, diagnostic examinations, and treatment methods were recorded. The patients were divided into 3 different age groups: 0-5, 6-11, 12-17 years old.

This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by local ethics committee with date 02.08.2022 and number 10769.

Statistical analysis

Descriptive statistical methods were used in analyzing the data. Normality tests including Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine the distribution of data. Normally distributed data were specified as mean ± standard deviation, and not normally distributed data were specified as median (25^{th}-75^{th} percentile). Categorical variables were expressed as number (n) and percentage (%). Statistical Package for Social Sciences (SPSS) Windows software (ver. 22; IBM SPSS, Chicago, USA) was used for all statistical analyses.

RESULTS

Of the 241 patients, 164 (68.0%) were male. The median age of the patients was 11.0 (3.0-15.0) years and the youngest age was 9 months, the oldest was 17 years. The highest number of patients was in the 12-17 age group with 117 (48.5%) patients and 7 (2.9%) of the patients were hospitalized (Table I).

The most common reason for the pediatric emergency visits was foreign body in the eye in 30.3% (n=73) of the cases and it was followed by redness in the eye with 10.8% (n=26), sticky eye with 8.3% (n=20) and swelling in the eyelid with 8.3% (n=20) (Table II).

Table I: Distribution of patients by demographic and clinical characteristics.

	n = 241
Gender, n (%)	
Female	77 (32.0)
Male	164 (68.0)
Age, median(25th-75th percentile), years	11.0 (3.0-15.0)
Groups by age range, n (%)	
0-5 years	86 (35.7)
6-11 years	38 (15.8)
12-17 years	117 (48.5)
Hospitalization status, n (%)	
Yes	7 (2.9)
No	234 (97.1)

Table II: Distribution of patients according to complaints.

Complaints	n (%)	Complaints	n (%)
Foreign body	73 (30.3)	Stinging sensation	3 (1.2)
Eye redness	26 (10.8)	Blurred vision	3 (1.2)
Sticky eye	20 (8.3)	Detergent splash	3 (1.2)
Swollen eyelid	20 (8.3)	Low vision	3 (1.2)
Eye bleeding	11 (4.6)	Metal fragment penetration	3 (1.2)
Swollen eye	11 (4.6)	Spray splash	3 (1.2)
Eye weld burn	10 (4.1)	Eye discharge	2 (0.8)
Headache	9 (3.7)	Soil splash	2 (0.8)
Trauma	8 (3.3)	Dust splash	2 (0.8)
Tree branch strike	6 (2.5)	Adhesives splash	2 (0.8)
Perfumes splash	4 (1.7)	Strabismus	2 (0.8)
Eye pain	4 (1.7)	Drug splash	1 (0.4)
Fly intrusion	4 (1.7)	Pen strike	1 (0.4)
Oil solvent splash	4 (1.7)	Plastic fragment penetration	1 (0.4)

Foreign body was the most common diagnosis in the ophthalmologic examinations of the patients (31.1%, n=75). It was followed by conjunctivitis (26.1%, n=63), corneal epithelial defect (10.0%, n=24), subconjunctival hemorrhage (5.8%, n=14) and preseptal cellulitis (3.3%, n=8). Considering the distribution of diagnoses by age groups, conjunctivitis was the most common in the 0-5 and 6-11 age groups, foreign body in the 12-17 age group. Normal ophthalmologic examination findings were present in 7.5% (n=18) of the patients (Table III).

It was observed that the biomicroscope method was mostly used (78.8%, n=190). While medical treatment was given to 59.3% (n=143) of the patients, intervention under local anesthesia was performed for 29.5% (n=71) of the patients. No treatment was required for the 18 (7.5%) patients with normal eye examination findings (Table IV).

Seven (2.9%) patients were hospitalized. Five of them were hospitalized for foreign bodies (Table V). The mean age of hospitalized patients was 3.4±1.5 years and all hospitalized patients were between 0-5 years old. While five of the hospitalized seven patients were treated with intervention under general anesthesia, two were treated with surgical treatment.

Table III: Distribution of diagnoses made after ophthalmology consultation according to age groups.

Diagnoses	0 – 5 years*	6 – 11 years*	12-17 years*	Total*
Foreign body	7 (2.9)	6 (2.5)	62 (25.7)	75 (31.1)
Conjunctivitis	37 (15.4)	10 (4.1)	16 (6.6)	63 (26.1)
Corneal epithelial defect	9 (3.7)	6 (2.5)	9 (3.7)	24 (10.0)
Normal eye	4 (1.7)	5 (2.1)	9 (3.7)	18 (7.5)
Subconjunctival hemorrhage	8 (3.3)	2 (0.8)	4 (1.7)	14 (5.8)
Preseptal cellulitis	5 (2.1)	1 (0.4)	2 (0.8)	8 (3.3)
Blepharitis	2 (0.8)	1 (0.4)	4 (1.7)	7 (2.9)
Allergic conjunctivitis	1 (0.4)	3 (1.2)	2 (0.8)	6 (2.5)
Hordeolum	3 (1.2)	1 (0.4)	1 (0.4)	5 (2.1)
Papilledema	0 (0.0)	0 (0.0)	4 (1.7)	4 (1.7)
Nasolacrimal duct obstruction	2 (0.8)	0 (0.0)	0 (0.0)	2 (0.8)
Herpes infection	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.8)
Keratitis	2 (0.8)	0 (0.0)	0 (0.0)	2 (0.8)
Corneal abrasion	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.8)
Entropion	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Visual impairment	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Hemangioma	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Hyphema	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Cataract	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Chemosis	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Corneal scar	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Pterygium	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Amblyopia	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Total	86 (35.7)	38 (15.8)	117 (48.5)	241 (100)

**n(%)*

Table IV: Distribution of diagnostic examinations and treatment methods applied to the patients.

	n (%)
Diagnostic examinations	
Biomicroscope	190 (78.8)
Ophthalmoscope	51 (21.2)
Total	241 (100)
Treatment methods	
Surgical treatment	2 (0.8)
Intervention under general anesthesia	5 (2.1)
Glasses treatment	2 (0.8)
Intervention under local anesthesia	71 (29.5)
Medication	143 (59.3)
No treatment	18 (7.5)
Total	241 (100)

Table V: Distribution of the diagnoses of hospitalized patients according to age groups.

	0-5 year n (%)	6-11 year n (%)	12-17 year n (%)	Total n (%)
Hordeolum	1 (14.3)	0 (0.0)	0 (0.0)	1 (14.3)
Cataract	1 (14.3)	0 (0.0)	0 (0.0)	1 (14.3)
Foreign body	5 (71.4)	0 (0.0)	0 (0.0)	5 (71.4)
Total	7 (100)	0 (0.0)	0 (0.0)	7 (100)

DISCUSSION

In this study, pediatric emergency visits due to eye complaints were most common between 12-17 years of age and the most common complaint for pediatric emergency visits was foreign bodies in the eye. Furthermore, the most common diagnoses were foreign body in the eye and conjunctivitis, respectively. In addition, all hospitalized patients were 0-5 years old and the most common reason for hospitalization was foreign bodies.

Shah et al. (7) found the male patient rate to be 68.3% in their study on closed-globe injuries. Singh et al. (8) reported that male patients were 68.6% and Archambault et al. (9) reported that male patients were 65.0% in their studies. In our study, pediatric patients who presented to the pediatric emergency department due to any eye complaint were examined. When the patients were evaluated in terms of gender, 164 (68%) patients were male and 77 (32%) patients were female. The fact that boys are more active and courageous and spend more time outside the home than girls may cause them to be more exposed to eye infections and injuries.

In the study of Alim et al. (10) including all age groups, conjunctivitis was the most common diagnosis, while in the study of Üstündağ et al. (11) it was conjunctival hyperemia. In our study, foreign body in the eye (31.1%) was the most frequently recorded emergency diagnosis, followed by conjunctivitis (26.1%) and corneal epithelial defect (10.0%). Considering the distribution of diagnoses by age groups, conjunctivitis was the most common in the 0-5 and 6-11 age groups, and foreign body in the 12-17 age group. Our interpretation of the foreign body and conjunctivitis being more common is as follows: Small objects are easier to enter into the eye because the eye is open to the external environment. Conjunctivitis can be seen more frequently because children do not follow hygiene rules.

In the study of Ligget et al.(12) it was reported that 1.3% of the emergency department visits were due to eye trauma. In the study of Alim et al. (10) this rate was found to be 2.3%. In our study, the rate of patients who visited the pediatric emergency department due to eye trauma was found to be 3.3%.

When the pediatric ophthalmic complaint related emergency department visits are examined in detail, the most common complaints were foreign body in eye (30.3%), eye redness (10.8%), sticky eye (8.3%) and swollen eyelid (8.3%). Kaplan et al. (13) found the exposure to chemical substance rate to be 5.8% in their study. In our study, it is seen that the number of patients who were exposed to chemicals such as detergents, drugs, perfumes, spray, oil solvents and adhesives into their eyes was 17 (7.1%).

In the study of Kaplan et al. (13) 90.1% of the patients were treated with simple medical intervention, 7.2% were treated with advanced medical treatment, 2.4% with simple surgical intervention and 0.3% with advanced surgical intervention. In our study, 59.3% of the patients were treated with medical treatment and 29.5% were treated under local anesthesia. Surgical treatment was performed in two patients; one for cataract and one for hordeolum. Foreign bodies were removed under general anesthesia in five patients because they were very young and examination of the patients were difficult.

One of the limitations of our study is that it is a single-center. The second is that it is a retrospective study. Another limitation is that, the patients who visited the pediatric emergency service with eye complaints and were treated by a pediatric emergency doctor were not included in our study.

CONCLUSION

Visits to the pediatric emergency department with eye complaints in children were most common between 12-17 years of age, and the most common cause was foreign bodies in the eye. All hospitalized patients were 0-5 years old and the most common reason for hospitalization was foreign bodies. Clinicians' awareness should be increased on common pediatric eye emergencies accordingly.

REFERENCES

1. Matsa E, Shi J, Wheeler KK, McCarthy T, McGregor ML, Leonard JC. Trends in US Emergency Department Visits for Pediatric Acute Ocular Injury. JAMA Ophthalmol 2018;136:895-903.
2. Qayum S, Anjum R, Rather S. Epidemiological profile of pediatric ocular trauma in a tertiary hospital of northern India. Chin J Traumatol 2018;21:100-3.
3. Zhang Y, Feng K, Yan H. Epidemiological Characteristics of Pediatric Ocular Trauma in China: A Multicenter Retrospective Hospital-Based Study. J Ophthalmol 2022;2022:4847027.Availablefrom:URL:https://www.hindawi.com/journals/joph/2022/4847027/
4. Puodžiuvienė E, Jokūbauskienė G, Vieversytė M, Asselineau K. A five-year retrospective study of the epidemiological characteristics and visual outcomes of pediatric ocular trauma. BMC Ophthalmol 2018;18:10.
5. Günaydın NT, Oral AYA. Pediatric traumatic cataracts: 10-year experience of a tertiary referral center. BMC Ophthalmol 2022;22:199.
6. Ahmadi H, Alizadeh Z, Karkhah S, Ghazanfari MJ. Prevalence of Pediatric Ocular Trauma in Northern Iran; An Epidemiological Cross-Sectional Study. Bull Emerg Trauma 2022;10:40-3.
7. Shah SM, Shah MA, Singh R, Rathod C, Khanna R. A prospective cohort study on the epidemiology of ocular trauma associated with

closed-globe injuries in pediatric age group. Indian J Ophthalmol 2020;68:500-3.

8. Singh S, Sharma B, Kumar K, Dubey A, Ahirwar K. Epidemiology, clinical profile and factors, predicting final visual outcome of pediatric ocular trauma in a tertiary eye care center of Central India. Indian J Ophthalmol 2017;65:1192-7.
9. Archambault C, Gabias C, Fallaha N, Bélanger C, Superstein R. Pediatric ocular injuries: a 3-year review of patients presenting to an emergency department in Canada. Can J Ophthalmol 2019;54:83-6.
10. Alim S. The clinical features of eye emergency patients that admitted to emergency department of Tokat State Hospital. J Contemp Med 2014;4:26-8.
11. Ustundag M, Orak M, Guloglu C, Sayhan M B, Ozhasanekler A. Retrospective evaluation of eye injury victims presented to emergency department. Turk J Emerg Med2007;7: 64 -7.
12. Liggett PE, Pince KJ, Barlow W, Ragen M, Ryan SJ. Ocular trauma in an urban population: review of 1132 cases. Ophthalmology 1990;97:581-4.
13. Kaplan AT, Kaymak NZ, Günaydın NT, Oral AY, Şimşek Ş. Epidemiological Evaluation of Pediatric Patients Admitted to the Emergency Ophthalmology Clinic. Bosphorus Med J 2018;5:58-61.

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Türkiye Çocuk Hastalıkları Dergisi

The Impact of the COVID-19 Pandemic On Long Term Behavior Problems in Typically Developing Preschool Children in Turkey

COVİD-19 Pandemisinin Türkiye'de Tipik Gelişen Çocukların Uzun Dönem Davranış Sorunları Üzerindeki Etkisi

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ABSTRACT

Objective: Pandemics such as COVID 19, cause severe stress for both parents and children due to social constraints, changes in daily routines, and economic challenges, and can lead to long-term developmental and behavioral problems in children. We evaluated the behavioral problems of typically developing healthy children at the end of the second year of the pandemic, as well as the effect of family sociodemographic characteristics.

Material and Methods: This case-control study included 28 children between the ages of 18 to 60 months who admitted to Hacettepe University İhsan Doğramacı Children's Hospital between January and February 2022 and 23 children from the pre-pandemic period. All of the children scored normally on the Ages and Stages Questionnaire (ASQ) in all developmental domains. The Child Behavior Check List (CBCL) was completed by parents.

Results: In terms of family sociodemographic characteristics, no significant difference existed between the two groups. Anxiety-depression scores were significantly higher in the post-pandemic group once CBCL scores were assessed (p=0.047). In the final stepwise multiple regression model, maternal education level was significantly associated with lower anxiety-depression scores (p=0.030). It was revealed that a maternal education level above high school reduced the anxiety-depression scores by 2.53 points in the post-pandemic group.

Conclusion: Families, pediatricians, and all other healthcare providers need to closely monitor preschoolers, who are among the groups most vulnerable to the negative effects of the pandemic. Additionally, new policies are required to eliminate health and social inequalities that deepen during the pandemic, especially in middle income and developing countries.

Key Words: Behavior problems, Children, COVID-19

ÖZ

Amaç: COVİD-19 gibi pandemiler sosyal kısıtlılıklar, günlük rutinlerdeki değişiklikler ve ekonomik zorluklara bağlı olarak hem ebeveynlerde, hem de çocuklarda strese neden olur ve çocuklarda uzun dönemde gelişimsel ve davranışsal

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Contribution of the Authors / Yazarların katkısı*: *ÖMERCİOĞLU E: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***HAJİYEVA A:*** Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study. ***METE YEŞİL A:*** Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study. ***ZENGİN AKKUŞ P:*** Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study. ***ÖZMERT EN:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar

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sorunlara yol açar. Çalışmamızda pandeminin ikinci yılında tipik gelişen sağlıklı çocuklarda davranış problemlerini ve bu sorunlara aile sosyodemografik özelliklerinin etkisini değerlendirdik.

Gereç ve Yöntemler: Bu vaka kontrol çalışmasına, Ocak ve Şubat 2022 tarihleri arasında Hacettepe Üniversitesi İhsan Doğramacı Çocuk Hastanesi'ne başvuran yaşları 18-60 ay arasında 28 çocuk ve pandemi öncesi dönemden 23 çocuk dahil edildi. Çocukların tümünün Erken Gelişim Evreleri Envanteri değerlendirme sonuçları tüm gelişim alanlarında normaldi. Çocuk Davranışlarını Değerlendirme Ölçeği ebeveynler tarafından dolduruldu.

Bulgular: Aile sosyodemografik özellikleri açısından iki grup arasında anlamlı fark yoktu. Çocuk Davranışlarını Değerlendirme Ölçeği puanları değerlendirildiğinde anksiyete-depresyon puanları pandemi sonrası grupta anlamlı olarak daha yüksekti (p=0.047). Çoklu regresyon modelinde, anne eğitim düzeyi düşük kaygı-depresyon puanları ile anlamlı bir şekilde ilişkiliydi (p=0.030). Anne eğitim düzeyinin lise üstü olmasının pandemi sonrası gruptaki çocuklarda anksiyete-depresyon puanlarını 2.53 puan azalttığı gösterildi.

Sonuç: Aileler, çocuk doktorları ve diğer tüm sağlık çalışanları pandeminin olumsuz etkilerine karşı en savunmasız gruplardan biri olan okul öncesi çocukları yakın izlemelidir. Ayrıca, özellikle orta gelirli ve gelişmekte olan ülkelerde pandemi sürecinde derinleşen sağlık ve sosyal eşitsizliklerin ortadan kaldırılması için yeni politikalara ihtiyaç duyulmaktadır.

Anahtar Sözcükler: Davranış sorunu, Çocuk, COVİD-19

INTRODUCTION

Since 2020, the COVID-19 pandemic has affected the entire world, and many countries have been caught off guard. Government closure measures and policies aimed at reducing population movement and the uncertainty of the pandemic period have led to negative outcomes at the child, family, and service levels. School closures, changes in daily routines, increased screen time, fewer physical activities, economic difficulties, job losses, increased domestic stress, and restricted access to health services all have the potential to damage children's growth and development as well as the mental health of both children and parents (1,2).

Children and adolescents are the most vulnerable groups in terms of mental health. Comprehensive studies have revealed that during shutdown periods, most children and adolescents have an increase in emotional-behavioral issues and are highly burdened by the COVID-19 pandemic (3,4). In preschool children, negative emotional-behavioral circumstances such as crying, sleeping problems/nightmares, oppositional-defiant behaviors, clinginess, and fear that family members could contract the infection were observed, in addition to internalization problems such as emotional reactivity, withdrawn, and anxiety-depression (3,5,6). Anxiety and depression symptoms in school-aged children; irritability, intense depressive symptoms, increased levels of stress, worry, concern, and fear associated with COVID-19 were prominent in adolescents (3,7,8). Studies on preschool children, who respond to stress with a wide range of symptoms due to age-related developmental characteristics and are the most vulnerable group for persistent mental problems if these symptoms are not recognized and treated early, are few in comparison to other age groups (3,6).

Developmental variations in cognitive, verbal, emotional, and social skills are critical for coping with stress, understanding and processing complicated situations such as routine changes and pandemic processes, and responding positively emotionally and behaviorally (3,9). In addition to the individual developmental-behavioral disadvantages of children with acute/chronic diseases, neurodevelopmental disorders, and special education needs, access restrictions to health services and private education institutions, as well as school closures, have exacerbated psychosocial problems. Considerable research has shown that these children had more mental health problems than healthy children during the pandemic's shutdown periods (8,10,11). The 'healthy children' in the research were those who were described as such by the families and who did not have a chronic illness. Studies on the impacts of the pandemic are needed, particularly in children who have been proven to have typical development and behaviors and whose stress coping skills are expected to be better.

Recent research suggests that the acute challenges associated with the COVID-19 pandemic will be long-lasting and the long-term effects of the pandemic on preschoolers are limited (12-14). The goal of this study was to evaluate the behavioral problems of children with typical development 2 years from the start of the pandemic, and to determine how these problems were related to family sociodemographic characteristics.

MATERIALS and METHODS

This study was conducted at Hacettepe University Faculty of Medicine Department of Developmental Pediatrics, and all parents who participated in this research provided written informed consent. The Ethics Committee of the Hacettepe University Faculty of Medicine approved this study (GO 22/615). Children aged 18 to 60 months who visited Hacettepe University general pediatric outpatient clinic for reasons apart from developmental-behavioral issues were evaluated using the Ages and Stages Questionnaire (ASQ) between January and February 2022. The patients evaluated were all term born children with normal growth and developmental milestones and no chronic disease. Furthermore, the children were not followed up on for any behavioral issues. The study group comprised of 28 children who had normal development in communication, gross motor, fine motor, problem solving, and personal social areas as a result of the developmental evaluation. Children

who had developmental delays in any area were monitored for further assessment and not included in this study. The sociodemographic characteristics of the study participants and their families, such as parental age and educational level, was obtained. The Child Behavior Check List (CBCL) was completed by parents. Likewise, the sociodemographic characteristics and CBCL scores of 23 control group children who met all of the following inclusion criteria were established from the control groups of two studies conducted at Hacettepe University Department of Developmental Pediatrics in 2019 (15,16). The following tools were used to conduct screening for developmental and behavioral issues.

The Ages and Stages Questionnaire (ASQ)

The ASQ, one of the most extensively used developmental screening tools in pediatric practice, evaluates children aged 3 to 72 months in the areas of communication, gross motor, fine motor, problem solving, and personal-social development (17). Although the ASQ was designed to be completed by parents, in this study, the researchers scored the items in the questionnaire by asking or observing the child in conjunction with the literature (18). While a score above the cutoff values in all domains is accepted typical development, children with a score below 2 SD in at least one domain are regarded to have a positive screening test for developmental delay. The sensitivity and specificity of the Turkish version of the ASQ are 0.94 and 0.85, respectively (19).

Child behavior checklist for ages 1.5 to 5 years (CBCL/1.5–5)

This instrument is used to identify behavioral and psychiatric issues in children aged 18 to 71 months, and the results are obtained by having parents score own children's behaviors. CBCL/1.5–5, that comprises 100 items, has seven syndrome scores as follows: (i) emotionally reactive, (ii) anxious/depressed, (iii) somatic complaints, (iv) withdrawn, (v) sleep problems, (vi) attention problems, and (vii) aggressive. High scores indicate more problematic behavior. Moreover, the combination of emotionally reactive, anxious/depressed, somatic complaints, and withdrawn scores constitute the "Internalizing Problems score" and the combination of attention problems and aggressive scores constitute the "Externalizing Problems score." The "Total Problems score" is composed of these scores, the seven syndrome scores, and the one item added by the parents (20). Parents completed the CBCL/1.5–5 to evaluate the behavioral difficulties of the children in this study (21, 22).

Statistical analysis

IBM SPSS Version 22.0 was used to perform the statistical analysis. The numerical variables were summarized as median (min–max, interquartile range (IQR)), while categorical variables were reported as frequencies and percentages. The Mann Whitney U test was used to determine the differences between the groups (prepandemic vs. postpandemic children) in continuous variables, whereas the Pearson Chi-square test or Fisher's exact test was used to determine such differences in categorical variables. The relationship among continuous variables was determined by the bivariate Spearman correlation coefficients. A multiple linear regression model was performed to test whether the family sociodemographic characteristics predict child behavior problems after the pandemic. A p-value of less than 0.05 was considered significant.

RESULTS

The median age of the 23 children in the pre-pandemic group was 42 months (IQR: 20), and the median age of the 28 children in the post-pandemic group was 37 months (IQR: 23), with no significant difference between the ages. In terms of family sociodemographic characteristics, no significant difference existed between the two groups (age, educational status, employment status, number of siblings, etc.) (Table I). Anxiety-depression scores were significantly higher in children in the postpandemic group once CBCL scores were assessed. The post-pandemic group had higher scores in the somatic complaints and sleep problems but they did not achieve statistical significance (Table II).

There was no relationship between sociodemographic variables (child age, maternal and paternal age, education level, employment, chronic disease condition, number of siblings and members of the family, birth order of the child) and CBCL scores in the pre-pandemic group. Table III shows the correlation between the sociodemographic characteristics and CBCL scores in the post-pandemic group. Children whose mothers had less than a high school education had significantly higher witdrawn (<high school median:3 IQR:3.5, >high school median:1 IQR:2) , anxiety-depression (<high school median:5 IQR:2.5, >high school median:3 IQR:2), internalization problem (<high school median:15 IQR:10, >high school median:7 IQR:4), and total problem scores (<high school median:43 IQR:34.5, >high school median:27 IQR:23) (respectively; p=0.026, p=0.002, p=0.008, p=0.034). Anxiety-depression (unemployed median:4 IQR:2, employed median: 2 IQR:2.75), somatic complaints (unemployed median:3.5 IQR:2.5, employed median:2 IQR:2.75), and internalizing problem (unemployed median:10 IQR:9, employed median:5.5 IQR:5.5) scores were also higher in children with unemployed mothers (respectively; p=0.006, p=0.038, p=0.017).

Stepwise multiple regression analyses were used to show the important risk factors related to anxiety-depression scores, so variables such as the number of siblings and household members, maternal education level and employment status, and child birth order were included in the model. In the final model, maternal education level was significantly associated with higher anxiety-depression scores (p=0.030). It was revealed that a maternal education level above high school

Table I : Sociodemographic Characteristics of Families

Variable, n(%) or median (minimum-maximum)	Pre-pandemic group (n=23)	Post-pandemic group (n=28)	p
Age (months)	42 (20-60)	37 (24-59)	0.353
Maternal age (years)	33 (25-41)	31 (22-40)	0.160
Maternal education (n)			0.603
≤High school	9 (39.1)	9 (32.1)	
>High school	14 (60.9)	19 (67.9)	
Maternal employment status			0.964
Employed	10 (43.5)	12 (42.9)	
Unemployed	13 (56.5)	16 (57.1)	
Chronic disease in mother			0.061
Yes	7 (30.4)	2 (7.1)	
Paternal age (years)	36 (28-43)	34.5 (27-44)	0.494
Paternal education (n)			0.914
≤High school	8 (34.8)	9 (39.1)	
>High school	15 (65.2)	18 (66.6)	
Paternal employment status			
Employed	23 (100)	26 (96.3)	1
Unemployed	0 (0)	1 (3.7)	
Chronic disease in father			0.270
Yes	6 (26)	3 (11.1)	
Number of sibling	0 (0-3)	0 (0-2)	0.559
Number of members in the family	3 (3-6)	3 (3-6)	0.639
Birth order of the child	1 (1-4)	1 (1-3)	0.817

Table II Distribution of the CBCL* scores before and after the COVID19 pandemic

Scores of child behavior checklist	Pre-pandemic group (n=23)	Post-pandemic group (n=28)	p
Emotionally reactive	2 (0-5)	2 (0-8)	0.794
Anxiety/depression	2 (0-6)	3 (0-8)	0.047
Somatic complaints	1 (0-9)	3 (0-9)	0.057
Withdrawn	1 (0-4)	1 (0-5)	0.590
Sleep problems	3 (0-7)	3.5 (0-14)	0.067
Attention problems	4 (0-6)	3 (0-7)	0.729
Aggressive behavior	7 (0-16)	8.5 (2-20)	0.171
Internalizing problem score	6 (0-19)	9 (1-26)	0.146
Externalizing problem score	9 (0-22)	11 (3-24)	0.271
Total problem score	26 (0-58)	31.5 (10-71)	0.097

Median value and minimum–maximum values are presented, p<0.05 is significant, ***** *Child Behavior Checklist*

reduced the anxiety-depression scores by 2.53 points (95% confidence interval (CI): (-4.143) – (-0.921)).

DISCUSSION

Pandemic periods, such as COVID-19, cause severe stress for parents and children due to social restrictions, infection risk, and economic difficulties, and could be considered as adverse childhood experiences (ACEs) (23,24). Eventually, toxic stress develops once children's negative experiences and stress load persist as well as in the absence of the protective buffering effect of a supportive caregiver relationship. It is critical to understand and identify the effects of the pandemic on preschool children, particularly given that toxic stress can cause permanent deterioration and changes in learning (cognitive, language, social emotional skills), behaviors, and physical health, particularly in early childhood when brain plasticity is at its peak (25). The mid-long-term effects of the pandemic following the acute closure processes are still being researched in this context.

In this study, preschoolers' anxiety-depression scores at the end of the second year of the pandemic were shown to be statistically significantly higher than they were prior to the pandemic. In the comprehensive COPSY South Tyrol 2021 study, which investigated children and adolescents aged 7

Table III: Correlations between the sociodemographic characteristics and CBCL scores in the post-pandemic group

		1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Child age	1.000													
2	Number of sibling	.166	1.000												
3	Birth order of the child	.137	.808**	1.000											
4	Number of members in the family	.066	.911**	.599**	1.000										
5	Emotionally reactive	.302	.270	.117	.254	1.000									
6	Anxiety/depression	.157	.478*	.326	.413*	.579**	1.000								
7	Somatic complaints	-.024	.244	.195	.210	.488**	.575**	1.000							
8	Withdrawn	.458*	.210	-.128	.222	.553**	.318	.232	1.000						
9	Sleep problems	.325	-.066	-.193	-.063	.457*	.521**	.296	.263	1.000					
10	Attention problems	-.131	-.218	-.384*	-.198	-.042	-.163	-.013	.153	-.005	1.000				
11	Aggressive behavior	-.166	.080	-.231	.166	.489**	.397*	.390*	.543**	.398*	.361	1.000			
12	Internalizing problem	.273	.356	.173	.330	.827**	.831**	.778**	.599**	.533**	-.064	.573**	1.000		
13	Externalizing problem	-.168	.024	-.284	.089	.414*	.295	.328	.514**	.340	.609**	.951**	.472*	1.000	
14	Total problem	.151	.181	-.080	.189	.706**	.658**	.650**	.627**	.642**	.218	.824**	.863**	.771**	1.000

**p<0.050, **p<0.010,*

to 19 at the end of the first year of the pandemic, behavior problems, anxiety, depressive symptoms, and psychosomatic symptoms all increased, and mental health issues were more affected negatively in young children (12). In like manner, in the second year of the pandemic, general mental health issues, anxiety, and depressive symptoms in children and adolescents were still greater than they were before the pandemic, according to the longitudinal German COPSY research (26). Preschoolers and school-age children both exhibited higher internalizing problems and post-traumatic stress symptoms in December 2021 than in March 2020, according to another comprehensive study that looked into the behavioral issues of children ages 3 to 13 at four different time points (14). In keeping with the literature, this study emphasizes the long-term impacts of the pandemic on children.

The socioeconomic status of the family and the mental health issues that children and adolescents experience are strongly correlated. These socioeconomic characteristics of the family play a significant role in the adjustment and behavior of both the child and the parents to stressful circumstances. Longitudinal studies revealed that children who lived in persistently low socioeconomic conditions were more susceptible to mental health issues than their peers who did not. The most potent predictors of these mental issues are low household income and low parental education, which are the most critical predictors of socioeconomic level (27, 28). In this study, children of mothers with lower education levels had significantly higher levels of withdrawn, anxiety-depression, internalization, and total problem scores, whereas children of unemployed mothers had significantly higher levels of withdrawn, anxiety-depression, somatic, and internalization problems. It has been demonstrated in studies looking at child behavioural problems during the pandemic that low parental education levels and socioeconomic status are linked to an increase in mental health issues (4,12,26). In addition to the stress caused by economic hardships in families with low socioeconomic status, this situation can be clarified by the relationship between low maternal education level and negative parental practices in areas like communication, child care, and positive discipline (29, 30). Anxiety-depression scores were higher as there were more family members and siblings present in the post-pandemic period, regardless of the fact that this finding did not achieve statistical significance in the multiple regression analysis. The increased number of children and family members at home all through pandemics can exacerbate sibling conflicts, create a complicated home environment, increase caregiver workload, reduce one-on-one time spent with children, and thus increase mental health problems in children (3,13,31).

One of our study's strengths is that it is one of the few studies looking at how the COVID-19 pandemic has affected preschoolers' behavioral issues over the mid-long term. Furthermore, unlike previous studies examining the effects of the pandemic on healthy children, the physical and developmental evaluations of the children in this study were performed using worldwide validated assessment tools, and then healthy children with typical development were included in the study (10, 11, 32). Another strength we have is that the pre-pandemic and post-pandemic groups are equivalent in terms of sociodemographic characteristics and developmental status. The small number of participants is one of the study's limitations. Moreover, having failed to evaluate parental stress, parental self-efficacy, and home environment characteristics, which may be closely related to the factors that cause of behavioral problems in children, was a limitation. As stress and anxiety levels may rise in mothers and fathers during the pandemic period regardless of education level and sociodemographic characteristics, one of the study's limitations is the lack of

information on this subject. Another limitation is the inability to obtain from the families the household income data necessary for a more accurate assessment of socioeconomic status.

It is noteworthy that at the end of the second year of the pandemic, anxiety-depression symptoms in children with typical development, who are thought to have relatively better coping mechanisms with stressful situations, proceed to be higher than prior to the pandemic. Given that it is well known that early behavioral problems frequently persist into adolescence and adulthood, it is crucial to identify and explore these issues. Families, pediatricians, and all other healthcare providers need to closely monitor preschoolers because they are one of the most vulnerable age groups to the extreme stress load that comes with the pandemic process and since they exhibit complex symptoms when stressed. Additionally, new policies are required to eliminate health and social inequalities that deepen during pandemic processes, especially in low-income and developing countries, given that low parental education and socioeconomic characteristics boost these mental problems.

REFERENCES

1. Wang G, Zhang Y, Zhao J, Zhang J, Jiang F. Mitigate the effects of home confinement on children during the COVID-19 outbreak. Lancet 2020;395:945-47.
2. Goldfeld S, O'Connor E, Sung V, Roberts G, Wake M, West S, et al. Potential indirect impacts of the COVID-19 pandemic on children: a narrative review using a community child health lens. Med J Aust 2022;216:364-72.
3. Schmidt SJ, Barblan LP, Lory I, Landolt MA. Age-related effects of the COVID-19 pandemic on mental health of children and adolescents. Eur J Psychotraumatol 2021;12:1901407.
4. Ravens-Sieberer U, Kaman A, Erhart M, Devine J, Schlack R, Otto C. Impact of the COVID-19 pandemic on quality of life and mental health in children and adolescents in Germany. Eur Child Adolesc Psychiatry 2022;31:879-89.
5. Jiao WY, Wang LN, Liu J, Fang SF, Jiao FY, Pettoello-Mantovani M, et al. Behavioral and emotional disorders in children during the COVID-19 epidemic. J Pediatr 2020;221:264-66. e1.
6. Frigerio A, Nettuno F, and Nazzari S. Maternal mood moderates the trajectory of emotional and behavioural problems from pre-to during the COVID-19 lockdown in preschool children. Eur Child Adolesc Psychiatry 2022. https://doi.org/10.1007/s00787-021-01925-0
7. Xie X, Xue Q, Zhou Y, Zhu K, Liu Q, Zhang J, et al. Mental health status among children in home confinement during the coronavirus disease 2019 outbreak in Hubei Province, China. JAMA Pediatr 2020;174:898-900.
8. Samji H, Wu J, Ladak A, Vossen C, Stewart E, Dove N, et al. Mental health impacts of the COVID-19 pandemic on children and youth–a systematic review. Child Adolesc Ment Health 2022;27:173-89.
9. Franks BA. Moving targets: A developmental framework for understanding children's changes following disasters. J Appl Dev Psychol 2011;32:58-69.
10. Tso WWY, Wong RS, Tung KTS, Rao N, Fu KW, Yam J, et al. Vulnerability and resilience in children during the COVID-19 pandemic. Eur Child Adolesc Psychiatry 2020;31:161-76.
11. Geweniger A, Barth M, Haddad AD, Högl H, Insan S, Mund A, et al. Impact of the COVID-19 Pandemic on Mental Health Outcomes of Healthy Children, Children With Special Health Care Needs and Their Caregivers-Results of a Cross-Sectional Study. Front Pediatr 2022;10:759066.
12. Barbieri V, Wiedermann CJ, Kaman A, Erhart M, Piccoliori G, Plagg B, et al. Quality of Life and Mental Health in Children and Adolescents after the First Year of the COVID-19 Pandemic: A Large Population-Based Survey in South Tyrol, Italy. Int J Environ Res Public Health 2022;19:5220 doi: 10.3390/ijerph19095220.
13. Prime H, Wade M, and Browne DT. Risk and resilience in family well-being during the COVID-19 pandemic. Am Psychol 2020;75:631-43.
14. Wenter A, Schickl M, Sevecke K, Juen B, Exenberger S. Children's Mental Health During the First Two Years of the COVID-19 Pandemic: Burden, Risk Factors and Posttraumatic Growth–A Mixed-Methods Parents' Perspective. Front Psychol 2022;13:901205.
15. Zengin Akkus P, Ciki K, Mete Yesil A, Ilter Bahadur E, Karahan S, et al. Developmental and behavioral outcomes of preschool-aged children with biotinidase deficiency identified by newborn screening. Eur J Pediatr 2021;180:217-24.
16. Zengin Akkus P, Gharibzadeh Hizal M, Ilter Bahadur E, Ozmert EN, Eryilmaz Polat S, Ozdemir G, et al. Developmental and behavioral problems in preschool-aged primary ciliary dyskinesia patients. Eur J Pediatr 2019;178:995-1003.
17. Squires J, Potter L, and Bricker D. The ASQ user's guide for the Ages & Stages Questionnaires: A parent-completed, child-monitoring system. 2nd ed. Baltimore: Paul H Brookes Publishing, 1999.
18. Small JW, Hix-Small H, Vargas-Baron E, Marks KP. Comparative use of the Ages and Stages Questionnaires in low-and middle-income countries. Dev Med Child Neurol 2019;61:431-43.
19. Kapci EG, Kucuker S, and Uslu RI. How applicable are Ages and Stages Questionnaires for use with Turkish children? Topics Early Child Spec Educ 2010;30:176-88.
20. Achenbach TM and Rescorla LA. Manual for the ASEBA preschool forms and profiles. Vol. 30. Burlington, VT: University of Vermont, Research center for children, youth, 2000.
21. Erol N, Simsek Z, Oner O, Munir K. Behavioral and emotional problems among Turkish children at ages 2 to 3 years. J Am Acad Child Adolesc Psychiatry 2005;44:80-7.
22. Yurduşen S, Erol N, and Gençöz T. The effects of parental attitudes and mothers' psychological well-being on the emotional and behavioral problems of their preschool children. Matern Child Health J 2013;17:68-75.
23. Araújo LAd, Veloso CF, Souza MdC, Azevedo JMCd, Tarro G. The potential impact of the COVID-19 pandemic on child growth and development: a systematic review. J Pediatr (Rio J) 2021;97:369-77.
24. Bellis MA, Hughes K, Ford K, Rodriguez GR, Sethi D, Passmore J. Life course health consequences and associated annual costs of adverse childhood experiences across Europe and North America: a systematic review and meta-analysis. Lancet Public Health 2019;4:517-28.
25. Shonkoff JP, Garner AS, Committee on Psychosocial Aspects of Child, Family Health Committee on Early Childhood Adoption,

Dependent Care, Section on Developmental Behavioral Pediatrics, et al. The lifelong effects of early childhood adversity and toxic stress. Pediatrics 2012;129:232-46.

26. Ravens-Sieberer U, Erhart M, Devine J, Gilbert M, Reiss F, Barkmann C, et al. Child and adolescent mental health during the COVID-19 pandemic: Results of the three-wave longitudinal COPSY Study. J Adolesc Health 2022;71:570-8.
27. Reiss F. Socioeconomic inequalities and mental health problems in children and adolescents: a systematic review. Soc Sci Medi 2013;90:24-31.
28. Sun J, Singletary B, Jiang H, Justice LM, Lin TJ, Purtell KM. Child behavior problems during COVID-19: Associations with parent distress and child social-emotional skills. J Appl Dev Psychol 2022;78:101375.
29. Altafim ERP, McCoy DC, and Linhares MBM. Relations between parenting practices, socioeconomic status, and child behavior in Brazil. Child Youth Serv Rev 2018; 89:93-102.
30. Fox RA, Platz DL, and Bentley KS. Maternal factors related to parenting practices, developmental expectations, and perceptions of child behavior problems. J Genet Psychol 1995;156:431-41.
31. Fitzpatrick O, Carson A, and Weisz JR. Using mixed methods to identify the primary mental health problems and needs of children, adolescents, and their caregivers during the coronavirus (COVID-19) pandemic. Child Psychiatry Hum Dev 2021;52:1082-93.
32. Cantiani C, Dondena C, Capelli E, Riboldi EM, Molteni M, Riva V. Effects of COVID-19 lockdown on the emotional and behavioral profiles of preschool Italian children with and without familial risk for neurodevelopmental disorders. Brain Sci 2021;11:477.

Relationship Between Obesogenic Family Environment, Children's Smartphone Usage, and Depressive Symptoms

Obezojenik Aile Ortamı ile Çocukların Akıllı Telefon Kullanımı ve Depresif Belirtileri Arasındaki İlişki

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ABSTRACT

Objective: Childhood obesity has become a most common public health problem. We aimed to examine the relationship between obesogenic family practices for childhood obesity, children's obesity, smartphone usage times, and depressive symptoms.

Material and Methods: In the present study, we conducted on 96 families and their children aged 6-14 who applied to our pediatric clinic from October 2020 to July 2021. Parents and children who agreed to participate in the study filled out an online questionnaire containing sociodemographic data, children's weight, and height information, "The Children's Depression Inventory (CDI)," and "Family Nutrition and Physical Activity Screening Tool (FNPA)."

Results: The present study found 80.2% (n=77) of the children were primary school students, and 19.8% (n=19) of them were secondary school students. We found a significant negative correlation between FNPA score and depressive symptoms in primary school students (r and p values; r=-0.276, p=0.015). Obesogenic family environment was correlated with higher depressive scores in primary school children. We also confirmed that primary and secondary school children with obesogenic family environments spent more time on smartphones (p respectively p=0.009, p=0.031).

Conclusion: The FNPA is an easily applicable tool to determine obesogenic family factors. Children with an obesogenic family environment should be carefully evaluated for depressive symptoms and smartphone usage time.

Key Words: Behavior, Children, Depression, Family Environment, Nutrition, Smartphone Use

ÖZ

Amaç: Çocukluk çağı obezitesi günümüzde en yaygın halk sağlığı sorunu haline gelmiştir. Çocukluk obezitesi için obezojenik aile uygulamalarının, çocukluklardaki obezite, akıllı telefon kullanım süresi ve depresif belirtiler ilişkisini incelemeyi amaçladık.

Gereç ve Yöntemler: Bu araştırmayı, Ekim 2020 - Temmuz 2021 tarihleri arasında çocuk kliniğimize başvuran 6-14 yaş aralığında olan 96 çocuk ve onların ailesi ile gerçekleştirdik. Çalışmaya katılmayı kabul eden ebeveynler ve çocuklar, sosyodemografik verilerini, çocukların kilo ve boy bilgilerini, "Çocuklar İçin Depresyon Envanteri (CDI)" ve "Aile Beslenmesi ve Fiziksel Aktivite Tarama Aracı (FNPA)" içeren bir online anketi doldurdular.

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Bulgular: Bu araştırmada çocukların %80.2'sinin (n=77) ilkokul öğrencisi, %19.8'inin (n=19) ortaokul öğrencisi olduğu saptanmıştır. İlkokul öğrencilerinde FNPA puanı ile depresif belirtiler arasında negatif yönde anlamlı bir ilişki bulduk (r ve p değerleri; r=-0.276, p=0.015). İlkokul çocuklarında, obezojenik aile ortamı daha yüksek depresif puanlarla ilişkiliydi. Obezojenik aile ortamına sahip olan ilkokul ve ortaokul çocuklarının akıllı telefonu daha uzun süreli kullandıklarını doğruladık (sırasıyla p=0.009, p=0.031).

Sonuç: FNPA, obezojenik aile faktörlerini belirlemede kolay uygulanabilir bir araçtır. Obezojenik aile ortamına sahip çocuklar, depresif belirtiler ve akıllı telefon kullanım süreleri açısından dikkatle değerlendirilmelidir.

Anahtar Sözcükler: Davranış, Çocuklar, Depresyon, Aile Ortamı, Beslenme, Akıllı telefon kullanımı

INTRODUCTION

Childhood obesity is one of the most critical public health challenges nowadays. Obesity and its related diseases are largely preventable. Thus the prevention of obesity in children requires high priority (1). Ihmels et al. (2) developed the Family Nutrition and Physical Activity (FNPA) tool to determine risky family environmental factors for childhood obesity. Peyer et al. (3) showed the FNPA tool to have high validity in screening for childhood obesity risk. The previous study, conducted in the United States, identified the applicability of the FNPA tool for preventing and treating obesity by determining obesogenic risk factors in normal-weight children and roles as a guide for health professionals to initiate treatments with those currently overweight or obese. Some researchers showed a relationship between the FNPA score and obesity in children (4). We can get information about the obesogenic family environment via this tool.

Childhood obesity treatment is based on some medical and nonpharmacological treatment recommendations. The most critical step in nonpharmacological treatment is identifying the barriers in the family environment that may go against lifestyle changes (5). Some researchers suggested that the family environment plays an essential role in more effective prevention and intervention of childhood obesity (6). In this respect, it is essential to recognize risky family behaviors for childhood obesity, especially in school-age children, and to take precautions to prevent children from obesity (7).

Obesity can bring together other physical and psychological comorbidities (8). An evaluation of 13 longitudinal studies' meta-analyses confirmed the bidirectional relationship between obesity and depression. They found that depressed adolescents had a 70% higher risk of obesity whereas obese adolescents had a 40% higher risk of depression (9). The Centers for Disease Control and Prevention has emphasized the increase in depression in children in recent years and that depression can result in suicide in children (10). Panchal et al. (11) confirmed that parent-child communication was protective against depression in children. Similarly, Whittle et al. (12) suggested the importance of parents in influencing children's health.

Other conditions related to childhood obesity are increasing children's screen time and decreasing physical activity. In the digital world, the child has frequently become using smartphones (13). Children's problematic smartphone use had been associated with poorer mental health and obesity in children (13,14).

The present study aimed to evaluate the relationship between the obesogenic family environment with obesity, smartphone usage, and depressive symptoms in primary and secondary school students.

METHODS

We conducted the present prospective cross-sectional study on children between the ages of 6-14 and their families who applied to the university pediatric clinics between October 01, 2020, and January 01, 2021. We predicted that approximately a total of "600 children" would refer to the outpatient clinic during the study, and we calculated the target sample size to be at least "68"(15).

We planned to include the present study with seven-year-old children because the "Children's Depression Inventory" can be conducted above seven years old. One hundred twenty children family pairs applied to our pediatric clinic; 24 did not fill out the questionnaire, and 96 children and their families who filled out an online questionnaire were included in the study.

We sent these questionnaire forms to families via e-mail. The online questionnaire consisted of the families' sociodemographic characteristics, children's height and weight information, "The Children's Depression Inventory (CDI)," and "Family Nutrition and Physical Activity Screening Tool." Participants (families-children) filled out the online questionnaire. The children and their families filled together the "Children's Depression Inventory", and the parents completed the rest.

According to parents-reported, we recorded the children's weight and height as values on March 2020 and March 2021. The body mass index (BMI) was calculated using the weight/height2 formula. The percentiles of the BMI were grouped according to Turkish children's reference values (16). We classified children's weight status according to de BMI percentiles. We defined underweight (below the 5th percentile), normal (the 5th-85th percentile), overweight (the 85-95 percentile), and obese (above the 95th percentile). We recorded the children's values in March 2020 as their weight status before the pandemic and their values in March 2021 as their weight status during the pandemic.

We asked about the children's smartphone usage times except for study and homework. Responses scored; less than an hour/day =1 point, 1-2 hour= 2 points, 2-3 hours/day=3 points, >3 hour=4 points.

Ihmel et al. (2) developed the Family Nutrition and Physical Activity Screening Tool (FNPA) to determine the obesogenic family and child practices. Özdemir et al. (17) conducted Turkish validity and reliability study of FNPA. The FNPA contains ten risk factors with two items each (Family meals, family eating habits, food preferences, beverage preferences, restriction/reward, screen time, healthy environment, family activity, child activity, and family schedule/sleep pattern). The FNPA aims to determine risky family and child behaviors regarding child nutrition and obesity. The FNPA scores ranged from 20 to 80. There is no cut-off value for FNPA scores. Higher scores show a less obesogenic family environment. The present study's mean FNPA score was 57.7±7.1 (39-73).

The Children's Depression Inventory (CDI) is a 27-item tool to determine depressive symptoms in children aged 7–17. Oy (18) conducted the reliability and validity of The CDI in Turkish children. The items are scored as 0, 1, or 2. Higher total scores show increased depressive symptoms in children. We used the Children's Depression Inventory (CDI) to determine the children's depressive symptoms.

The study was approved by Başkent University Medical and Health Sciences Research Board (28.04.2021-21/82).

Statistical Analysis

Numerical variables were evaluated for normality of data distribution by performing the Shapiro- Wilk test. Categorical measurements were summarized as numbers (n) and percentages (%), whereas numerical measurements were summarized as the mean±standard deviation and median (minimum-maximum). Since the assumption of normal distribution was not met, Kruskal Wallis tests were applied to compare the differences among the response groups regarding scale variables. The relationship between the scale scores was used with the Spearman correlation test. The categorical data analysis was done using the Pearson Chi-Square test and Generalized Fisher (Fisher-Freeman-Halton) Exact test. The Mc-Nemar-Bowker test was used to analyze the relationship between the children's screen time before and during the pandemic. Values with a $p < 0.050$ were considered statistically significant in all tests. Statistical analyses were conducted using SPSS v25.0 software (SPSS Inc., IBM, USA).

RESULTS

The present study found 80.2% (n=77) of the children were primary school students, and 19.8% (n=19) of them were secondary school students (Table I). There was no difference between the two groups in terms of the male/female ratio (p=0.437).

Table I: Sociodemographic data

Sociodemographic data of the parents and children	Frequency n (%)
Mother's Educational Status	
High School and below	21 (21.9)
University	48 (50.0)
Post-graduate	27 (28.1)
Father's Educational Status	
High School and below	19 (19.7)
University	42 (43.8)
Post-graduate	35 (36.5)
Family's Monthly Income	
2800 TL and below	1 (1.0)
2801-5600 TL	15 (15.6)
5600-8400 TL	19 (19.8)
8400 TL and above	61 (63.6)
Marital Status	
Married	84 (87.5)
Divorced	12 (12.5)
Number of Siblings	
-	25 (26.0)
1	65 (67.7)
2	6 (6.3)
Children's Educational Status	
Primary school	77 (80.2)
Secondary school	19 (19.8)
The male/female ratio of the children	
Primary school	37/40
Secondary school	9/10

TL: *Turkish Lira*

We found that 78.1% of mothers and 80.3% of fathers graduated from university or graduate school, most parents (87.5) were married, and most parents' (63.9) monthly income was more than three times the minimum wage. Table I represents the sociodemographic factors of the parents and children. The mean age of the children was 9.0±2.0 (6-14) years, and Female/Male was 1.23 in terms of gender distribution. We analyzed children's depressive scores and FNPA scores according to primary school children (7-10 years old) and secondary school students (11-14).

We found no significant relationship between the sociodemographic characteristics of the parents with the children's educational status (primary school or secondary school), smartphone usage time, and depressive symptom levels (p>0.050).

Table II represents the weight status of primary and secondary school students. We found higher obesity rates in primary school students during the pandemic than before the pandemic (p=0.025). On the other hand, there were no differences in the obesity rates of secondary school children before and during the pandemic (p=0.564).

We found no relationship between primary and secondary school students' obesity with FNPA scores (p values respectively; p= 0.127, p=0.643).

Table III represents the FNPA scores of primary and secondary school students. We confirmed a higher obesogenic family environment in secondary school students than in primary school children (p=0.004). The mean FNPA scores of the primary school children were 58.82±7.02 (Table III).

The present study found that children who more spent time on smartphones had a higher risky family environment for obesity (p=0.009). Similar to primary school students, there was a significant relationship between children's smartphone usage time, and obesogenic family environment in secondary school students (p=0.031). Table IV represents the relationship between FNPA scores and smartphone usage times of the children.

We found a significant negative correlation between FNPA score and depressive symptoms in primary school students (r and p values; r=-0.276, p=0.015). This finding expressed that primary school children with higher obesogenic family environments had more depressive symptoms. But we showed no relationship between obesogenic family environment and depressive symptoms in secondary school students (r and p values; r=-0.457, p=0.065)

We also showed higher depressive symptoms in secondary school students than in primary school children (p=0.018). The CDI scores of the secondary school students were 11.4±8.46 (Table III). We found no relationship between children's obesity and depressive symptoms (p=0.647). We found no significant relationship between children's smartphone usage times, and depressive scores (p=0.162).

Table II: The weight status of primary and secondary school children

Body Mass Percentile	Before the pandemic	During the pandemic	p
Primary School Students			
Underweight*	5 (6.5)	5 (6.5)	
Normal*	41 (53.2)	37 (48.1)	0.025
Overweight*	20 (26.0)	13 (16.9)	
Obese*	11 (14.3)	22 (28.6)	
Secondary School Students			
Underweight*	-	-	
Normal*	13 (68.4)	14 (73.7)	0.564
Overweight*	4 (21.1)	3 (15.8)	
Obese*	2 (10.5)	2 (10.5)	

***** *n(%)*

Table III: Depressive symptoms and obesogenic family environment of the primary and secondary school students

Scores	Primary School Students	Secondary School Students	p
FNPA Total Score			
Mean ± SD	58.82±7.02	53.55±6.08	0.004*
Median (min-max)	59 (39-73)	56 (42-62)	
Beck Total Score			
Mean ± SD	7.61±5.94	11.4±8.46	0.018*
Median (min-max)	6 (1-30)	9.5 (1-37)	

***p<0.050, Mann-Whitney U test, **min**: Minimum, **max:** Maximum, **SD:** Standart Deviation*

Table IV: The relationship between smartphone usage time and FNPA scores of the primary and secondary school children

Smartphone Usage Time	FNPA Scores		
	Mean ± SD	Median (min-max)	p
Primary School Children's Smartphone Usage Times			
< 1 hour	61.8±6.3	62.50 (51-73)	0.009*
1-2 hours	58.18±5.8	59.00 (47-70)	
2-3 hours	55.75±6.2	56.00 (49-67)	
> 3 hours	54.71±7.7	55.50 (39-69)	
Secondary School Children's Smartphone Usage Times			
< 1 hour	57.8±3.3	58.5 (52-62)	0.031*
1-2 hours	-	-	
2-3 hours	58.0±0.1	58.0 (58-59)	
> 3 hours	50.8±6.2	53.1 (42-58)	

***p<0.050, **SD:** Standart Deviation, **min**: Minimum, **max:** Maximum*

DISCUSSION

The family environment plays a critical role in the mental and physical health of the children. Childhood obesity was associated with an obesogenic family practice (4). In this regard, children might be protected from obesity and obesity-related comorbidities by interfering with family practices. To our knowledge, no study examined the relationship between obesogenic family practice with children's depressive symptoms and digital media use. The present study examined the relationship between the obesogenic family environment with obesity, smartphone usage, and depressive symptoms in primary and secondary school students.

Ihmel et al. (2) developed the Family Nutrition and Physical Activity Screening Tool (FNPA) to determine the obesogenic family and child practices. This scale provides information about the high-risk family environment and child behaviors regarding children's obesity. Herbenict et al. (19) suggested that implementing the FNPA tool at a school-based clinic might effectively determine children at high risk for obesity . Tucker et al. (4) conducted a study on 564 5-18 age children; they found a relationship between lower FNPA scores and severe obesity odds in children . On the other hand, Peyer et al. (3) suggested that The FNPA is also used to inform the arrangement of family-centered obesity treatment for children. Unlike previous studies, our present study did not find a relationship between FNPA scores, and obesity in children. We might explain this finding by that we recorded children's weight and height according to the parent's self-report. They might not accurately remember their children's weights and heights.

Risky behavior for obesity in children increased during the COVID-19 pandemic (20,21). The present study confirmed higher obesity rates in primary school students during the pandemic than before. However, we found no differences in the obesity rates of secondary school children before and during the pandemic. Only 19 of the children were secondary school students. Due to this, we might not find a significant increase in obesity rates among secondary school children during the pandemic. Some studies showed that obese children had a high risk for depression or depressive children were more likely to be obese (9). In the literature, there was no study to examine the relationship between obesogenic family environment and children's psychological status. The present study found that primary school children with higher obesogenic family environments had more depressive symptoms. This situation can be explained as follows, a family that shows careless behavior in terms of obesity may also be inattentive in terms of the emotional needs of their child. However, future studies that examine other factors related to the psychological state of the children are needed. We thought this finding contributed to the literature. Unlike primary school children, we showed no relationship between obesogenic family environment and depressive symptoms in secondary school students. The small sample size of secondary school children might explain no significant differences in secondary school children.

In the present study, we found no significant difference between the sociodemographic characteristics of the parents and the children's smartphone usage time and depressive symptom levels. Current studies showed the relationship between family sociodemographic data and children's screen use and behavior (22). Some studies showed that depressive symptoms in school children are associated with certain socio-demographic factors, family socioeconomic status, and family relationships (23,24). The parents conducted in our study had similar sociodemographic characteristics that may have affected this situation. We believe that participants with similar characteristics might make our study meaningful by excluding parenteral factors related to children's depressive symptoms.

Another critical issue is that smartphone use has become popular among children. Children spend more time on smartphones nowadays (25,26). Our present study found that more smartphone usage time was associated with a higher obesogenic family environment in primary and secondary school children. In this process, how long children use smartphones gains importance. Problematic smartphone use can bring some negative consequences. Some studies showed that problematic smartphone use for entertainment was positively associated with obesity (14). Sohn et al. (27) evaluated 41 studies as a systematic review, and they found a significant relationship between depression and problematic smartphone use in adults. Lee et al. (28) found that smartphone addiction was positively related to depression among low-income male students . The present study revealed no relationship between children's smartphone usage time with obesity though there was a relationship between the obesogenic family environment and smartphone usage time of the children. Children with an obesogenic family environment may have healthy body mass index at now, but these children may become obese later in life. The present cross-sectional study might not show the relationship between smartphone use, obesity, and depressive symptoms. Re-evaluating these children after a few years will be more meaningful to determine the long-term effects of the obesogenic family environment like obesity.

On the other hand, the present study showed some differences between primary and secondary school students. We confirmed that higher obesogenic environment, and more depressive symptoms in secondary school students than primary school children. Similar to our study, some studies showed that depression symptoms were more common in older children (29). These differences might be explained small sample size of secondary school students. Future studies with more primary and secondary school students are needed.

In summary, FNPA is a feasible tool in well-child visits to determine risky family environments for childhood obesity. It is known the relationship between FNPA score, and obesity in children. The present study showed a relationship between FNPA scores, children's smartphone usage time, and depressive symptoms. Health professionals might be careful about children with lower scores of FNPA regarding obesity, smartphone use, and psychological status.

CONCLUSION

We found that the risky family environment for childhood obesity was associated with depressive symptom levels in primary school children. The present study also confirmed that obesogenic family practices were related to more smartphone usage time in primary and secondary school students. To our knowledge, no study examined the relationship between obesogenic family practices, smartphone usage time, and depressive symptoms in children. We believe that our research will contribute to science. Future comprehensive studies on parental attitudes, children's behavior, and mental health are needed.

LIMITATIONS

There are several limitations of the present study. The first limitation was the small sample size of secondary school children. We examined the children's weight and height according to the parent's self-report. Families may not remember precisely this information retrospectively. Small sample sizes may overestimate the FNPA impact on children's depression levels. Another limitation of our study is determining the psychological well-being of children using scales Children's

Depression Inventory. We determined the levels of depressive symptoms, not to diagnose depression. For this reason, future studies may need to include child psychiatrists and evaluate the psychological status of the children more clearly.

REFERENCES

1. World Health Organization (WHO). Erişim tarihi: 11 Kasım 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
2. Ihmels MA, Welk GJ, Eisenmann JC, Nusser SM. Development And Preliminary Validation Of A Family Nutrition And Physical Activity (FNPA) Screening Tool. The Int J Behav Nutr Phys Act 2009; 6:14.
3. Peyer KL, Bailey-Davis L, Welk G. Development, Applications, and Refinement of the Family Nutrition and Physical Activity (FNPA) Child Obesity Prevention Screening. Health Promot Pract 2021; 22: 4: 456–61.
4. Tucker JM, Howard K, Guseman EH, Yee KE, Saturley H, Eisenmann JC. Association between the Family Nutrition and Physical Activity Screening Tool and obesity severity in youth referred to weight management. Obes Res Clin Pract 2017;11: 3, 268-75.
5. Morales Camacho WJ, Molina Díaz JM, Plata Ortiz S, Plata Ortiz JE, Morales Camacho MA, Calderón BP. Childhood obesity: Aetiology, comorbidities, and treatment. Diabetes Metab Res Rev 2019; 35: 8: 3203.
6. Bates CR, Buscemi J, Nicholson LM, Cory M, Jagpal A, Bohnert AM. Links between the organization of the family home environment and child obesity: a systematic review. Obes rev 2018; 19: 5: 716-27.
7. Yee KE, Pfeiffer KA, Turek K, Bakhoya M, Carlson JJ, Sharman M, et al. Association of The Family Nutrition and Physical Activity Screening Tool with Weight Status, Percent Body Fat, and Acanthosis Nigricans in Children From A Low Socioeconomic, Urban Community. Ethn Dis2015; 25: 4: 399–404.
8. Smith JD, Fu E, Kobayashi MA. Prevention and management of childhood obesity and its psychological and health comorbidities. Annu Rev Clin Psychol 2020; 16: 351-78.
9. Mannan M, Mamun A, Doi S, Clavarino A. Prospective associations between depression and obesity for adolescent males and females- a systematic review and meta-analysis of longitudinal studies. PLoS One 2016;11: 0157240.
10. Centers For Disease Control And Prevention (CDC). Erişim tarihi: 10 Ekim 2022. Available from: https://www.cdc.gov/Childrensmentalhealth/Depression.Html.
11. Panchal U, Salazar de Pablo G, Franco M, Moreno C, Parellada M, Arango C, et al. The impact of COVID-19 lockdown on child and adolescent mental health: a systematic review. Eur Child Adolesc Psychiatry 2021: 1–27.
12. Whittle S, Bray K, Lin S, Schwartz O. Parenting and child and adolescent mental health during the COVID-19 pandemic. PsyArXiv 2020 https://doi.org/10.31234/osf.io/ag2r7
13. Park JH. Smartphone use patterns of smartphone-dependent children. Child Health Nurs Res 2020; 26: 47-54.
14. Ma Z, Wang J, Li J, Jia Y. The association between obesity and problematic smartphone use among school-age children and adolescents: a cross-sectional study in Shanghai. BMC public health 2021; 21: 2067. doi: 10.1186/s12889-021-12124-6.
15. Alpar R. Uygulamalı İstatistik Ve Geçerlilik-Güvenirlilik. 6. Baskı. Ankara, Detay yayıncılık, 2020.
16. Neyzi O, Günöz H, Furman A, Bundak R, Gokcay G. Türk Çocuklarinda Vücut Ağirliği, Boy Uzunluğu, Baş Çevresi ve Vücut Kitle İndeksi Referans Değerleri. Çocuk Sağlığı ve Hastalıkları Dergisi 2008;51:1-14.
17. Ozdemir S, Terzi O, Dundar C. The Family Nutrition and Physical Activity (Fnpa) Screening Tool: Psychometric Characteristics, Reliability, and Validity in The Turkish Population. J Public Health (Berl) 2021; 30:1-7. DOI:10.1007/s10389-021-01540-y.
18. Oy B. Depression Inventory for Children: A Validity And Reliability Study. Turkish Journal of Psychiatry 1991;2:132-7.
19. Herbenick SK, James K, Milton J, Cannon D. Effects of family nutrition and physical activity screening for obesity risk in school-age children. J Spec Pediatr Nurs 2018; 23: e12229.
20. Stavridou A, Kapsali E, Panagouli E, Thirios A, Polychronis K, Bacopoulou F, Tsitsika A. Obesity in children and adolescents during COVID-19 pandemic. Children 2021; 8: 135.
21. Nogueira-de-Almeida CA, Del Ciampo LA, Ferraz IS, Del Ciampo IR, Contini AA, Ued FDV. COVID-19 and obesity in childhood and adolescence: a clinical review. J Pediatr (Rio J) 2020; 96: 546-58.
22. Aguilar-Farias N, Toledo-Vargas M, Miranda-Marquez S, Cortinez-O'ryan A, Cristi-Montero C, Rodriguez-Rodriguez F, et al. Sociodemographic Predictors Of Changes In Physical Activity, Screen Time, And Sleep Among Toddlers And Preschoolers In Chile During The Covid-19 Pandemic. Int J Environ Res Public Health 2020;18:176.
23. Wang L, Feng Z, Yang G, Yang Y, Wang K, Dai Q, et al. Depressive symptoms among children and adolescents in western China: an epidemiological survey of prevalence and correlates. Psychiatry Res 2016; 246: 267-74.
24. Zhou Q, Fan L, Yin Z. Association between family socioeconomic status and depressive symptoms among Chinese adolescents: Evidence from a national household survey. Psychiatry Res 2018; 259: 81-8.
25. Razak Özdinçler A, Azim Rezaei D, Şeker Abanoz E, Atay C, Aslan Keleş Y, Tahran Ö, et al. The Effect of Technology Addiction on Posture and Body Awareness in School Age Children. Journal of Dependence 2019; 20: 185-96.
26. Dutta K, Mukherjee R, Sen D, Sahu S. Effect Of Covid-19 Lockdown On Sleep Behavior And Screen Exposure Time: An Observational Study Among Indian School Children, Biological Rhythm Research 2020;53: 628-39.
27. Sohn SY, Rees P, Wildridge B, Kalk NJ, Carter B. Prevalence of problematic smartphone usage and associated mental health outcomes amongst children and young people: a systematic review, meta-analysis, and GRADE of the evidence. BMC Psychiatry 2019; 19: 356.
28. Lee J, Lim H, Allen J, Choi G, Jung J. Smartphone Addiction and Depression among Low-Income Boys since COVID-19: The Moderating Effect of Being an Only Child. Healthcare (Basel, Switzerland) 2021;9:1350.
29. Ghandour RM, Sherman LJ, Vladutiu CJ, Ali MM, Lynch SE, Bitsko RH, Blumberg SJ. Prevalence and treatment of depression, anxiety, and conduct problems in US children. J Pediatr 2019; 206: 256-67.

The Relationship of Screen Exposure with Sleep Quality and Self-Regulation Skills in Preschool Children

Okul Öncesi Çocuklarda Ekran Maruziyeti ile Uyku Kalitesi ve Öz-Düzenleme Becerileri Arasındaki İlişki

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ABSTRACT

Objective: We aimed to investigate possible links between screen time, self-regulation skills and sleep quality in preschool children.

Material and Methods: The study was carried out with 140 mothers with 4-6 years old children who visited the family medicine outpatient clinic between March and May 2022. Children's age, gender, existing chronic diseases, the most used technological product, purpose of use, time and duration were recorded. Children's sleep habits were evaluated with the "Children's Sleep Habits Questionnaire (CSHQ)", and their self-regulation skills were evaluated with the "Self-Regulation Skills Scale for 4-6 Years-Old Children (Mother Form) (SrSS)".

Results: The median age of the children in our study was 60 (48-72) months. 75/140 of the participants were girls. The most used technological product at home was the smartphone (48.2%). 64% of the participants reported less than 2 hours screen time, 21.6% of them reported between 2-4 hours and 14.4% of them reported over 4 hours. Educational status of mothers (p=0.003) and fathers (p<0.001) of those with a lot of screen exposure was lower. Delay in falling asleep score, one of the CSHQ subscales, was higher in those with screen exposure over 4 hours (p<0.001). Self-regulation skills scale total score (p=0.001), attention (p=0.014), inhibitory control-emotion (p=0.004), and inhibitory control-behavior (p=0.029) sub-scale scores were lower in children with longer screen time.

Conclusion: Excessive screen exposure in preschool children is associated with delay in falling asleep and low self-regulation skills.

Key Words: Preschool children, Screen exposure, Self-regulation skills, Sleep

ÖZ

Amaç: Bu çalışmanın amacı okul öncesi çocuklarda ekran maruziyeti ile uyku kalitesi ve öz-düzenleme becerileri arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: Çalışma Mart-Mayıs 2022 tarihleri arasında aile hekimliği polikliniğe başvuran 4-6 yaşında çocuğu olan 140 anne ile gerçekleştirildi. Çocukların yaş, cinsiyet, mevcut kronik hastalıkları, en çok kullanılan teknolojik ürün, kullanım amacı, zamanı ve süreleri sorgulandı. Çocukların uyku alışkanlıkları "Çocukların Uyku Alışkanlıkları Ölçeği (CSHQ)" ile, öz-düzenleme becerileri ise 4-6 Yaş Çocuklarına Yönelik Öz-Düzenleme Becerileri Ölçeği (Anne Formu) ile değerlendirildi.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Kütahya Health Sciences University, Non-Interventional Clinical Research Ethics Committee (18.01.2022/ 2022/01-11).

Contribution of the Authors / Yazarların katkısı*: ÖZDEMİR ÇAĞLA:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***KELEŞ S: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study.

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Bulgular: Çalışmamızda çocukların median yaşı 60 (48-72) aydı. Katılımcıların 75/140'ı kadındı. Evde en çok kullanılan teknolojik ürün telefondu (% 48.2). Ekran süresi %64'ünün 2 saat altında; %21.6'sının 2-4 saat arasında; %14.4'ünün 4 saat üzerindeydi. Ekran maruziyeti çok olanların anne (p=0.003) ve babalarının (p<0.001) eğitim durumu daha düşüktü. CSHQ alt ölçeklerinden uykuya dalmada gecikme skoru ekran maruziyeti 4 saat üzerinde olanlarda daha yüksekti (p<0.001). Öz-düzenleme becerileri ölçeği total skor (p=0.001), dikkat (p=0.014), engelleyici kontrol-duygu (p=0.004) ve engelleyici kontrol-davranış (p=0.029) alt-ölçek skorları ekran süresi fazla olan çocuklarda daha düşüktü.

Sonuç: Okul öncesi çocuklarda aşırı ekran maruziyeti uykuya dalmada gecikme ve düşük öz düzenleme becerileri ile ilişkilidir.

Anahtar Sözcükler: Okul öncesi çocuklar, Ekran maruziyeti, Öz-düzenleme becerileri, Uyku

INTRODUCTION

With the increase in the use of electronic/digital screens in recent years, the benefits or harms of children's screen exposure have been the subject of scientific debate. The use of display technologies, the accessibility of devices and total screen exposure are increasing. However, concerns about children's health are also rising due to increased screen time (1).

Screen time is associated with elevated energy intake, metabolic syndrome and obesity, and decreased physical activity in children (2-4). In addition to its physical effects, psychological effects such as restlessness, mood changes and decreased educational performance have also been reported (5). Children's screen time has increased dramatically with the COVID-19 pandemic, so the potential harms of excessive screen time may increase. In line with this, The American Academy of Pediatrics recommends avoiding media use for children younger than 24 months; and limiting it to one hour per day for children aged 2-5 (6,7).

Sleep parameters such as sleep time, bedtime and sleep quality, which are determinants of children›s well-being, are affected by screen time (8-10). Sleep problems not only affect children's cardiometabolic health, but also cause poor cognitive activity and mood disorders (11,12). Although the effect of screen time on sleep is well known, there is limited data on self-regulation skills (13,14).

Self-regulation is a multidimensional concept that includes adapting, avoiding inappropriate behaviors, delaying requests, controlling and regulating emotions, and maintaining attention (15). Self-regulation is often a skill that children develop themselves with external factors. Children's self-regulation skills shape their later life and are associated with academic success (16,17).

The consequences of screen exposure in the preschool period, when self-regulation skills are shaped, may be greater and longer lasting. As a result of excessive screen exposure, maladaptive emotion-regulation may occur in adulthood. The aim of our study is to evaluate the relationship of screen time with sleep and self-regulation skills in preschool children.

MATERIALS and METHODS

This study was designed as a cross-sectional descriptive study and was conducted in a primary health care facility between March and May 2022. The study was approved by Kütahya Health Sciences University, Non-Interventional Clinical Research Ethics Committee (18.01.2022/ 2022/01-11). Mothers with children aged 4-6 years registered in a primary health care institution were informed about the study and 140 mothers consented to participate in the study.

Data collection

Children's Sleep Habits Questionnaire (CSHQ) and Self-regulation Skills Scale (SrSS) were filled out by mothers. Preschool children›s total screen time and time of the day in which the screen exposure occurs (daytime[08:00-17:00], evening [17:00-24:00] or all-day) were asked separately. Screen exposure time was determined by the mother›s statement. Preschool children with physical or mental disabilities or their mothers were not included in the study. Preschool children›s age, gender, screen exposure time, duration, sleep duration and the educational status of parents were also recorded. Screen times were categorized as under 2 hours, 2-4 hours, and over 4 hours.

Children's Sleep Habits Questionnaire

"Children's Sleep Habits Questionnaire (CSHQ)" was used to assess preschool children's sleep habits. Owens et al.(18) developed the questionnaire in 2000 to detect sleep problems in children aged 4-10 years. The scale consists of 33 questions and 6 subscales: parasomnias, sleep anxiety, sleep delay, sleep duration, sleep disruption, bedtime resistance, night awakenings, and daytime sleepiness. Each question is scored between 1-3 (3:Usually; 2:Sometimes; 1:Never/rarely). High scores indicate sleep problems. Fiş et al. (19) conducted a Turkish validity and reliability study in 2010.

Instrument for Measuring Self-Regulation Skills

Preschool children›s self-regulation skills "Self-Regulation Skills Scale for 4-6 Years-Old Children (Mother Form) (SrSS)" was administered. This scale, developed by Erol and İvrendi in 2018, consists of 20 items. The scale has 4 sub-dimensions: inhibitory control-emotion (ICE), working memory, attention, and inhibitory control-behavior (ICB) (20). Each item is scored

between 1-5 (1:Never, 2:Rarely, 3:Sometimes, 4:Often, 5:Always). High scores indicate higher self-regulation ability.

Statistical Analysis

SPSS version 21 (IBM®, Chicago, USA) was used to perform statistical analysis. The normal and abnormal distribution of the variables was analyzed with the 'Shapiro-Wilk test'. Descriptive statistics were expressed as mean and standard deviation in normally distributed numerical data, median (minimum-maximum) in abnormally distributed data, number and percentage in nominal data. "Student's T- test" and "One-way ANOVA" were used in the analysis of normally distributed numerical variables, and "Mann-Whitney U" and "Kruskal-Wallis test" were used in the analysis of non-normally distributed variables. Nominal data were compared using "Chi-square analysis". A p value below 0.05 was considered significant in statistical analyses.

RESULTS

The study was carried out with 140 participants. The mean age of the participants was 58. ±9.7 months (range 48-72 months). The female/male ratio was 1.15/1. The education level of 21.4% of the mothers and 17.1% of the fathers was primary education. The most frequently used technological devices by preschool children were smartphones (47.9%) and TV (35%). Technological devices were frequently used during the daytime (73.6%). Education was cited as the reason for screen exposure in only 8.6% of preschool children. Screen time was less than 2 hours in 64.3% of children, 2-4 hours in 21.4%, and over 4 hours in 14.3%.

Table I shows the demographic characteristics, screen exposures, SrSS and CSHQ results of preschool children.

When preschool children were grouped according to screen time, no difference was observed in terms of age and gender. However, the education level of mothers (p=0.003) and fathers (p<0.001) of those with a screen time of 4 hours or more was lower. Sleep time delay score from CSHQ subscales was higher than those with screen time of 4 hours or more.

When categorized according to the duration of screen exposure, there were significant differences between the groups in terms of total score and; ICE, attention, and ICB subscales of the SrSS. ICE, ICB and attention were significantly lower in those with screen exposure over 4 hours compared to those with less than 2 hours of screen exposure. Self-regulation skills total score (p=0.001), attention (p=0.014), ICE (p=0.004) and ICB (p=0.029) scores were lower in those with a screen time longer than 4 hours (Table II).

Table I: Descriptive characteristics of the participants.

Characteristic n=140	n (%)
Gender, girls	75 (53.6)
Mother's education level	
High school or above	110 (78.6)
Primary education	30 (21.4)
Father's education level	
High school or above	116 (82.9)
Primary education	24 (17.1)
Monthly income of the family*	
> minimum wage	106 (75.7)
< minimum wage	34 (24.3)
The most used technological product by children	
Phone	67 (47.9)
Television	49 (35.0)
Tablet or computer	22 (15.7)
Other	2 (1.4)
Children's exposure time	
Daytime	103 (73.6)
Evening	33 (23.6)
All-day	4 (2.9)
Children's intended use	
Watching videos	77 (55.0)
Playing games	58 (41.4)
Education	12 (8.6)
Children's screen time	
< 2 hours	90 (64.3)
2-4 hours	30 (21.4)
>4 hours	20 (14.3)
Sleep time (hours)†	10 (5-14)
SrSS†	78.5 (37-100)
Attention	24 (3-40)
Working memory	22 (5-25)
ICE	20 (5-25)
ICB	13 (4-21)
CSHQ†	50 (36-68)
Bedtime resistance	12 (6-18)
Sleep anxiety	7 (4-15)
Sleep duration	5 (3-9)
Delay in falling asleep	2 (1-3)
Night awakenings	4 (3-8)
Parasomnias	8 (6-19)
Asleep respiratory disturbance	3 (3-9)
Daytime sleepiness	11 (6-21)

:** *4.250 TL (Year 2022),* **†:** *Median (Min-Max,* ***CSHQ: *Children's Sleep Habits Questionnaire,* ***SrSS:*** *Self-regulation Skills Scale,* ***ICE:*** *Inhibitory control emotion,* ***ICB:*** *Inhibitory control behavio.*

DISCUSSION

Excessive screen time in preschool children is associated with delay in speech development, lack of physical activity, obesity, attention deficit and hyperactivity, and decrease in cognitive functions (21-23). A rise in screen time has been observed in preschool children during the coronavirus pandemic. Therefore, the possible consequences of screen exposure in preschool children have become more significant. Although there is a large amount of data on the negative effects of screen exposure, its

Table II: The relationship between screen time and demographic characteristics, sleep habits and self-regulation skills.

Characteristic	Screen time			p	
	<2 hours	2-4 hours	>4 hours		
Age†	57.7±9.6	59.4±11.0	60.6±8.2	0.438	A** B** C**
Gender, girls§	53 (58.9)	14 (46.7)	8 (40)	0.214	A** B** C**
Sleep duration (hours)‖	10 (5-14)	10 (8-12)	10 (9-12)	0.548	A** B** C**
Mother's education level, Primary education§	15 (16.7)	5 (16.7)	10 (50.0)	0.003	A** B* C*
Father's education level, Primary Education§	8 (8.9)	4 (13.3)	12 (60)	<0.001	A** B* C*
CSHQ ‖	50 (38-68)	51.5 (36-66)	48 (40-64)	0.134	A** B** C**
Bedtime resistance	11 (6-17)	12 (6-18)	11.5 (9-15)	0.309	A** B** C**
Sleep anxiety	7 (4-15)	8 (4-12)	6 (4- 11)	0.174	A** B** C**
Sleep duration	5 (3-9)	6 (3-8)	7 (3-8)	0.205	A** B** C**
Delay in falling asleep	1 (1-3)	2 (1-3)	3 (1-3)	<0.001	A** B* C*
Night awakenings	4 (3-8)	4 (3-7)	3 (3-7)	0.366	A** B** C**
Parasomnias	8 (6-14)	8 (7-14)	8 (7-19)	0.788	A** B** C**
Asleep respiratory disturbance	3 (3-9)	3 (3-8)	3 (3-5)	0.702	A** B** C**
Daytime sleepiness	12 (6-21)	12 (8-20)	11 (8- 13)	0.123	A** B** C**
SrSS ‖	80 (46-100)	77 (57-94)	67.5(37-95)	0.001	A** B* C*
Attention	24.5 (7-40)	24 (5-30)	19.5 (3-31)	0.014	A** B* C**
Working memory	22.5 (14-25)	22.5 (15-25)	22 (5-25)	0.796	A** B** C**
ICE	20 (5-25)	20 (15-25)	15 (5-24)	0.004	A** B* C*
ICB	14 (4-21)	13 (7-20)	11.5 (4-19)	0.029	A** B* C**

***CSHQ** :Children's Sleep Habits Questionnaire, **SrSS:** Self-regulation Skills Scale, **ICE:** Inhibitory control emotion, **ICB:** Inhibitory control behavior.†:Mean±SD, §:n (%),‖: Med (min-max), **A:** <2 hours to 2-4 hours, **B:** <2 hours to >4 hours, **C:** 2-4 hours to >4 hours, *p<0.05; **p>0.05*

relationship to sleep habits and self-regulation skills is not fully known (24-26).

Preschool children›s self-regulation skills are an important developmental stage. Self-regulation, which is the ability to control behavior, thoughts and emotions, is a determinant in academic success and social-emotional competence in later life. However, screen exposure can negatively affect self-regulation skills. In our study, it was observed that preschool children with more screen exposure had worse self-regulation skills. More screen time was also associated with worse self-regulation skills in attention, emotion, and behavioral control. A limited number of studies evaluated screen exposure and self-regulation skills (13, 14). Screen exposure can affect the self-regulation skills of preschoolers, leading to negative consequences in their later lives. Munzer et al. (13) evaluated the effect of screen time on various self-regulation skills in preschool children. In the study, it was reported that the ability to delay gratification time decreased as the screen time increased. Self-regulation skills are provided by the integration and functionality of many emotional and behavioral patterns. Oflu et al. (25) recently reported that excessive screen exposure was associated with emotional lability. Cliff et al. (14) reported that screen exposure in early childhood is associated with self-regulation skills later in life. This study in a prospective design evaluated 2-year-old children. Unlike Cliff et al. (14), we evaluated self-regulation skills with systematic scales in our study.

Due to the cross-sectional nature of this study, directionality cannot be determined. Screen exposure can be a factor in poor self-regulation skills, but this relationship can also be inverse or bidirectional. Linebarger et al. (27) reported that screen time was more for calming in children with difficult temperament, while Cliff et al. (14) stated that the relationship between self-regulation skills and screen exposure was bidirectional. In prospective studies, the cause-effect relationship between screen exposure and self-regulation skills can be clarified.

Screen time can affect children›s sleep habits. Excess screen time is associated with circadian discrepancy of sleep, disturbed sleep, and later bedtimes (28-30). In our study, the CSHQ subscale delay in falling asleep score was higher in children with a screen time of more than 4 hours. Foley et al. (31) reported that participants with a later sleep onset had significantly greater engagement in screen time.

In our study, screen time was 2-4 hours in 21.4% of pre-school children, and over 4 hours in 8.6%. The American Academy of Pediatrics (AAP) guidelines state that for children aged 2-5 years, screen time should be limited to about one hour per weekday, and three hours on the weekends (32). By limiting screen time, the possibility of developmental delay, behavioral problems, and poorer vocabulary acquisition can be reduced (33).

As the accessibility of technology has increased, screen exposure has increased in families from low socioeconomic

status. In our study, screen exposure was higher in children of parents with a low educational level. Previous studies demonstrate that preschoolers from low socioeconomic status engage in more screen time (34). Identifying mechanisms to explain the relationship between socioeconomic status and screen time exposure may be beneficial for the health of preschool children.

Our study had some limitations. Screen time, SrSS and CSHQ scales were filled out by the parents. Children›s actual screen time may differ. There is a need for studies that evaluate screen time with objective criteria. And the causality between screen time and self-regulation skills can be clarified by studies in the prospective design.

In conclusion, high screen time in preschool children is associated with low self-regulation skills and sleep problems. Reported screen times were more than the recommended amount for a significant proportion of preschool children. By reducing screen time, self-regulation skills and sleep quality can be improved.

REFERENCES

1. Stiglic N, Viner RM. Effects of screentime on the health and well-being of children and adolescents: a systematic review of reviews. BMJ Open 2019 ;9:e023191. doi: 10.1136/bmjopen-2018-023191
2. Marsh S, Ni Mhurchu C, Maddison R. The non-advertising effects of screen-based sedentary activities on acute eating behaviors in children, adolescents, and young adults. A systematic review. Appetite 2013;71:259-73.
3. Jahangiry L, Aune D, Farhang MA. Screen time and the risk of metabolic syndrome among children and adolescents: A systematic review and dose-response meta-analysis. Nutr Metab Cardiovasc Dis 2022;32:2483-92.
4. Iannotti RJ, Janssen I, Haug E, Kololo H, Annaheim B, Borraccino A; HBSC Physical Activity Focus Group. Interrelationships of adolescent physical activity, screen-based sedentary behavior, and social and psychological health. Int J Public Health 2009;54 Suppl 2(Suppl 2):191 8.
5. Domingues-Montanari S. Clinical and psychological effects of excessive screen time on children. J Paediatr Child Health 2017;53:333-8.
6. Trott M, Driscoll R, Irlado E, Pardhan S. Changes and correlates of screen time in adults and children during the COVID-19 pandemic: A systematic review and meta-analysis. Ecclinical Medicine 2022;48:101452.
7. American Academy of Pediatrics. (2016, 01 November). Access: https://pediatrics.aappublications.org/content/138/5/e20162591/tab-article-info. Access date: 06.10.2022.
8. Twenge JM, Hisler GC, Krizan Z. Associations between screen time and sleep duration are primarily driven by portable electronic devices: evidence from a population-based study of US children ages 0-17. SleepMed 2019;56:211-8.
9. Kahn M, Schnabel O, Gradisar M, Rozen GS, Slone M, Atzaba-Poria N, et al. Sleep, screen time and behavior problems in preschool children: an actigraphy study. Eur Child Adolesc Psychiatry 2021;30:1793-802.
10. Zhu R, Fang H, Chen M, Hu X, Cao Y, Yang F, et al. Screen time and sleep disorder in preschool children: identifying the safe threshold in a digital world. Public Health 2020;186:204-10.
11. Short MA, Blunden S, Rigney G, Matricciani L, Coussens S, M Reynolds C, et al. Cognition and objectively measured sleep duration in children: a systematic review and meta-analysis. SleepHealth 2018;4:292-300.
12. Goodlin-Jones B, Tang K, Liu J, Anders TF. Sleep problems, sleepiness and daytime behavior in preschool-age children. Journal of Child Psychology Psychiatry 2009;50:1532-40.
13. Munzer TG, Miller AL, Peterson KE, Brophy-Herb HE, Horodynski MA, Contreras D, et al. Media Exposure in Low-Income Preschool-Aged Children Is Associated with Multiple Measures of Self-Regulatory behavior. J Dev Behav Pediatr 2018;39:303-9.
14. Cliff DP, Howard SJ, Radesky JS, McNeill J, Vella SA. Early Childhood Media Exposure and Self-Regulation: Bidirectional Longitudinal Associations. Acad Pediatr 2018;18:813-9.
15. Eisenberg N, Sulik MJ. Emotion-Related Self-Regulation in Children. Teach Psychol 2012;39:77-83.
16. Cuartas J, Hanno E, Lesaux NK, Jones SM. Executive function, self-regulation skills, behaviors, and socioeconomic status in early childhood. PLoS One 2022;17:e0277013.
17. Raver CC, Carter JS, McCoy DC, Roy A, Ursache A, Friedman A. Testing models of children's self-regulation within educational contexts: implications for measurement. Adv Child Dev Behav 2012;42:245-70.
18. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep 2000;23:1043-51.
19. Fiş NP, Arman A, Ay P, Topuzoğlu A, Güler AS, İmren SG, et al. The validity and the reliability of Turkish Version of Children's Sleep Habits Questionnaire. Anatolian Journal of Psychiatry 2010; 11: 151-60.
20. Erol A, Ivrendi A. Developing an Instrument for Measuring Self-Regulation Skills of 4-6 Year -Old Children (Mother Form). PUJE 2018: 44; 178-95.
21. Varadarajan S, Venguidesvarane AG, Ramaswamy KN, Rajamohan M, Krupa M, Christadoss SBW. Prevalence of excessive screen time and its association with developmental delay in children aged <5 years: A population-based cross-sectional study in India. PLoS ONE 2021;16:e0254102.
22. Hosokawa R, Katsura T. Association between mobile technology use and child adjustment in early elementary school age. PLoS ONE 2018;13:e0199959.
23. Raj D, Mohd Zulkefli N, Mohd Shariff Z, Ahmad N. Determinants of Excessive Screen Time among Children under Five Years Old in Selangor, Malaysia: A Cross-Sectional Study. Int J Environ Res Public Health 2022;19:3560.
24. Tezol O, Yildiz D, Yalcin S, Oflu A, Erat Nergiz M, Caylan N, et al. Excessive screen time and lower psychosocial well-being among preschool children. Arch Pediatr 2022;29:61-6.
25. Oflu A, Tezol O, Yalcin S, Yildiz D, Caylan N, Ozdemir DF, et al. Excessive screen time is associated with emotional lability in preschool children. Arch Argent Pediatr 2021;119:106-13.
26. Felix E, Silva V, Caetano M, Ribeiro MVV, Fidalgo TM, Rosa Neto F, et al. Excessive Screen Media Use in Preschoolers Is Associated with Poor Motor Skills. Cyberpsychol Behav Soc Netw 2020;23:418-25.

27. Linebarger DL, Barr R, Lapierre MA, Piotrowski JT. Associations between parenting, media use, cumulative risk, and children›s executive functioning. Journal of developmental and behavioral pediatrics: JDBP 2014;35:367–77.
28. Lan QY, Chan KC, Yu KN, Chan NY, Wing YK, Li AM, et al. Sleep duration in preschool children and impact of screen time. SleepMed 2020;76:48-54.
29. Lin YY, Lee WT, Yang HL, Weng WC, Lee CC, Jeng SF, et al. Screen Time Exposure and Altered Sleep in Young Children With Epilepsy. J Nurs Scholarsh 2020;52:352-9.
30. Hiltunen P, Leppänen MH, Ray C, Määttä S, Vepsäläinen H, Koivusilta L, et al. Relationship between screen time and sleep among Finnish children: results from the DAGIS study. SleepMed. 2021;77:75-81.
31. Foley LS, Maddison R, Jiang Y, Marsh S, Olds T, Ridley K. Presleep activities and time of sleep onset in children. Pediatrics. 2013;131:276-82.
32. American Academy of Child & Adolescent Psychiatry. Media Habits During COVID-19: Children & Teens on Screens in Quarantine. AACAP. 2020. [Accessed on: Dec 4, 2022]. Available in: https://www.aacap.org/App_ Themes/AACAP/Docs/resource libraries/covid-19/ Screen-Time-During-COVID.pdf.
33. McArthur BA, Tough S, Madigan S. Screen time and developmental and behavioral outcomes for preschool children. Pediatric Res. 2022;91:1616-1621.
34. Cameron AJ, Spence AC, Laws R, Hesketh KD, Lioret S, Campbell KJ. A review of the relationship between socioeconomic position and the early-life predictors of obesity. Curr Obes Rep 2015;4:350–62.

Evaluation of Child Development Knowledge Among Medical Students

Tıp Öğrencilerinin Çocuk Gelişimi Bilgilerinin Değerlendirilmesi

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ABSTRACT

Objective: With the developments in the world, a significant decrease in the death rates of chronic or fatal diseases causes the problems that affect the development of children to be seen more frequently. Physicians must be aware of the basic developmental stages and information of children during medical education for early diagnosis and intervention. This study aimed to determine the knowledge of medical students about child development.

Material and Methods: A total of 482 3rd and 4th-year medical faculty students who did not take the Developmental Pediatrics lecture in the Department of Pediatrics of İnönü University Faculty of Medicine between 2018 and 2019 were included in the study. Our study included socio-demographic information and questions on "Caregiver Knowledge of Child Development Inventory".

Results: 227 (47.09%) 3rd year and 255 (52.90%) 4th-year students were included in the study. The mean Caregiver Knowledge of Child Development Inventory total score was 14.44±5.89 for 3rd-year students and 16.10 ± 5.90 for 4th-year students. More than 50% of the third and fourth year students answered 5 of the 10 questions in the developmental skills component section correctly. It was observed that the developmental skills and stimulation component knowledge of the third and fourth year medical students were not sufficient. It was also understood that the general pediatrics courses given in the third year did not increase the knowledge of the fourth year students about child development.

Conclusion: Evaluating the child development knowledge of medical students is important for interventions and studies to ensure that medical students are familiar with and detect developmental delays in infancy and early childhood.

Key Words: Medical Students, Child Development, Medical Education, Developmental Behavioral Pediatrics, Early Childhood Development

ÖZ

Amaç: Dünyada gelişmelerle birlikte, kronik ya da ölümcül hastalıkların ölüm oranlarında önemli bir azalma görülmesi; çocukların gelişimlerini etkileyen sorunların daha sık görülmesine neden olmaktadır. Erken tanı ve müdahalenin

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Ethics Committee of the Faculty of Medicine of Inonu University (11.04.2019/2019-8-24).

Contribution of the Authors / Yazarların katkısı*: *GÜVEN BAYSAL Ş: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***GÜMÜŞ DOĞAN D:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***ARSLAN FN:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study. ***KORTAY CANALOĞLU S:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study.

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gerçekleşmesi için, hekimlerin temel gelişim basamaklarından haberdar olması ve bu tür bilgilerin tıp eğitimi sırasında edinilmesi gerekir. Bu çalışmanın amacı, tıp öğrencilerinin çocuk gelişimi hakkındaki bilgilerini belirlemektir.

Gereç ve Yöntemler: Çalışmaya, 2018- 2019 yılları arasında İnönü Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıklarında Gelişimsel Pediatri dersi almamış toplam 482 3.sınıf ve 4.sınıf tıp fakültesi öğrencileri dahil edilmiştir. Çalışmamızda 1. bölüm sosyo-demografik bilgileri, 2. bölüm; "Bakım Verenlerin Bebeklik ve Erken Çocukluk Dönemi Gelişimi ve Gelişimin Desteklenmesi Bilgisi'ni (CKCDI) ile ilgili soruları içermektedir.

Bulgular: Çalışmaya 227 (%47.09) 3. sınıf, 255 (%52.90) 4.sınıf olmak üzere toplam 482 tıp öğrencisi dahil edildi. Ortalama CKCDI toplam puanı 3 sınıf öğrencileri için 14.44±5.89, 4 sınıf öğrencilerinde ise 16.10 ± 5.90'di. Üçüncü ve 4. Sınıf öğrencilerinin %50'sinden fazlası gelişim basamakları bileşeni bölümündeki 10 sorunun 5'ini doğru yanıtladığı ancak gelişimsel uyaranla destekleme bileşeni bölümündeki 10 sorudan 3. Sınıfların sadece 1 soruya (sayı saymayı öğretme) ve 4. sınıfların ise (sayı saymayı, renkleri öğretme) 2 soruya doğru cevap verdiği ortaya çıkmıştır. Üçüncü ve dördüncü sınıf tıp öğrencilerinin, gelişim becerileri ve uyarılma bilgilerinin yeterli düzeyde olmadığı görülmüştür. Üçüncü sınıfta verilen genel pediatri derslerinin dördüncü sınıf öğrencilerinin çocuk gelişimi hakkındaki bilgilerini artırmadığı da anlaşılmıştır.

Sonuç: Tıp öğrencilerinin çocuk gelişimi bilgilerini değerlendirmek bebeklik ve erken çocukluktaki gelişimsel gecikmelere aşina olmalarını ve gecikmeleri tespit edebilmelerini sağlamak için yapılacak müdahaleler ve çalışmalar için önem arz etmektedir.

Anahtar Sözcükler: Tıp Öğrencileri, Çocuk Gelişimi, Tıp Eğitimi, Gelişimsel Pediatri, Erken Çocukluk Gelişimi

INTRODUCTION

Childhood development is described as an interactive process that results in the progress of cognitive, language, motor, socio-emotional, and self-regulation skills. (1). In order for the early childhood period to be at an optimal level and the developmental trajectory that will continue throughout the life of the child, it is important to monitor development in health services, to identify developmental risks and difficulties early, and to provide individualized and family-centered support (2). The American Academy of Pediatrics recommends all children to be evaluated in terms of developmental risks at certain age periods and states that early diagnosis and intervention of developmental difficulties are critical for the well-being of children and this is the responsibility of physicians (3). Primary care physicians are positioned to play a crucial role in the system of early diagnosis and intervention for young children with developmental delays (4). However, studies show that the knowledge and confidence of primary health care workers are insufficient in the diagnosis and management of children with developmental delays (5).

The focus of the child pediatric traineeships and medical curriculum is acute illness and hospital care. This situation also shows the contradictory situation in medical education (6). Identification of children with developmental delay and health needs are rarely emphasized during medical education (7). Medical students and residents should learn basic concepts related to the development of the child, recognize developmental delays, and develop clinical reasoning skills with appropriate further evaluation (8, 9). There are studies showing that teaching about development and developmental delays improves the knowledge of medical students (8, 10). For example, in a study conducted in Australia at Western Sydney University Faculty of Medicine in 2018, the education and training of medical students regarding child development and developmental disability during the period of pediatric internships were organized in the last decade and it was found to be beneficial as a result (6). Students were more motivated to approach neurodevelopmental examination and developmental stages more competently after this training. This educational opportunity has helped most students to understand developmental follow-up and delay and to understand the shared care provided by educators, parents, and healthcare providers.

Most of the studies on " Knowledge of Child Development" have focused on mothers because the person who can make the diagnosis at the earliest is mothers (11). Apart from mothers, it was also studied with fathers, adults, both parents and pediatric residents (12-16). There are very few studies about medical students' knowledge.

Since today's students will be tomorrow's doctors, it is critical to assess medical students' knowledge of infancy and early childhood development. In this study, it was aimed to determine the level of knowledge of third and fourth year medical students on this subject.

MATERIALS and METHODS

3rd and 4th year students of İnönü University Faculty of Medicine between 2018 and 2019 were included in the study. Required approval was obtained from the university ethics committee. Written consent was obtained from the students. It was observed that 28 of 510 medical students in total did not complete the questionnaire and were excluded from the study. A total of 482 (94.50%) medical students were included in the study.

'Caregiver Knowledge of Child Development Inventory' (CKCDI) was given to 3rd and 4th year medical students who did not receive any training with knowledge of child development. In our faculty, four hours of theoretical and eight hours of practical training are given in the field of developmental pediatrics during the pediatric internship training in the 4th year. As of 2019, a one-

hour 'Introduction to Developmental Pediatrics and Monitoring Child Development' lecture has been started for all 3rd year.

Our study consists of 28 questions. The first 8 questions contain socio-demographic information. Remaining 20 questions consist of CKCDI questions developed in 2007 by Ertem et al (17). Section 1 is the Developmental Skills Component consisting of 10 questions and Section 2 is the Developmental Stimulation Component consisting of 10 questions.

Survey Instrument

CKCDI consists of 20 items, it is easy to apply, understandable and the application time takes about 10 minutes. The scale consists of two components; In the Developmental Skills Component, the person's knowledge about the basic developmental stages of their infants or children is measured. In the Developmental Stimulation Component, the knowledge of when caregivers should provide appropriate stimuli to support the development of their children is measured. The age range of each item in the scale is determined by reference to the "International Guide for Monitoring Child Development (GMCD)"(2). The answers given by the caregivers receive a score of "2" if they are within the specified age range for each item, and a score of "1" if they are 1 month younger or older than the specified age range. All other answers are considered incorrect and receive a score of "0". Results are between 0-40 and a high score is considered as high caregiver knowledge. The internal consistency of the instrument was measured with Cronbach α and its validity was verified with factor analysis (α: 0.61).

Statistical Evaluation of Data

Statistical evaluation of the data was made by using the "Statistical Package For Social Sciences (SPSS 25)" package program. Qualitative variables were expressed as numbers (percentage). Quantitative variables were summarized as mean ± standard deviation. Mann-Whitney U test was used for comparison of the groups. The bivariate relationships between categorical variables were examined using Pearson's Chi-square test. The results with p values below 0.05 were considered statistically significant.

RESULTS

Sociodemographic characteristics

A total of 482 medical students, 227 (47.09%) 3rd year and 255 (52.90%) 4th year, were included in the study. The average age of all students was 22.69 ± 1.42. 49.4% (n: 238) of the students were girls. There was no significant difference in both classes in terms of gender distribution, number of siblings, and family structure (p> 0.050). The sociodemographic information of the cases is given in Table I.

Table I: Descriptive Statistics on Sociodemographic Data

	3th year	4th year	Test statistics*
Number of participants n:482	227 (47.1)‖	255(52.9%)	
Gender			
Female	112 (49.3) ‖	126 (49.4)	p= 0.987
Male	115 (50.7)	129 (50.6)	
Age(years)	22 (20-28)†	23 (20-30)	p< 0.001
Number of siblings ‖			
No sibling	9 (0.003)	8 (0.03)	p= 0.871
One	52 (22.9)	74 (29.01)	
≥ Two	166 (73.1)	173 (67.8)	
Family Structure ‖			
Nuclear	216 (95.2)	236 (95.2)	p= 0.238
Extended	11 (4.84)	19 (7.5)	

**Mann-Whitney U test, †Median (min-max),‖ %*

The average CKCDI total score was 15.32±5.95 for all students, 14.44±5.89 for 3rd year students, and 16.10±5.90 for 4th year students (the highest out of 40). A significant difference was found between 3rd and 4th year students in terms of all scores. The mean score of the section 1 was 9.49±3.47 for all students, 8.85±3.52 and 10.05±3.33 for 3rd year and 4th year students (the highest out of 20). The mean score for section 2 was 5.83 ± 3.78 for all students, 5.59±3.64 and 6.04±3.89 for 3rd year and 4th year students. (the highest out of 20). The total CKCDI score of male students is 14.12±5.65, and the total score of female students is 16.55±6.0. The developmental skills component scores of female and male students were 9.58±3.44 and 9.13±3.47, respectively. A significant difference was found between the scores of the developmental skills component between female students and male students (p= 0.044). The scores of the developmental stimulation component of female and male students were 6.69±3.88 and 4.99±3.48, respectively. A significant difference was found between the scores of the developmental stimulation component (p <0.001), there was also a significant difference between the total CKCDI scores (p <0.001).

More than 50% of the 3rd and 4th year students correctly answered 5 of the 10 questions in the developmental skills component part. Most of the students had insufficient knowledge of the correct age of the developmental stages. It was revealed that only half of all students gave correct answers to only 2 questions out of 10 questions in the part of the developmental stimulation component. (teaching counting (55.0%) and teaching colors (50.2%)). Details are given in Table II.

When the study was evaluated in terms of 3rd year and 4th year students and gender, a significant difference was found between the developmental skills component of female students and male students and the correlation coefficients of the developmental stimulus component scores. In total students, a significant difference was found between correlation coefficients

Table II: The Caregiver Knowledge of Child Development Inventory questions.

	Correct Answers	Medical students' correct answers Total n: 482 n (%)
1. When does a child's brain begin to develop and learn?	in utero or birth	365 (75.7)
2. When do children begin to see?	in utero or birth	303 (62.9)
3. When do children begin to follow a moving person or toy, with their eyes?	birth to 2 months	169 (35.1)
4. When do children begin to vocalise in response to someone talking to them?	birth to 2 months	36 (7.5)
5. When do children begin to smile socially, that is smile into the face of another person?	birth to 2 months	69 (14.3)
6. When do children begin to say single meaningful words?	9–14 months	298 (61.8)
7. When do children begin to play imaginary play like feeding a doll or driving a toy car?	12–24 months	267 (55.4)
8. When do children begin to reach for a toy in front of them?	4–5 months	45 (9.3)
9. When do children begin to grasp tiny things like raisins, with their fingertips?	7–9 months	77 (16.0)
10. When do children begin to walk alone with good co-ordination?	10–15 months	321 (66.6)
11. When should mothers begin to talk to children?	in utero or birth	154 (32.0)
12. When should mothers begin to show colourful objects to children to help them practise reaching? ?	0–4 months	148 (30.7)
13. When should mothers begin to teach children to count?	12–24 months	265 (55.0)
14. When should mothers begin to teach children colours?	12–24 months	242 (50.2)
15. When should mothers start to give children a spoon or a fork to let them eat by themselves?	9–12 months	79 (16.4)
16. When should mothers begin to give children paper and crayons to draw and colour?	12–24 months	196 (40.7)
17. When should mothers begin to let children sit with support?	3–4 months	19 (3.9)
18. When should mothers begin to give children clean and safe objects or toys which they can mouth?	4–6 months	161 (33.4)
19. When should mothers begin to look at childrens' books with their children?	0–6 months	30 (6.2)
20. When should mothers begin to give children clean and safe household items to play with?	4–6 months	45 (9.3)

Table III: Correlations.

	The Developmental Skills Component total score Spearman's rho		
	n	r	p
Developmental Stimulation Component Total Score			
Third year	227	.338	0.000
Fourth year	255	.337	0.000
Boys	244	.315	0.000
Girls	238	.348	0.000
Total	482	.341	0.000

of the developmental skills component and the developmental stimulation component scores (r: 0.341 (p = 0.000)) (Table III)

DISCUSSION

This study is the first to examine the knowledge of medical students about child development in Turkey. The tool we use is in line with the "Care for Development" that WHO promotes worldwide and can be used in conjunction with this intervention (18). We planned to learn how much the 3rd and 4th year medical students know about early childhood basic developmental skills and supporting child development. As a result, while there was a significant difference between the developmental skills component and the total CKCDI scores in terms of both gender and medical education year, a significant difference was found between the scores of the developmental stimulus component scores only in terms of gender. Considering both gender and medical education year, it is seen that the total CKCDI average scores are low. Most of the students knew that brain development and vision began very early in life. They did not know when it should be normal to make sounds when spoken and developmental skills such as social smiling. It was not known by most of the students when the developmental stimulation components should be done.

In the study conducted by Ertem et al. (17), it was determined that many mothers in a representative mothers group in which

1055 mothers were included in two provinces of Turkey did not know when the basic developmental skills of infants and young children emerged and they did not know when to start simple practices that support child development. In this study by Ertem et al.(17), the average CKCDI questionnaire score was 19.2 ± 5.6; It has been found that mothers with higher education and fewer children have higher CKCDI scores. In countries where maternal development information was evaluated by using CKCDI, the total CKCDI scores were found in Turkey (19.2 ±5.6), Nepal (20±4.8) and Tanzania (at the beginning of the study they applied CKCDI to three different groups. The scores are 17.2 ± 4.4/ 13.8 ± 5.0/ 15.7±5.2) (17,19,20). However, in studies conducted in Pakistan (five questions about CKCDI and developmental steps taken by the North American Association of Pediatric Orthopedics on child development), no scores were specified (21). The fact that our scores are lower than mothers in our study can be associated with mothers' efforts to gain knowledge on this issue.

The questions most correctly answered by the students participating in our research in the developmental skills component are "When does a child's brain begin to develop and learn? (75.7% correct answer), When do children start walking? (66.0% correct answer) and When do children start seeing?" (62.9% correct answer). In the research of Ertem et al. (17), most of the mothers (80%) answered the question "When do children start walking?" correctly. In Nepal and Pakistan studies, "When do children start walking?" was the question answered most correctly by mothers (19,21). This can be interpreted as the strong social importance given to young children's mobility skills and the belief by society that the skills in these areas are a critical indicator of whether a child is developing "normally". It also suggests that caregivers may follow the basic developmental steps of movement development and keep them in mind for a long time.

The questions that the students who participated in our study answered at least correctly in the developmental skills component were "When do children begin to vocalize in response to someone talking to them?" (7.5% correct answer), "When do children begin to reach for a toy in front of them?" (9.3% correct answer). Similar to our study, the question " When do children begin to vocalize in response to someone talking to them?" was answered correctly by only one-fifth of the mothers in the study of Ertem et al. (17). In Nepal and Pakistan studies, these questions are among the least correct questions, very similar to our research (19,21). As the reasons for the least correct answers to these questions; children respond by using voices when talking to them over a long period of time, starting almost from the first months and it can be thought that the step of reaching out to the object in front of them may be difficult to observe and determine exactly when this behavior started, especially if the games are not played for this purpose.

The questions most correctly answered by the students participating in our research in the developmental stimulation component were " When should mothers begin to teach children to count? (55%) and " When should mothers begin to teach children colors?" (50.2%). Similarly, in the study of Ertem (17) and Shrestha et al. (19), these questions are among the most correctly answered questions. In the study of Rehman et al.(21), these questions were answered correctly by 57% of the mothers. The most incorrectly answered questions in the developmental stimulation component of the students participating in our research were " When should mothers begin to let children sit with support?" (3.9% correct answer) and " When should mothers begin to look at children's books with their children?" (6.2% correct answer). In the studies of Shrestha et al., these questions are among the least correctly answered questions, similar to our study (19). However, in the research of Rehman. et al. (21), the question "When should mothers begin to let children sit with support? was answered correctly by more than half of the mothers.

It was found that more than 50% of the students gave incorrect answers to 8 questions out of 10 in the section of developmental stimulation component. In the study of Sheresta et al. (19), similar to our study, more than half of the mothers gave incorrect answers in 7 out of 10 items of the developmental stimulation component. In the study of Rehman et al. (21), more than half of the mothers gave incorrect answers to six questions.

The result of not knowing when developmental skills emerge is a missed opportunity to detect developmental delay. In countries where a developmental survey is not easily provided in health services, determining the developmental delay in children falls to the first physician they meet. Primary healthcare providers play an important role in early childhood development, especially as an important access point for children and parents, especially in the process of monitoring child development and identifying children with delays (22). Early detection of developmental problems is an ongoing process of monitoring a child's development. The process, which starts from the moment the child receives primary health care, consists of high-impact strategies. (23). In the study conducted by Ertem et al. (17), mothers identified healthcare professionals as the first resource from which they wanted to get information about the development of their children. Parenting knowledge is thought to be associated with the cognitive and social-emotional development of children, as it allows caregivers to better understand and interact with their children in an appropriate and enriching manner (24).

Children's developmental problems are variable and some are easier to describe than others (25). Recognition of child development and developmental delay provides timely questioning and intervention for children with developmental delay. Despite this, child development and developmental delay were not emphasized in the medical curriculum (6). Little attention is paid to identifying children with developmental delay and their health needs (7). In the study conducted by Comley et al. (26), it was shown that there are important gaps

in knowledge about early child development among newly graduated family physicians. In the study of Çelen Yoldaş et al. (27); 86% of the pediatric residents stated that they did not have sufficient knowledge about child development and they encountered various difficulties in early diagnosis and learning of developmental guidelines. Potential gaps in the early childhood development curriculum were identified at the McMaster University School of Medicine, the Early Years Program was initiated and it was concluded that the overall purpose of this program was achieved (28) Medical faculties should play a very important role in the process of raising knowledgeable doctors about recognizing those with developmental delay, but the medical education curriculum in Turkey does not include teaching child development and developmental delays. Only three universities have a discipline of Developmental Behavioral Pediatrics, and medical students are trained on this subject in these universities (29,30)

In order for early diagnosis and intervention, physicians should be aware of basic diagnostic criteria and such information should be acquired during medical education. The findings in a study conducted by medical students at St George's Hospital Medical School in 2001 with all first and fourth year students show that even towards the end of medical school education, correct knowledge about autism is very limited (31). Primary care physicians play a central role in identifying children with developmental delays. They regularly see children in their early years and therefore have the opportunity to relate children with suspected developmental delay in their practice with appropriate services. However, physicians have acknowledged that they have a role in facilitating children's access to school-based special education services, but that they do not fully understand the eligibility requirements for these services, cannot rely on their knowledge or skills, and do not have the skills to identify children who may be eligible for special education services (32,33).

Identification of children who may be eligible to benefit from healthcare services requires understanding their development needs and special education eligibility criteria. It is also possible that some of the lack of confidence in their knowledge and skills is due to their failure to understand the eligibility criteria (32). This situation may be attributed to the lack of sufficient educational opportunities in child development during and after medical school education (33).

This study has some limitations. Instead of the direct observation method, we used a questionnaire reported from students, which may negatively affect the results to some extent. We did not check whether the knowledge of students increased by applying questionnaires again after the developmental behavioral pediatrics traineeship. We took a sample of students from a single university for the study, so we cannot generalize it for Turkey with these data. Despite these limitations, we believe our findings have invaluable implications for medical curriculum.

CONCLUSION

Medical students need to learn the basic concepts of child development and developmental delay, identify developmental delays and children with special needs through medical history taking and clinical examination and develop appropriate further evaluation and clinical reasoning skills. This study, which observes medical students' knowledge of child development, is important for interventions and studies that will enable medical students to become familiar with and detect developmental delays in infancy and early childhood.

REFERENCES

1. Black MM, Walker SP, Fernald LCH, Andersen CT, DiGirolamo AM, Lu C, et al. Early childhood development coming of age: science through the life course. Lancet 2017;389:77-90.
2. Ozturk Ertem I, Krishnamurthy V, Mulaudzi MC, Sguassero Y, Bilik B, Srinivasan R, et al. Validation of the International Guide for Monitoring Child Development demonstrates good sensitivity and specificity in four diverse countries. Acta paediatrica 2019;108:1074-86.
3. Lipkin PH, Macias MM. Promoting Optimal Development: Identifying Infants and Young Children With Developmental Disorders Through Developmental Surveillance and Screening. Pediatrics 2020;145: e20193449.
4. Sices L, Feudtner C, McLaughlin J, Drotar D, Williams M. How do primary care physicians manage children with possible developmental delays? A national survey with an experimental design. Pediatrics 2004;113:274-82.
5. Clark B, Andrews D, Taghaddos S, Dinu I. Teaching child development to medical students. Clin Teach 2012;9:368-72.
6. McDonald J. Twelve tips for teaching child development and disability to medical students. Med Teach 2018;40:135-9.
7. Trollor JN, Ruffell B, Tracy J, Torr JJ, Durvasula S, Iacono T, et al. Intellectual disability health content within medical curriculum: an audit of what our future doctors are taught. BMC Med Educ 2016;16:105.
8. Fox G, Katz DA, Eddins-Folensbee FF, Folensbee RW. Teaching development in undergraduate and graduate medical education. Child and Adolesc Psychiatr Clin 2007;16:67-94
9. Yeleswarapu S. Padmini PKA, Lourdes MD. Evaluation of a developmental paediatrics teaching programme for medical students. The Asia Pacific Scholar 2019;4: 25–31.
10. Ryan T. Medical students' attitudes towards healthcare for people with learning disabilities (thesis). London: University College London, 2014.
11. Chen Y, Tu B, Huang C-C, Huang C. Improving parenting knowledge through caregiver education in China. Child Care, Health Dev 2021;47:261-8.
12. Scarzello D, Arace A, Prino LE. Parental practices of Italian mothers and fathers during early infancy: The role of knowledge about parenting and child development. Infant Behavior and Dev 2016;44:133-43.
13. Habbash AS, Qatomah A, Al-Doban R, Asiri R. Parental knowledge of children's developmental milestones in Aseer, Saudi Arabia. J Family Med Prim Care 2022;11:5093-5102.

14. McBride DL. The Role of Fathers' in the Care and Development of Their Children. J Pediatr Nurs 2016;31:740-1.
15. Nolan M. A Survey of English Sixth Formers' Knowledge of Early Brain Development. Int Q Community Health Educ 2017;38:27-35.
16. Hammond B, Pressman AW, Quinn C, Benjamin M, Luesse HB, Mogilner L. Evaluating the Keystones of Development-An Online Curriculum for Residents to Promote Positive Parenting in Primary Care. Acad Pediatr 2022;22:151-9.
17. Ertem I, Atay G, Dogan D, Bayhan A, Bingoler B, Gok C, et al. Mothers' knowledge of young child development in a developing country. Child Care, Health and Dev 2007;33:728-37.
18. World Health Organization. Care for child development: improving the care of young children. 2012.
19. Shrestha M, Ulak M, Strand T, Kvestad I, Hysing M. How much do Nepalese mothers know about child development? Early Child Development and Care 2017;189:1-8.
20. Sudfeld CR, Bliznashka L, Ashery G, Yousafzai AK, Masanja H. Effect of a home-based health, nutrition and responsive stimulation intervention and conditional cash transfers on child development and growth: a cluster-randomised controlled trial in Tanzania. BMJ Global Health 2021;6:e005086.
21. Rehman AU, Kazmi SF, Munir F. Mothers' Knowledge about Child Development. Pak Pediatr J 2016;40:176-81.
22. Bauer SC, Smith PJ, Chien AT, Berry AD, Msall M. Educating pediatric residents about developmental and social–emotional health. Infants & Young Children 2009;22:309-20.
23. Figueiras AC, Souza N, Rios VG, Benguigui Y. Monitoring child development (0-6 years) in the IMCI context. Second Edition Washington DC: Pan American Health Organization, 2012.
24. Yue A, Wu M, Shi Y, Luo R, Wang B, Kenny K, et al. The relationship between maternal parenting knowledge and infant development outcomes: Evidence from rural China. Chinese J Sociol 2017;3:193-207.
25. Lin LY, Cherng RJ, Lee IC, Chen YJ, Yang HM, Chen YJ. The agreement of caregivers' initial identification of children's developmental problems with the professional assessment in Taiwan. Res Dev Disabil 2011;32:1714-21.
26. Comley L, Janus M, Marshall D, Niccols A. The early years: child development in undergraduate medical school training. Can Fam Physician 2008;54:876,876.e1-4.
27. Yoldaş TÇ, Şenel S, Abuş HM, Yücel H, Özmert E. Identification of the Place of Developmental Issues in the Educational and Clinical Practices of Pediatric Residents and Affecting Factorsi. Turkish J Pediatr Dise 2021;15:59-64.
28. McCain MN, Mustard JF. The early years study three years later: From early child development to human development: Enabling communities: Founders' Network of the Canadian Institute for Advanced Research; 2011.
29. Dogan D. Gelişimsel Pediyatriye Giriş. In: Yakıncı C, Topal E (ed). Çocuk Sağlığı ve Hastalıkları 2. İnönü Üniversitesi Yayınları, 2020: 187-91.
30. Pekcici EBB, Dogan DG, Akin EO, Buyukavci A, Akpinar F, Hayran G, et al. Referral Trends in Two Pioneering Developmental-Behavioral Pediatric Centers in Turkey. J Dev Behav Pediatr 2021;42:227-33.
31. Shah K. What Do Medical Students Know about Autism? Autism 2001;5:127-33.
32. Hastings EA, Lumeng JC, Clark SJ. Primary care physicians' knowledge of and confidence in their referrals for special education services in 3- to 5-year-old children. Clin Pediatr (Phila) 2014;53:166-72.
33. Nicol P. Using the Ages and Stages Questionnaire to teach medical students developmental assessment: a descriptive analysis. BMC Med Educ 2006;6:29.

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The Reason of Increasing Puberty Precocious Cases During the Pandemic Period: Obesity or Not?

Pandemi Döneminde Artan Puberte Prekoks Vakalarının Nedeni: Obezite mi Değil mi?

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ABSTRACT

Objective: Publications have shown increased rate of precocious puberty and rapidly progressing puberty during the pandemic period. During the pandemic period, obesity has become widespread in children due to sedentary life, an increase in the time spent at home, and prolonged use of mobile devices. Obesity is a significant contributor to early puberty in females.We aimed to investigate whether obesity is a factor in the increase of puberty precocious cases during the pandemic.

Material and Methods: In the study, female patients diagnosed with Puberty precocious /Rapidly Progressive Puberty in our clinic were divided into three groups August 2019-February 2020 before the pandemic (Group1-G1), August 2020-February 2021 during the pandemic (online education - Group2-G2), August 2021-February 2022 during the pandemic (face-to-face education -Group3-G3). The groups were retrospectively compared in terms of clinical, laboratory, and imaging findings.

Results: A total of 495 female patients were included in the study. There was no difference between the groups in terms of age at the presentation. The most common complaint at presentation in the three groups was thelarche. Also, presentation with combination of thelarche and pubarche was more common in G3, and presentation due to menarche was more common in G2 (p=0.011). No difference was found between the groups regarding body weight SDS, and height SDS. The BMI SDS was 0.69±1 SD for all patients, 0.78±0.94 SD for G1, 0.67±1 SD for G2, and 0.67±1 for G3, and the BMI SDS of the groups were comparable (p=0.630). The majority of patients at the presentation were Breast Tanner stage 3. G2 (9%) and G3 (9%) were presented with Breast Tanner stage 4 at a higher frequency compared to G1 (2%). There was no difference between the groups' FSH, LH, estradiol, LHRH test peak FSH, peak LH, and LH/FSH values. There was no difference between the bone ages of the groups at the presentation. The uterus size, right and left ovary volumes of G2 and G3 were significantly bigger than those of G1 (p=0.001). No difference was found between the groups in the rates of precocious puberty and rapidly progressing puberty cases.

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Contribution of the Authors / Yazarların katkısı*: GÜNDOĞAN SÇ:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***KILINÇ UĞURLU A: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***GÜRBÜZ F:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results. ***BÜYÜKYILMAZ G:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***YARDIMCI G:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***BİTKAY A:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***ÖZER E:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***TOKSOY ADIGÜZEL K:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***IŞIK E:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***KOCAAY P:*** Taking responsibility in logical interpretation and conclusion of the results. ***TEPE D:*** Taking responsibility in logical interpretation and conclusion of the results. ***POYRAZ M:*** Reviewing the article before submission scientifically besides spelling and grammar.

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Conclusion: In our study, the age at presentation and BMI were similar pre-pandemic group G1 and during the pandemic, online education (G2) and pandemic face-to-face education (G3). We determined that obesity may not be one of the factors triggering precocious puberty cases during the pandemic period.

Key Words: Covid -19 Pandemic, Obesity, Ovarian size, Puberty precocious, Uterus size

ÖZ

Amaç: Pandemi döneminde puberte prekoks ve hızlı ilerleyen ergenlik olgularında artış olduğunu gösteren yayınlar mevcuttur. Pandemi döneminde sedanter yaşam, evde kalınan sürede artış ve mobil cihaz kullanım sürelerinin uzaması nedeni ile obezite çocuklarda yaygınlaşmıştır. Obezite, kızlarda ergenliği öne çeken önemli bir faktördür. Bu çalışmada pandemi döneminde puberte prekoks ve hızlı ilerleyen ergenlik vakalarının artışında obezitenin bir faktör olup olmadığını araştırılması amaçlanmıştır.

Pandemi döneminde puberte prekoks ve hızlı ilerleyen ergenlik olgularında artış olduğunu gösteren yayınlar mevcuttur. Pandemi döneminde sedanter yaşam, evde kalınan sürede artış ve mobil cihaz kullanım sürelerinin uzaması nedeni ile obezite çocuklarda yaygınlaşmıştır. Obezite, kızlarda ergenliği öne çeken önemli bir faktördür. Bu çalışmada pandemi döneminde puberte prekoks ve hızlı ilerleyen ergenlik vakalarının artışında obezitenin bir faktör olup olmadığını araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmada kliniğimizde Puberte Prekoks/Hızlı ilerleyen ergenlik tanısı alan kız olgular pandemi öncesi Ağustos 2019-Şubat 2020 (Grup1-G1), pandemi dönemi Ağustos 2020-Şubat 2021 (çevirimiçi eğitim- Grup2-G2), pandemi dönemi Ağustos 2021-Şubat 2022 (yüzyüze eğitim-Grup3-G3) olarak üç gruba ayrıldı. Gruplar klinik, laboratuvar ve radyolojik bulguları açısından retrospektif olarak karşılaştırıldı.

Bulgular: Toplam 495 kız hasta çalışmaya alındı. Gruplar arasında başvuru yaşı açısından fark saptanmadı. Üç grubun başvuru şikayetleri en sık telarş iken (n:76) iken, telarş ve pubarş birlikteliği ile başvuru Grup 3' te, menarş nedeni ile başvuru Grup 2' de diğer gruplara göre daha fazla saptandı (p=0.011). Gruplar arasında vücut ağrılığı, boy ve vücut kitle indeksi SD açısından fark saptanmadı. Başvuru esnasındaki meme tanner evrelemesi en sık evre üçtü. Grup 2 ve Grup 3' te meme evre 4 ile başvuru Grup1'e göre daha sık gözlendi. Grupların FSH, LH, östrodiol, LHRH testi pik FSH ve pik LH, LH/FSH değerleri arasında fark saptanmadı. Grupların başvurudaki kemik yaşları arasında fark saptanmadı. Grup 2 ve Grup 3'ün uterus boyutu, sağ ve sol over hacimleri Grup 1'e göre daha büyüktü (p=0.001). Gruplar arasında puberte prekoks ve hızlı ilerleyen ergenlik olgularının oranları arasında fark saptanmadı.

Sonuç: Pandemi döneminde tanı alan puberte prekoks ve hızlı ilerleyen ergenlik olgularında artıştan obezite ve mobil cihaz maruziyeti ön planda bahsedilmektedir Çalışmamızda pandemi öncesi Grup 1, pandemi dönemi (çevirimiçi eğitim) Grup 2 ve (yüzyüze eğitim) Grup 3' ün başvuru yaşı ve VKI benzerdi. Pandemi döneminde obezitenin erken ergenlik vakalarını tetikleyen faktörlerden biri olmayabilir

Anahtar Sözcükler: COVİD-19 pandemi, Obezite, Over boyut, Puberte prekoks, Uterus boyut

INTRODUCTION

Puberty is a crucial and multifaceted phase that involves significant physiological maturation and variance. The timing of puberty and the rate of development are complicated processes influenced by interactions between genetic, dietary, and environmental factors (1,2). Obesity is one of the factor of precocious puberty in females (3). Home quarantine has significantly impacted people's daily lives because of the global coronavirus disease 2019 (COVID-19) pandemic, including dietary changes, exercise patterns, work and rest routines, and medical care access. Schools around our country were closed between March and June (4). Children were kept out of school during the lockdown, and their daily physical routines were severely restricted. Studies have reported an increase in puberty precocious and rapidly progressing puberty during the pandemic period, which is associated with a sedentary life, increased obesity with an increase in the time spent at home, and prolonged use of mobile devices (5,6). While obesity is generally highlighted as the risk factor with the most potential to disrupt the physiology of puberty, research has shown that physical inactivity, excessive screen time, altered sleep patterns, and psychological issues may also directly contribute to the issue (6,7)compared to subjects observed in the same period of the previous year. Design: The study population (490 children. In this study, we evaluated the pre-pandemic and pandemic periods of the patients diagnosed with puberty precocious in our clinic, clinical features, laboratory findings, and whether obesity is a factor.

MATERIALS and METHODS

In the study, female patients diagnosed with Puberty precocious / Rapidly Progressive Puberty in our clinic were divided into three groups August 2019-February 2020 before the pandemic (Group 1), August 2020-February 2021 during the pandemic (Group 2), August 2021-February 2022 during the pandemic (Group 3).

Among the study groups, Group 1 (G1) covers the pre-pandemic period, Group 2 (G2) covers the whole closure period during the pandemic period, and Group 3 (G3) covers the face-to-face education period with partial closure during the pandemic period. The groups were retrospectively compared in terms of clinical, laboratory, and radiologic findings.

The study was conducted as a single-center retrospective case-based study. Two pediatric endocrinology specialists recorded demographic information, physical examination findings, hormone tests, and radiological imaging information from the

files of these patients diagnosed with puberty precocious.

Precocious puberty is defined as puberty stage 2 and above according to Marshall and Tanner staging, pubertal gonadotropin levels (basal LH > 0.3 IU/L, stimulated LH > 5 IU/L, and LH/FSH > 0.6), advanced bone age and pubertal findings on pelvic imaging (uterus > 35 mm, ovary > 2cc) before the age of 8 years. Progressive precocious puberty is defined as pubertal stage advancement from one stage to another in 3-6 Months or Growth velocity Accelerated >6 cm/year or bone age, typically advanced, variable, at least two years, predicted adult height, below target height or decreasing on serial determinations (8). Patients with peripheral puberty precocity and organic pathology on cranial MRI were excluded from the study.

Height and weight were measured, body mass index (BMI) was calculated using the standard formula [weight in kg/(height in m), and the respective standard deviation score (SDS) was calculated based on Turkish reference data (9). Obesity was defined percentile for age z-score 1.64, equivalent to 95 th percentile. Bone age (x-ray of the left hand) was assessed according to the method of Greulich and Pyle. FSH, LH, and estradiol (ATELLİCA System, Siemens) concentrations were measured using immunochemiluminometric assay (ICMA). The Ethics Committee of Ankara City Hospital approved this study. (27.05.2022/E2-22-1926).

SPSS 26 program was used for statistical analysis. Descriptive statistics were used to evaluate demographic and clinical characteristics. Data were described as a percentage and mean ± standard deviation (SD) or median (minimum-maximum) and categorical data. ANOVA, Kruskal-Wallis test and χ^2 tests were used according to data distribution. The “Kruskal-Wallis” test was used when comparing the medians of three independent groups in the data that did not fit the normal distribution, and the “Mann-Whitney U” test was used when comparing the medians of two independent groups. All data are given as mean ± SD Bonferroni correction was used in post hoc tests. Statistically, p<0.050 was considered significant.

RESULT

A total of 495 patients diagnosed with precocious puberty and rapidly progressive puberty were included in the study. The patients in the groups were as follows: n: 98 in G1, n: 194 in G2, n: 203 in G3. The median (min-max) age at presentation was 8.3 (5.4-9.8) years in G1, 8.4 (5-9.9) years in G2, 8.3 (5.6-10) years in G3 and the age at presentation was similar in the groups (p=0.160) (Table I). The most common complaint at presentation in the three groups was thelarche, and presentation with combination of thelarche and pubarche were more common in G3 than in the other groups (p>0.050) (Figure 1). In comparison to the other groups, G2 had a significantly higher incidence of menarche (p=0.011) (Figure 1).

No difference was found between the groups regarding body weight SD and height SD (p>0.05). The BMI SD was 0.69±1 SD for all patients, 0.78±0.94 SD for G1, 0.67±1 SD for G2, and 0.67±1for G3, and the BMI SDS of the groups were comparable (p=0.630) (Table I).

In the physical examination findings at the presentation, the most common breast staging was Tanner stage 3. Breast Tanner stage 4 was detected more frequently in G2 and G3 than in G1 (p=0.057). In pubis Tanner staging, stage 1 and stage 2 were at the same rate in G1 (36.7%); the most common presentation was with Tanner stage 2 (38.7%) in G2; and the most prevelant manifestation was with Tanner stage 1 (38.4%) in G3 (Figure 2).

No difference was found between the groups’ FSH, LH, estradiol, LHRH test peak FSH, peak LH, and LH/FSH values (p> 0.050) (Table II). There was no difference between the bone ages of the groups at presentation (p> 0.050). The uterine size, right and left ovarian volumes and endometrium thickness of G2 and G3 were larger than G1 (p=0.001) (Table II).

Ratio of puberty precocious to rapid progressive puberty cases 1:1.9 in G1, 1:2.2 in G2, 1:2.9 in G3. There was an increase in the incidence of rapid progressive puberty compared to puberty precocious during the pandemic, but no difference was found between the groups in the rates of puberty precocious and rapid progressive puberty cases (p = 0.239) (Table III).

DISCUSSION

Many publications have been shared about the increase in puberty precocious cases from different continents of the world during the pandemic (5,10–13). This increase during the pandemic is associated with increased obesity and screen exposure due to closure and sedentary life (10). Our study

Table I: Age and Anthropometric Findings of the Patients

	Total n:495	G1 n:98	G2 n: 194	G3 n:203	p
Age at application (years)	8.3 (5-10)	8.3 (5.4-9.8)	8.4 (5-9.9)	8.3 (5.6-10)	0.160
Age at treatment (years)	8.6 (5-10)	8.5 (5.4-9.8)	8.6 (5-10)	8.6 (6-10)	0.430
Weight (sds)	0.99±1.08*	1±1.1*	0.9±1.1*	1±1*	0.560
Height (sds)	0.96±1.1*	0.92±1.1*	0.88±1.1*	1±1*	0.300
BMI (sds)	0.69±1*	0.78±0.94*	0.67±1*	0.67±1*	0.630

Values represent median (minimum-maximum), Values represent mean ± SD*

Table II: Laboratory Results, Bone Age, and Pelvic Ultrasonography Findings of the Groups

	Total	G1	G2	G3	p
FSH (U/L)	5 (0.7-19)	5.3 (0.7-17)	5.1 (1.3-19)	4.9 (0.7-11.8)	0.770
LH (U/L)	0.9 (0.05-49)	0.8 (0.1-7.3)	1 (0.1-49)	0.9 (0.05-6.1)	0.280
Estradiol (pmol/l)	30 (8.2-345)	29.5 (12-345)	31 (8.2-257)	29 (12-91)	0.460
LHRH test					
Peak FSH (U/L)	15 (1.8-48)	14.8 (5.4-30)	15.5 (7.5-48)	14 (1.8-41)	0.210
Peak LH (U/L)	10.5 (3.2-93)	9.9 (4.4-47)	10.4 (4.8-78)	10.6 (3.28-93)	0.750
LH/FSH	0.8 (0.1-5.9)	0.8 (0.3-1.9)	0.7 (0.3-3.6)	0.9 (0.1-5.9)	0.56
Imaging findings					
Bone Age (years)	10.2 (5-13)	10 (5.4-12.5)	10 (5-13)	12.5 (6.8-13)	0.720
Uterine size (mm)	33 (13-67)	26 (15-59)	35 (15-67)	34.5 (13-66)	**0.001**
Right ovary (cc)	2.7 (0.5-24)	2.39 (0.5-19.7	2.5 (0.5-24)	3 (0.9-10.5)	**0.001**
Left ovary (cc)	2.5 (0.5-20.2)	2.2 (0.5-6.5)	2.45 (0.5-20.2)	2.9 (0.9-8.4)	**0.038**
Endometrial thickness (mm)	0 (0-17)	0 (0-6.5)	0 (0-17)	0 (0-12)	**0.041**

Values represent median (minimum-maximum)

Table III: Distribution of puberty precocious and rapidly progressive puberty diagnoses in the groups

	Puberty Precocious n (%)	Rapidly Progressive Puberty n (%)	Total n (%)
G1	33 (33.7)	65 (66.3)	98 (100)
G2	60 (30.9)	134 (69.1)	194 (100)
G3	51 (25.1)	152 (74.9)	203 (100)
Total	144 (29.1)	351 (70.9)	495 (100)

showed that the BMI SD of the cases with puberty precocious who presented during the pandemic did not differ from those who presented before the pandemic. With this study, we have determined that obesity is not a factor of puberty precocious during the pandemic.

Nutrition is an accepted factor in sexual maturation (14). Although BMI has frequently increased during the epidemic due to decreased physical activity, this increase is often not noteworthy (5,15). Therefore, it is questionable whether a slight rise in BMI alone may account for the reported increase in the prevalence of precocious puberty in clinics. When we analyzed our patients in terms of obesity, which is defined as an essential factor in the increase in the frequency of cases in this period, the BMI SDS of the groups were similar. The balance of leptin and ghrelin is essential for eating, obesity, and puberty. Puberty is indicated by increased leptin and lower ghrelin levels in obese individuals (16). Chen et al. (3) found no difference in leptin levels between pandemic and pre-pandemic cases while finding similar BMI SD in pre-pandemic and pandemic. However, they found that ghrelin levels were lower in cases during the pandemic period. Since a positive correlation was discovered between serum ghrelin and serum MKRN3 concentrations, the researchers hypothesize that the lower concentrations of ghrelin may have downregulated the concentrations of MKRN3 and subsequently upregulated the pulsatile secretion of GnRH to promote the onset of puberty. In addition to psychological distress, dietary changes, and pandemic-related food changes, it is also required to incorporate alterations in microbiota, the microRNA network, and DNA methylation in the previously described (17). And all of these factors may affect the mediators and signaling pathways involved in the onset of puberty. At this point, rather than obesity itself being a factor, the foods prefered, like antioxidant foods which used to protect from Sars-Covid19-B may also be a factor. Glutathione peroxidase, one of the enzymatic antioxidants, plays a role in cell differentiation and proliferation in gametes and those are related to the onset of puberty (18).

Screen exposure, which is mentioned as an important reason for the increase in the incidence of precocious puberty, may be explained by the suppression of melatonin and the elimination of the inhibitory effect of melatonin on GnRH. In our study, the screen exposure of the cases was not questioned individually, but G2 group in the study reflects the period when children were most exposed to the screen due to online education. In the literature, screen exposure time increased in children during the pandemic. Some studies questioned daily screen exposure before sleeping and daily screen exposure in puberty precocious cases and have shown increase in both parameters (5,19).

In our study, the ages at the presentation of the patients who presented before and during the pandemic period were similar to each other. In studies in the literature, studies are showing that the ages of the cases admitted during the pandemic period were younger (11,12,20).

While the most common complaint at presentation was thelarche, an especially increased number of patients in the G2

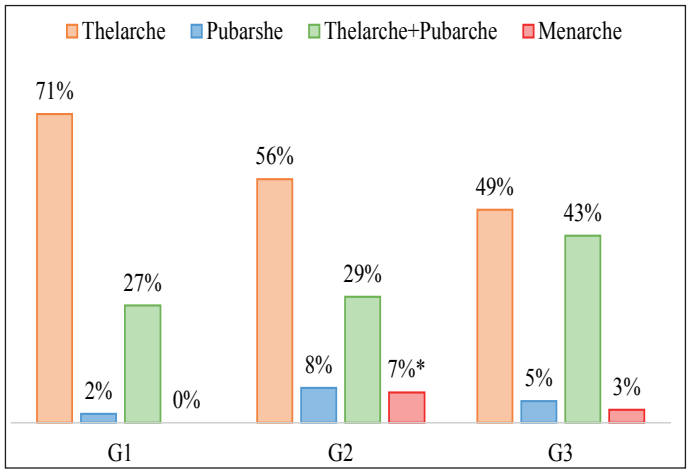

Figure 1: Application Complaints of Groups.
***Menarche was detected more in Group 2 compared to other groups (p=0.011)**

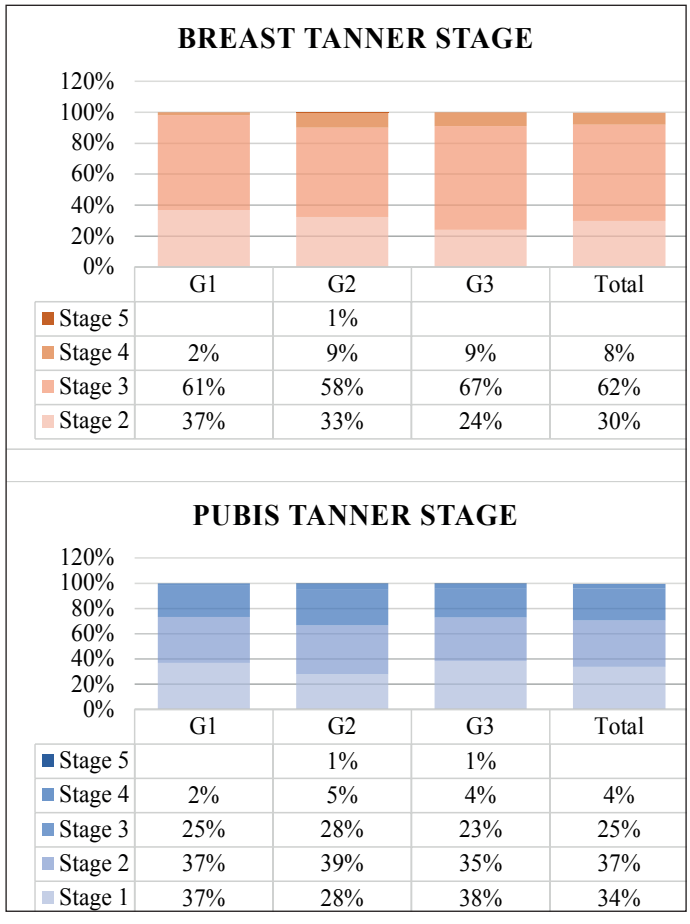

Figure 2: Pubertal Examination Tanner Staging of the Group.

group and G3 group, who were admitted with menarche after the complete closure period, were observed. This was thougth to be the effect of closures, fear of virus and late admission to hospital for puberty concerns. In addition, the increase in the G2 group was also statistically significant. In support of these cases, in the physical examination findings, a high percentage of patients presenting with breast tanner stage 4 and an increase in uterine size and ovarian volumes in pelvic ultrasonography were detected in the pandemic period groups compared to the pre-pandemic period. The emergence of the first findings of the G2 and G3 pandemic period groups may have occurred earlier, or the puberty tempo may have progressed faster. Although there was no difference between the LH and Estradiol concentrations of the cases.

The strengths of our study are that the groups defined as the pandemic period in the groups taken in the literature's reflections cover the pandemic's initial period. Puberty development is a process, and the cases in that period reflect the pre-pandemic period. However, G2, one of our study groups, reflects the period in which we saw the effects of full closure; G3 reflects the period in which we saw the impact of the partial closure - face-to-face education continued process in which the pandemic effect.

In our study, we aimed to investigate whether obesity was a factor rather than an increase in the number of cases during the pandemic. In addition, we did not make a subjective evaluation in our study to learn the screen time of the instances one-to-one. However, it includes the period when the online education process and the time spent in front of the screen increased significantly in our country's G2 group of prepubertal children. Still, in the G3 group, out-of-home and in-school activities increased with a partial closure but were more limited compared to the pre-pandemic period.

In conclusion, obesity, increased screen exposure time, and immobility are shown as factors for the increase of puberty precocious during the pandemic. In our study, the BMI of pandemic groups (G2-G3) was similar before the pandemic group(G1). Our study showed that obesity was not a factor in precocious puberty during the pandemic.

REFERENCES

1. Rubin C, Maisonet M, Kieszak S, Monteilh C, Holmes A, Flanders D, et al. Timing of maturation and predictors of menarche in girls enrolled in a contemporary British cohort. Paediatr Perinat Epidemiol 2009;23:492–504.
2. Clarkson J, Han S-K, Liu X, Lee K, Herbison AE. Neurobiological mechanisms underlying kisspeptin activation of gonadotropin-releasing hormone (GnRH) neurons at puberty. Mol Cell Endocrinol 2010;324:45–50.
3. Chen C, Zhang Y, Sun W, Chen Y, Jiang Y, Song Y, et al. Investigating the relationship between precocious puberty and obesity: A cross-sectional study in Shanghai, China. BMJ Open 2017;7:1–8.
4. https://en.wikipedia.org/wiki/Timeline_of_the_COVID-19_pandemic_in_Turkey.
5. Stagi S, De Masi S, Bencini E, Losi S, Paci S, Parpagnoli M, et al. Increased incidence of precocious and accelerated puberty in females during and after the Italian lockdown for the coronavirus 2019 (COVID-19) pandemic. Ital J Pediatr 2020;46:165.
6. Chioma L, Bizzarri C, Verzani M, Fava D, Salerno M, Capalbo D, et al. Sedentary lifestyle and precocious puberty in girls during

the COVID-19 pandemic: an Italian experience. Endocr Connect 2022;11: e210650.

7. Street ME, Sartori C, Catellani C, Righi B. Precocious Puberty and Covid-19 Into Perspective: Potential Increased Frequency, Possible Causes, and a Potential Emergency to Be Addressed. Front Pediatr 2021;9 734899.
8. Rosenfield RL, Cooke DW, Radovick S. Puberty in the female and its disorders. in: Sperling Pediatric Endocrinology. Elsevier 2021:528–626.
9. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, et al. Reference values for weight, height, head circumference, and body mass index in Turkish children. J Clin Res Pediatr Endocrinol 2015;7:280-93.
10. Fu D, Li T, Zhang Y, Wang H, Wu X, Chen Y, et al. Analysis of the Incidence and Risk Factors of Precocious Puberty in Girls during the COVID-19 Pandemic. Int J Endocrinol 2022;2022:9229153.
11. Yesiltepe Mutlu G, Eviz E, Haliloglu B, Kirmizibekmez H, Dursun F, Ozalkak S, et al. The effects of the covid-19 pandemic on puberty: a cross-sectional, multicenter study from Turkey. Ital J Pediatr 2022;48:144.
12. Mondkar SA, Oza C, Khadilkar V, Shah N, Gondhalekar K, Kajale N, et al. Impact of COVID-19 lockdown on idiopathic central precocious puberty - Experience from an Indian centre. J Pediatr Endocrinol Metab 2022;35:895–900.
13. Oliveira Neto CP de, Azulay RS de S, Almeida AGFP de, Tavares M da GR, Vaz LHG, Leal IRL, et al. Differences in Puberty of Girls before and during the COVID-19 Pandemic. Differences in Puberty of Girls before and during the COVID-19 Pandemic. Int J Environ Res Public Health 2022;19:4733.
14. Calcaterra V, Cena H, Regalbuto C, Vinci F, Porri D, Verduci E, et al. The role of fetal, infant, and childhood nutrition in the timing of sexual maturation. Nutrients 2021;13:419.
15. Verzani M, Bizzarri C, Chioma L, Bottaro G, Pedicelli S, Cappa M. Impact of COVID-19 pandemic lockdown on early onset of puberty: experience of an Italian tertiary center. Ital J Pediatr 2021;47:52.
16. Wagner I V, Sabin MA, Pfäffle RW, Hiemisch A, Sergeyev E, Körner A, et al. Effects of obesity on human sexual development. Nat Rev Endocrinol 2012;8:246–54.
17. Ju M, Yang L, Zhu J, Chen Z, Zhang M, Yu J, et al. MiR-664-2 impacts pubertal development in a precocious-puberty rat model through targeting the NMDA receptor-1. Biol Reprod 2019;100:1536–48.
18. Giannattasio A, Girotti M, Williams K, Hall L, Bellastella A. Puberty influences expression of phospholipid hydroperoxide glutathione peroxidase (GPX4) in rat testis: Probable hypophysis regulation of the enzyme in male reproductive tract. J Endocrinol Invest 1997;20:439–44.
19. Chioma L, Bizzarri C, Verzani M, Fava D, Salerno M, Capalbo D, et al. Sedentary lifestyle and precocious puberty in girls during the COVID-19 pandemic: an Italian experience. Endocr Connect 2022;11: e210650.
20. Umano GR, Maddaluno I, Riccio S, Lanzaro F, Antignani R, Giuliano M, et al. Central precocious puberty during COVID-19 pandemic and sleep disturbance: an exploratory study. Ital J Pediatr 2022;48:60.

Bloody Stool in Infants: A Pediatric Allergy View

İnfantlarda Kanlı Gayta: Pediatrik Alerji Bakışı

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ABSTRACT

Objective: The prevalence of food allergy (FA) has gradually increased. Bloody stool is among the symptoms associated with non-immunoglobulin E (IgE) mediated FA in infants. In our study, we shared the clinical characteristics of the patients who applied to our clinic with bloody stool.

Material and Methods: The data of the patients with bloody stool were reviewed. Patients' characteristics and the time of onset of tolerance in patients with FA were recorded, retrospectively.

Results: The 110 patient files were reviewed. 68% of the patients were diagnosed with FA (63 proctocolitis/12 enterocolitis), 22% with an anal fissure, and 9% with nonspecific colitis. The most common causative food was cow milk (57%), the second was the combination of egg and milk (24.2%), and the third was egg (18.2%). The presence of atopic dermatitis (AD) and eosinophil count at the time of admission did not affect tolerance development time but it was shown that skin prick test (SPT) positivity and the high level of total IgE at the time of admission delayed the development of tolerance [(p=0.02), (r=0.510, p=0.009)].

Conclusion: Bloody stool is one of the common complaints in infants. It does not always indicate a FA. The clinic is mild when the underlying disease is non-IgE mediated FA. However, accompanying IgE-type sensitivities negatively affect the prognosis. Elevated total IgE and SPT positivity at the time of diagnosis may give an impression that tolerance of baked products could be delayed in this type of allergy.

Key Words: Atopic dermatitis, Food allergy, Gastrointestinal hemorrhage, Infant, Proctocilitis

ÖZ

Amaç: Besin alerjisi (BA) sıklığı giderek artan bir hastalıktır. Kanlı gayta yakınması infantlarda non immunoglobulin E (IgE) aracılı BA ile ilişkilendirilen semptomlar arasındadır. Çalışmamızda kanlı gaita nedeniyle kliniğimize başvuran hastaların klinik özellikleri paylaşılmıştır.

Gereç ve Yöntemler: Kanlı gaitası olan hastaların verileri incelendi. Hastaların özellikleri ve BA saptanan hastalarda toleransın ne zaman geliştiği restrospektif kaydedildi.

Bulgular: 110 hastanın kayıtları incelendi. Bunlardan %68'i BA (63 proktokolit/12 enterokolit), %22'si anal fissür, %9'u nonspesifik kolit tanısı aldı. Şüpheli besin olarak en sık inek sütü (%57), ikinci sıklıkta yumurta ve süt birlikteliği (%24.2), üçüncü sıklıkta yumurta (%18.2) saptandı. Atopik dermatit (AD) olması, başvuru anındaki eozinofil sayısı tolerans zamanını

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Dokuz Eylül University ethics committee with a decision number 2021/003-33 and with the date 01.02.2021.

Contribution of the Authors / Yazarların katkısı*: *ATAKUL G: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results. ***KÖSE ŞİRİN S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***ATAY Ö:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***BOYACIOĞLU KANGALLI Ö:*** Taking responsibility in logical interpretation and conclusion of the results. ***AL S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***ASİLSOY S:*** Constructing the hypothesis or idea of research and/or article, Reviewing the article before submission scientifically besides spelling and grammar. ***UZUNER N:*** Planning methodology to reach the Conclusions. ***KARAMAN Ö:*** Organizing, supervising the course of progress and taking the responsibility of the research/study.

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etkilemezken deri prick test (DPT) pozitifliği ve başvuru anındaki yüksek total IgE düzeyinin toleransı geciktirdiği bulundu [(p=0.020), (r=0.510, p=0.009)].

Sonuç: Kanlı gaita, infantil dönemde sık karşılaşılan şikayetlerden biridir. Her zaman besin alerjisine işaret etmez. Altta yatan hastalık non-IgE kaynaklı BA olduğunda klinik ılımlıdır .Ancak eşlik eden IgE tipi duyarlılıklar prognozu olumsuz etkiler. Tanı anındaki total IgE yüksekliği ve DPT pozitifliği bu tip alerjilerde fırınlanmış ürün toleransının geç olacağı yönünde fikir verebilir.

Anahtar Sözcükler: Atopik dermatit, Besin alerjisi, Gastrointestinal hemoraji, İnfant, Proktokolit

INTRODUCTION

Food allergy (FA) is defined as an adverse food reaction which developed as a result of immune-mediated mechanisms. These mechanisms could be immunoglobulin E (IgE) mediated, cellular (non-IgE) and both IgE-mediated and cellular (mixed) (1). Although its prevalence increases worldwide, it varies between 2-8% among children (2).

Signs of non-IgE-mediated FAs occur from several hours to several days later after exposure. Symptoms are usually associated with the gastrointestinal system, such as blood in stool, vomiting, diarrhoea, abdominal discomfort and constipation. The most common food allergens are cow's milk, egg, soy and wheat in non–IgE-mediated FA (3). It is not always easy to distinguish these symptoms from other gastrointestinal system (GIS) diseases. Bloody stool in children is a common clinical problem; indeed, it is reportedly the presenting complaint for approximately 0.3% of children in the emergency department (4). In infants, allergic colitis and anorectal fissures represent the most common causes, besides, non-specific colitis, duplication of bowel, volvulus, Hirschsprung's disease, necrotizing enterocolitis and bleeding diathesis are the other causes of lower GIS bleeding (5). Bloody stool is a common finding in patients referred to pediatric allergy clinics. Food protein-induced allergic proctocolitis (FPIAP) was diagnosed from the presence of bloody stools or occult blood in 163 (18%) of 903 infants over a period of 3 years, and from the presence of occult blood alone in 63 (7%), in a recent prospective study (6). FPIAP is believed to resolve rapidly but a study of 257 infants with FPIAP in Turkey showed that 60% of children developed tolerance in the first year of life, although 99% did so within 3 years (7). SPT and specific IgE (sIgE) tests for food allergens are usually negative. However, about 20% of children with FPIAP may show sensitization or develop IgE-mediated allergy to offending foods over time (8).

In this study, laboratory and clinical characteristics of the patients who applied to and followed up in our clinic with bloody stool were reviewed.

MATERIALS and METHODS

File records of 110 patients were analysed who applied to our pediatric immunology and allergy outpatient clinic with bloody stool between January 2020-2021. Patients with chronic diseases and immunodeficiency were excluded from the study. Patients' demographic characteristics, accompanying findings, laboratory results, and time of the tolerance development in patients with FAs were recorded.

The infants with bloody stool and no accompanying complaints like weight loss, fever and whose symptoms disappeared with the elimination of suspected allergen from diet but whose symptoms reappeared with the addition of allergen to diet were considered FPIAP (3).

While infants who have profuse and repetitive vomiting 1-4 hours after food intake, followed by fatigue and lethargy were considered acute food protein-induced enterocolitis syndrome (FPIES), those with chronic diarrhea, intermittent vomiting, growth retardation, hypoalbuminemia, and anemia were considered as chronic FPIES (3).

Skin-prick tests (SPT) were performed in accordance with the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) using commercial extracts of the most common food allergens (ALK-Albello ®, Canada) such as cow's milk, eggs, soy, peanuts, and wheat flour. Such allergens were applied with a negative saline and positive histamine control (Histamindihydrochloride 0.1%) (9). Punctures were performed on the inner side of the forearm, on the allergen microdroplets using appropriate lancets. The reading was performed with a ruler graduated in millimeters after 15 minutes. The test result was considered negative with a wheal of <3 mm and positive with the wheal of ≥3 mm.

Atopy patch tests (APT) were performed on non-lesional, untreated skin of the back, in accordance with the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) (10). A technique similar to conventional patch tests have been used by performing atopy patch testing – IQ Ultimate TM (IQ-UL chambers,Chemotechnique MB,Vellinge,Sweden). The volume of each chamber was 32 µL and the inner area of the chamber was 64 mm^2. The APTs with native egg's white and yolk, peanuts, soy, cow's milk and wheat were applied. Wheat powder and soy powder were used with vehicle-distillated water (1 g of wheat powder or soya powder in 10 ml of distillated water), egg's white, yolk, cow's milk and peanuts were used in the native form as the fresh foods without any dilution. Single vehicle (distillated water) has been used as a negative control. The occlusion time of APTs was 48 h, the first results were evaluated 20 min after removal of the tests and the second results were analysed 72 h after the application of the tests. The APT results were graded according to European

Task Force on Atopic Dermatitis (ETFAD) standards (10): no reaction or erythema without infiltration (–), erythema and infiltration (+), erythema and few papules (++), erythema and many or spreading papules (+++), erythema, papules and vesicles (++++).

Statistics: The data were analyzed with SPSS 22.0. The Chi-square test and Fischer Exact Test were used for categorical variables. Numerical parameters were tested for normal distribution and the independent samples T-test was performed for pairwise group comparison and one-way Anova test was used for multi group comparisons among those normally distributed; and Mann Whitney U test was performed for pairwise group comparison and Kruskal Wallis test was used for multi group comparisons among those not normally distributed. $p < 0.05$ was considered statistically significant.

The study was approved by Dokuz Eylül University ethics committee with a decision number 2021/003-33 and with the date 01.02.2021.

RESULTS

The data of 110 patients were analysed and 75 of them (68%) were followed with the diagnosis of FA (63 proctocolitis/12 enterocolitis), 35 of them had no food allergy (32%); 25 had an anal fissure, and 10 had gastrointestinal complaints which are temporary and unrelated to food intake. These patients were considered as non-specific colitis. Statistical analyses were performed in patients who were diagnosed with FA (n:75). Fifty-two percent of the patients with FA were male, the median age of onset was 3 months, 74.7% were born with cesarean section and 14.7% were born prematurely. Sixty percent of them had atopic dermatitis (AD). The demographic data of patients were summarized in Table I. The causative food allergens in our study group and features of tolerance were summarized in Table II and Table III.

Table I: Clinical and laboratory data of patients.

Parameters	Median (25-75 per)
Age (month)	6 (5-10)
Age of onset of complaints (month)	3.2 (2-6)
Age of tolerance to baked products (n:28)	12 (8.2-14)
Follow-up duration of the patients (month)	10 (4-25)
Age of full tolerance (month) (n:17)	14 (12-20)
Total IgE (IU/ml) (n:65)	13.7 (5.3-38.5)
Eosinophil (%) (n:75)	3.3 (2.1-5)
Eosinophil (#) (n:75)	300 (200-500)
Specific IgE (kU/lt) (n:71)	0.23 (0-1.4)
Cow's milk (n:23,>0.35 kU/lt)	0 (0-0.55)
Egg positive (n:17,>0.35 kU/lt)	0 (0-0.31)
Patch test (n:27)	
Negative	23 (85.2)
Positive	4 (14.8%)
Skin prick test (n:66)	
Negative	39 (59.1)
Positive	27 (40.9%)
Tolerance (months)	
Baked products	12 (8-13)
Full tolerance	14 (11-18)
Formula	
None	42 (56)
Amino acid	21 (28)
Extensively hydrolyzed	12 (15)

Table II: Causative Food Allergens.

Causative Foods	n (%)
Cow's milk	42 (57)
Cow's milk + Egg	18 (24)
Egg	14 (18)
Others	
Cow's milk+ walnut	2 (2.7)
Cow's milk + egg+ wheat	2 (2.7)
Cow's milk +Sesame	2 (2.7)
Egg + Red meat	2 (2.7)
Egg + Banana	1 (1.4)

Table III: Comparison of cases by causative food allergens and features of tolerance.

	Cow's milk	Egg	Cow's milk+Egg	p
AD*				
Without	20(47)	0 (0)	7 (38)	0.013
With	22 (53)	14 (100)	11 (62)	
Age of onset of symptoms (months)†	3 (2-6)	4(2-5)	3.5 (2-6)	0.392
	Baked Tolerance	**Full Tolerance**		
SPT†				
Negative	9 (7.5-12)	12(10-18)		0.020
Positive	13 (12-16)	15.5 (13.5-27)		
AD*				
Without	21 (75)	13 (80)		>0.050
With	7 (25)	4 (20)		

AD: *Atopic dermatitis,* ***SPT:*** *skin prick test,* n(%), †median (25-75p)*

For patients with milk allergy and formula-fed, the type of formula used did not affect the age of onset of tolerance to baked products or full tolerance ($p > 0.050$). There was no significant relationship between the percentage of eosinophil and the time of tolerance to baked products or full tolerance ($p > 0.050$). We observed that there is a statistically significant positive correlation between mean total IgE value at admission and the mean age of tolerance to baked products ($r = 0.510$, $p = 0.009$) but no correlation between total IgE level and the mean age of full tolerance $p > 0.050$).

DISCUSSIONS

FA is a common disease and has an increasing prevalence among worldwide (1). On the other hand, bloody stool is not always associated with FAs. We presented 68% of patients have diagnosed with FA who applied to our clinic with the suspicion of non-IgE mediated FA and short-term follow-up data. We have showed that the most common food allergens were cow's milk and egg in infants presenting with bloody stools.

The symptoms of FPIAP generally start in the first weeks of life, while the clinical findings of FPIES generally vary with causative food (11,12). Although the clinical findings in our patients occured at a median of three months of age and minimum of two months of age.

AD was observed in 13% of the patients in a multicenter study conducted with FPIAP patients in our country, Turkey (7). FPIAP rate was found 60% in our patient group and it is quite higher than their rate. The pathogenesis of non-IgE and mixed-type food allergies are still unclear. It's known that the clinical course of FA varies from society to society and from region to region. AD is not only caused by a FA but could also be affected by many environmental factors. These factors may be the reason of this high rate that we have found.

Suspicious food allergens in FA are affected by the nutritional habits of societies (2). In parallel to many studies conducted in our country, the most common causative food in our study was cow's milk protein followed by egg protein (7,14-16).

Formulas are not recommended to more than half of the patients with cow's milk protein allergies. Due to varying breastfeeding rates in several countries, formula-fed infants' rate has been affected. The age of tolerance to baked products was not different in formula fed infants compared to breastfed infants (p=0.445). Breast feeding is still preferred primarily rather than formulas in infants with FA. Formula feeding does not play an essential role in improving the prognosis of the disease (17).

The prognosis of non-IgE mediated FA is generally favourable and non-IgE FAs usually resolve between the ages of three to five before the school-age (18). FPIAP generally resolves at the ages of 1-2 years. In a study with large sample size, infants were able to consume cow's milk protein at the age of 11 months (6). Tolerance ages in our study were compatible with the literature and the median age of baked food tolerance was found to be 12 months (8-13 months) and the median age to end all extensive elimination diets was 14 months (12-20 months).

Egg sensitivity is closely related to AD, especially in infants who developed AD in their first year of life (19). AD was presented in all patients with egg allergy and in 52.8% of patients with milk allergy (p = 0.013). The prognosis of the disease is not affected by accompanying AD and there was no statistically significant difference between patients with AD (12 [9-13.8] months) and without AD in terms of the mean age of tolerance to baked products (p = 0.592).

IgE-mediated FA tends to be persistent (7). Our data also supported this view in our study and food tolerance time was significantly delayed in the patients who have positive SPTs compared to negative SPTs (p = 0.020). Although our study group included patients with non-IgE mediated FAs like FPIAP and FPIES, positive SPT results were presented in 40.9% of patients (n = 27). The SPT positivity rate may have been high due to patients with AD in our study group. AD is classified under mixed-type reactions with findings of FA and SPT positivity may be seen (2).

In our study which we analysed parameters that could predict prognosis, it was determined that the higher the total IgE at admission had positive correlation with delayed tolerance (r=0.510, p=0.009). Although total IgE is accepted as a biomarker for allergic disease, it has not proven an influence on the prognosis of FA (20). The applicability of these results to the general population was limited, as it is a study based on single center experiences and included only patients presenting to a tertiary health care center. It should be studied with larger sample sizes.

CONCLUSION

There are still many unknowns in non-IgE mediated FAs. It should be kept in mind that not all infants with bloody stool have a FA. In infants with bloody stool who have FA diagnosis, the most common food allergens are cow's milk and eggs. Non-IgE mediated FAs have a favourable prognosis, but IgE-type sensitizations have negative effect on the prognosis. Total IgE level at the admission and a positive SPT may help predicting the prognosis.

REFERENCES

1. Labrosse R, Graham F, Caubet JC. Non-IgE-Mediated Gastrointestinal Food Allergies in Children: An Update. Nutrients 2020;12:2086.
2. Cianferoni A. Non-IgE Mediated Food Allergy. Curr Pediatr Rev 2020;16:95-105.
3. Meyer R, Chebar Lozinsky A, Fleischer DM, Vieira MC, Du Toit G, Vandenplas Y, et al. Diagnosis and management of Non-IgE gastrointestinal allergies in breastfed infants-An EAACI Position Paper. Allergy 2020;75:14-32.
4. Osman D, Djibré M, Da Silva D, Goulenok C. Management by the intensivist of gastrointestinal bleeding in adults and children. Ann Intensive Care 2012;2:46.
5. Romano C, Oliva S, Martellossi S, Miele E, Arrigo S, Graziani MG, et al. Pediatric gastrointestinal bleeding: Perspectives from the Italian Society of Pediatric Gastroenterology. World J Gastroenterol 2017; 23:1328-37.

6. Martin VM, Virkud YV, Seay H, Hickey A, Ndahayo R, Rosow R, et al. Prospective Assessment of Pediatrician-Diagnosed Food Protein-Induced Allergic Proctocolitis by Gross or Occult Blood. J Allergy Clin Immunol Pract 2020;8:1692-9.e1.
7. Buyuktiryaki B, Kulhas Celik I, Erdem SB, Capanoglu M, Civelek E, Guc BU, et al. Risk Factors Influencing Tolerance and Clinical Features of Food Protein-induced Allergic Proctocolitis. J Pediatr Gastroenterol Nutr 2020;70:574-9.
8. Cetinkaya PG, Ocak M, Sahiner UM, Sekerel BE, Soyer O. Food protein-induced allergic proctocolitis may have distinct phenotypes. Ann Allergy Asthma Immunol 2021;126:75-82.
9. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, et al. The skin prick test - European standards. Clin Transl Allergy 2013;3:3.
10. Turjanmaa K, Darsow U, Niggemann B, Rance F, Vanto T, Werfel T. EAACI/GA2LEN position paper: present status of the atopy patch test. Allergy 2006;61:1377-84.
11. Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome and allergic proctocolitis. Allergy Asthma Proc 2015; 36:172– 84.
12. Caubet JC, Ford LS, Sickles L, Järvinen KM, Sicherer SH, Sampson HA, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy Clin Immunol 2014;134:382-9.
13. Lyons JJ, Milner JD, Stone KD. Atopic dermatitis in children: clinical features, pathophysiology, and treatment. Immunol Allergy Clin North Am 2015;35:161-83.
14. Arik Yilmaz E, Soyer O, Cavkaytar O, Karaatmaca B, Buyuktiryaki B, Sahiner UM, et al. Characteristics of children with food protein-induced enterocolitis and allergic proctocolitis. Allergy Asthma Proc 2017;38: 54-62.
15. Sirin Kose S, Asilsoy S, Uzuner N, Karaman O, Anal O. Outcomes of Baked Milk and Egg Challenge in Cow's Milk and Hen's Egg Allergy: Can Tolerance Be Predicted with Allergen-Specific IgE and Prick-to-Prick Test?. Int Arch Allergy Immunol 2019;180:264-73.
16. Guler N, Cokugras FC, Sapan N, Selimoglu A, Turktas I, Cokugras H et al. Diagnosis and management of cow's milk protein allergy in Turkey: Region-specific recommendations by an expert-panel. Allergol Immunopathol (Madr) 2020;48:202-10.
17. Ahmadipour S, Najafi M, Motamed F, Rahmani P. Feeding-based treatment of allergic proctocolitis and associated clinical outcomes. Clin Nutr ESPEN 2020;40:237-41.
18. Caubet J, Cianferoni A, Groetch M, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome. Clin Exp Allergy 2019:9:1178–90.
19. Čelakovská J, Bukač J, Vaňková R, Krejsek I, Krcmova C. Andrýs. Egg allergy in atopic dermatitis patients-analysis of results of specific extract IgE and specific IgE to molecular components. Bird-egg syndrome, Food Agric Immunol 2021;32:265-82.
20. Cetinkaya PG, Kahveci M, Karaatmaca B, Esenboga S, Sahiner UM, Sekerel B, et al. Predictors for late tolerance development in food protein-induced allergic proctocolitis. Allergy Asthma Proc 2020;41:11-8.

Relation of Antioxidant Native Thiol Level with Inflammatory Markers and Disease Activity Index in Pediatric Ulcerative Colitis

Pediatrik Ülseratif Kolit Hastalarında Antioksidan Native Tiyol Düzeyinin İnflamatuar Markırlar ve Hastalık Aktivite İndeksi ile İlişkisi

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ABSTRACT

Objective: Pediatric ulcerative colitis (PUC) is an inflammatory disease. PUC pathogenesis is associated with an imbalance between reactive oxygen species and antioxidant activity which creates oxidative stress. Native thiol (NT) level is antioxidant capacity which is practical and repeatable marker of inflammation and antioxidan level. We aimed to analyse the relation of NT level with inflammatory markers and pediatric ulcerative colitis activity index (PUCAI).

Material and Methods: Thirty-eight PUC patients (SG) and 33 control group (CG) participants were included in the study. PUC patients grouped as in remission, mild, moderate and severe activity according to disease activity according to PUCAI. NT, hemoglobin (Hb), white blood cell (WBC), platelet (PLT), mean platelet volume (MPV), albumin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin 6 (IL-6) levels of all participants were measured at the time they were enrolled in the study and recorded.

Results: Mean age and gender ratio of groups were similar (p>0.050). NT level of SG statistically high compared to CG (p=0.001). Hb, PLT, MPV, CRP, ESR, IL-6 levels of SG were statistically different than CG (p=0.045, p=0.026, p=0.001, p=0.001, p=0.001, p=0.001). NT level of SG was positively correlated with Hb, MPV, albumin (p=0.001, for all). NT level of SG was negatively correlated with PLT, CRP, ESR, IL-6 and PUCAI (p=0.001).

Conclusion: NT level of PUC is significantly lower than CG. NT level of SG was positively correlated with albumin which is a good prognostic factor in PUC patients. NT may be repeatable, noninvasive candidate serum biomarker for PUC management.

Key Words: Activity, Antioxidant, Children, Thiol, Ulcerative colitis

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ÖZ

Amaç: Pediatrik ülseratif kolit (PÜK) inflamatuar bir hastalıktır. PÜK patogenezinde oksidatif stres oluşturan antioksidan aktivite ile reaktif oksijen türleri arasındaki dengesizlik ile ilişkilidir. Native tiyol (NT) seviyesi, iltihaplanma ve antioksidan seviyesinin pratik ve tekrarlanabilir belirteci olan antioksidan kapasitedir. NT düzeyinin inflamatuar belirteçler ve pediatrik ülseratif kolit aktivite indeksi (PÜKAI) ile ilişkisini incelemeyi amaçladık.

Gereç ve Yöntemler: Çalışmaya 38 PÜK hastası (ÇG) ve 33 kontrol grubu (KG) katılımcısı dahil edildi. PÜK hastaları, PUKAI'ye göre hastalık aktivitesi remisyonda, hafif, orta ve şiddetli olarak gruplandı. Tüm katılımcıların NT, hemoglobin (Hb), beyaz kan hücresi (WBC), trombosit (PLT), ortalama trombosit hacmi (MPV), albümin, C-reaktif protein (CRP), eritrosit sedimantasyon hızı (ESH), interlökin 6 (IL-6) seviyeleri ölçüldü ve kaydedildi.

Bulgular: Grupların ortalama yaş ve cinsiyet oranları benzerdi (p>0.050). ÇG'nin NT düzeyi, KG'ye göre istatistiksel olarak yüksek (p=0.001). ÇG'nin Hb, PLT, MPV, CRP, ESR, IL-6 düzeyleri istatistiksel olarak KG'den farklıydı (p=0.045, p=0.026, p=0.001, p=0.001, p=0.001, p=0.001). ÇG'nin NT düzeyi Hb, MPV, albümin ile pozitif korelasyon gösterdi (p=0.001). ÇG'nin NT düzeyi PLT, CRP, ESR, IL-6 ve PUCAI ile negatif korelasyon gösterdi (p=0.001).

Sonuç: PÜK hastalarında NT seviyesi, KG'den anlamlı olarak düşük bulundu. ÇG'nin NT düzeyi PÜK hastalarında iyi bir prognostik faktör olan albümin ile pozitif korelasyon gösterdi. NT ölçümü PÜK yönetimi için tekrarlanabilir, noninvaziv bir serum biyobelirteç olabilir.

Anahtar Sözcükler: Aktivite, Antioksidan, Çocuk, Native tiyol, Ülseratif kolit

INTRODUCTION

Pediatric ulcerative colitis (PUC) is a chronic relapsing systemic idiopathic disease. Most of the findings of PUC are similar to an adult-onset disease. PUC incidence and prevalence rate tends to increase worldwide and up to one-fourth of cases have a more severe disease course and longer duration than inflammatory bowel disease (IBD) diagnosed in adulthood. It is widely known that pathogenesis and progression of the inflammatory cascade in this disease are often attributed to genetic, environmental factors (1,2). For successful treatment of PUC, early diagnosis and follow disease activity is important but there is no well established ideal serum biomarker for PUC, yet.

Lately oxidative stress has been considered to be one of the important steps in disease pathogenesis (3,4). In ulcerative colitis (UC), excessive immune response due to chronic inflammation and impaired tissue perfusion due to mucosal damage lead to excessive production of reactive oxygen and nitrogen species (ROS/RNS) and amount of these oxidative stress markers in UC were found as correlated with the severity of mucosal inflammation (5-7).

In healthy state, there is equilibrium between oxidant and antioxidant mechanisms in the body. Thiols are organic antioxidants since they possess a sulfhydryl group. Thiol groups can form reversible disulfide bridges by the effect of oxidants in plasma (6). The formed disulfide bridges can be reduced to thiol groups again via the antioxidant systems in the organism. Thus, dynamic native thiol-disulfide balance is maintained. The thiol-disulfide balance plays a critical role in antioxidant defense, detoxification, apoptosis, regulation of enzyme activities, and mechanisms of transcription and cellular signal transduction, proliferation and immunity (6,7). In inflammatory diseases, oxidant radicals increases due to oxidative stress and this equilibrium is disturbed (6). To measure levels of all oxidant radicals and antioxidant molecules separately is very time-consuming and expensive and also not really possible since interaction of these substances is always ongoing during all the time in the body (3,4,6).

Native thiol (NT) is the main element of the antioxidant defense and measurement of serum NT level is a good indicator of total amount of antioxidant capacity (6-9). For this reason, a new method was developed to determine native thiol-disulfide balance. Native thiol balances oxidative stress by reducing the levels of reactive oxygen species or by accelerating their inactivation (6,8-10).

We propose that, NT level may be a possible candidate biomarker for PUC diagnosis and follow up. The aim of the study was to determine the relation between NT levels and widely used inflammatory markers and pediatric ulcerative colitis activity index (PUCAI).

MATERIAL and METHODS

This study was carried out in the Pediatric Gastroenterology, Hepatology and Nutrition Clinic of Ankara Bilkent City Hospital, between October 2021 and March 2022. This study was approved by Ankara Bilkent City Hospital Second Ethical committee (10.10.2021/E2-20-106). The written informed consent was received from the family for every child who were included into the study.

This prospective study included two groups; the study group (SG) consisted of 38 children (male 19, female 19) diagnosed and treated with a diagnosis of PUC, and the control group (CG) consisted of 33 healthy children (male 16, female 17) who were admitted for a routine check-up. The diagnosis of UC was made according to clinical, endoscopic, and histopathological criteria of ESPGHAN (11). PUC patients were grouped as in remission, mild, moderate, and severe activity according

to PUCAI score; a non-invasive multi item UC activity index to differentiate the disease activity states accurately and to assess change over time, without the need for colonoscopic assessment for pediatric patients accepted as objective by clinical authorities (12). Patients with any complications related to UC and other chronic or systemic disease and patients with any infection were excluded from the study.

Results of NT, hemoglobin (Hb), white blood cell (WBC), platelet (PLT), mean platelet volume (MPV), albumin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin 6 (IL-6) levels of all participants were measured at the time they were enrolled in the study and recorded. Blood samples were taken to measure NT levels with a newly developed method by Erel/ Neselioglu and NT levels were measured using an automated clinical chemistry analyzer (Roche, Cobas 501, Mannheim, Germany) (8).

Hemoglobin, WBC and PLT were measured by an automatic analyzer (Sysmex XE-2100, USA) within five minutes of sampling. C-reactive protein (Siemens BN II System, Germany), ESR (Therma NE, Spain), and albumin (Roche Cobas 8000, Mannheim, Germany) levels were measured using commercial kits. IL-6 levels were measured by using an enzyme-linked immunosorbent assay kit (Affymetrix Ebioscience).

Statistical Analysis

Statistical Package for Social Sciences (SPSS) 22 for Windows (IBM SPSS Inc.,Chicago, USA) program was used for statistical analyses. Kolmogorov Smirnov test was used to determine the distribution of data. Categorical variables were expressed as numbers and percentage. Continuous variables were compared with independent sample t-test, ANOVA, Mann Whitney U test, and Kruskal-Wallis test where appropriate. Post- Hoc analysis was implemented within subgroups, including PUCAI score, NT level, MPV, PLT, IL-6. Chi-square test and Fisher's exact chi-square test were used to compare categorical variables. The relationship between the numeric parameters was analyzed by Pearson and Spearman correlation analysis. A $p<0.05$ was considered significant for statistical analyses.

RESULTS

During the study in 15 months, a total of 71 children were included. The demographic characteristics and laboratory results of the two groups are summarized in Table I. There were 38 UC patients; 19 (50 %) male and 19 (50 %) girls in SG. CG was consisted of 33 healthy children, 17 (51.5 %) girls, and 16 (48.5 %) boys. The mean ages ± SD were 13.6±3.3 years in SG and 13.3±4.1 years in CG. No statistically significant difference was observed between the SG and CG with respect to age, and gender ratio ($p> 0.050$). NT, Hb, MPV, albumin levels were significantly lower in SG compared to CG ($p=0.001$, $p=0.045$, $p=0.001$, $p=0.015$, respectively). PLT, CRP, ESR, IL-6 were significantly higher in SG compared to CG ($p=0.026$, $p=0.001$, $p=0.001$, $p=0.001$, respectively) (Table I).

Table I: Demographic and laboratory findings of Study and Control groups

	SG (mean±SD) n=38	CG (mean±SD) n=33	p
Gender (male)*	19 (50)	16 (48.5)	0.899
Age (yr)	13.6±3.3	13.3±4.1	0.351
Hb (g/dL)	12.2±1.97	13±1.4	0.045
WBC (x10^9/L)	7.18±2.23	6.96±1.65	0.602
PLT (x10^9/L)	380.9±172.4	309.4±57.3	0.026
MPV (fL)	7.9±1.1	8±1.4	0.001
Albumin g/L)	44.3±5.2	46.9±3.2	0.015
Native Thiol (µmol/l)	489±93	592.7±80.3	0.001
CRP (g/L)	8.97±10.96	1.93±1.4	0.001
ESR (mm/hour)	12.1±6.8	6.2±3.4	0.001
IL-6 (pg/mL)	8.8±8.3	3.9±1.8	0.001

***:** *n (%),* ***SG:** *Study Group,* ***CG:** *Control Group,* ***Hb:** *Hemoglobin,* ***WBC:** *White Blood Cell,* ***MPV:** *Mean Platelet Volume,* ***PLT:** *Platelet,* ***CRP:** *C-reactive protein,* ***ESR:** *Erythrocyte Sedimentation Rate,* ***IL-6:** *Interleukin 6*

In order to determine the relation between the inflammatory parameters with NT levels of PUC patients with different disease activity level, SG subdivided into groups as remission, mild attack, moderate or severe attack groups that defined according to PUCAI score. But since the number of patients in severe attack group was low, we combined moderate and severe attack cases as one group in order to make comparisons. Mean NT level in subgroups were all different than CG (remission vs control; $p=0.038$, mild vs control; $p=0.002$, moderate-severe vs control; $p=0.001$, respectively) (Table II and Figure I).

Results of correlation analysis of NT and PUCAI, Hb, WBC, PLT, MPV, albumin, CRP, ESR, IL-6 were summarized in Table III. There was a significant correlation between NT level with PUCAI and albumin level ($r=-0.336$, $p=0.039$; $r= 0.573$, $p=0.001$, respectively). Results of correlation analysis of disease severity and NT, Hb, WBC, PLT, MPV, albumin, CRP, ESR, IL-6 were summarized in Table IV.

DISCUSSION

To the best of our knowledge, this is the first case-control prospective study that investigated NT as a novel repeatable and practical biomarker of oxidative capacity in PUC patients. In our study, we demonstrated that the mean level of NT which is reflecting the antioxidant capacity of the body is significantly lower in SG as compared to CG. Our study results showed that, NT level gives fairly precise information about antioxidant capacity of the PUC patients. Measurement of all antioxidant molecules separately is very time-consuming and expensive and need some invasive techniques like biopsy. In a study

Table II: The Relationship Between Disease Severity and Inflammatory Markers

	Control mean±SD (n=33)	Remission mean±SD (n=10)	Mild mean±SD (n=18)	Moderate-Severe mean±SD (n=10)	ANOVA	Post hoc p	
Native Thiol (µmol/l)	592.7±80.3	506.3±120.9	497.9±77.9	462.6±88.7	0.001	p* p† p‡	0.00 0.002 0.000
IL-6 (pg/mL)	3.9±1.83	6.19±5.7	9.04±6.98	11.02±11.99	0.004	p* p† p‡	NS 0.029 0.003
ESR (mm/hour)	6.24±3.44	10.4±4.24	11.11±7.56	15.5±6.75	0.001	p* p† p‡	NS 0.015 0.000
Albumin (g/L)	46.92±3.2	45.2±6.43	44.76.±4.4	42.67±5.4	0.051	p* p† p‡	NS NS 0.045
CRP (g/L)	1.93±1.39	8.6±9.62	7.27±9.79	12.4±14.1	0.002	p* p† p‡	NS NS 0.003
PLT (x10^9/L)	309.4±57.3	420±130.6	330.5±123.7	432.7±257.8	0.019	p* p† p‡	NS NS 0.049
MPV (fL)	8.7±1.4	8.2±1.5	7.97±0.9	7.5±0.71	0.044	p* p† p‡	NS NS 0.051

IL-6: *Interleukin 6,* ***ESR:*** *Erythrocyte Sedimentation Rate,* ***CRP:*** *C-reactive protein,* ***PLT:*** *Platelet,* ***MPV:*** *Mean Platelet Volume,* ***NS:*** *Not Significant,* ****:*** *Remission vs control,* ***†:*** *Mild vs control,* ***‡:*** *Moderate-severe vs control*

Table III: Correlation of Native Thiol and Laboratory Parameters

	r	p
Hb (g/dL)	0.538	0.001
WBC (x10^9/L)	-0.177	0.139
PLT (x10^9/L)	-0.468	0.001
MPV (fL)	0.408	0.001
Albumin (g/L)	0.573	0.001
CRP (g/L)	-0.566	0.001
ESH (mm/hour)	-0.414	0.001
IL-6 (pg/mL)	-0.504	0.001

Hb: *Hemoglobin,* ***WBC:*** *White Blood Cell,* ***MPV:*** *Mean Platelet Volume,* ***CRP:*** *C-reactive protein,* ***PLT:*** *Platelet,* ***ESR:*** *Erythrocyte Sedimentation Rate,* ***IL-6:*** *Interleukin-6*

Table IV: Correlation of pediatric ulcerative colitis severity and laboratory parameters

	r	p
Hb (g/dL)	-0.051	0.76
WBC (x10^9/L)	-0.047	0.778
PLT (x10^9/L)	0.056	0.737
MPV (fL)	-0.254	0.124
Albumin (g/L)	-0.383	0.017
Native Thiol (µmol/l)	-0.336	0.039
CRP (g/L)	0.078	0.640
ESR (mm/hour)	0.282	0.087
IL-6 (pg/mL)	0.037	0.824

Hb: *Hemoglobin,* ***WBC:*** *White Blood Cell,* ***PLT:*** *Platelet,* ***MPV:*** *Mean Platelet Volume,* ***CRP:*** *C-reactive protein,* ***ESR:*** *Erythrocyte Sedimentation Rate,* ***IL-6:*** *Interleukin-6*

done in biopsy material, Holmes and Tsunada et al. (13,14) demonstrated that oxidized glutathione (GSSG) in inflamed mucosa from patients with active UC was increased. Holmes et al. (13) also found that the tissue GSSG content of the mucosa showed a significant positive correlation with clinical and histological indices of disease severity among UC patients. NT is used to maintain reduced glutathione level in the body. Our study reported that there is a significant decrease in NT level in PUC patients. Our study results support the results of biopsy study by Holmes et al. (13) but our technique is superior since there is no need for tissue biopsy. An adult study using our technique by Erel, demonstrated that there was a significant decrease in antioxidant capacity reflected by a decrease in NT level (15).

To our knowledge, there is only one pediatric study reported that active PUC patients and controls which are composed of children with functional bowel disease had similar antioxidant levels in gastrointestinal tract tissue biopsies. They had used a different, manual immunodiagnostic technique with 4% intraassay variability, and also the control group was not healthy children (10). Although measurement of the level of GSSG in tissue needs some special techniques and tissue biopsy,

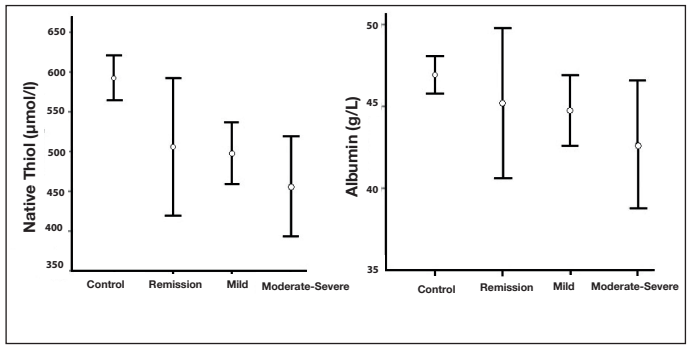

Figure I: Relation of Native Thiol Level and Albumin with Disease Activity.

measurement of serum NT level is a practical, repeatable and automated technique and could be used in PUC patients easily.

Our study results also demonstrated that there is a weak but statistically significant negative correlation between the activity of disease as scaled by PUCAI and NT (r=-0.336, p=0.039). Our study also demonstrated that NT level was also positively correlated with albumin; (r= 0.573, p=0.001). NT level of remission group was significantly lower than CG, NT level of mild activity group significantly lower than control group, means that NT level measurement is fairly precise enough to differentiate these groups (p=0.038).

Our results showed that there is also a statistically significant correlation between NT level and Hb, CRP which reflects an indirect confirmation of the NT level value in this patient group.

Our results suggested that NT level measurement by the Erel technique, it would be possible to measure antioxidant capacity more definitely by measuring NT level and help to early diagnosis of PUC and follow-up purposes as a predictor of the activation in PUC cases. We believe that larger-scale case-control studies with this new Erel technique would help to understand and clarify the progression, diagnosis of recurrence, and pathogenesis of PUC. With this technique, it would be possible to increase the diagnostic accuracy in deciding the disease severity in PUC cases.

The mean Hb level of SG was statistically lower than CG. This finding was similar to literature findings (16). Anemia in PUC patients is probably caused by inadequate intake, malabsorptive state, and chronic blood loss by mucosal ulcerations.

Although WBC was defined as a strong predictor of severe clinical disease as measured by PUCAI, we could not find a statistically important difference between the study and control group (17). This finding of our study would be related to the presence of cases with remission in our study group.

MPV is an indicator of platelet activity and aggregation capacity (16). The mean MPV result of the SG was lower than the CG. There was also positive correlation of NT level with MPV in our study. There are multiple adult studies revealed that MPV decreased in active UC patients compared to the control group (17-19). There is no pediatric study about relation of MPV and NT level. Our study was also novel in pediatric PUC literature.

The platelet count of the study group was significantly higher than the control group. This finding supports the hypothesis that in chronic diseases, number, shape, and functions of platelets are important in the amplification of the disease severity (20). According to Chen et al. (19) chronic disease activity and iron deficiency anemia lead to thrombocytosis. Our study results support the idea that iron deficiency would cause thrombocytosis. The mean level of CRP in our SG was significantly higher than the CG which is similar to the findings of Cifci et al. (21). Although CRP was accepted as a classical parameter for IBD patients but our study results showed that CRP level was not correlated with disease activity levels as similar to the literature findings (22).

As expected, the mean level of ESR in our SG was significantly higher than CG which is parallel to the finding of Croft et al. (23). But the correlation with PUCAI was not significant. This finding supports the idea that ESR could not be used for follow-up purposes efficiently.

Our study results showed that the mean IL-6 level was found significantly higher in SG. According to a study by Feng, the life span of T lymphocytes was extended with the help of IL-6 and also IL-6 was defined as a marker of recurrence development in IBD patients who were treated (24). Karaskova et al. (25) also demonstrated that in pediatric IBD patients the level of IL-6 decreased after treatment. Our study results about IL-6 were parallel to the findings of pediatric and adult studies in literature (24,25).

Limitation of our study: Since antioxidant capacity of body would be affected from dietary factors, standard diet would be recommended before measurements. Generally, our patients use grossly similar nutrients since they were given similar instructions and recommendations about diet at the diagnosis time, but we did not check the diet of the children in detail. This study was limited by relatively small sample size in severe PUC cases. And PUCAI that we used to differentiate subgroups, accepted as subjective according to some authorities.

CONCLUSION

This is the first study demonstrating antioxidant NT level of PUC is significantly lower than healthy children. NT level also showed a good correlation with known inflammatory biomarkers, albumin and MPV. There is a significant negative correlation between disease activity defined by PUCAI and NT level. NT level would be a good candidate serum biomarker for PUC patients at the diagnosis and follow-up period without the need of a tissue biopsy. But there is a need for larger and more definitive studies for making decision about the place of NT level measurement in diagnostic and follow-up workup of PUC.

REFERENCES

1. Rubalcava NS, Gadepalli SK. Inflammatory Bowel Disease in Children and Adolescents. Adv Pediatr 2021; 68:121-42.
2. Turner D. Severe acute ulcerative colitis: the pediatric perspective. Dig Dis 2009;27:322-6.
3. Karp SM, Koch TR. Oxidative stress and antioxidants in inflammatory bowel disease. Dis Mon 2006; 52: 199– 207.
4. Hamouda HE, Zakaria SS, Ismail SA, Khedr MA, Mayah WW. p53 antibodies, metallothioneins, and oxidative stress markers in chronic ulcerative colitis with dysplasia. World J Gastroenterol 2011; 17: 2417–23.
5. Pravda J. Radical induction theory of ulcerative colitis. World J Gastroenterol 2005; 11: 2371–284.
6. Winther JR, Thorpe C. Quantification of thiols and disulfides. Biochim Biophys Acta 2014;1840: 838-46.
7. Rodosskaia NK, Chernousova GM. Immune system and thiols: some peculiarities of thiol exchange. Comp Immunol Microbiol Infect Dis 2010; 33: 65-71.
8. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem 2014; 47: 326-32.
9. Patlevič P, Vašková J, Švorc P Jr, Vaško L, Švorc P. Reactive oxygen species and antioxidant defense in human gastrointestinal diseases. Integr Med Res 2016; 5: 250-8.
10. Grzybowska-Chlebowczyk U, Wysocka-Wojakiewicz P, Jasielska M, Cukrowska B, Więcek S, Kniażewska M, et al. Oxidative and Antioxidative Stress Status in Children with Inflammatory Bowel Disease as a Result of a Chronic Inflammatory Process. Mediators Inflamm 2018:4120973.
11. Birimberg-Schwartz L, Zucker DM, Akriv A, Cucchiara S, Cameron FL, Wilson DC, et al. Development and Validation of Diagnostic Criteria for IBD Subtypes Including IBD-unclassified in Children: a Multicentre Study From the Pediatric IBD Porto Group of ESPGHAN. J Crohns Colitis 2017; 11:1078-84.
12. Turner D, Otley AR, Mack D, Hyams J, de Bruijne J, Uusoue K, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology 2007; 133:423-32.
13. Holmes EW, Yong SL, Eiznhamer D, Keshavarzian A. Glutathione content of colonic mucosa: evidence for oxidative damage in active ulcerative colitis. Dig Dis Sci 1998; 43:1088-95.
14. Tsunada S, Iwakiri R, Ootani H, Aw TY, Fujimoto K. Redox imbalance in the colonic mucosa of ulcerative colitis. Scand J Gastroenterol 2003; 38:1002-3.
15. Neselioglu S, Keske PB, Senat AA, Yurekli OT, Erdogan S, Alisik M, et al. The relationship between severity of ulcerative colitis and thiol-disulphide homeostasis. Bratisl Lek Listy 2018;119: 498-502.
16. Mahadea D, Adamczewska E, Ratajczak AE, Rychter AM, Awada A, Eder P, et al. Iron Deficiency Anemia in Inflammatory Bowel Diseases-A Narrative Review. Nutrients 2021;13:4008.
17. Holtman GA, Lisman-van Leeuwen Y, Day AS, Fagerberg UL, Henderson P, Leach ST, et al. Use of Laboratory Markers in Addition to Symptoms for Diagnosis of Inflammatory Bowel Disease in Children: A Meta-analysis of Individual Patient Data. JAMA Pediatr 2017;171:984-91.
18. Kapsoritakis AN, Koukourakis MI, Sfiridaki A,Potamianos SP, Kosmadaki MG, Koutroubakis IE, et al. Mean platelet volume: a useful marker of inflammatory bowel disease activity. Am J Gastroenterol 2001; 96: 776-81.
19. Chen Z, Lu Y, Wu J, Zhang H. Clinical significance of blood platelets and mean platelet volume in patients with ulcerative colitis. J Int Med Res 2021; 49: 3000605211009715.
20. Voudoukis E, Karmiris K, Koutroubakis IE. Multipotent role of platelets in inflammatory bowel diseases: a clinical approach. World J Gastroenterol 2014; 20:3180-90.
21. Cifci S, Ekmen N. Prediction of Mucosal Health by NLR, CRP x NLR and MPV in Ulcerative Colitis: Can Their Availability Change According to Treatment Options? Cureus 2021; 13:e19942.
22. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut 2006; 55: 426-31.
23. Croft A, Lord A, Radford-Smith G. Markers of systemic inflammation in acute attacks of ulcerative colitis: What level of C-reactive protein constitutes severe colitis? J Crohns Colitis 2022;11:jjac014.
24. Feng JS, Yang Z, Zhu YZ, Liu Z, Guo CC, Zheng XB. Serum IL-17 and IL-6 increased accompany with TGF-β and IL-13 respectively in ulcerative colitis patients. Int J Clin Exp Med 2014; 7:5498-04.
25. Karaskova E, Volejnikova J, Holub D, Velganova-Veghova M, Spenerova M, Mihal V, et al. Changes in serum hepcidin levels in children with inflammatory bowel disease during anti-inflammatory treatment. J Paediatr Child Health 2020; 56: 276-82.

Congenital Genitourinary Profile and Management of Syrian Children: Single-Center Experience

Suriyeli Çocukların Konjenital Genitoüriner Profili ve Yönetim Şekli: Tek Merkez Deneyimi

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ABSTRACT

Objective: Aim of the study is to evaluate congenital genitourinary tract anomaly prevalence in Syrian refugee children population and detect difficulties in management of this population.

Material and Methods: Syrian refugee patients who applied to Adana City Training and Research Hospital Pediatric Urology and Pediatric Nephrology outpatient clinics between February 2020 and June 2022 were retrospectively analyzed. Patients aged between 1 month and 18 years with the diagnosis of congenital genitourinary disease were included in the study. Age, gender, application dates, follow-up periods, surgical needs, and hospitalization needs of the patients were recorded from the electronic patient files.

Results: A total of 288 Syrian refugee children (183 male/105 female) with the diagnosis of congenital genitourinary disease were included in the study. Among 288 Syrian refugee children, congenital anomalies of the kidney and urinary tract (CAKUT) was the leading congenital urogenital disease with 175 patients (60.8%). This was followed by nonspecific hydronephrosis in 61 patients (21.2%), urogenital anomaly in 47 patients (16.3%), and cystic kidney disease in 5 patients (1.7%).

Conclusion: As a conclusion, we think that close cooperation between health personnel, social workers, and interpreters will not only protect patients from long-term complications and provide a better quality of life, but also protect the health system from additional financial burden. Interdisciplinary training on cultural sensitivity and special problems of refugees should be established in treatment centers. We believe that special education programs for patients and their families can improve understanding of the disease and its treatment.

Key Words: CAKUT, Children, Syrian refugee

ÖZ

Amaç: Çalışmanın amacı, Suriyeli mülteci çocuk popülasyonunda konjenital genitoüriner sistem anomali prevalansını değerlendirmek ve bu popülasyonun yönetimindeki zorlukları tespit etmektir.

Gereç ve Yöntemler: Şubat 2020-Haziran 2022 tarihleri arasında Adana Şehir Eğitim ve Araştırma Hastanesi Çocuk Ürolojisi ve Çocuk Nefrolojisi polikliniklerine başvuran Suriyeli mülteci hastalar retrospektif olarak değerlendirildi. Çalışmaya 1 ay ile 18 yaş arasında konjenital genitoüriner hastalık tanısı alan hastalar dahil edildi. Hastaların yaş, cinsiyet, başvuru tarihleri, takip süreleri, cerrahi ihtiyaçları ve yatış ihtiyaçları elektronik hasta dosyalarından kaydedildi.

Bulgular: Konjenital genitoüriner hastalık tanısı almış toplam 288 Suriyeli mülteci çocuk (183 erkek/105 kız) çalışmaya dahil edildi. İki yüz seksen sekiz Suriyeli mülteci çocuk arasında konjenital böbrek ve üriner sistem anomalileri (CAKUT)

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by Adana City Training and Research Hospital Ethic Committee on 21 April, 2022 (Ethics committee approval number 1911).

Contribution of the Authors / Yazarların katkısı*: *EKBERLİ G: Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***TANER S:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results.

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175 hasta (%60.8) ile önde gelen konjenital ürogenital hastalıktı. Bunu 61 hasta ile (%21.2) nonspesifik hidronefroz, 47 hasta ile(%16.3) ürogenital anomali ve 5 hasta ile (%1.7) kistik böbrek hastalığı izledi.

Sonuç: Sonuç olarak sağlık personeli, sosyal hizmet uzmanları ve tercümanlar arasındaki yakın işbirliği, hastaları uzun vadeli komplikasyonlardan koruyarak daha iyi bir yaşam kalitesi sağlamanın yanı sıra sağlık sistemini ek mali yükten de koruyacağını düşünüyoruz. Tedavi merkezlerinde kültürel duyarlılık ve mültecilerin özel sorunlarına yönelik disiplinler arası eğitimler oluşturulmalıdır. Hastalar ve aileleri için özel eğitim programlarının, hastalığın ve tedavisinin, hasta ve yakınları tarafından anlaşılmasını kolaylaştırabileceği kanısındayız.

Anahtar Sözcükler: CAKUT, Çocuk, Suriyeli mülteciler

INTRODUCTION

Turkey is one of the countries facing the enormous amount of refugee population after the beginning of the civil war in Syria on March 11, 2011. Syrian people thought to be under ''temporary protection", but nowadays in 2022 this population became permanent especially in cities bordering Syria. The most important problem brought by human migration is the burden added to the existing health system. Missing medical records of patients, communication problems, logistic problems, lack of literature information about relevant society are factors which make the physician's diagnosis and treatment process challenging. To determine the congenital disease profile of refugee population may be meaningful for the host country in preventive and curative health care.

Because of the preventable nature of especially congenital renal problems proper follow up is mandatory. Expected obstacles after irregular migration of Syrian children may result in end-stage renal disease. In this study we aimed to evaluate congenital genitourinary disease profile, follow-up compliance and difficulties in management of refugee population.

MATERIAL and METHODS

Syrian refugee patients who applied to Adana City Training and Research Hospital Pediatric Urology and Pediatric Nephrology outpatient clinics between February 2020 and June 2022 were retrospectively analyzed. Patients aged between 1 month and 18 years with the diagnosis of congenital genitourinary disease were included in the study. Age, gender, application dates, follow-up periods, surgical needs, and hospitalization needs of the patients were recorded from the electronic patient files.

Chronic Kidney Disease (CKD) was defined as on the 'The Kidney Disease: Improving Global Outcomes (KDIGO)' clinical practice guidelines.

This study was approved by Adana City Training and Research Hospital Ethic Committee on 21 April, 2022 (Ethics committee approval number 1911).

Statistical Analyses

All statistical analyses analyzed by SPSS version 21 software package. Data collection and definitions are described below. Normal distribution of numeric variables was tested with Kolmogorov-Smirnov test. Continuous data were defined by means of mean± SD under the parametric conditions and median (interquartile range-IQR) under the nonparametric conditions. P values less than 0.050 were statistically significant.

RESULTS

Patients

A total of 288 Syrian refugee children (183 male/105 female) with the diagnosis of congenital genitourinary disease were included in the study. Median age of the patients was 48.3 months (IQR 90 months) and the median follow-up time was 8 months (IQR 10 months). Of them, 54.5% (157 patients) did not come to their regular follow-ups or scheduled surgical interventions. Surgical intervention was performed in 23.6% (68 patients) of the admitted patients. Among 288 Syrian refugee children, congenital anomalies of the kidney and urinary tract (CAKUT) was the leading congenital urogenital disease with 175 patients (60.8%). This was followed by nonspecific hydronephrosis in 61 patients (21.2%), urogenital anomaly in 47 patients (16.3%), and cystic kidney disease in 5 patients (1.7%).

Congenital Anomalies of The Kidney and Urinary Tract

In 175 CAKUT patients, the three most common etiologies were vesicoureteral reflux (VUR) in 47 patients (26.9%), neurogenic bladder (NB) in 40 patients (22.9%), and obstructive pathologies

Table I: The etiological distribution of the patients with Congenital Anomalies of The Kidney and Urinary Tract

CAKUT (n=175)	Number of the patients, (%)
Vesicoureteral reflux	47 (26.9)
Neurogenic bladder	40 (22.9)
Obstructive pathologies	36 (20.6)
Ureteropelvic junction obstruction	23 (13.1)
Posterior urethral valve	7 (4.0)
Ureterovesical junction obstruction	6 (3.4)
Hypodysplasia/ atrophy	13 (7.4)
Agenesis	12 (6.9)
Ectopic kidney	10 (5.7)
Multicystic dysplastic kidney	8 (4.6)
Others	9 (5.1)
Megaureter	4 (2.3)
Duplex collecting system	3 (1.7)
Bladder diverticulum	1 (0.6)
Horseshoe kidney	1 (0.6)

Table II: Detailed information of end-stage renal disease (ESRD) patients

	Age (months)	Sex	Etiology	Surgery	Surgery country
1	186	F	NB+ ARM	Uretero-cutaneous ostomy	Turkey
2	211	F	NB+ Wolfram Syndrome	-	-
3	186	F	NB+ AA	-	-
4	95	M	PUV	PUV ablation /Nephrostomy	Syria/Turkey
5	194	M	NB+ AA	-	-
6	184	M	NB	-	-
7	174	F	VUR nephropathy	-	-
8	32	M	VUR nephropathy	-	-
9	56	M	PUV	PUV ablation	Tukey
10	125	M	PUV	PUV ablation	Syria
11	124	M	Hypoplasia	-	-

***F:** Female, **M:** Male, **NB:** neurogenic bladder, **ARM:** Anorectal malformation, **PUV:** posterior urethral valve, **AA:** aplastic anemia, **VUR:** vesicoureteral reflux*

Table III: Urogenital Anomaly profile of Syrian Refugee Children

Urogenital Anomaly (n=47)	Number of the patients, (%)
Hypospadias	27 (57.4)
Distal Hypospadias	15 (31.8)
Penoscrotal Hypospadias	6 (12.8)
Penile Hypospadias	6 (12.8)
Cryptorchidism	5 (10.6)
Inguinal hernia	4 (8.5)
Chordee	4 (8.5)
Hydrocele	2 (4.3)
Exstrophy vesica	2 (4.3)
Others	3 (6.3)
Epispadias	1 (2.1)
Meatal stenosis	1 (2.1)
Megameatus intact prepuce	1 (2.1)

in 36 patients (20.6%). The etiological distribution of CAKUT patients was shown in Table I. Chronic kidney disease (CKD) was found with a frequency of 54.3% in CAKUT patients. The frequencies of CKD patients were, Stage 1 CKD 58.9%, Stage 2 CKD 21.1%, Stage 3 CKD 7.4%, Stage 4 CKD 1.1% and Stage 5 CKD (end-stage renal disease) 11.6%, respectively. Detailed information of end-stage renal disease (ESRD) patients is shown in Table II.

Among 47 patients with VUR, 31 (66%) had high-grade reflux, and 23 (48.9%) had bilateral reflux. Median age at diagnosis of the patients was 49 months (IQR 106 months. When the kidney functions of patients with VUR were evaluated, 83% had CKD and only 5% of them were ESRD patients. Of the 26 patients who underwent surgical intervention, ten underwent subureteric injection, six had ureteroneocystostomy (UNC), three had subureteric injection and UNC, one had vesicostomy and one had cystoscopy.

The leading cause of NB was neuro-spinal dysraphism with 33 (80%) patients; of these 32 was myelomeningocele, one was anorectal malformation. Other causes were transverse myelitis, Guillain-Barre syndrome, Wolfram syndrome and post-traumatic injury (firearm injury, traffic accident and spinal operation), respectively. The frequency of CKD in patients with NB is 47.5% and 12.5% of them are ESRD. The frequency of patients not complying with clean intermittent catheterization treatment was 65%. Surgical intervention was performed in 4 patients: vesicostomy in two, ureterocutaneous ostomy in one, and cystolithotripsy in one.

In patients with obstructive pathologies, 75% were male. The frequency of CKD was 58.3% and 8.3% of them are ESRD. Surgical intervention was performed in 80.6% of the patients (59% in our center/ 41% external or Syria), and the remaining patients did not come to the scheduled surgery appointment or did not give consent for the surgery. Ureteropelvic junction obstruction (UPJO) constituting 65.7%, was the most frequent reason of the obstructive pathologies. Of these, 65.2% were left UPJO, 30.4% were right, and 4.3% were bilateral. Of the 6 ureterovesical junction obstruction, four were left-sided, one was right-sided, and one was bilateral.

Urogenital Anomaly

Among the urogenital anomalies, hypospadias was the most common with 57.4%, and distal hypospadias constituted more than half of the patients (55.6%) with a diagnosis of hypospadias. Other urogenital anomalies are shown in Table III. The median age of patients diagnosed with hypospadias was 30 months (IQR 47 months). Surgical intervention was performed in 15 (55.6%), 9 patients (33.3%) did not come to the scheduled surgery day. Of the remaining 3 patients (11.1%), 2 were waiting for the operation day, and 1 was waiting for the decision of the sex determination commission.

DISCUSSION

Defects in embryonic kidney development can lead to congenital anomalies of kidney and urinary tract (CAKUT). In developed countries CAKUT represents %20-30 of all antenatally detected pathologies and prevalence reported to rang between three and six per 1000 births (2). With the development of technology, the expected significant increase in the rate of prenatal diagnosis and treatment makes CAKUT diagnosis more common than in the past. Even positive predictive value of ultrasound in detection of urogenital anomaly such as hypospadias has been reported as 72% (3). The available data on CAKUT from Arabic population are very scanty and extracted. There are only few studies evaluating CAKUT or other kidney related diseases. (4,5). But lately, studies have been reported from Turkish centers in Syria neighborhood regarding refugee population (6-9).

National and regional registries in Europe reported CAKUT to be the leading cause of end-stage renal disease (41.3%) (10). CAKUT (especially obstructive anomalies and renal dysplasia) is reported to be most frequent etiological factor of Chronic Kidney Disease (CKD) in neonatal period and may require prompt surgical intervention (11). A retrospective study from Saudi Arabia evaluated etiological factors of CKD in full term neonates. Obstructive uropathies are reported to be the most common underlying etiology of CKD (5). But very small percentage of these patients required renal replacement therapy (RRT). Most of the patients reported to had ongoing urine production and managed without dialysis after respiratory complications. Bongdaji et al. reported another study from Saudi Arabia regarding congenital genitourinary anomalies. As a conclusion they claimed that, genitourinary anomalies diagnosed in the antenatal period constituting 38.6% of all anomalies diagnosed in that center (5). Among 288 Syrian refugee children, congenital anomalies of the kidney and urinary tract (CAKUT) was the leading congenital urogenital disease with 175 patients (60.8%). Obstructive urinary pathologies (ureteropelvic junction obstruction, ureterovesical junction obstruction and posterior urethral valve) constitute 20.6% of all study population. Raboei et al. (12) in their study conducted with 23.000 babies reported urinary tract malformation incidence to be 7:1,000. This incidence is higher than the studies reported from Sweden or England (13,14). An explanation for this significant difference is high degree of consanguinity in Arabic population (4,12). Resent studies reported no decrease in consanguinity marriage (15). Bongdaji reported 57 (40.4%) of affected fetuses to be products of consanguineous marriages. Although, we do not have data about consanguinity marriage in our study group because of communication problems with study population. Considering the factor that consanguineous marriages are not uncommon in our region awareness rising programs can be helpful for populations with overmentioned traditions.

Chronic kidney disease (CKD) was found with a frequency of 54.3% in CAKUT patients. Frequency of CAKUT related ESRD in presented study is 11.6%. The three most common etiologies were vesicoureteral reflux (VUR) in 47 patients (26.9%), neurogenic bladder (NB) in 40 patients (22.9%), and obstructive pathologies in 36 patients (20.6%). Among patients with obstructive pathologies the frequency of CKD was 58.3% and 8.3% of them are ESRD. All of the identified etiological factors can be prevented with early and proper management.

In presented study of 288 patients with congenital genitourinary anomaly 157 (54.5%) detected to be incompatible with treatment, follow-up and scheduled surgical interventions.

The reasons for bad compliance for follow-up and treatment can be explained by multiple factors such as: socioeconomical factors, cultural reasons, religious issues, communication problems, logistic problems. Lemke et al. (16) in their educational review discussed different challenges which health care professionals may encounter during pediatric refugee patient with renal replacement. Language challenges, perception challenges, social/cultural challenges, medical history, mental health, dietary/medication issues, administrative problems are determined as the factors which hinder access to adequate health services (16). All Syrian people can receive health care in government hospitals for free in Turkey. So, it can be claimed that access to health services by the patient or caregiver in not sufficient for proper management. This group of patients should be managed with holistic perspective and awareness should be raised in caregivers regarding vulnerabilities of children with genitourinary pathology requiring close follow-up or surgical intervention.

Hypospadias is one of the most commonly detected genitourinary pathologies in our study population (57.4). None of the patients had antenatal diagnosis. In concordance with literature majority of patients had distal hypospadias. Most of the reported studies prefer intervention of hypospadias to be before the rise of genital awareness (17). The median age of patients diagnosed with hypospadias was 30 months (IQR 47 months). In patients with proximal hypospadias staged repair prolongs period of surgery. Surgery and hospitalization in advanced ages have many negative aspects, especially post-operative complications.

Hypospadias repair was performed in 15 (55.6%), 9 patients (33.3%) did not come to the scheduled surgery day. We do not have data to explain the reason for not coming to the planned surgery. Education programs for this population about the problems that hypospadias surgery may cause in the older age group may be a solution.

While evaluation of study population's compliance during pre and postsurgical period, it can be said that despite all the advantages provided by the health system, the reason why some patients do not continue their follow-up and treatment and do not neglect their planned surgical interventions is closely related to the socio-cultural structure and education level of the patient population.

CONCLUSION

Our findings support the need for robust and multidisciplinary screening that addresses congenital genitourinary anomalies, taking into account their forced migration experiences, socio-cultural backgrounds and belief systems, in order to facilitate and contribute to the lives of refugee children.

Close cooperation between health personnel, social workers, and interpreters will not only protect patients from long-term complications and provide a better quality of life, but also protect the health system from additional financial burden. Interdisciplinary training on cultural sensitivity and special problems of refugees should be established in treatment centers. Special education programs for patients and their families can improve understanding of the disease and its treatment.

REFERENCES

1. Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158:825-30.
2. Queisser-Luft A, Stolz G, Wiesel A, Schlaefer K, Spranger J. Malformations in newborn: Results based on 30,940 infants and fetuses from the mainz congenital birth defect monitoring system (1990-1998). Arch Gynecol Obstet 2002;266:163-7.
3. Epelboym Y, Estrada C, Estroff J. Ultrasound diagnosis of fetal hypospadias: accuracy and outcomes. J Pediatr Urol 2017;13:484.
4. Kari JA, Sharief SN, El Desoky SM, Alhasan KA, Albanna AS. Etiology, ethics, and outcomes of chronic kidney disease in neonates. Saudi Med J 2018;39:361-7.
5. Bondagji NS. Antenatal diagnosis, prevalence and outcome of congenital anomalies of the kidney and urinary tract in Saudi Arabia. Urol Ann 2014;6:36-40.
6. Balat A,Demircioğlu Kiliç B, Aksu B, Akbalik Kara M, Büyükçelik M, Kara Eroğlu F, et al. Kidney disease profile and encountered problems during follow-up in Syrian refugee children: a multicenter retrospective study. Pediatr Nephrol 2022;37:393-402.
7. Çelakıl M, Çoban Y. Etiologic-sociodemographic assessment and comparison of dialysis modalities in pediatric Syrian migrants with chronic kidney disease. Braz J Nephrol 2022;44:68-74.
8. Akbalik Kara M, Demircioglu Kilic B, Col N, Ozcelik AA, Buyukcelik M, Balat A. Kidney Disease Profile of Syrian Refugee Children. Iran J Kidney Dis 2017;11:109-14.
9. Karadağ ŞG, Sönmez HE, Demir F, Çakan M, Öztürk K, Tanatar A, et al. Rheumatic diseases in Syrian refugee children: a retrospective multicentric study in Turkey. Rheumatol Int 2020;40:583-9.
10. Chesnaye N, Bonthuis M, Schaefer F, Groothoff JW, Verrina E, Heaf JG, et al. Demographics of paediatric renal replacement therapy in Europe: a report of the ESPN/ERA–EDTA registry. Pediatr Nephrol 2019;29:2403–10.
11. Phua YL, Ho J. Renal dysplasia in the neonate. Curr Opin Pediatr 2016;28:209-15.
12. Raboei E, Abou-Seoud M, Abou-Nassef N, Mehboob F, Saggaf A, Luoma R. Prenatal ultrasound screening of the urinary tract is useful. Pediatr Surg Int 2002;18:432–4.
13. Livera LN, Brookfield DS, Eggington JA, Hawnaur JM. Antenatal ultrasonography to detect fetal renal abnormalities: a prospective screening programme. BMJ 1989;27:1421–3.
14. Rosendahl H. Ultrasound screening for fetal urinary tract malformations: a prospective study in the general population. Eur J Obstet Gynecol Reprod Biol 1990;36:27–33.
15. Warsy AS, Al-Jaser MH, Albdass A, Al-Daihan S, Alanazi M. Is consanguinity prevalence decreasing in Saudis?: A study in two generations. Afr Health Sci 2014;14:314-21.
16. Lemke J, Schild R, Konrad M, Pape L, Oh J. Members of the German Society of Pediatric Nephrology (GPN). Distribution and management of the pediatric refugee population with renal replacement: A German pediatric cohort. Pediatr Nephrol 2021;36:271-7.
17. van der Horst HJ, de Wall LL. Hypospadias, all there is to know. Eur J Pediatr 2017;176:435-41.

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Acute Rhabdomyolysis Due To Levetiracetam in A Two-Year-Old Girl

İki Yaşındaki Kız Çocuğunda Levetirasetama Bağlı Akut Rabdomiyoliz

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ABSTRACT

Levetiracetam is one of the safest drugs which is used for the treatment of focal and generalized seizures during childhood. Until now, few patients have been reported with the diagnosis of acute rhabdomyolysis due to levetiracetam and our case is the youngest patient in the literature. Two-year old girl followed with atypical Rett syndrome (CDKL 5 deficiency) was admitted to our hospital with pneumonia and respiratory insufficiency. She was receiving intravenous antibiotics and levetiracetam therapy. During follow-up, the increase of creatine kinase levels continued, intravenous hydration and alkalinization was added on therapy. As we could not find any etiology explaining the raising creatine kinase levels in our patient, levetiracetam was thought to be the cause of rhabdomyolysis and withdrawn. After discontinuation of levetiracetam, creatine kinase levels began to decline within 24 h and returned to normal levels in one week.

Levetiracetam-induced rhabdomyolysis is quite rare but is a life-threatening condition and should be kept in mind especially during childhood. The creatine kinase levels and renal function tests of all patients should be followed in the first week of levetiracetam therapy. Early diagnosis and supportive therapy is very important in order to prevent acute kidney injury. CDKL 5 deficiency can be a protective factor which might prevent acute kidney injury in our patient but more research is needed about this topic.

Key Words: , CDKL5, Levetiracetam, rhabdomyolysis

ÖZ

Levetirasetam çocukluk çağında fokal ve jeneralize nöbetlerin tedavisi için kullanılan en güvenilir antiepileptik ilaçlardan birisidir. Şimdiye kadar levetirasetama bağlı akut rabdomiyoliz tanılı az sayıda hasta bildirilmiştir ve vakamız literatürde bildirilmiş en genç vakadır. Atipik Rett sendromu (CDKL5 eksikliği) tanısıyla izlenen iki yaşındaki kız hasta pnömoni ve solunum yetmezliği nedeniyle hastanemize kabul edildi. İntravenöz antibiyotik ve levetirasetam tedavisi alıyordu. Klinik izleminde kreatin kinaz düzeylerinde yükselme devam etti, intravenöz hidrasyon ve alkalinizasyon tedavisine eklendi. Kreatin kinaz düzeylerinde yükselmeyi açıklayacak neden bulamadığımız için hastamızda rabdomiyolizin levetirasetama bağlı olabileceği düşünüldü ve levetirasetam tedavisi kesildi. Levetirasetam kesildikten sonra 24 saat içerisinde kreatin kinaz düzeyi düşmeye başladı ve bir hafta içersinde normal düzeylerine döndü.

Levetirasetama bağlı rabdomiyoliz çok nadir fakat hayatı tehdit eden bir durum olup özellikle çocukluk çağındaki hastalarda akılda tutulmalıdır. Levetirasetam tedavisinin ilk haftasındaki tüm hastaların kreatin kinaz düzeyleri ve böbrek fonksiyon testleri izlenmelidir. Erken tanı ve tedavi akut böbrek hasarını önlemek açısından çok önemlidir. CDKL5 eksikliği hastamızda akut böbrek hasarını önleyecek koruyucu faktör olabilir ancak bu konuyla ilgili daha fazla sayıda araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Çocuk, CDKL5, Levetirasetam, rabdomiyoliz

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INTRODUCTION

Levetiracetam (LEV) is a second-generation anti-epileptic which regulates the synaptic neurotransmitters by binding to synaptic vesicle protein 2A. Its side effects mainly include somnolence, headache, fatigue, dizziness, vomiting, and behavioral alterations. Rhabdomyolysis as a rare adverse effect of LEV was reported firstly from Japan in the literature in 2014 (1,2).

Rhabdomyolysis results from the rapid breakdown of skeletal muscle fibers which leads to leakage of potentially toxic cellular content into the systemic circulation. Although consensus criteria are lacking, the most-used definition of rhabdomyolysis is a serum creatine kinase level greater than 5 times the upper limit of normal or greater than 1000 U/L. Some of the common causes of rhabdomyolysis include trauma, strenuous exercise, seizures, hypothermia, malignant hyperthermia, electrolyte imbalances (hypokalemia, hypocalcemia, hypophosphatemia), myositis, inherited metabolic diseases such as dystrophies/myopathies, glycogenolysis/glycolysis metabolism disorder, mitochondrial disorders, and certain drugs (statins and succinylcholine). Febrile illnesses and exercise are common triggers of rhabdomyolysis (3).

Rhabdomyolysis may be due to a combination of underlying genetic disorder and environmental triggers. Genetic disorders underlying rhabdomyolysis cause a diagnostic challenge due to their rarity, marked heterogeneity, and nonspecific clinical features requiring a high index of suspicion. Acquired causes are frequently observed. The underlying pathophysiology of this adverse effect is unknown. The increase of intracellular calcium concentration by direct injury to sarcolemma (acquired causes) or the failure of energy production (inherited causes) leading to Na/K-ATPase and Ca2+ATPase pumps dysfunction and skeletal muscle fiber necrosis are pathopysiologic mechanisms causing rhabdomyolysis (4).

We report 2-year-old girl who developed rhabdomyolysis 24 hours after the initiation of LEV, and improved rapidly after withdrawal of this drug.

CASE REPORT

Two-year old girl was admitted to our clinics with pneumonia and respiratory insufficiency. She has been followed with the diagnosis of atypical Rett syndrome (CDKL deficiency) at a different center. She was receiving no antiepileptic drugs and investigated for all inherited metabolic diseases.

She was hospitalized for pneumonia at a different center. She was born after an uncomplicated full-term pregnancy. She had generalized tonic-clonic seizures lasting 20-30 seconds since two months. Phenobarbital, klonazepam, vigabatrin and ACTH were given but seizures did not respond to these drugs. After the diagnosis of CDKL5 deficiency, all antiepileptic drugs were withdrawn because atypical Rett syndrome was thought to be refractory to all antiepileptics. During clinical follow-up, she had seizure lasting for 4-5 minutes and levetiracetam was given with loading dose to treat seizure and antimicrobial therapy (ceftriaxone) for pneumonia. Due to clinical and laboratory (increase in CK,AST,ALT levels) deterioration, she was transferred to our hospital. At our hospital, LEV was continued, cefotaxim and vancomycin were given. Thorax ultrasonography showed bilateral pleural effusion so diagnostic tab was performed and chest tube was inserted by pediatric surgeons. The patient improved remarkably after pleural drainage and control ultrasonography revealed bilateral minimal pleural effusion. During the follow-up, raising CK levels were observed, Intravenous (IV) hydration (1/3 SF) and alkalinization (4 meq/kg NaHCO3,after two days decreased to 2 meq/kg) was added on therapy. After IV hydration and bicarbonate, CK levels continued to rise and reached a level of 71280 U/L (N:33-211). Laboratory investigations revealed high levels of liver function tests (AST:1502 U/L, N:0-46; ALT: 410 U/L, N:8-32). We could not measure serum or urine myoglobin levels. We did not observe dark urine. There was no history of prolonged convulsion. Viral serology was negative. The result of all the metabolic tests were normal. We could not find out any explanation for this unexpected and resistant increase in CK level, for this reason LEV was thought to be the cause of acute rhabdomyolysis and withdrawn. After discontinuation of LEV, CK and liver function tests began to decrease. (CK, AST, ALT levels respectively 32000,949,511; 9211,281,309; 1752,107,166; 731,68,110; 298,59,49). The laboratory tests returned to normal levels at the end of ten days and she was discharged. We diagnosed the patient as rhabdomyolysis induced by LEV based on the clinical course.

DISCUSSION

We present the youngest patient with rhabdomyolysis due to LEV in the literature. Though causality can't be completely established, on the basis of the previously reported side effect of LEV and temporal relationship between clinical and laboratory improvement after discontinuation of this drug, it was likely LEV that caused the rhabdomyolysis in our patient. Fever and serious infection were also important triggers which caused severe acute myolysis with a CK level > 50.000U/L.

Up to date, fourteen patients with LEV-induced rhabdomyolysis were reported and most of them were observed in young and adolescent patients in the literature (5-10). In a recent review analyzing 13 patients, all the patients had elevation in CK level

within 12–36 h after initiation of LEV, supporting the importance of close follow-up, particularly during the initial treatment phase (11). The time duration from initiation of LEV to peak CK elevation was 3–5 days. After the medication was discontinued, improvement in CK levels was observed in all patients. Peak CK levels observed in these cases ranged between 1368 IU/L - 49 539 IU. Our patient is the youngest case with the highest CK level (71280 IU/L) in the literature. Some reports support the idea that there is a relationship between muscle mass and peak CK levels, but our case is inconsistent with this idea.

The myoglobin level rises before CK level, can be measured in serum or urine to confirm the diagnosis but has some limitations and disadvantages. Because it has a half-life of only 1-3 hours and causes a high false-negative rate. Unfortunately, serum or urine myoglobin could not be measured in our patient. The goal of of the treatment for rhabdomyolysis is to preserve renal functions and prevent acute kidney injury (AKI). There is consensus that this can be achieved by administration of IV fluids. There is no set guideline for adult or pediatric patients but normal saline is the most commonly used fluid choice. Animal studies have shown that alkalinization of urine decreases cast formation in the acute management of rhabdomyolysis (12). Early hydration and alkalinization therapy might be a protective factor which prevented the development of AKI in our case. Mortality rate is higher especially in the patients with acute renal failure. Fortunately, renal functions were normal and there was no need for renal replacement therapy in our case.

The present case was diagnosed with atypical Rett syndrome at a different center. CDKL5 deficiency disorder (CDD) is a complex of clinical symptoms resulting from the presence of non-functional CDKL5 protein, i.e., serine-threonine kinase (previously referred to as STK9), or its complete absence. The clinical picture is characterized by epileptic seizures which initiates within the first three months of life and mostly do not respond to pharmacological treatment, epileptic encephalopathy secondary to seizures, and retardation of psychomotor development, which are often observed in the first months of life (13). An interesting study investigating the relationship between CDKL5 and rhabdomyolysis by Kim et al. (14) identified cyclin-dependent kinase-like 5 (Cdkl5), as a critical regulator of renal tubular epithelial cell (RTEC) dysfunction associated with nephrotoxic and ischemia-associated AKI. In this study, the researchers examined the role of Cdkl5 in rhabdomyolysis-associated AKI and found the activation of Cdkl5 in RTECs early during the development of rhabdomyolysis-associated AKI by using activation-specific antibodies and kinase assays. RTEC dysfunction and cell death are among the key pathological features of AKI. Diverse stress conditions such as sepsis, rhabdomyolysis, nephrotoxic drugs can trigger RTEC dysfunction. On the basis of this knowledge, we can propose that CDKL5 deficiency might be a protective factor which prevented rhabdomyolysis-associated renal impairment in our patient but more research is needed about this topic.

Lipin-1 deficiency has been reported as the second most common cause of early-onset rhabdomyolysis after primary fatty acid oxidation disorders. Phosphatidate phosphatase-1 (lipin-1) is encoded by LPIN1gene. LPIN1-related rhabdomyolysis occurs usually in children less than 6 years. Lipin-1 is highly expressed in myocardium and involved in fatty acid metabolism in the cardiomyocytes. After exclusion of primary fatty acid oxidation disorders, lipin-1 deficiency should be suspected in the presence of recurrent rhabdomyolysis, positive family history, exercise intolerance or recurrent muscle cramps (15). We planned to investigate lipin-1 deficiency if recurrent rhabdomyolysis occurs in our patient.

In conclusion, LEV-induced rhabdomyolysis is quite rare but is a life-threatening condition and should be kept in mind especially during childhood. To our current knowledge, this is one of the few reports of rhabdomyolysis due to LEV therapy in children. Early diagnosis and supportive therapy is very important. The CK levels and renal function tests of all patients should be followed in the first week of therapy. Although our patient had risk factors such as young age, serious infection treated with nephrotoxic agent (vancomycin), very high CK levels, she did not develop AKI. CDKL 5 deficiency can be a protective factor which might prevent AKI in our patient, but more research is needed about this topic.

REFERENCES

1. Akiyama H, Haga Y, Sasaki N, Yanagisawa T, Hasegawa Y. A case of rhabdomyolysis in which levetiracetam was suspected as the cause. Epilepsy Behav Case Rep 2014; 2: 152–5.
2. Rastogi V. Rhabdomyolysis: A Rare Adverse Effect of Levetiracetam. Cureus 2018;10:e2705.
3. Hamel Y, Mamoune A, Mauvais FX, Habarou F, Lallement L, Romero NB, et al. Acute rhabdomyolysis and inflammation. J Inherit Metab Dis 2015;38:621-8.
4. Shapiro ML, Baldea A, Luchette FA. Rhabdomyolysis in the intensive care unit. J Intensive Care Med 2012;27:335-42.
5. Di Lorenzo R, Li Y. Rhabdomyolysis associated with levetiracetam administration. Muscle Nerve 2017; 56: E1–2.
6. Singh R, Patel DR, Pejka S. Rhabdomyolysis in a hospitalized 16-year-old boy: A rarely reported underlying cause. Case Rep Pediatr 2016; 7873813.
7. Kubota K, Yamamoto T, Kawamoto M, Kawamoto N and Fukao T. Levetiracetam-induced rhabdomyolysis: A case report and literature review. Neurol Asia 2017;22: 275–8.
8. Aslan N, Yildizdas D, Huseyınlı B, Horoz OO, Mert GG, Ekinci F, et al. Levetiracetam Treatment-Associated Acute Rhabdomyolysis in an Adolescent. J Pediatr Intensive Care 2020;9:139–40.

9. Incecik F, Herguner OM, Besen S, Altunbasak S. Acute rhabdomyolysis associated with levetiracetam therapy in a child. Acta Neurol Belg 2016 ;116:369-70.
10. Rota E, Arena L, Celli L, Testa L, Morelli N. Levetiracetam-induced rhabdomyolysis: the first Italian case. Neurol Sci 2018;39:1629-30.
11. Moinuddin IA. Suspected Levetiracetam-Induced Rhabdomyolysis: A Case Report and Literature Review. Am J Case Rep 2020;21:e926064.
12. Szugye HS. Pediatric Rhabdomyolysis. Pediatr Rev 2020;41:265-75.
13. Jakimiec M, Paprocka J, Śmigiel R. CDKL5 Deficiency Disorder—A Complex Epileptic Encephalopathy. Brain Sci 2020;10:107.
14. Kim JY, Bai Y, Jayne LA, Cianciolo RE, Bajwa A, Pabla NS. Involvement of the CDKL5-SOX9 signaling axis in rhabdomyolysis-associated acute kidney injury. Am J Physiol Renal Physiol 2020;319:F920-9.
15. Indika NLR, Vidanapathirana DM, Jasinge E, Waduge R, Shyamali NLA, Perera PPR. Lipin-1 Deficiency-Associated Recurrent Rhabdomyolysis and Exercise-Induced Myalgia Persisting into Adulthood: A Case Report and Review of Literature. Case Rep Med 2020;27:7904190.

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COVID-19-Associated Acute Immune Thrombocytopenic Purpura: An Unusual Pediatric Case

COVİD-19 İlişkili Akut İmmün Trombositopenik Purpura: Sıradışı Pediatrik Bir Olgu

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ABSTRACT

Immune thrombocytopenic purpura (ITP) is a hematological disease manifested by isolated thrombocytopenia. Viral infections in the last month are often found in its etiology. After COVID-19 infection, various hematological complications can be seen, as well as the development of ITP. In this article, a case of pediatric acute ITP who was diagnosed during COVID-19 infection and had no signs of bleeding is presented.

Key Words: COVID-19, Children, Immune thrombocytopenic purpura (ITP), Without petechiae

ÖZ

İmmün trombositopenik purpura (İTP), izole trombositopeni ile kendini gösteren hematolojik bir hastalıktır. Etiyolojisinde son bir aydaki viral enfeksiyonlar sıklıkla bulunur. COVİD-19 enfeksiyonu sonrası çeşitli hematolojik komplikasyonların yanı sıra ITP gelişimi de görülebilmektedir. Bu yazıda COVİD-19 enfeksiyonu sırasında teşhis edilen ve kanama bulgusu olmayan bir çocuk akut ITP olgusu sunulmaktadır.

Anahtar Kelimeler: COVİD-19, Çocuklar, İmmün trombositopenik purpura (İTP), Peteşi olmadan

INTRODUCTION

Immune thrombocytopenic purpura (ITP) is a hematological disorder that generally manifests with petechial/purpuric lesions defined by a platelet count <100000/mm^3. Viral infections in the last month are frequently included in its etiology (1).

ITP has been identified after various viral infections including hepatitis B/C viruses (HBV/HCV), cytomegalovirus (CMV), varicella zoster virus (VZV), human immunodeficiency virus (HIV) (2). A new one has been added to these viral infection agents with the start of reporting of COVID-19 related immune thrombocytopenic purpura cases (3-5).

CASE REPORT

Previously, a healthy 6-month-old baby girl applied to the emergency service with the complaint of fever that had been going on for two days. The patient did not have any other complaints on her application. In her vital signs and physical examination, he had no abnormal findings other than 38°C body temperature. A COVID-19 nasopharyngeal swab PCR test was requested from the patient, as he had a history of close contact with a father, aunt and cousin known to be infected with COVID-19. There was no history of drug use, previous viral infection or vaccination in the past

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month. No hematologic disease was identified in her family history in her first-degree relatives. He was admitted to the pediatric infectious diseases service for observation due to a symptomatic COVID-19 infection. In the hemogram taken on the first day of hospitalization, the white blood cell count was 8240/mm^3, the absolute neutrophil count: 4610/mm^3, the absolute lymphocyte count: 2030/mm^3, hemoglobin: 11.8 g/dL, and the platelet count: 21.000/mm^3. In the hemogram of the patient, which was taken two weeks ago, it was seen that the platelet count was 200.000 /mm^3. In the peripheral smear, the platelet count was consistent with 20.000/mm^3, platelet morphology was normal, and no atypical cells were found. The patient was consulted with the pediatric hematology-oncology department, immune thrombocytopenic purpura (ITP) was considered, and tests for autoimmune and infectious etiology were requested. ANA, anti-double-stranded DNA, indirect and direct Coombs test, antiphospholipid antibody, anti-cardiolipin antibody tests requested for autoimmune etiology were negative. HBsAg, Anti-HIV, Anti HCV, brucella rose bengal, brucella IgM and IgG, CMV IgM and IgG, toxoplasma IgM and IgG, rubella IgM and IgG, salmonella tube agglutination, parvovirus IgM and IgG infectious etiology tests resulted negative. The COVID-19 nasopharyngeal swab PCR test was positive. Fever continued for two more days in clinical follow-up and responded to intravenous paracetamol administration. No fever was observed in the following days. Our patient was accepted as COVID-19-associated acute ITP because of exclusion of other causes and COVID-19 nasopharyngeal swab PCR positivity. Intravenous immunoglobulin (IVIG) infusion (1 g/kg) was administered, and the control platelet count at the 48th hour after the end of the infusion was 162000/mm^3. Response to intravenous immunoglobulin infusion was observed. Her family was advised to apply a two-week home quarantine. After the end of home quarantine, pediatric hematology outpatient clinic and hemogram control were recommended. On the 15th day after discharge, the platelet count checked in the pediatric hematology-oncology outpatient clinic was 196.000/mm^3, and other hemogram values were within normal limits. During the six-month outpatient follow-up period, the patient's platelet count and other hemogram parameters were found to be within normal limits.

DISCUSSION

Viral infections and other immunological triggers can be counted among the causes of ITP that can be detected (6). Approximately two-thirds of newly diagnosed ITPs have a history of viral infection in the past month (1). In our case, there was no history of viral infection in the last month, but there was a history of close contact with family members and relatives infected with COVID-19 at home, and the diagnosis was made with a positive nasopharyngeal swab PCR test. Especially after the measles-mumps-rubella (MMR) vaccine, which is one of the early childhood vaccines, ITP development can be seen with a small percentage, and ITP development is not expected after other early childhood vaccines (7). In our case, there was no history of vaccination in the last month before hospitalization.

Immune thrombocytopenic purpura is a diagnosis made by excluding other causes (8). Viral infections (HIV, HCV, CMV, parvovirus), hematological diseases (leukemia, autoimmune hemolytic anemia, etc.), systemic autoimmune diseases (systemic lupus erythematosus, etc.) are diagnoses that should be excluded (9). In our case, the tests requested for autoimmune etiology for other causes of ITP were negative, except for the COVID-19 nasopharyngeal swab PCR test, which is one of the tests requested for infectious etiology, all others were negative. IVIG infusion was given to our case due to near-severe thrombocytopenia, and a positive platelet count response was observed in the hemogram control after the infusion, supporting the diagnosis of ITP. In the six-month follow-up of our patient after discharge, it was observed that the platelet count and other hemogram parameters were normal. All these findings supported the diagnosis of acute ITP associated with COVID-19 in our case.

The platelet count <100.000/mm^3 is used to define thrombocytopenia in ITP. The platelet count of our patient was 21.000/mm^3 and platelet morphology was normal in the peripheral smear. Mild thrombocytopenia can usually be seen in COVID-19 infection (10). However, in severe COVID-19 infection, severe thrombocytopenia can be seen in proportion to the severity of the disease (11). However, in cases where the platelet count is <100.000/mm^3 or the platelet count has decreased by more than 50%, autoimmune causes (especially ITP) should be considered first.

In a systematic review (15), three pediatric cases (12-14) presenting as COVID-19-related ITP in different age groups were mentioned. The clinical features of these cases, their treatments for ITP and clinical follow-up information will be given below, respectively.

A 10-year-old female patient, who was healthy before the first case, applied to the emergency department with the complaint of a one-day rash. The rash has spread from his lower extremities bilaterally to his chest and neck within 24 hours. On the morning of admission, he had purple lesions and new bruises in his mouth. 3 weeks ago, the patient had been mildly ill with 2 days of fatigue, non-productive cough and fever up to 38.3°C in the setting of SARS-CoV-2 exposure. She then felt completely fine for 2.5 weeks until the rash developed. She had severe thrombocytopenia (5000/mm^3) at her admission. SARS-CoV-2 nasopharyngeal swab PCR test was positive. (1g/kg) received an intravenous IVIG infusion. He was discharged from the hospital the next morning. The hemogram control after two weeks and at the second month was normal (12).

The second case, a 16-year-old male patient, presented with rash and mouth sores. SARS-CoV-2 nasopharyngeal

swab PCR test could not be performed, COVID-19 IgG test was positive. Both of her parents reported flu-like symptoms that they had quarantined at home 3-4 weeks ago. At her admission, she had extensive petechiae of the skin and oral mucosal purpura, and moderate thrombocytopenia (45.000/mm^3). One day after discharge, petechiae and purpura, and platelet count decreased to 4000/mm^3. It started with clinical improvement with corticosteroid treatment, and the platelet count increased to 73.000/mm^3 after one week (13).

The third case, a 12-year-old girl, presented with complaints of fever, cough and vomiting for 5 days. In her application, the SARS-CoV-2 nasopharyngeal swab PCR test was positive. He was treated with IVIG (1 g/kg) and steroids (1.5 mg/kg MPZ). While the platelet count was 10.000/mm^3 at admission, it increased to 143.000/mm^3 after the treatments. Because the patient had severe acute respiratory distress syndrome, mechanical ventilation support, tocilizumab and remdesivir were given. The patient was discharged on the 14th day of hospitalization (14).

Apart from the three pediatric cases mentioned in the systematic review, two more pediatric cases (fourth and fifth cases) were reported. The clinical features of these cases (16,17), treatments applied for ITP, and clinical follow-up information are given below.

The fourth case, an 11-year-old male patient, was admitted with the complaint of diffuse petechiae and ecchymosis. She had severe thrombocytopenia (5000/mm^3) on her admission and SARS-CoV-2 nasopharyngeal swab PCR test was positive. Fever and cough preceded the onset of petechial rash approximately 4 weeks. Intravenous immunoglobulin infusion was administered (800 mg/kg), partial response was initially obtained (platelet count 45.000/mm^3) 48 hours after the end of the infusion. A second IVIG infusion was administered four days after the first infusion, resulting in a complete response (platelet count 216.000/mm^3 48 hours after the end of the infusion). Three weeks later, the patient was discharged and followed up in the outpatient clinic. It was reported that he was in optimal clinical condition and his complete blood count was normal in his nine-month follow-up (16).

The fifth case, a 1-year-old 5-month-old female patient, presented with fever and ecchymosis that had been going on for two weeks in her limbs. She had a mild history of COVID-19 five weeks ago. In her application, her platelet count was 20.000/mm^3. COVID-19 IgG antibodies were positive. A single dose of intravenous IVIG (1 g/kg) was administered. One week later, the platelet count was 100.000/mm^3 in the hemogram control. Platelet count completely normalized in 10 weeks. He completed his three-month follow-up and was in full remission (17).

In our case, there was no sign of bleeding in the physical examination at admission and during the follow-up period. At the time of admission, the platelet count was 21.000/mm^3, and the SARS-CoV2 nasopharyngeal swab test was positive. The duration of symptoms before admission was two days. Complete response to intravenous immunoglobulin treatment was obtained, and in the 6-month follow-up after discharge, she was clinically stable and her platelet count was within normal limits.

Although the diagnosis of ITP was made in the second and third weeks after the onset of COVID-19 disease, there were cases of ITP that started in the first week. This may be due to the inability of patients to recognize or report the symptoms of COVID-19 disease (15). In a systematic review, ITP is among the autoimmune diseases that can develop after COVID-19 infection, and the time between the symptoms of COVID-19 disease and the onset of autoimmune symptoms ranges from 2 days to 33 days (18). In our case, the time between the onset of symptoms and diagnosis was as short as two days.

It is remarkable that our case was diagnosed with ITP very soon after the symptoms of COVID-19 appeared and there was no sign of bleeding at the time of diagnosis.

In conclusion, when sudden thrombocytopenia is detected in children diagnosed with COVID-19 disease, the diagnosis of COVID-19 associated with ITP should be kept in mind even if there is no evidence of bleeding. Although the development of ITP is expected 2-3 weeks after the diagnosis of COVID-19 infection, it should be kept in mind that the development of ITP may occur days after the onset of symptoms.

REFERENCES

1. Kühne T, Buchanan GR, Zimmerman S, Michaels LA, Kohan R, Berchtold W, et al. Intercontinental Childhood ITP Study Group; Intercontinental Childhood ITP Study Group. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the Intercontinental Childhood ITP Study Group. J Pediatr 2003;143:605-8.
2. Zeller B, Rajantie J, Hedlund-Treutiger I, Tedgård U, Wesenberg F, Jonsson OG, et al. NOPHO ITP. Childhood idiopathic thrombocytopenic purpura in the Nordic countries: epidemiology and predictors of chronic disease. Acta Paediatr 2005;94:178-4.
3. Zulfiqar AA, Lorenzo-Villalba N, Hassler P, Andrès E. Immune Thrombocytopenic Purpura in a Patient with Covid-19. N Engl J Med 2020;382:e43.
4. Lévesque V, Millaire É, Corsilli D, Rioux-Massé B, Carrier FM. Severe immune thrombocytopenic purpura in critical COVID-19. Int J Hematol 2020;112:746-50.
5. Bomhof G, Mutsaers PGNJ, Leebeek FWG, Te Boekhorst PAW, Hofland J, Croles FN, et al. COVID-19-associated immune thrombocytopenia. Br J Haematol 2020;190:e61-4.
6. D'Orazio JA, Neely J, Farhoudi N. ITP in children: pathophysiology and current treatment approaches. J Pediatr Hematol Oncol 2013;35:1-13.
7. O'Leary ST, Glanz JM, McClure DL, Akhtar A, Daley MF, Nakasato C, et al. The risk of immune thrombocytopenic purpura after vaccination in children and adolescents. Pediatrics 2012;129:248-55.

8. British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol 2003;120:574-96.
9. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.
10. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.
11. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta 2020;506:145-8.
12. Tsao HS, Chason HM, Fearon DM. Immune Thrombocytopenia (ITP) in a Pediatric Patient Positive for SARS-CoV-2. Pediatrics 2020;146:e20201419.
13. Rosenzweig JD, McThenia SS, Kaicker S. SARS-CoV-2 infection in two pediatric patients with immune cytopenias: A single institution experience during the pandemic. Pediatr Blood Cancer 2020;67:e28503.
14. Patel PA, Chandrakasan S, Mickells GE, Yildirim I, Kao CM, Bennett CM. Severe pediatric COVID-19 presenting with respiratory failure and severe thrombocytopenia. Pediatrics 2020;146:e20201437.
15. Bhattacharjee S, Banerjee M. Immune Thrombocytopenia Secondary to COVID-19: a Systematic Review. SN Compr Clin Med 2020;2:2048-58.
16. Ceglie G, De Ioris MA, Mercadante S, Olivini N, Del Bufalo F, Marchesani S, et al. Immune thrombocytopenia in a child with COVID-19: Is it the calm after the (cytokine) storm? Pediatr Blood Cancer 2022;69:e29326.
17. Vadakkekara J, Mathew R, Khera S. COVID-19-Associated Immune Thrombocytopenia in a Toddler. Indian J Pediatr 2022;89:623.
18. Saad MA, Alfishawy M, Nassar M, Mohamed M, Esene IN, Elbendary A. COVID-19 and Autoimmune Diseases: A Systematic Review of Reported Cases. Curr Rheumatol Rev 2021;17:193-204.

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Chest Pain in Children

Çocuklarda Göğüs Ağrısı

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ABSTRACT

Chest pain is one of the most common reasons for admission to the emergency department, pediatrics and pediatric cardiology clinics in childhood. While pain is not usually caused by a serious cause, it can be of concern to the patient and their parents. Clinicians should inform the family of the benign nature of chest pain, unless they consider an important underlying cause. Routine referral of these patients to the cardiology department is not recommended, as it increases family and patient anxiety and may cause unnecessary evaluation. Chest pain can occur at any age, but its incidence increases after 10 years of age. The most frequent causes are costochondritis, chest wall muscle pain due to trauma or muscle strain and respiratory tract diseases. Cardiac reasons are rare with a prevalence of less than 6% and further diagnostic studies does not always necessary.

Key Words: Chest pain, Children, Pediatric cardiology

ÖZ

Göğüs ağrısı, çocukluk çağında acil servis, pediatri ve çocuk kardiyoloji kliniklerine en sık başvuru nedenlerinden biridir. Ağrı genellikle ciddi bir nedenden kaynaklanmasa da, hasta ve ebeveynleri için endişe kaynağı olabilir. Klinisyenler, altta yatan önemli bir neden olduğunu düşünmedikçe, aileyi göğüs ağrısının iyi huylu doğası hakkında bilgilendirmelidir. Aile ve hasta kaygısını arttırdığı ve gereksiz değerlendirmelere neden olabileceği için bu hastaların rutin olarak kardiyoloji bölümüne sevk edilmesi önerilmemektedir. Göğüs ağrısı her yaşta ortaya çıkabilir, ancak 10 yaşından sonra görülme sıklığı artar. En sık nedenler kostokondrit, travma veya kas gerilmesine bağlı göğüs duvarı kas ağrısı ve solunum yolu hastalıklarıdır. Kardiyak nedenlerin prevalansı %6'dan daha azdır ve daha ileri tanısal çalışmalar her zaman gerekli değildir.

Anahtar Kelimeler: Göğüs ağrısı, Çocuklar, Pediatrik kardiyoloji

INTRODUCTION

Chest pain is one of the most common reasons for admission to the emergency department, pediatrics and pediatric cardiology clinics in childhood (1, 2). While pain is not usually caused by a serious cause, it can be of concern to the patient and their parents. Clinicians should inform the family of the benign nature of chest pain, unless they consider an important underlying cause. Routine referral of these patients to the cardiology department is not recommended, as it increases family and patient anxiety and may cause unnecessary evaluation (3).

Chest pain can occur at any age, but its incidence increases after 10 years of age. The most frequent causes are costochondritis, chest wall muscle pain due to trauma or muscle strain and respiratory tract diseases. Although cardiac causes have been shown to be as high as 17% in pediatric cardiology outpatient admissions, they are rare with a prevalence of less than 6% in pediatric polyclinics and pediatric emergency department

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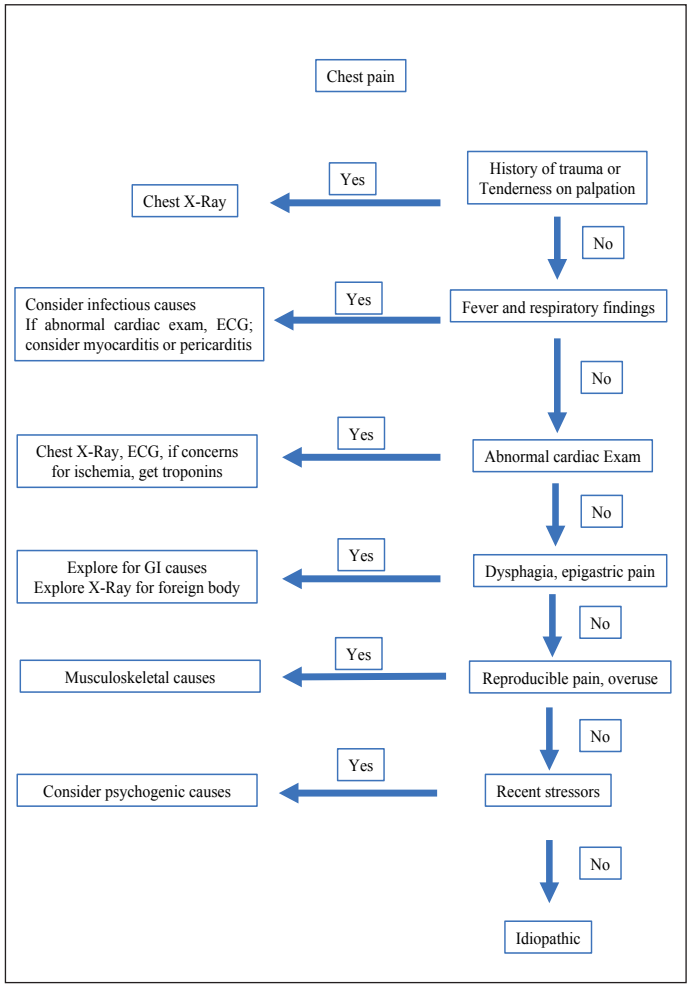

Figure 1: Chest pain diagnostic algorithm

admissions, and further diagnostic studies are not always necessary (2, 4-6) (Figure 1). Table I lists common non-cardiac causes of chest pain in children.

Noncardiac Chest Pain

Chest pain is noncardiac in origin in more than 98% of children (7). Causes are most often found on thorax and respiratory system (3). Noncardiac causes can be classified as musculoskeletal, pulmonary, gastrointestinal, and miscellaneous.

Musculoskeletal / Chest-Wall Pain

The most common cause of chest pain in children is chest-wall pain. The prevalence can reach up to 31% (8). idiopathic causes being the most frequent; costochondritis, Tietze syndrome, trauma and muscle strain, xiphoid pain are the main causes.

Costochondritis is characterized by unilateral sharp pain along upper costochondral joints. It is more common in girls older than 12 years of age. Pain is usually exaggerated by deep breathing or a specific position and lasts from a few seconds to minutes. Tenderness on palpation on the affected area is diagnostic. There is no sign of inflammation. It is a benign, self-limited situation but pain can persist for several months.

Table I: Non-cardiac Causes of Chest Pain in Children

Musculoskeletal
Costochondritis
Muscle trains
Trauma to chest wall
Abnormalities of the thoracis spine
Tietze syndrome
Respiratory
Asthma
Pneumonia
Pleural effusion
Pneumothorax or pneumomediastinum
Pulmonary embolism
Gastrointestinal
Gastroesophageal reflux disease
Peptic ulcers
Esophageal spasm
Esophagitis-gastritis
Cholecystitis
Pancreatitis
Psychogenic
Anxiety
Panic
Somatoform disorder(conversion)
Depression
Emotional distress
Miscellaneous
Mastalgia
Herpes zoster
Sickle cell disease
Precordial catch
Slipping rib syndrome
Pleurodynia
Thoracis tumor

Tietze's syndrome is nonsuppurative inflammation of the costochondral, costosternal or sternoclavicular joints particularly the second and third costochondral junctions, characterized by swelling and tenderness of the affected area. It can be preceded by a respiratory tract infection with coughing or retching (9). Symptoms are usually accompanied by radicular arm pain. It is usually self-limited and analgesics can be used. In its chronic, medically refractory form intercostal nerve block or surgical intervention has been suggested (10).

Musculoskeletal chest pain is caused by strains of the muscles after exercise, coughing, trauma as well as continued muscle strain from video gaming. Rest and reassurance are the primary treatments but for the patients who have severe pain non-steroidal anti-inflammatory drugs for 1 week can be helpful.

Respiratory

The prevalence of chest pain due to air-way and pulmonary causes is 10% to 20% (3). Pulmonary pain can be originated from the main air-ways, parietal pleura, chest-wall muscles or diaphragm.

Asthma and exercise-induced bronchospasm are common causes of respiratory chest pain and should be considered in patients particularly with history or family history of asthma,

eczema, allergies. In these patients, chest pain is usually benign, not localized, retrosternal, and most likely secondary to chest-wall muscle strain after excessive cough and, dyspnea or hyperinflation (11). Rarely it is secondary to serious causes like pneumothorax or pneumomediastinum (5).

Chest pain in patients with pneumonia, parapneumonic effusion, pleuritis is typically sharp, and can be localized laterally. However, these patients are usually unwell. Respiratory pain can be resent as ipsilateral shoulder pain as a result of diaphragmatic irritation of the phrenic nerve.

Pulmonary embolism is extremely rare in children. It has been reported in children with hypercoagulation syndromes and female adolescents using oral contraceptives. It may manifest as hypoxia with the symptoms of dyspnea, pleuritic pain, cough, and fever(12).

Psychogenic

Psychogenic chest pain is a diagnosis of exclusion, and should be considered after a thorough history taking and follow-up examination. Its incidence is higher in teenagers, especially girls (8, 14). Recent psychologic or emotional stress can trigger the pain and it may last longer than 6 months. It is more common in children with a family history of cardiac disease (15). This kind of pain is vague and may be localized over the heart and radiate to the left arm. It may occur at rest and does not worsen with exercise. Often, the parents are extremely anxious, while the child exhibits the classic indifference seen in many psychosomatic disorders.

Anxiety-related hyperventilation is a very common form of psychogenic pain. Although the cause is psychological, a hypocapnoeic alkalosis after dysfunctional breathing can cause coronary artery vasoconstriction, resulting in real physical pain (16). Physiotherapist can help the patient learn breathing techniques to prevent dysfunctional breathing.

Anxiety-related hyperventilation is a very common form of psychogenic pain. Although the cause is psychological, a hypocapnoeic alkalosis after dysfunctional breathing can cause coronary artery vasoconstriction, resulting in real physical pain (10). Physiotherapist can help the patient learn breathing techniques to prevent dysfunctional breathing.

Miscellaneous

- *Breast development*

  During puberty can cause pain in girls and boys with gynecomastia. Trauma, mastitis and particularly in post pubertal girls, breast cysts may lead to localized pain.

- *Herpes Zoster*

  It can produce sharp, localized pain due to intercostal neuralgia. Pain can be present before the skin lesions and worsens with deep breathing and movement. With healing of skin eruptions, the pain typically resolves however postherpetic neuralgia may persist. In these cases, gabapentin or local anesthetic blocks can be considered.

- *Precordial Catch Syndrome (Texidor's twinge)*

  This is a sharp, brief, well-localized pain, most commonly seen in healthy individuals between 6 and 12 years of age (17). It is an extremely common but etiology is unknown. The origin of the pain may come from the parietal pleura or chest-wall muscles (18). The pain is typically localized below the left breast or left sternal border, rarely lasts longer than 1 min, does not radiate and usually worsens with deep inspiration (17). Careful history-taking is necessary to reveal diagnostic features of the syndrome. The pain may recur frequently. No treatment is needed but reassurance is helpful (19).

- *Slipping-Rib Syndrome*

  It is an infrequent cause of recurrent chest or abdominal pain in children. It occurs as a result of luxation of the costal cartilage as a result of inadequacy or rupture of the interchondral fibrous ligaments in the 8th, 9th and 10th ribs which does not attach directly to the sternum (20). This can cause rib laxity and intercostal nerve entrapment. The hooking maneuver, a reproduction of the pain and producing a clicking and popping sound by pulling inferior ribs slightly superiorly, and anteriorly, is positive in these patients. Rest and anti-inflammatory medications may be helpful. In severe cases local anesthetic blocks, and surgery can be performed.

- *Pleurodynia (Devil's grip)*

  Pleurodynia is also known as Bornholm disease, is a rare underdiagnosed etiology of chest pain in adolescents. It is caused by enterovirus infections, most commonly of the Coxsackie B group. It is characterized by sudden episodes of pleuritic and abdominal pain. The pain may be accompanied by fever, myalgia, and upper respiratory symptoms. It is self-limited and usually resolves within 1 to 7 days.

Cardiac Causes of Chest Pain

Chest pain, although only 2% to 5% of children are of cardiac origin, is a concern for the patient and their parents (3). One study reported that up to 56% of adolescents with chest pain believed they had heart disease (21). Cardiac causes was found to be statistically significant in patients with chest pain accompanied by fever, dyspnea, palpitations, pallor and pathological murmur on examination (22). Patients feel the pain in the precordial or substernal area as a deep, heavy pressure sensation, and the pain may radiate to the neck, jaw, arms, back, or the abdomen. Pericardial or myocardial inflammatory diseases, coronary artery abnormalities, increased myocardial demand or decreased supply, medication or drug abuse that may induce coronary vasoconstriction are the main causes of cardiac chest pain in children (23) (Table II).

Table II: Cardiac Causes of Chest Pain in Children
Inflammatory
Pericarditis
Myocarditis
Post-pericardiotomy syndrome
Ischemic
Coronary artery diseases
Kawasaki disease
Congenital coronary artery abnormalities
Cycle cell disease
Hypertension
Severe aortic stenosis, pulmonary stenosis
Eisenmenger's syndrome
Hypertrophic obstructive cardiomyopathy
Dilated cardiomyopathy
Mitral valve prolapse
Drug abuse
Aortic dissection (Marfan syndrome, Turner syndrome, Noonan syndrome)
Arrhythmias
Supraventricular tachycardia
Frequent premature ventricular contractions

Inflammatory Causes: Pericarditis, Myocarditis

Pericardial inflammation may occur in viral, bacterial, rheumatological causes and post-pericardiotomy syndrome after recent open-heart surgery. Patients identify a sharp, constant precordial pain, typically worsens by lying down and relieved by sitting or bending forward. ECG may show low QRS voltages due to pericardial effusion, widespread ST-T segment elevation, deflection of the PR segment in the direction opposite to P wave.

Myocarditis is a serious cause of chest pain in children. In children over 10 years of age, lightheadedness, syncope are more frequent, whereas respiratory presentations are more common in younger children (24). Tachypnoea, hepatomegaly and tachycardia are frequently present on physical examination. Common ECG findings include tachycardia, T wave and ST segment changes.

Ischemic Myocardial Diseases

In these diseases in which the oxygen demand of the heart or oxygen supply to the heart is diminished, chest pain typically tends to worsen with exercise and relieve with rest. Acute myocardial infarction is rarely seen in children. It can be seen in children with coronary artery diseases (Kawasaki disease, anomalous origin of coronary arteries, coronary arteriovenous or coronary cameral fistulae, Williams syndrome), familial hypercholesterolemia, previous heart transplant, sickle cell disease, cardiac myxoma, hypercoagulable states, drug abuse, and metabolic diseases such as homocystinuria and mucopolysaccharidosis. Cardiac examination may be normal but ECG may show ST-T segment changes or old myocardial infarction. For the diagnosis, computed tomography or coronary angiography may be indicated.

Severe congenital obstructive lesions such as aortic or subaortic stenosis, and pulmonary stenosis may result in chest pain because of increased oxygen demand from tachycardia and increased pressure work of the ventricle. A prominent murmur is heard on examination and ventricular hypertrophy or strain pattern is found on ECG. Echocardiography is diagnostic.

Pulmonary arterial hypertension is a rare but serious clinical condition and can cause chest pain. It can be difficult to diagnose and often has a fatal course. It may be secondary to congenital heart diseases, pulmonary and collagen tissue diseases or it may be idiopathic. The most common symptom in these patients is dyspnea, especially with exercise, but 3% may have chest pain (25).

Hypertrophic or dilated cardiomyopathy can cause chest pain because of ischemia or arrhythmias.

About 3.5% of aortic dissection cases occur in the adolescent period (26). It is more common in patients with coarctation of the aorta, aortic stenosis, Turner's syndrome, Marfan's, Ehler-Danlos and Noonan's syndrome (27). Trauma, cocaine use and weight lifting are other risk factors. Echocardiography or computed tomography is helpful for diagnosis.

Vague, brief chest pain not associated with exercise has been identified in 20% of patients with mitral valve prolapse (3). The etiology is not clearly understood, but it is thought to be due to tension of the papillary muscles.

Arrhythmias

Arrhythmia is a common cause of chest pain of cardiac origin in children. It has been found to occur with a frequency of 2% in children presenting to the emergency department with chest pain (22). Especially in tachyarrhythmias, it occurs due to both increased oxygen demand of the heart and decreased blood supply due to shortened diastole time.

Approach to the Pediatric Patient with Chest Pain

In children with chest pain, care should be taken to ensure that the pain is not due to a cardiac or other important etiology. Even though a detailed anamnesis and physical examination are usually sufficient for this, further investigations may be performed in patients in whom the cause cannot be identified.

History

As organic causes are more common in acute pain, the onset of pain should be questioned in history. In patients with pain that awakens from sleep and is exacerbated by exercise, organic causes have been found to be more common. Factors such as eating, exercise, trauma, and psychological stressors that aggravate or elicit pain should be questioned. Children may not always be able to describe the sensation of pressure, crushing and squeezing radiating to the neck, which are typical characteristics of cardiac pain. Causes involving the chest wall increase with motion, whereas in patients with pericarditis, the pain relieves when the patient sits or leans forward and worsens when lying down.

Cardiac causes are more common in patients with palpitations and syncope. History of fever may be due to cardiac causes such as myocarditis, pericarditis as well as other diseases such as pneumonia.

In addition, drug use such as oral contraceptives or the use of drugs that cause coronary vasospasm in adolescents should be questioned.

Medical history should include Kawasaki disease, asthma, diabetes mellitus, sickle cell disease, connective tissue disease, and Marfan syndrome. Family history should focus on the presence of a family member with unexplained or sudden death.

Physical Examination

Physical examination should start with vital signs, followed by the patient's general appearance in terms of anxiety, skin color, and level of alertness. Tachycardia or tachypnea may be identified in patients with severe cardiac or respiratory organic disease. In patients with fever, infectious or inflammatory causes may be underlying. In children with familial hypercholesterolemia, xanthomas can be detected on the skin, especially on the palms, elbows, knees and buttons. Attention should be paid to the presence of stigmas of Marfan syndrome and other connective tissue diseases, which can potentially lead to serious heart disease.

Palpation of the chest wall is usually painful in patients with musculoskeletal problems. Subcutaneous emphysema may be present over the neck and supraclavicular region in patients with pneumomediastinum. In patients with coarctation or aortic dissection, there is a pressure gap between the upper and lower extremities and the femoral pulse is weak or absent.

On lung auscultation, wheezing, crackles, decreased breath sounds are found in patients with lung disease. The heart should be auscultated to identify murmurs, rhythm irregularities, gallop rhythm and rub. Distant heart sounds, jugular venous distention and narrow pulse pressure can be found in significant pericardial effusion.

Hepatomegaly may suggest heart failure. A study found epigastric tenderness in 33% of patients presenting to a pediatric cardiology outpatient clinic with chest pain, with endoscopic abnormalities identified in 98% of them (28).

Investigations

In the majority of patients, history and physical examination are usually satisfactory, but in a minority of patients, several investigations may be performed when a cardiac disease is strongly suspected.

Chest radiography should be obtained in patients with respiratory distress, abnormal heart or lung auscultation findings. It can reveal useful findings about the size of the heart, pericardial and pleural effusion and pulmonary pathologies.

ECG should be acquired in patients with syncope or pain with activity, abnormal cardiac auscultation finding, or in patients with clinically suspected myocarditis or pericarditis. ECG may reveal rhythm disturbances; ST-PR segment, T wave changes and low voltage in inflammatory or ischemic diseases; ventricular hypertrophy or strain sign in diseases such as valvular stenosis and aortic coarctation (29).

Laboratory tests are rarely necessary. Complete blood count and acute phase reactants may be useful in infectious diseases. Cardiac enzymes are helpful in ischemic or inflammatory disorders such as myocarditis. One study showed that troponin levels were found to be elevated in 54% of patients with myocarditis (30, 31). It can also be elevated in myopericarditis. D-Dimer can be high in patients with pulmonary thromboembolism.

Echocardiography is recommended especially in patients with exertional chest pain, abnormal ECG findings, family history of cardiomyopathy or sudden/unexplained death (32). Structural heart diseases, cardiomyopathies and most of the coronary artery diseases can be diagnosed with the help of echocardiography. It is not recommended in patients with benign family history, absence of ECG abnormalities and tenderness on chest wall palpation. Further cardiac imaging such as CT or MRI may be needed in patients whom echocardiographic imaging is not diagnostic.

Treatment

Treatment of chest pain is based on the underlying cause. Since most patients have myalgia, it is usually helpful to inform the patient and family that the pain is not cardiac in nature and to reduce their anxiety related to the pain. Medication is usually not necessary but nonsteroidal anti-inflammatory drugs may be useful. If a cardiac etiology is suspected, referral to a further center is recommended.

REFERENCES

1. Yeh TK, Yeh J. Chest pain in pediatrics. Pediatric Annals 2015;44:e274-e8.
2. Öztürk K, Çetin İl, Ekici F, Kocabaş A, Şaylı TR. Etiology of Chest Pain in Children. Turkish J Pediatr Dis 2015;9:248-53.
3. Park MK. Child with Chest Pain. Pediatric cardiology for practitioners E-Book: Elsevier Health Sciences 2014.
4. Fyfe DA, Moodie DS. Chest pain in pediatric patients presenting to a cardiac clinic. Clinical pediatrics 1984;23:321-4.
5. Öztürk K, Çetin İ, Özışık K, Ekici F, Şaylı TR. A Rare Cause of Chest Pain in Children: Spontaneous Pneumomediastinum. Turkish J Pediatr Dis 2013;7:1-3.
6. Chun JH, Kim TH, Han MY, Kim NY, Yoon KL. Analysis of clinical characteristics and causes of chest pain in children and adolescents. Korean J Pediatr 2015;58:440.
7. Johnson JN, Driscoll DJ. Chest pain in children and adolescents. Moss and Adams' Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adult: Ninth Edition: Wolters Kluwer Health Adis (ESP); 2016.

8. Selbst SM, Ruddy RM, Clark B, Henretig FM, Santulli Jr T. Pediatric chest pain: a prospective study. Pediatrics 1988;82:319-23.
9. Aeschlimann A, Kahn M. Tietze's syndrome: a critical review. Clin Exp Rheumatol 1990;8:407-12.
10. Fishman SM. Bonica's management of pain: 4th ed. Philedelphia: Lippincott Williams & Wilkins; 2012.
11. Ives A, Daubeney P, Balfour-Lynn I. Recurrent chest pain in the well child. Arch Dis Child 2010;95:649-54.
12. Agha BS, Sturm JJ, Simon HK, Hirsh DA. Pulmonary embolism in the pediatric emergency department. Pediatrics 2013;132:663-7.
13. Berezin S, Medow M, Glassman M, Newman L. Chest pain of gastrointestinal origin. Arch Dis Child1988;63:1457-60.
14. Kenar A, Örün UA, Yoldaş T, Kayalı Ş, Bodur Ş, Karademir S. Anxiety, depression, and behavioural rating scales in children with non-cardiac chest pain. Cardiol Young 2019;29:1268-71.
15. Pillay A, Lalloo M. Psychogenic pain disorder in children. S Afr Med J 1989;76:195-6.
16. Neill WA, Hattenhauer M. Impairment of myocardial O_2 supply due to hyperventilation. Circulation 1975;52:854-8.
17. Gumbiner CH. Precordial catch syndrome.(Featured CME Topic: Precordial Catch Syndrome). South Med J 2003;96:38-42.
18. Fam AG, Smythe HA. Musculoskeletal chest wall pain. CMAJ 1985;133:379-89.
19. Aygun E, Aygun ST, Uysal T, Aygun F, Dursun H, Irdem A. Aetiological evaluation of chest pain in childhood and adolescence. Cardiol Young 2020;30:617-23.
20. Saltzman DA, Schmitz ML, Smith SD, Wagner CW, Jackson RJ, Harp S. The slipping rib syndrome in children. Pediatr Anesth 2001;11:740-3.
21. Pantell RH, Goodman Jr BW. Adolescent chest pain: a prospective study. Pediatrics 1983;71:881-7.
22. Massin MM, Bourguignont A, Coremans C, Comté L, Lepage P, Gérard P. Chest pain in pediatric patients presenting to an emergency department or to a cardiac clinic. Clin Pediatr 2004;43:231-8.
23. Veeram Reddy SR, Singh HR. Chest pain in children and adolescents. Pediatr Rev 2010;31:e1-e9.
24. Freedman SB, Haladyn JK, Floh A, Kirsh JA, Taylor G, Thull-Freedman J. Pediatric myocarditis: emergency department clinical findings and diagnostic evaluation. Pediatrics 2007;120:1278-85.
25. van Loon RLE, Roofthooft MT, van Osch-Gevers M, Delhaas T, Strengers JL, Blom NA, et al. Clinical characterization of pediatric pulmonary hypertension: complex presentation and diagnosis. J Pediatr 2009;155:176-82. e1.
26. Fikar CR, Amrhein JA, Harris JP, Lewis ER. Dissecting aortic aneurysm in childhood and adolescence: case report and literature review. Clin Pediatr 1981;20:578-83.
27. Care RP. Health supervision for children with Marfan syndrome. Pediatrics 2013;132:e1059-e72.
28. Sabri M, Ghavanini A, Haghighat M, Imanieh M. Chest pain in children and adolescents: epigastric tenderness as a guide to reduce unnecessary work-up. Pediatric Cardiol 2003;24:3-5.
29. Friedman KG, Alexander ME. Chest pain and syncope in children: a practical approach to the diagnosis of cardiac disease. J Pediatr 2013;163:896-901. e3.
30. Durani Y, Egan M, Baffa J, Selbst SM, Nager AL. Pediatric myocarditis: presenting clinical characteristics. Am J Emerg Med 2009;27:942-7.
31. Brown JL, Hirsh DA, Mahle WT. Use of troponin as a screen for chest pain in the pediatric emergency department. Pediatr Cardiol 2012;33:337-42.
32. Chamberlain RC, Pelletier JH, Blanchard S, Hornik CP, Hill KD, Campbell MJ. Evaluating appropriate use of pediatric echocardiograms for chest pain in outpatient clinics. J Am soc Echocardiogr 2017;30:708-13.