Original Articles / *Özgün Araştırmalar*

Case Reports / *Olgu Sunumları*

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

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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

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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).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with the COPE guidelines.

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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.

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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.

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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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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.

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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.

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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

Review articles are comprehensive analyses of the specific topics in medicine, which are written upon the invitation due to extensive experience and publications of authors on the review subjects. All invited review articles will also undergo peer review prior to the acceptance.

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

While citing publications, the preference should be given to the latest, most up-to-date publications. Authors should avoid using references that are older than ten years. The limit for the old reference usage is 20% in the journal. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of the references. Reference numbers should be indicated at the end of the sentences in the text as superscripts and references should be numbered consecutively in the order that they are mentioned in the text. Journal names should be abbreviated as listed in "Index Medicus" or in "ULAKBIM/Turkish Medical Index". References should be typed in consistence with the following examples. Native references should be used as much as possible.

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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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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Tablolar, referans listeden sonra ana belgeye dahil edilmelidir ana metin içine yarleştirilmemelidir. Ana metinde atıfta bulundukları sırayla numaralandırılmalıdır. Tabloların üzerine açıklayıcı bir başlık konulmalıdır. Tablolarda kullanılan kısaltmalar ana metinde tanımlansalar bile tabloların altında dipnotlarla tanımlanmalıdır. Tablolarda sunulan veriler, ana metinde sunulan verilerin tekrarı olmamalı, ancak ana metni desteklemelidir. Kısaltmalar için aşağıdaki semboller sırayla kullanılmalıdır: *, †, ‡, §, ||, ¶, **, ††, ‡‡.

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Tüm referanslar, tablolar ve şekiller ana metin içinde belirtilmeli ve ana metin içinde belirtildikleri sırayla numaralandırılmalıdır. Orijinal makalelerin kısıtlılıkları tartışma bölümü içinde sonuç paragrafından önce belirtilmelidir.

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Medicus" veya "ULAKBIM/Turkish Medical Index" de listelendiği gibi kısaltılmalıdır. Mümkün olduğunca yerel referanslar kullanılmalıdır. Kaynaklar aşağıdaki örneklere uygun olarak yazılmalıdır.

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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.

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

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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.

Kaynak toplantıda sunulan bildiri ise;

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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

Cardiological Findings of Babies Born to Mothers with Connective Tissue Disease

Bağ Dokusu Hastalığı Olan Annelerden Doğan Bebeklerin Kardiyolojik Bulguları

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ABSTRACT

Objective: Cardiac conduction system is affected and heart blocks can be seen in newborns whose mothers have connective tissue disease, especially with systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). Anti-SS-A (Ro), and anti-SS-B (La) antibodies in the mother's circulation are responsible for this situation. In this study, it was aimed to evaluate the clinical features and long-term follow-up results of babies born to mothers with connective tissue disease in our hospital.

Material and Methods: Patients who were hospitalized in the neonatal intensive care unit between January 2001 and January 2016 due to the diagnosis of SLE, SS or connective tissue disease in their mothers were retrospectively screened, and their demographic and clinical characteristics and electrocardiographic findings were recorded.

Results: A total of 49 babies from 48 mothers were included in the study. The mean age of mothers at birth was 30.8±5.0 years (28-41), the mean gestational week of patients was 35.8±2.5 weeks (28-41), mean birth weight was 2614±680 g (730-3810 g). Ten newborns (20.4%) had 3rd degree atrioventricular (AV) block, and 1 baby had 1st degree AV block. A permanent pacemaker was implanted in five patients in the neonatal period, two of these patients died in the neonatal period. A pacemaker was inserted in a patient who was followed up with AV block in the 6th month. One baby who had no cardiac conduction problem died due to reasons related to prematurity. The mean follow-up period of 46 living babies was 4.6±3.1 (1.2-10.75) years, and the follow-up period of the patients with complete AV block and without a pacemaker was 5.6±2 years.

Conclusion: Complete AV block in the neonatal period is a serious cardiac problem that requires rapid intervention. Expectant mothers with known connective tissue disease should be followed in tertiary care centers and the fetus should be followed closely. It is possible for newborns in need to return to their normal lives by inserting pacemakers.

Key Words: Atrioventricular (AV) Block, Sjögren's Syndrome, Systemic Lupus Erythematosus

0000-0001-5932-7372 : SEL K
0000-0002-1725-0722 : ÇELİK HT
0000-0002-6607-0568 : ERTUĞRUL İ
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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 Hacettepe University, Non-Invasive Clinical Research Ethics Committee (17.01.2017/GO 17/39).

Contribution of the Authors / Yazarların katkısı*: *SEL K: 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 logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study. ***ÇELİK HT:*** Constructing the hypothesis or idea of research and/or article, 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. ***ERTUĞRUL İ:*** Planning methodology to reach the Conclusions, Taking responsibility in logical interpretation and conclusion of the results. ***AYKAN HH:*** Planning methodology to reach the Conclusions, Taking responsibility in logical interpretation and conclusion of the results. ***ÖKTEM A:*** Constructing the hypothesis or idea of research and/or article, 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. ***AKAL C:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, responsibility in necessary literature review for the study. ***YİĞİT Ş:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar. ***ALEHAN D:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar. ***YURDAKÖK M:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar. ***KARAGÖZ T:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar.

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ÖZ

Amaç: Başta sistemik lupus eritematozus (SLE) ve Sjögren sendromlu (SS) olmak üzere annelerinde bağdokusu hastalığı olan yenidoğanlarda kardiyak iletim sistemi etkilenmekte ve kalp blokları görülebilmektedir. Bu durumdan annenin dolaşımındaki anti-SS-A (Ro), anti- SS-B (La) antikorları sorumludur. Bu çalışmada hastanemizde bağ dokusu hastalığı olan annelerden doğan bebeklerin klinik özellikleri ve uzun dönem takip sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Yenidoğan yoğun bakım ünitesinde Ocak 2001 ile Ocak 2016 arasında annelerinde SLE, SS veya bağ dokusu hastalığı tanısı olması nedeniyle yatırılarak izlenen hastalar geriye dönük olarak tarandı, demografik ve klinik özellikleri ile elektrokardiyografik bulguları kayıt edildi.

Bulgular: Çalışmaya toplam 48 anneden 49 bebek alındı. Annelerin doğum sırasında ortalama yaşı 30.8±5.0 yıl (28-41), hastaların ortalama gestasyonel haftası 35.8±2.5 hafta (28-41), ortalama doğum ağırlığı ise 2614±680 gr (730-3810 gr)'dı. On yenidoğanda (%20 .4) 3. derece atrioventriküler (AV) blok, bir bebekte ise 1. derece AV blok tespit edildi. Beş hastaya yenidoğan döneminde kalıcı kalp pili takıldı, bu hastalardan ikisi yenidoğan döneminde yaşamını yitirdi. AV blok ile takip edilen bir hastaya ise 6. ayında kalp pili takıldı. Kardiyak iletim sorunu olmayan bir bebek ise prematüriteye bağlı nedenler ile yaşamını yitirdi. Yaşayan 46 bebeğin ortalama takip süresi 4.6±3.1 (1.2-10.75) yıl, bunlardan AV tam bloklu olup kalp pili takılmadan izlenen hastaların takip süresi 5.6±2 yıldı.

Sonuç: Yenidoğan döneminde görülen tam AV blok hızlı müdahale edilmesi gereken ciddi bir kardiyak problemdir. Bilinen bağ dokusu hastalığı olan anne adayları üçüncü basamak merkezlerde izlenmeli, fetüs yakın takip edilmelidir. Gereken yenidoğanlara kalp pili takılarak normal yaşamlarına dönmeleri mümkündür.

Anahtar Sözcükler: Atrioventriküler blok, Sjögren sendromu, Sistemik lupus eritamatozus

INTRODUCTION

The incidence of a complete congenital atrioventricular block (CCAVB) in surviving newborns is 1/20000 (1). The most common cause is the presence of autoimmune disease in the mother. Complete congenital atrioventricular blocks occur especially in infants born to mothers with systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) who has anti-SS-A (Ro), anti-SS-B (La), or both, and are the most serious clinic of neonatal lupus syndrome (2). It has been reported that these antibodies also cause inflammatory myocarditis, endocardial fibroelastosis, and late-onset dilated cardiomyopathy (3). On the other hand, only 1-2% of infants of mothers with positive anti-La/SSB and anti-Ro/SSA antibodies have CCAVB, and most infants have normal heart conduction (4). In addition, clinical findings related to autoimmune disease have not yet emerged in most of the mothers who have children with CCAVB, and serological findings are observed in approximately half of them (5).

In this study, short and long-term follow-up results and cardiac findings of babies born to mothers with diagnoses of SLE, SS or connective tissue disease in our hospital were evaluated retrospectively.

MATERIAL and METHOD

Patients who were hospitalized in the neonatal intensive care unit of Hacettepe University İhsan Doğramacı Children's Hospital between January 2001 and January 2016 due to the diagnosis of SLE, SS or connective tissue disease in their mothers were retrospectively screened. Babies with at least one-year follow-up were included in the study. The demographic and neonatal data of the babies, their mothers' diagnoses, presence of antibodies, fetal and transthoracic echocardiographic findings, electrocardiographic (ECG) findings, presence of AV block and permanent pacemaker needs were recorded in the case form. The study was approved by Hacettepe University, Non-Invasive Clinical Research Ethics Committee (17.01.2017/GO 17/39).

RESULTS

A total of 49 (22 girls) babies born to 48 mothers with one twin pregnancy were included in the study. A total of 38 mothers were diagnosed with SLE, 5 mothers with SS, 3 mothers with SLE and SS, 1 mother with SLE and Raynaud, and 1 mother with SLE and rheumatoid arthritis. The mean age of the mothers at the time of delivery was 30.8±5.0 years (28-41), the mean gestational week of the patients was 35.8±2.5 weeks (28-41), and the mean birth weight was 2614±680 g (730-3810). The birth weights of 15 of our patients were below 2500 g (30%) and the gestational ages of 17 patients were below 37 weeks (34%). A total of 5 patients had low birth weight (SGA) for gestational age. The demographic characteristics of the patients in the study are shown in Table I.

Transthoracic echocardiography examinations revealed a ventricular septal defect in one patient, thin patent ductus arteriosus in one patient, and mild pulmonary stenosis in one patient. ECG was taken for all babies after the study. In total, 10 (20.4%) of 49 infants had 3rd degree AV block/ CCAVB and 1 infant had 1st degree AV block (Table II). All patients with CCAVB were diagnosed in fetal echocardiographic evaluation. Hydrops did not develop in any of these patients. Of the 10 patients with AV block, four of the mothers had SS-A (+) alone, and four had both SS-A (+) and SS-B (+). No antibodies were detected in the mothers of the two patients. Serological findings of mothers of newborns included in the study are shown in Figure 1.

A total of 11 patients with AV block in their ECGs underwent 24-hour Holter electrocardiogram examination. Since the mean heart rate of five patients was <55/min, a permanent

Table I: Demographic characteristics of the patients in the study

	All patients (n=49)	CCAVB + (n=10)	Normal cardiac rhythm (n=39)
Mother'sage (years)	30.8±5.0 (28-41)	27.5±3.5	31.7±5.0
Gestation (weeks)	35.8±2.5 (28-41)	35.8±3.7	35.8±2.2
Birth weight (gr)	2614±680 (730-3810)	2495±914	2644±617
Gender (F/M)	22 F / 27 M	4 F/ 6 M	18 F/ 21 M

***M:** male, **F:** female, **CCAVB:** complete congenital atrioventricular block*

Table II: Findings of newborns with AV block

Patient	Gender	Mother'sage (years)	Diagnosis of the mother	Age of gestation	Fetal echocardiography	Birth weight	ANA	SS-A	SS-B	Diagnosis after birth	Followup
1	M	31	SLE	30	Fetal brady cardia, nosign of heart failure	1650 gr	320	-	-	Complete AV block	5.5 y, no complaints
2	M	24	SLE	38	Normal	2950 gr	160	-	-	Complete AV block	6y, no complaints
3	F	27	SLE	37	-	2620 gr	100	-	-	1st degree AV block	3y, no complaints
4	F	32	SLE	28	Fetal AV block, cardiomegaly	730 gr	320	+	+	Complete AV block, external pacemaker	Exitus due to severe prematurity
5	F	24	SS	38	Fetal bradycardia, cardiomyopathy	3400 gr	320	+	+	Complete AV block, permenant pacemaker at 3rd day	6 y, no complaints
6	F	21	SLE	37	CCAVB	2500 gr	1000	+	+	Complete AV block, permenant pacemaker at 1st day	10 y, cardiomyopathy related to pacemaker
7	M	29	SLE	38	CCAVB, no sign of heart failure	3100 gr	160	+	-	Complete AV block, permenant pacemaker at 5th day	9y, no complaints
8	F	30	SS	39	CCAVB, no sign of heart failure	3750 gr	320	+	-	Complete AV block	8 y, no complaints
9	M	30	SLE	37	Cardiomyopathy	2180 gr	160	+	-	Complete AV block, cardiomyopathy	Permenant pacemaker at 6th months
10	M	26	SLE	38	CCAVB, no sign of heart failure	2890 gr	320	+	-	Complete AV block, permenant pacemaker at 1st day	7 y, no complaints
11	M	28	SLE	35	CCAVB, no sign of heart failure	1800 gr	320	+	+	Complete AV block, permenant pacemaker at 1st day	Exitus due to neonatal sepsis

***M:** Male, **F:** Female, **SLE:** Systemic Lupus Erythematosus, **SS:** Sjögren's syndrome, **CCAVB:** Complete congenital atrioventricular block, **Y:** years*

pacemaker was inserted in these patients in the neonatal period. A pacemaker was implanted in a patient who followed up with CCAVB at 6 months.

Three out of 49 patients died in the neonatal period. A patient with CCAVB, born at the 28th week of pregnancy with a weight of 720 g, in the first day of life; a patient with CCAVB, born at the 35th week of pregnancy with a weight of 1800 g, was placed on an emergency pacemaker, but on the 4th day of his life due to neonatal sepsis; a 29-week-old, 1150-g born patient who had no AV conduction problem, whose mother had HELLP syndrome was able to live up to the 12th day of her life due to reasons related to prematurity. The mean follow-up period of the other 46 patients was 4.6±3.1 years (1.2-10.75). No cardiological problem developed in the follow-ups of 4 patients with pacemakers. Holter ECG follow-ups of four patients with CCAVB who did not need a pacemaker because they were asymptomatic had a mean heart rate of >55/min, and the mean follow-up period of these patients was 5.6±2 years.

Of the infants without CCAVB in the neonatal period; AV block didn't develop in the one-year follow-up of the children of 3 mothers with both SS-A (+) and SS-B (+) antibodies, 2 mothers with only SS-A (+) and 1 mother with only SS-B (+) antibodies.

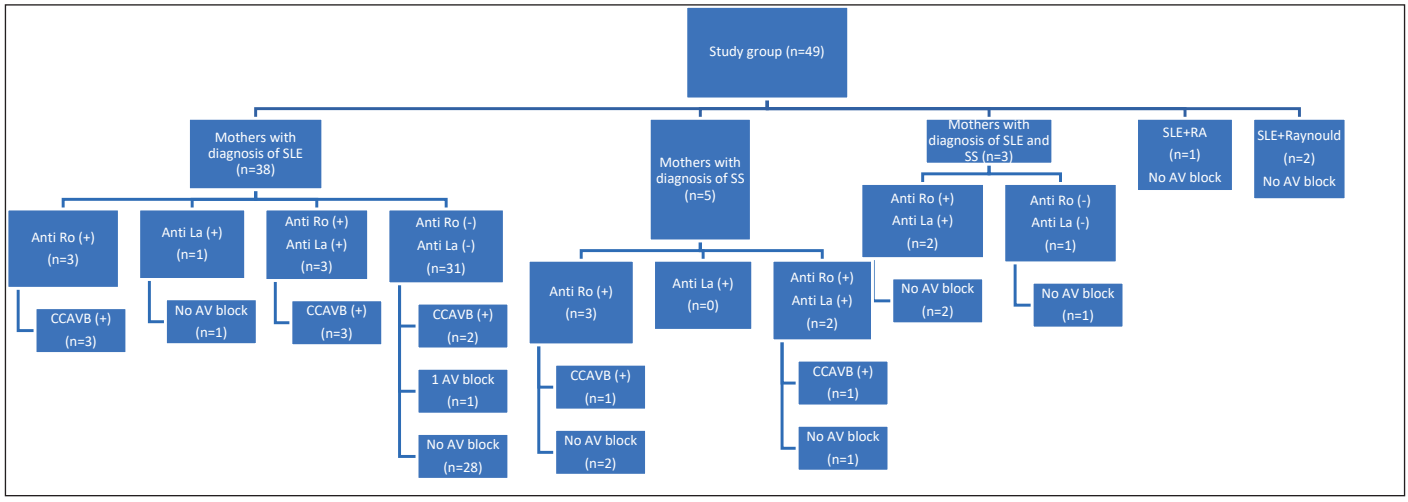

Figure 1: Serological findings of mothers of newborns included in the study.
SLE: Systemic Lupus Erythematosus, ***SS:*** Sjögren's syndrome, ***CCAVB:*** Complete congenital atrioventricular block

AV block was not observed in the babies of 34 mothers who did not have either SS-A or SS-B antibodies. Cardiomyopathy developed in the first year of life in a baby without CCAVB and whose mother was negative for SS-A and/or SS-B antibodies. In the last echocardiography performed at the age of 1.5 years, the ejection fraction was measured as 50%. This patient is being followed up.

In our study, there were five newborns with non-cardiac findings; hepatic enzyme elevation was observed in one newborn, pancytopenia in one newborn and skin findings in 3 newborns.

DISCUSSION

Third-degree AV block is the most serious problem of neonatal lupus. It is irreversible and carries a high risk of morbidity and mortality. In this most serious and life-threatening form called complete block the electrical activity does not pass from the atriums to the ventricles and the ventricles contract independently through a focus from within. Symptoms generally depend on the ventricular rate, which can vary between 30-100/min. The closer the ventricular rate is to the normal mean heart rate for age, the more likely the patient is to be asymptomatic (6). Heart contractility and the ratio of atrial and ventricular rates are also factors affecting the patient's symptomatic. The lower the fetal heart rate during pregnancy, the higher the probability of neonatal heart failure, hydrops, and fetal or neonatal death. This possibility is especially high at ventricular rates below 55/min (7).

All types of heart block can be found in babies born to mothers with lupus. Infants with affected cardiac conduction systems have >80% complete block, other types of the block are less common; second-degree (10-16%) and first-degree blocks (3%) have also been reported (7). In this study, our patients were predominantly 3rd degree AV block (complete block) (90.9%). One patient had 1st degree AV block. In the follow-up of this patient, the PR distance did not shorten, but it did not progress to a more advanced AV block. No such progress has been reported in the literature (8, 9).

It has not been shown that any degree of AV block develops in the future in babies without CCAVB in the neonatal period. In our study, also no block was found in the follow-up in babies who did not have AV block in the neonatal period.

The rate of CCAVB in babies born to mothers with connective tissue disease has been reported to be around 2% (4). In our study, the rate of patients with AV block (20.4%) was found to be higher than that reported in the publications. This can be explained by our hospital is a tertiary reference hospital. All mothers in our study were diagnosed with connective tissue disease. All of our patients with AV block were diagnosed by fetal echocardiography. Fetal hydrops did not develop in any of them. In 5 of these patients, a pacemaker had to be inserted in the neonatal period, since the mean heart rate was below 55/min due to 24-hour rhythm holter evaluation. A permanent pacemaker was implanted in a patient born with CCAVB in the 6th month.

Anti-Ro is the antibody most associated with CCAVB.When antinuclear antibody (ANA) passes from women with active connective tissue disease to the fetus, it damages the fetal thyroid and myocardial conduction system together with anti-Ro/SSA (10,11). While the rate of CCAVB in infants whose mothers have anti-La antibodies alone is less than 1%, it has been reported that the incidence increases up to 5% in infants of mothers with both positive anti-Ro and anti-La antibodies (7,10,12). In our study, 8 of 14 infants whose mothers were positive for one or both of these antibodies had CCAVB (57%). Of the 35 babies whose mothers did not have either of these antibodies, only 2 had CCAVB (5.7%). With these findings, it can be said that the risk of developing CCAVB increases approximately 10 times in babies whose mothers are positive for either or both of these antibodies.

In Sjögren's and mixed connective tissue disease, the risk of CCAVB was found to be higher than in babies of mothers with SLE (3,13). Supporting this finding in our series, two of the five infants whose mothers had Sjögren's syndrome alone had CCAVB (40%), while eight of 38 infants (21%) whose mothers had only SLE had CCAVB.

Criteria for pacing indications have been determined in patients with complete AV block (14). Possible pacemaker implantation risks and complications should be considered when evaluating the indication. Two-thirds of infants with CCAVB require a pacemaker until the first year of life, and this rate reaches 90% until the age of 20 (15). We had five patients who were found to have AV block in the neonatal period but did not need a pacemaker. The patients were followed closely and rhythm holter evaluations were performed intermittently. A pacemaker was implanted in one of our patients when he was six months old. The other four patients were followed up without a pacemaker, as their mean heart rate was higher than 55/min and were clinically and echocardiographically normal.

All of the mothers participating in our study were previously diagnosed with connective tissue disease and were referred to our hospital during pregnancy follow-up. Perinatology follow-ups and fetal echocardiography were performed. It is of great importance for maternal and infant health that these patients are referred to tertiary centers with experienced perinatology, neonatology, pediatric cardiology and pediatric cardiovascular surgery specialists, where they can insert an urgent pacemaker when necessary. More than half of the mothers of newborns with complete atrioventricular block are diagnosed with connective tissue disease later (7). Since the clinical signs and symptoms of connective tissue disease in mothers are often not fully manifested, maternal autoantibodies should be investigated when a complete AV block is detected in the baby.

Apart from heart rhythm problems, it is also reported that 15-20% of babies of mothers with lupus have conditions in which myocardial function is affected such as cardiomyopathy and endocardial fibroelastosis (EFE) (8). These findings can cause severe heart failure and death in infants. In a meta-analysis evaluating a total of 14 studies, EFE was reported up to 20%, even in infants without CCAVB (7). Although the cause is unclear, changes in the fetal immune response are thought to be responsible. Cardiomyopathy developed after one year of age in a patient whose mother had a diagnosis of SLE, had negative anti-Ro or anti-La antibodies, and did not have CCAVB. We thought that this may be due to the mother's SLE or myocarditis in the process.

Problems related to prematurity and intrauterine growth restriction increase the risks of morbidity and mortality in newborns whose mothers have connective tissue disease (7). Fetal-neonatal mortality rates in infants of mothers with lupus are close to 20% (16). Causes of death have been reported as prematurity, hydrops and cardiomyopathy. In our study, three patients (6.1%) died, and all three had prematurity and intrauterine growth restriction. No mortality was detected in the patients followed up after the neonatal period.

Apart from cardiac findings, in babies of mothers with lupus, Sjögren, or mixed connective tissue disorder various findings may occur, including skin findings, liver involvement, and hematological findings. These are often temporary and not life-threatening. The skin lesions and hematological findings usually disappear spontaneously in sixth-ninth month, due to decreasing titer of maternally transmitted autoantibodies in the baby's circulation (17). Among our patients, one newborn had pancytopenia and one had mild hepatic enzyme elevation. Various skin lesions were seen in three patients. All of these non-cardiac findings improved over time.

CONCLUSION

CCAVB seen in newborns is a rare but serious cardiac problem that needs to be well managed because of the potential morbidity and mortality risk. Currently, there is no proven preventive treatment. Therefore, all mothers with known SS-A or SS-B antibody positivity should undergo fetal echocardiography in the early period and require close monitoring with perinatology. Since these pregnant women are at high risk for maternal and infant health, their referral to centers which has pediatric cardiology, pediatric cardiovascular surgery, third-fourth level neonatal intensive care units that can install pacemakers, and planned delivery in these centers are important in decreasing death rates.

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Clinical Evaluation of Pediatric Patients Diagnosed with Membranous Glomerulonephritis

Çocukluk Çağı Membranöz Glomerülonefrit Tanılı Hastaların Klinik Değerlendirmesi

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ABSTRACT

Objective: Membranous nephropathy (MN) is a rare immune complex disease in pediatric population then adults. The prognosis of MN is variable, ranging from spontaneous complete remission to end-stage renal disease (ESRD). The lack of large multicenter studies precludes the possibility of examining in detail the treatment options and clinical outcomes in these patients. The present study aimed to expand the literature on the clinical findings, treatment, and prognosis of MN in pediatric patients.

Material and Methods: This single-center retrospective study included 13 patients with a diagnosis of primary and secondary membranous nephropathy.

Results: The mean age of the sample was 12.29±3.67 years. Complete remission occurred in 7 (53.8%) patients (of which 1 case was spontaneous remission), and partial remission occurred in 4 (30.8%) patients. In long-term follow-ups; one patient had chronic kidney disease (CKD) and one patient had end-stage renal disease (ESRD). At the last-follow up, proteinuria was noted in 6 (46.2%) patients and microscopic hematuria was noted in 4 (30.8%) and 9 patients were still using low-dose steroids.

Conclusion: The current findings have not identified any significant risk factors associated with the prognosis of MN in pediatric patients, but are thought to contribute to the limited data on pediatric MN. Most of the available data on the natural history, treatment options, and long-term outcomes of MN in the pediatric population consists of small, uncontrolled case series. Therefore, we think that larger-scale clinical trials are necessary to clearly elucidate the factors related to the prognosis of pediatric MN.

Key Words: Childhood, Membranous glomerulonephritis, Nephrotic syndrome, Nephritic syndrome

ÖZ

Amaç: Membranöz nefropati (MN), pediatrik popülasyonda erişkin dönemden daha nadir görülen bir immün kompleks hastalığıdır. MN'nin prognozu, spontan tam remisyondan son dönem böbrek hastalığına (SDBY) kadar değişkendir. Çok merkezli geniş çalışmaların olmaması, bu hastalarda tedavi seçeneklerinin ve klinik sonuçların ayrıntılı olarak incelenmesi olasılığını engellemektedir. Bu çalışma, pediatrik hastalarda MN'nin klinik bulguları, tedavisi ve prognozu hakkındaki literatür verilerine katkı sağlamayı amaçlamaktadır.

Gereç ve Yöntemler: Bu çalışmaya primer ve sekonder MN glomerülonefrit tanılı 13 çocuk hasta dahil edilmiştir.

Bulgular: Yaş ortalaması 12.29±3.67 yıldı. Yedi (%53.8) hastada (1 olgu spontan remisyon) tam remisyon, 4 (%30.8) hastada kısmi remisyon meydana geldi. 13 hastanın 2'sinde (%15.4) böbrek yetmezliği gelişti. Son kontrolde 6 (%46.2) hastada proteinüri, 4 (%30.8) hastada mikroskobik hematüri saptandı ve 9 hasta halen düşük doz steroid kullanıyordu.

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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. Approval was obtained from the Clinical Research Ethics Committee of Sami Ulus Obstetrics, Gynecology and Pediatrics Training and Research Hospital (E-22/06-356 / 15.06.2022).

Contribution of the Authors / Yazarların katkısı*: *KARAKAYA D: Constructing the hypothesis or idea of research and/or article. ***YAZILITAŞ F:*** Planning methodology to reach the Conclusions, ***KARGIN ÇAKICI E:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, ***GÜNGÖR T:*** Taking responsibility in logical interpretation and conclusion of the results, ***ÇELİKKAYA E:*** Reviewing the article before submission scientifically besides spelling and grammar. ***BÜLBÜL M:*** Taking responsibility in necessary literature review for the study.

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Sonuç: Mevcut bulgular, pediatrik hastalarda MN'nin prognozu ile ilişkili herhangi bir önemli risk faktörü belirlememiştir, ancak pediatrik MN ile ilgili sınırlı verilere katkı sağlayacağı düşünülmektedir. Pediyatrik popülasyonda MN'nin doğal seyri, tedavi seçenekleri ve uzun dönem sonuçları ile ilgili mevcut verilerin çoğu küçük, kontrolsüz vaka serilerinden oluşmaktadır. Bu nedenle, pediatrik MN'nin prognozu ile ilgili faktörleri açık bir şekilde aydınlatmak için daha büyük ölçekli klinik araştırmaların gerekli olduğunu düşünüyoruz.

Anahtar Sözcükler: Çocukluk çağı, Membranöz glomerülonefrit, Nefrotik sendrom, Nefritik sendrom

INTRODUCTION

Membranous nephropathy (MN) is an immune complex disease. The prevalence of MN in adults is much higher than in the pediatric population (1,2). The incidence is 8 to 10 cases per 1 million population worldwide (3). MN has a wide range of clinical manifestations, from subnephrotic proteinuria to severe proteinuria and nephrotic syndrome.

MN can develop primarily (idiopathic) or secondary to systemic diseases, neoplasms, chronic infections, or drugs (4,5). It is often associated with concomitant diseases in children, such as systemic lupus erythematosus (SLE), hepatitis B or C infection, and drug use (4). After excluding secondary causes, idiopathic MN (IMN) is extremely rare. There are few data on the prognosis and optimal treatment of MN in children and adolescents.

The prognosis of MN is variable, ranging from spontaneous complete remission to end-stage renal disease (ESRD) (6-8). The lack of large multicenter studies precludes the possibility of examining in detail the treatment options and clinical outcomes in these patients. The present study aimed to expand the literature on the clinical findings, treatment, and prognosis of MN in pediatric patients.

MATERIALS and METHODS

This single-center study was carried out in the pediatric nephrology department of a tertiary pediatric hospital. The records of MN patients aged <18 years at the time of diagnosis between 1 January 2010 and 1 January 2022 were retrospectively reviewed. MN was diagnosed based on histopathological renal biopsy findings. Gender, age at presentation, family history, physical examination findings, and laboratory results were obtained from the patients' medical records, and were then analyzed. Physical examination findings included body weight, height, blood pressure, and the presence or absence of edema. Hypertension was defined according to the American Academy of Pediatrics 2017 Hypertension Guideline, based on gender, age, and height percentiles (9).

Laboratory findings included the serum creatinine, albumin, and cholesterol levels, complement 3 (C3) and complement 4 (C4) levels, the phospholipase A2 receptor (PLA2R) antibody level, anti-nuclear antibody (ANA) and anti-double stranded DNA (dsDNA) positivity, and hematuria. Hematuria was defined as the presence of >5 erythrocytes in urine sediment in a microscopic field. Proteinuria was defined as urinary protein level >4 $mg/m^{-2}/h^{-1}$ or a protein/creatinine ratio >0.2 g g^{-1}. Proteinuria in the nephrotic range was defined as a urinary protein level >40 $mg/m^{-2}/h^{-1}$ or a protein/creatinine ratio >2 g g^{-1}. Complete remission was defined as proteinuria <4 $mg/m^{-2}/h^{-1}$ and a protein/creatinine ratio <0.5 g g^{-1}, and partial remission was defined as a ≥50% decrease in proteinuria, as compared to baseline. The estimated glomerular filtration rate (eGFR) was calculated using the Schwartz equation. Chronic kidney disease (CKD) was defined as an eGFR <60 $mL/min^{-1}/1.73\ m^{-2}$ based on 2 consecutive exams performed ≥3 months apart (10).

Light and immunofluorescence microscopy were used for pathological evaluation of renal tissue samples. The presence or absence of interstitial disease and predominant immunoglobulin accumulation in the subepithelial space were noted with renal biopsy results. Antibodies against IgM, IgA, IgG, C4, C3, C1q, lambda, kappa, and fibrinogen were used to stain renal tissue sections.

Treatment and follow-up times were recorded for each patient. For the treatment of MN prednisolone was used together with angiotensin-converting enzyme (ACE) inhibitors for antiproteinuric effect, and second-line immunosuppressive agents (cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine and rituximab) were used according to the response to prednisolone. The study approval was obtained from the Clinical Research Ethics Committee of Sami Ulus Obstetrics, Gynecology and Pediatrics Training and Research Hospital (E-22/06-356 / 15.06.2022).

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows v.21 (IBM Corp., Armonk, NY, USA). Data are presented as mean ± SD. The level of statistical significance was set at $p<0.050$.

RESULTS

The study included 13 patients with a mean age at presentation of 12.29 ± 3.67 years (range: 3-16 years); 3 of the patients were aged ≤10 years. The female-to-male ratio was 1.6:1. Mean follow-up time was 35.23 ± 21.69 months. In total, 7.7% of the patients had a family history of proteinuria, hematuria, or CKD. Among the patients, 5 had an underlying secondary cause of MN, as follows: hepatitis B virus infection (n = 2); hepatitis C virus infection (n = 1); SLE (n = 2). At presentation 7 (53.8%) patients had microscopic hematuria, 10 (76.9%) had peripheral edema, 11 (84.6%) had nephrotic-range proteinuria, 3 (23.1%) had hypertension, and 3 (23.1%) had macroscopic hematuria.

Table I: Baseline characteristics of the children diagnosed with MN

Characteristic	Value
Gender female*	8 (53.3)
Patient age, years,†	12.29±3.67
Follow up time, months,†	35.23±21.69
Family history*	1 (7.7)
Seconder MN*	5 (38.46)
HCV	1 (7.7)
HBV	2 (15.4)
SLE	2 (15.4)
Presenting clinical symptoms*	
Edema	10 (76.9)
Macroscopic hematuria	3 (23.1)
Microscopic hematuria	7 (53.8)
Elevated blood pressure	3 (23.1)
Nephrotic proteinüria	11 (84.6)
Laboratory findings	
24-hour protein excretion,†	202.98±124.95
Nephrotic range proteinuria*	11 (84.6)
Hypoalbuminemia*	9 (69.2)
Serum albumin levels, gr/dl,†	2.49±1.31
Serum creatinine levels, mg/dl,†	0.6±0.13
eGFR, mL/min/1.73 m^2,†	104.69±16.34
Renal insufficiency*	2 (15.4)
Treatment responses	
Complete remission*	7 (53.8)
Partially remission CKD*	4 (30.8)
KBH*	2 (15.4)

:** *n (%),* **†:** *mean ± SD,* ***eGFR: *estimated glomerular filtration rate*

At the time of presentation mean 24-h protein excretion was 202.98 ± 124.95 mg/m^{-2}/h^{-1} and 84.6% of the patients had nephrotic-range urine protein excretion. In all, 9 (69.2%) patients had hypoalbuminemia and hypercholesterolemia, with a mean serum albumin level of 2.49 ± 1.31 g dL^{-1}. The mean serum creatinine level was 0.6 ± 0.13 mg dL^{1} and the mean eGFR was 104.69 ± 16.34 mL/min^{-1}/1.73 m^{-2}. PLA2R antibodies were present in 3 (23.1%) of the 4 patients that were tested. In addition, only the 2 patients with SLE had low C3 and C4 levels. Moreover, ANA and anti-dsDNA positivity were noted in the 2 patients that developed MN secondary to SLE (Table I). Patients with primary and secondary MN, it was observed that there was no significant difference between the initial symptoms of the patients (hypertension, edema, nephrotic level proteinuria, hematuria), and laboratory findings (albumin, creatinine, and eGFR) (p>0.050).

The mean interval between referral to pediatric nephrology and kidney biopsy was 13.46 ± 4.73 day. The mean glomeruli count was 27.46 ± 15.40. Characteristic histopathological findings of MN were observed in glomeruli in all specimens. Thickening of the glomerular basement membrane was noted in 9 (69.23%) patients, of which 6 had glomerulosclerosis and 2 had tubulointerstitial minimal infiltration and tubular atrophy. Biopsy findings showed that 8 (61.5%) patients had subepithelial deposits and 5 (38.5%) had intramembranous changes.

Table II: Biopsy findings in patients with MN

Characteristic	Value
İnterstisial infiltration*	2 (15.4)
Tubular atrophy*	2 (15.4)
Presence of thickening of GBM*	9 (69.2)
Mesangial enlargement*	3 (23.1)
Glomerular sclerosis*	6 (46.1)
Subepithelial deposits*	8 (61.5)
İntramembranous deposits*	5 (38.5)
Presence of thickening of the CBM*	5 (38.5)

:** *n (%),* ***CBM: *Capillary basement membrane,* ***GBM:*** *Glomerular basal membrane*

Among these patients the predominant immunoglobulin in the subepithelial or intramembranous deposits was IgG in the 4 (30.8%), 5 (38.5%) patient had combined IgG and IgM deposition, and 4 (30.8%) had IgG, IgM, and IgA deposition (Table II).

In total, 3 (23.1%) patients were given antiviral treatment, 10 (76.9%) received an ACE inhibitor or angiotensin receptor blocker (ARB), and 10 (76.9%) patients were given prednisoloneas the first-line immunosuppressive therapy. Additional immunosuppressive therapy was not used in cases developing secondary to viral infection. The criteria for the use of prednisolonewere persistence of proteinuria after initiation of treatment with an ACE inhibitor and/or ARB. Mean duration of prednisone treatment was 16.4 ± 19.8 months. Among the patients treated with prednisolone, 8 subsequently received ≥1 second-line drug, as follows: cyclophosphamide (n = 3); cyclosporine (n = 5); tacrolimus (n = 2); mycophenolate mofetil (n=1) and azathioprine (n = 1). The 1 patient that was positive for the PLA2R antibody and resistant to treatment was given rituximab. During the study period there was a lack of consistent criteria and clinical guidelines for the administration of these agents. The cumulative duration of secondary immunosuppressive therapy was 35.50 ± 17.91 months for cyclosporine, 15.00 ± 12.72 months for tacrolimus, 6 months for cyclophosphamide, and 32.00 ± 8.48 months for mycophenolate mofetil/azathioprine. In all 3 patients with positive phosphalipase A2 receptor antibody; in addition to corticosteroid treatment, calcineurin inhibitors (CNI) were preferred as the first choice, and rituximab treatment was given in one of them. In other primary MN cases, as a second immunosuppressive (IS) treatment; CNI was and MMF was preferred.

Complete remission occurred in 7 (53.8%) patients (of which 1 case was spontaneous remission), and partial remission occurred in 4 (30.8%) patients. At the last follow-up visit the mean creatinine level was 0.91 ± 0.41 mg dL^{-1}, the mean eGFR was 92.41 ± 35.35 mL/min^{-1}/1.73 m,$^{-2}$ and the mean albumin level was 3.29 ± 0.98 g dL^{-1}. Proteinuria was noted in 6 (46.2%) patients and microscopic hematuria was noted in 4 (30.8%). At the last follow-up visit 9 patients were still using low-dose steroids. Hypertension was present in 5 patients (38.46%) and

Table III: Distribution and treatment of patients with MN

Patent Number	Age	Seconder MN	Etiology	Phosphalipase A2 receptor antibody positivity	Treatment	Remission	Complication
1	13	-	-	+	CS + CSA + Cyclophosphamide	CR	-
2	12.6	+	SLE	-	CS + Azathioprine	CR	-
3	3	+	Hepatitis B	-	Antiviral	-	ESRD + Thrombosis (Moyamoya disease)
4	15	-	-	-	CS + CSA	PR	-
5	7	+	Hepatitis C	-	Antiviral	PR	-
6	10	-	-	-	CS + CSA + Cyclophosphamide	PR	HT
7	12.9	-	-	+	CS + CSA + Tacrolimus + Rituximab	CR	HT
8	13.6	+	SLE	-	CS + Cyclophosphamide + MMF	-	CKD
9	15.6	-	-	+	CS + CSA + Tacrolimus	CR	Renal vein thrombosis
10	13.4	-	-	-	CS	CR	-
11	16	-	-	-	-	CR	-
12	14.9	-	-	-	CS	PR	-
13	12.9	+	Hepatitis B	-	An#viral	CR	-

MN: *Membranous nephropathy,* ***eGFR:*** *Estimated glomerular filtration rate,* ***CS:*** *Corticosteroid,* ***CSA:*** *Cyclosporine,* ***SLE:*** *Systemic lupus erythematosus,* ***ESRD:*** *End stage renal disease,* ***HT:*** *Hypertension,* ***CR:*** *Complete remission,* ***PR:*** *Partial remission*

edema was present in 3 (23.07%). In long-term follow-ups; one patient had CKD and one patient had ESRD. None of the clinical features at presentation, including age, gender, presence of hematuria, nephrotic-range proteinuria, or hypertension, had any predictive value for renal insufficiency. Treatment-related complications were as follows: elevated serum creatinine with cyclosporine (n = 1); and leukopenia with cyclophosphamide (n = 1). Steroid related complications as decreased bone density developed in 3, short stature developed in 1 and cataract developed in 1 patient respectively. In all, 2 patient had a history of thromboembolic events. Renal vein thrombosis was found in one patient and Moyamoya disease was found in the other. A summary of baseline characteristics and the treatments administered of MN patients is given in the Table III.

When primary MN cases with and without phosphalipase A2 receptor antibody were compared, there was no significant difference between long-term treatment responses (amount of proteinuria, albumin level, eGFR) and complete/partial remission rates. Similarly, when the cases secondary to lupus were compared with the others, it was observed that there was no significant difference between the long-term response to treatment (amount of proteinuria, albumin level, eGFR, creatinine) and the frequency of remission.

DISCUSSION

MN occurs less frequently in children than in adults. Its estimated incidence is 8-10 cases per million (11). The present single-center retrospective study included 13 MN patients over a 12-year period. Data in the literature on the prognosis of MN are limited. The present study evaluated patients in terms of prognostic factors, but a significant risk factor for renal insufficiency was not identified.

Mean age in the present study coincided with adolescence, as reported earlier (1). In 75%-80% of patients MN occurs in the absence of identifiable causes and is therefore referred to as primary MN (11). Immunohistology and disease course can differ significantly between those with primary and secondary MN; however, in children the association between MN and secondary causes is more common than primary MN (1,11,12). Particularly in patients aged <10 years the MN lesion is more often secondary to a systemic condition, with hepatitis B infection or systemic lupus SLE being the most common (3). In the present study underlying secondary causes, including hepatitis B and C virus infection, and SLE, were noted in 38.4% of the patients. While adult primary MN is seen twice as often in boys than in girls, there is no gender difference similar to our study in pediatric population generally (12).

Although MN is thought to have a more insidious onset than other glomerular diseases, it is known that approximately 80% of the cases may show signs of nephrotic syndrome (13). Hematuria accompanying proteinuria is more common in children than adults. In this study, the most common form of presentation of the patients was nephrotic syndrome. In addition, 7 (53.8%) patients had microscopic hematuria and 3 (23.1%) patients had macroscopic hematuria. Also studies on

the presence of hypertension at the time of admission in MN patients have reported that approximately 25% of them have hypertension at the time of diagnosis (1). Similarly, 3 (23.1%) patients were hypertensive when MN was diagnosed in our study. As previously reported, also in the present study the creatinine level and eGFR at the time of presentation were normal for age (1,12). In addition, patients with primary and secondary MN, it was observed that there was no significant difference between the initial symptoms of the patients (hypertension, edema, nephrotic level proteinuria, hematuria), and laboratory findings (albumin, creatinine, and eGFR) ($p>0.050$).

Autoantibodies to the M-type PLA2R initially described in adult MN patients have now been identified in children and adolescents with MN, and serve as a useful diagnostic and monitoring tool in such patients. Between 70% and 80% of patients presumed to have primary MN have PLA2R1 antibody positivity (1,11). A small percentage of patients with secondary MN also have anti-PLA2R1 antibody positivity. More importantly, it was reported that PLA2R antibody positivity has prognostic significance (1). Patients with positive PLA2R antibody titers at the time of biopsy have a lower rate of complete remission (14). Beck and Salant (15) also observed that PLA2R1 antibody titers became undetectable before proteinuria completely remitted. Anti-PLA2R1 immunosuppressive therapies have been shown to reduce PLA2R antibody titers (16). In the present study PLA2R antibody positivity was noted in 3 (23.1%) of the 4 patients tested, of which 2 had normal levels after treatment; however, complete remission of proteinuria was not observed in 1 of these patients despite a decrease in antibodies.

Based on immunofluorescence and electron microscopy, MN is morphologically characterized by thickening of the glomerular basement membrane, subepithelial immune complex deposits, and deletion of the podocyte foot process (17). Endocapillary proliferation, crescents, and necrosis are rare, except for cases with SLE. IgG deposits are subepithelial and located on the outer surface of the glomerular capillary wall (11). In addition to subepithelial deposits, the presence of electron-dense immune deposits at mesangial and/or subendothelial positions are suggestive of secondary MN. Characteristic histopathological findings of MN were observed in glomeruli in all specimens in the present study and thickening of the glomerular basement membrane was detected in 9 (69.23%) patients. In total, 6 of the presented patients had glomerulosclerosis, of which 2 also had minimal tubulointerstitial infiltration and tubular atrophy. Moreover, 8 (61.5%) patients had subepithelial deposits based on biopsy findings and 5 (38.5%) had intramembranous changes.

The first step in the treatment of MN is to differentiate between primary and secondary MN, as the treatment of secondary MN is directed towards the underlying cause. Next is supportive therapy and targeted therapy, if MN is primary. Evidence supports the use of an ACEI/ARB in cases of primary MN, and supportive treatment is recommended immediately following diagnosis to minimize protein excretion (11). In the present study antiviral treatment was administered to 3 (23.1%) patients and 10 (76.9%) patients received an ACEI or ARB. Some children diagnosed with MN can require nothing more than conservative treatment, unless severely symptomatic, but immunosuppressive therapy should be considered in patients at high risk for progressive disease or severe nephrotic syndrome (1, 11). Cyclosporine or tacrolimus are considered alternative first-line therapeutic agents.

The extent to which pediatric MN responds to steroid monotherapy is unclear. Several case series show that pediatric MN can eventually respond to corticosteroids. Valentini et al. (18) observed in a small series of idiopathic MN cases that 50% did not respond to steroids, whereas 50% had a complete or partial response. In the present study 10 (76.9%) patients were given immunosuppressive therapy with prednisolone as the first-line therapy, but 8 of these patients required ≥1 second-line drugs, as follows: cyclophosphamide (n = 3); cyclosporine (n = 5); tacrolimus (n = 2); mycophenolate mofetil (n=1) and azathioprine (n = 1).

Therapeutic agents such as rituximab are a new therapeutic option that should be considered for the treatment of primary MN (11). Some case reports describe the use of rituximab for pediatric primary/idiopathic MN. According to Malatesta et al. (19), 2 adolescent MN patients with nephrotic proteinuria and an elevated anti-PLA2R level failed to achieve remission with steroids, but were subsequently successfully treated with rituximab. In the present study rituximab was given to 1 patient with PLA2R antibody positivity that was treatment resistant, but complete remission was not achieved.

The natural course of MN is highly variable. Although spontaneous disease remission can occur in 30% of patients, MN-associated nephrotic syndrome can negatively affect renal survival, with 33% of patients progressing to ESRD within 10 years of diagnosis, although progression to ESRD is rare in the pediatric population (6,20,21). Other established risk factors for progression to ESRD included age, male gender, and a low GFR at presentation (22). It was also reported that the initial serum creatinine level alone is important for predicting progression to CKD (23).

In the present study 7 (53.8%) patients had complete remission (of which 1 had spontaneous remission) and 4 (30.8%) had partial remission. Furthermore, renal insufficiency developed in 2 (15.4%) of the 13 patients; one patient had CKD and one patient had ESRD. Evaluation of patients with and without renal insufficiency showed that there was no significant difference for age, gender, hematuria, nephrotic level proteinuria, or hypertension at first admission. The present study has some limitations, including a small patient population and retrospective design.

In conclusion, the present findings did not identify any significant risk factors associated with the prognosis of MN in

pediatric patients, but they do make a valuable contribution to the limited data on pediatric MN. Most of the available data on the natural history, treatment options, and long-term outcomes of MN in the pediatric population come from small, uncontrolled case series; therefore, we think larger scale clinical research is necessary to more clearly elucidate the association between risk factors and the prognosis of pediatric MN.

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Reasons For Requesting the Test in Antinuclear Antibody-Positive Patients and Final Diagnosis of Patients

Antinükleer Antikor Pozitif Hastalarda Test İsteme Nedenleri ve Hastaların Nihai Tanıları

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ABSTRACT

Objective: The aim of this study was to determine the reasons for the request for antinuclear antibody (ANA) in ANA-positive patients and to determine the final diagnosis of these patients and whether they developed a rheumatologic disease.

Material and Methods: In this retrospective study, the files of 559 patients with positive ANA were reviewed. Demographic, laboratory and clinical characteristics of the patients were noted. At the end of follow-up, the final diagnosis was recorded.

Results: The study included 346 patients. 233 of the patients were female, and 113 were male. The mean age at the time of ANA positivity was 9.4±4.7 years, and the mean follow-up period was 19±5.7 months. The most common symptom was myalgia/arthralgia (21.7%). Other common reasons were urticaria, abdominal pain, thrombocytopenia, and proteinuria. Extractable nuclear antigens (ENA) panel results were negative in 170 patients (49.1%). In the ENA panel, dense fine speckled antigen 70 antibodies were most frequently positive in 135 patients (39.2%). At the end of follow-up, 234 patients had no disease. One hundred and one patients were diagnosed with non-rheumatologic diseases, and 11 patients were diagnosed with rheumatologic diseases. Eleven patients with rheumatologic diseases were girls. Rash was the most common symptom in patients with rheumatologic diseases. The positive predictive value of ANA positivity for rheumatologic disease was 3.2% and 1.7% for systemic lupus erythematosus.

Conclusion: Due to the low positive predictive value of ANA testing, patients at risk for autoimmune diseases should be identified and carefully evaluated before ANA is requested.

Key Words: Antinuclear antibody, DFS 70, Systemic lupus erythematosus

0000-0003-0403-151X : ÖNER N
0000-0003-0129-4410 : ÇELİKEL E
0000-0002-5446-667X : EKİCİ TEKİN Z
0000-0002-9838-2603 : GÜNGÖRER V
0000-0003-2568-9329 : COŞKUN S
0000-0002-8012-2774 : KAPLAN MM
0000-0002-2987-1980 : KARAGÖL C
0000-0002-2235-4489 : TEKGÖZ N
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Contribution of the Authors / Yazarların katkısı*: *ÖNER N: 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. ***ÇELİKEL E:*** 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 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. ***EKİCİ TEKİN Z:*** 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. ***GÜNGÖRER V:*** 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 the writing of the whole or important parts of the study. ***COŞKUN S:*** 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. ***KAPLAN MM:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results. ***KARAGÖL C:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results. ***TEKGÖZ N:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results. ***SEZER M:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results. ***POLAT MC:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results. ***ÇELİKEL ACAR B:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the researchstudy, Reviewing the article before submission scientifically besides spelling and grammar.

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ÖZ

Amaç: Bu çalışmanın amacı antinükleer antikor (ANA)-pozitif hastalarda ANA istenmesinin nedenlerini belirlemek ve bu hastaların son tanılarını ve romatolojik bir hastalık geliştirip geliştirmediklerini saptamaktır.

Gereç ve Yöntemler: Bu çalışmada ANA pozitif 559 hastanın dosyaları geriye dönük incelendi. Hastaların demografik, laboratuvar ve klinik özellikleri kaydedildi. Takip sonunda son tanıları kaydedildi.

Bulgular: Çalışmaya 346 hasta dahil edildi. Hastaların 233'ü kadın, 113'ü erkekti. ANA pozitifliği saptandığında, ortalama yaş 9.4±4.7 yıl ve ortalama takip süresi 19±5.7 aydı. En sık görülen semptom miyalji/artraljiydi (%21.7). Diğer yaygın nedenler ürtiker, karın ağrısı, trombositopeni ve proteinüriydi. Ekstrakte edilebilir nükleer antijenler (ENA) panel sonuçları 170 hastada (%49.1) negatifti. ENA panelinde en sık 135 hastada (%39.2) yoğun ince benekli antijen 70 antikorları pozitif bulundu. Takip sonunda 234 hastada hastalık yoktu. Yüz bir hastaya romatolojik olmayan hastalık, 11 hastaya ise romatolojik hastalık tanısı konuldu. Romatolojik hastalığı olan 11 hasta kızdı. Romatolojik hastalığı olan hastalarda döküntü en sık görülen semptomdu. ANA pozitifliğinin romatolojik hastalıklar için pozitif prediktif değeri %3.2 ve sistemik lupus eritematozus için %1.7'di.

Sonuç: ANA testinin pozitif prediktif değerinin düşük olması nedeniyle, otoimmün hastalıklar açısından risk altında olan hastalar ANA istenmeden önce belirlenmeli ve dikkatle değerlendirilmelidir.

Anahtar Sözcükler: Antinükleer antikor, DFS 70, Sistemik lupus eritematozus

INTRODUCTION

Anti-nuclear antibody (ANA) is a type of antibody that is found in the serum of patients with several rheumatic diseases and is directed against structures in the cell nucleus, such as DNA, histones, and centromeres (1). Although ANA was initially discovered in systemic lupus erythematosus (SLE) patients, it has also been found to be associated with many other autoimmune diseases such as systemic sclerosis, scleroderma, Sjogren's syndrome, and juvenile idiopathic arthritis (JIA) (2). ANA is a frequently used laboratory test for autoimmune disease screening, especially in patients with musculoskeletal complaints or skin symptom (3).

Anti-nuclear antibody can be detected using the enzyme-linked immunosorbent assay (ELISA) method or the immunofluorescence technique using Human Epithelial type 2 (HEp-2) cells as a substrate. The results of the test are reported in two sections: the titer of the antibodies, and the staining pattern produced by the antibodies. The titer of the antibodies is measured in dilutions, such as 1:80, 1:100, 1:320, 1:1000, or 1:3200 and a positive result is considered as a titer of 1:80 or higher. The staining pattern can be homogeneous, granular, diffuse, nucleolar, or speckled (4). Recently, a new staining pattern called 'anti-dense fine speckled antigen70' (anti-DFS70) has been described, in which the nucleoplasm is densely speckled. ANA test is commonly requested in patients suspected of having rheumatological disease. However, ANA positivity can also be found in varying frequencies in healthy individuals (5-7). A positive ANA test is not always an indicative of a rheumatological disease and further testing and a detailed clinical evaluation of the patient is needed to establish a diagnosis.

Identifying the patients in whom ANA should be requested and its indications will increase knowledge on the rational use of laboratory tests. The aim of this study was to evaluate the reasons for requesting ANA in patients who admitted to a tertiary pediatric rheumatology clinic with ANA positivity or were found to be positive during follow-up. We also aimed to determine the final diagnosis of patients with ANA positivity and to reveal whether they developed a rheumatologic disease.

MATERIAL and METHODS

The medical records of children who were admitted to the pediatric rheumatology department with ANA positivity or who were found to be ANA positive during follow-up between January 2019 and December 2022 were retrospectively analyzed.

Inclusion-Exclusion Criteria

Patients with ANA positivity who were followed up for more than 1 year were included in the study. Patients with missing medical records, those followed up for less than 1 year, and those who had ANA positivity in another center but tested negative in our center were excluded. Also, patients who had ANA positivity detected during the course of other rheumatological diseases [juvenile idiopathic arthritis (JIA), SLE, Raynaud phenomenon] were also excluded from the study. ANA positivity with cytoplasmic and mitotic staining pattern, which is not expected in rheumatologic diseases, was excluded from the study.

Data Collection

The demographic characteristics (age, gender, age of diagnosis), family history (presence of SLE or other autoimmune disease) were recorded.

Laboratory findings including complete blood count (neutropenia, lymphopenia, anemia, thrombocytopenia), acute phase reactants [Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver enzymes (AST-ALT), and kidney function tests [blood urea nitrogen (BUN) and creatinine (Cr)], complement 3, complement 4, direct Coombs, and urinalysis (hematuria, proteinuria) were noted.

ANA positivity was determined using the indirect immunofluorescence method with HEp-2 cells. ANA titer was recorded as 1:100, 1:320, 1:1000, 1:3200.

According to ANA titer, positivity was defined as:

- <1:100 = Negative
- 1:100 = Weak positive
- 1:100-1:320 = (1+) positive
- 1:320- 1:1000 = (2+) positive
- 1:1000- 1:3200= (3+) positive
- >1:3200= (4+) positive

Different (between 1-3) staining patterns and titers reported in the same patient were noted separately. In terms of staining pattern on HEp-2 cells;

- ***Nuclear:*** Homogeneous, DFS, fine speckled, coarse speckled, centromere, few dots, many dots
- ***Cytoplasmic:*** Fibrillar, speckled, AMA, golgi, rods and rings
- ***Mitotic:*** Centrosome, intercellular bridge, fine filaments, mitotic chromosomes.

Other autoantibodies [Anti-dsDNA (antibodies against double-stranded DNA), extractable nuclear antigens (ENA) panel] and the final diagnosis during follow-up were recorded.

ENA panel, rRNP/Sm, Sm, SS-A, Ro-52, SS-B, Scl-70, Pm-Scl, Jo-1, CENP B, PCNA, DsDNA, nucleosome, histon, ribosomal P Protein, AMA-M2, and DFS 70 antibodies were evaluated using the immunoblotting method.

Anti-dsDNA was evaluated by both the ELISA method and an ENA panel. Anti dsDNA was <99.99 RU/ml negative and >100 positive in ELISA method.

According to the final diagnosis, patients were divided into two groups: those with and without a rheumatological disease. The patients without a rheumatological disease were further divided into two subgroups: healthy individuals and those with other diseases that caused ANA positivity. The definition of a healthy individual was the absence of any signs of disease after further investigation and follow-up.

The study was approved by the Ethics Committee of Ankara City Hospital (04/01/2023, E2-23-3099) and followed the principles of the Helsinki Declaration.

Statistical Analysis

Statistical analysis was performed using version 26 of the Statistical Package for Social Sciences (SPSS). Continuous variables were expressed as mean±standard deviation and categorical variables as n(%). The normal distribution of continuous parameters was tested using the Kolmogorov-Smirnov or Shapiro-Wilk test.

RESULTS

In this study, the medical records of 559 patients with positive ANA were reviewed. 164 patients were excluded from the study due to missing data, a follow-up period of less than 1 year, ANA positivity diagnosed in another center but found negative in our center, and cytoplasmic and mitotic staining pattern. Forty-nine patients with SLE, Raynaud phenomenon or JIA were not included in the study.

The study was conducted in 346 patients. There were 233 girls and 113 boys, with a female to male ratio of 2:1. The mean age at the time of ANA positivity was 9.4±4.7 years and the mean follow-up period was 19±5.7 months. In family history, 24 patients had a first-degree relative with an autoimmune disorder, and 47 patients had a second-degree relative with an autoimmune disorder.

Table I: Reasons and rates of ANA positivity by departments

Departments	Patient n= 346, n (%)
Pediatric Rheumatology	82 (23.7)
Arthralgia/ Myalgia	64 (18.5)
Alopecia	5 (1.4)
Lymphadenopathy	5 (1.4)
Recurrent oral aphthous ulcer	4 (1.2)
Rash	4 (1.2)
Pediatric Allergy	66 (19)
Urticaria	43 (12.4)
Prolonged coughing	16 (4.6)
Rash	7 (2)
Pediatric Nephrology	50 (14.5)
Proteinuria	26 (7.5)
Hematuria	18 (5.2)
Abdominal pain	6 (1.8)
Pediatric Hematology	48 (13.9)
Thrombocytopenia	27 (7.8)
Anemia	8 (2.3)
Leukopenia	6 (1.8)
Neutropenia	5 (1.4)
Lymphadenopathy	2 (0.6)
Pediatric Gastroenterology	41 (11.8)
Abdominal pain	24 (6.9)
Stomachache	7 (2)
Elevated liver transaminase levels	7 (2)
Autoimmune hepatitis	3 (0.9)
Pediatric Neurology	25 (7.2)
Headache	11 (3.2)
Convulsion	7 (2)
Sudden loss of vision	5 (1.4)
Sudden hearing loss	2 (0.6)
Pediatrics	19 (5.5)
Arthralgia/ Myalgia	9 (2.6)
Fatigue	7 (2)
Urticaria	3 (0.9)
Dermatology	11 (3.2)
Rash	8 (2.3)
Urticaria	3 (0.9)
Other Departments	4 (1.2)
Pediatric cardiyology (Arthralgia/ Myalgia)	2 (0.6)
Pediatric endocrinology (Autoimmune thyroiditis)	1 (0.3)
Ophthalmology (Uveitis)z	1 (0.3)

Table II: Patients with rheumatologic disease among patients with ANA positivity

Patient No	Sex	Age, years	Symptom	Department	Diagnosis	WBC, (10^3/µL)	Hb, (g/dL)	PLT, (10^3/µL)	ANA-1, titer (positivity)/ staining patterns	ANA 2, titer (positivity)/ staining patterns	ANA 3, titer (positivity)/ staining patterns	Anti-dsDNA, RU/ml	ENA panel	C3 g/L	C4 g/L	Direct Coombs	Urinalysis	ESR, (mm/h)	CRP, (g/L)
1	Female	16	Recurrent oral aphthous ulcer	Pediatric Rheumatology	UCTD	7.7	12.7	322	320 (++)/ homogeneous	320 (++)/ granular	1000 (+++)/ fine speckled	Negative	Negative	1.1	0.2	Negative	Normal	10	10
2	Female	8.9	Rash	Pediatric Allergy	SLE	3.3	12.8	200	3200 (++++)/ granular	-	-	143	rRNP/Sm, sm, dsDNA	0.6	0.1	2+	Normal	21	0
3	Female	10.3	Arthralgia/ Myalgia	Pediatric Rheumatology	SLE	4.2	12.1	318	3200 (++++)/ homogeneous	3200 (++++)/ granular	-	307	Nucleosome	1.5	0.3	Negative	Normal	41	50
4	Female	16.5	Rash	Dermatology	Livedoid vasculopathy	7.6	12.5	361	100 (+)/ granular	-	-	Negative	Negative	1.1	0.1	Negative	Normal	5	0
5	Female	11.5	Fatigue	Pediatric Rheumatology	AFAS	10.6	13.5	293	1000 (+++)/ fine speckled	100 (+) DFS	-	Negative	Pm-Scl, DFS70	1.3	0.3	Negative	Normal	8	0
6	Female	16.6	Rash	Pediatric Rheumatology	CL	5.7	13.1	253	100 (+)/ granular	-	-	Negative	Ro-52, Jo-1	1.1	0.2	Negative	Normal	5	0
7	Female	16.6	Rash	Pediatric Allergy	SLE	3.4	9.3	245	3200 (++++)/ homogeneous	-	-	>800	dsDNA, nucleosome, histon	0.3	0.1	2+	Proteinuria + Hematuria	60	1.7
8	Female	8.4	Rash	Pediatric Rheumatology	SLE	2.9	12.3	457	320 (++)/ homogeneous	-	-	>800	Ro-52, Scl-70, nucleosome, histon, AMA-M2	0.9	0,1	2+	Normal	28	40
9	Female	15.6	Arthralgia/ Myalgia	Pediatric Rheumatology	SLE	3.6	13.5	277	320(++)/ DFS	-	-	Negative	DFS70	0.7	0.2	Negative	Normal	6	0
10	Female	12.7	Lymphadenopathy	Pediatric Rheumatology	SLE	7.6	12.2	326	3200 (++++)/ homogeneous	3200 (++++)/ granular	-	>800	Nucleosome	0.3	0	2+	Normal	30	12
11	Female	9.3	Rash	Pediatric Rheumatology	CL	5.2	12.5	260	1000 (+++)/ DFS	-	-	Negative	DFS70	0.9	0.2	Negative	Normal	3	0

AFAS: *Antiphospholipid antibody syndrome,* ***ANA:*** *Antinuclear antibody,* ***Anti-dsDNA:*** *antibodies against double-stranded DNA (RU/ml <99.99: negative ³100: positive),* ***CL:*** *Cutaneous lupus erythematosus,* ***CRP:*** *C-reactive protein,* ***C3:*** *Complement 3 [Reference range: (0.9-1.8 g/L)],* ***C4:*** *Complement 4 [Reference range: (0.1-0.4 g/L)],* ***DFS70:*** *Dense fine speckled antigen70,* ***ENA:*** *Extractable nuclear antigens,* ***ESR:*** *Erythrocyte sedimentation rate,* ***Hb:*** *hemoglobin,* ***PLT:*** *Platelet,* ***SLE:*** *Systemic lupus erythematosus,* ***UCTD:*** *Undifferentiated connective tissue disease,* ***WBC:*** *White blood cell.*

The departments that referred patients to our center were as follows: 66 patients (19%) from pediatric allergy, 50 (14.5%) from pediatric nephrology, 48 (13.9%) from pediatric hematology, 41 (11.8%) from pediatric gastroenterology, 25 (7.2%) from pediatric neurology, 19 (5.5%) from pediatrics, 11 (3.2%) from dermatology, and 4 (1.2%) from other departments (pediatric cardiology, pediatric endocrinology, ophthalmology). ANA positivity was detected in 82 patients (23.7%) in the pediatric rheumatology department.

The most common reason for ANA testing was myalgia/arthralgia (n=75, 21.7%). Other common reasons were urticaria, abdominal pain, thrombocytopenia, and proteinuria (14.2%, 8.7%, 7.8%, and 7.5% respectively). Table I summarizes the rates and reasons for requesting ANA in positive patients according to departments.

Two hundred and forty-two patients had ANA positivity with a single, 79 with 2 different, and 25 with 3 different staining patterns and titers. In terms of antibody titer, there were 274 patients with 1:100, 119 patients with 1:320, 59 patients with 1:1000, and 23 patients with 1:3200. Forty-three patients had weak positive ANA, 246 patients had 1+ positive ANA, 111 patients had 2+ positive ANA, 55 patients had 3+ positive ANA, and 20 patients had 4+ positive ANA. In terms of staining pattern, 170 patients had DFS, 129 had homogenous, 64 had granular, 56 had fine granular, 33 had nucleolar, 14 had centromeric, and 9 had speckled fine.

ENA panel was negative in 170 patients (49.1%). rRNP/Sm antibodies in 8 patients (2.3%), Sm antibodies in 12 patients (3.5%), SS-A antibodies in 11 patients (3.2%), Ro-52 antibodies in 7 patients (2%), SS-B antibodies in 18 patients (5.2%), Scl-70 antibodies in 23 patients (6.7%), DsDNA antibodies in 22 patients (6 4%), nucleosome antibodies in 5 patients (1.5%), histone antibodies in 12 patients (3.5%), ribosomal P protein antibodies in 4 patients (1.2%), AMA-M2 antibodies in 17 patients (4.9%), and DFS 70 antibodies in 135 patients (39.2%) were positive.

Twenty-two patients tested positive for anti-dsDNA in the ENA panel, while in the ELISA test, 16 patients tested positive for anti-dsDNA.

The final diagnoses of the patients were as follows: 234 patients had no disease. One hundred and one patients were diagnosed with non-rheumatologic diseases and 11 with rheumatologic diseases. Among the rheumatological diseases, there were 6 cases of SLE, 2 cases of cutaneous lupus erythematosus, 1 case of antiphospholipid antibody syndrome, 1 case of undifferentiated connective tissue disease and 1 case of livedoid vasculopathy. All patients were female. Among patients with rheumatologic diseases, 6 had rash, 2 had arthralgia/myalgia, 1 had lymphadenopathy, 1 had fatigue, and 1 had recurrent oral aphthous ulcer. Positive ANA findings were detected in 8 patients in pediatric rheumatology, 2 patients in pediatric allergy, and 1 patient in dermatology. The mean age at the time of ANA positivity was 12.3 ± 3.6 years. Five patients were positive for anti-dsDNA. Two patients had negative ENA panel. Four patients had low C3 and 1 patient had low C4. The demographic and detailed laboratory findings of these patients are given in Table II.

The positive predictive value of ANA positivity for rheumatologic disease was 3.2% and 1.7% for SLE. Of the 82 cases with ANA positivity in the pediatric rheumatology clinic, the rate of rheumatologic disease as the final diagnosis was 9.8%, which is the highest rate among the departments where ANA positivity was detected.

DISCUSSION

Antinuclear antibody testing is used in the diagnostic evaluation of autoimmune diseases; however, it can also be positive in many other diseases and even in healthy individuals (8). In this study, rheumatologic disease was diagnosed in 11 of 346 patients with positive ANA test. All patients diagnosed with rheumatologic diseases were female and adolescents. Among the departments that requested ANA testing, the highest ANA positivity rate was found in the rheumatology department. Regardless of the final diagnosis, musculoskeletal symptoms were the most common symptoms in ANA-positive patients, while rash was in patients with a final diagnosis of rheumatologic disease.

Both autoimmune diseases and ANA positivity are more common in females (9-11). Davis et al. (9) reported that 68.1% of ANA positive patients were female. Similarly, Racoubian et al. (10) found that the rate of female patients was 1.5–2.4 times higher than that of male patients in a prevalence study of 2860 patients with ANA positivity. Haşlak et al. (11) reported that 64.2% of 358 ANA positive patients were female. In this present study, the female rate was 67.3%.

Studies on ANA positivity in children have shown that positivity is generally more common in the adolescent age group (12-14). This may be due to the fact that SLE and other autoimmune diseases are more common in this age group of patients. In our study, the mean age of patients was 9.4±4.7 years. Moreover, the mean age of the patients diagnosed with rheumatologic diseases was 12.3±3.6 years, closer to adolescence.

ANA test can be positive in autoimmune rheumatologic diseases, autoimmune liver diseases, thyroid diseases, malignancies, drug exposure and even in healthy individuals (15,16). Therefore, ANA test is requested by clinicians from different departments. In our study, ANA positivity was most commonly requested from the pediatric rheumatology department (23.7%), followed by pediatric allergy (19%), pediatric nephrology (14.5%), pediatric hematology (13.9%), pediatric gastroenterology (11.9%), and other departments (17%). The most common indication for ANA testing was musculoskeletal system symptoms (21.7%), urticaria (14.2%), abdominal pain (8.6%), thrombocytopenia

(7.8%), proteinuria (6.9%). Abeles et al. (17) and Bilginer et al. (18) also reported that the most common reason for requesting ANA was musculoskeletal symptoms.

The titer and staining pattern should be taken into consideration in the evaluation of ANA positivity. For instance, a patient's ANA titer of 1:80 or higher is a mandatory criterion for the diagnosis of SLE. In healthy individuals, positivity at a titer of 1:40 is detected in 31.7% of the population, whereas at a titer of 1:320 this rate decreases to 3.3% (19). Wener et al. (13) reported that approximately 10% of healthy individuals were ANA positive when samples were tested at a dilution of 1:80, increasing to 20% when samples were tested at a dilution of 1:40. The higher the titer of ANA, the less likely it is to occur in healthy individuals. Kang et al. (12) tested 94,153 patients for ANA between 2010 and 2019, of which 14.4% were positive. 4.7% of ANA-positive patients were diagnosed with autoimmune rheumatological disease. This rate increases to 15.6% when ANA positivity is evaluated at a titer of 1:320.

Abeles et al. (17) found the positive predictive value of ANA test results to be 2.1% for lupus and 9.1% for any ANA-related rheumatologic disease in 232 patients.

Staining patterns also show clinical significance like titer. The most common staining pattern observed in healthy individuals is DFS pattern (5). The most commonly associated pattern with autoimmune diseases is homogenous, nucleolar pattern (8). All staining patterns and the conditions/diseases associated with ANA positivity can be accessed from the website https://anapatterns.org (20). This website offers multiple language options.

Karakeçe et al. (14) reported that nuclear pattern was observed in 425 of 755 ANA positive patients and the distribution of fine granular, coarse granular, homogeneous and nuclear membrane patterns were 69.4%, 14.1%, 15.1% and 1.4%, respectively. There is an association between some autoimmune diseases and antibodies in the ENA panel, such as anti-SS-A/Ro and anti-SS-B/La with SLE and Sjogren's syndrome; anti-Scl-70 and anti-CENP-B with scleroderma; anti-Jo-1 with polymyositis/dermatomyositis; anti-RNP with mixed connective tissue disease (21,22). In our study, 49.1% of all patients had a negative ENA panel, and the most common ENA antibody was DFS 70 antibody at 39.2%. The most common antibody found in the ENA panel of 6 patients with SLE was nucleosome at 66.7%.

This study has some limitations. The main limitation is its single center and retrospective design. Secondly, the follow-up period may need to be longer for the diagnosis of rheumatologic disease. However, emphasizing that the ANA test should be interpreted by considering the titer and staining pattern and revealing the ANA positivity rate in rheumatologic diseases are the strengths of our study.

In conclusion, this study demonstrated that the positive predictive value of ANA testing is low. The presence of rheumatologic disease should be carefully evaluated in adolescent girls with ANA positivity. The most common symptom in ANA positive patients with a final diagnosis of rheumatologic disease was rash. Multicenter studies including larger numbers of patients are needed to reflect population-based data.

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Reliability and Validity of the Turkish Version of the Nine-Item Avoidant/Restrictive Food Intake Disorder Screen (NIAS) Parent-Report

Dokuz Maddeli Kaçıngan/Kısıtlayıcı Gıda Alım Bozukluğu Tarama Ölçeği (NIAS) Ebeveyn Bildirimi'nin Türkçe Versiyonunun Geçerlik ve Güvenirliği

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ABSTRACT

Objective: The current study aimed to evaluate the psychometric properties of a Turkish version of The Nine Item Avoidant/Restrictive Food Intake Disorder Screen Parent Report (NIAS-PR), which measures the avoidant/restrictive food intake disorder (ARFID) symptoms by parents. NIAS-PR includes three subscales picky eating, poor appetite/limited interest in eating, and fear of aversive consequences from eating. Also, our secondary aim was to assess the relationship between ARFID-related eating behaviours and emotional-behavioural symptoms of children and parents' psychological status.

Material and Methods: The NIAS-PR was translated into Turkish with standard procedures. Two hundred sixty-eight children (133 girls, 49.6%; mean age 8.62, age range from 2 to 18 years) and parents (175 mothers, 65.2%) were included in the study. The factor structure was confirmed using confirmatory factor analysis (CFA). The results were compared to the validated Turkish Children's Eating Behavior Questionnaire (CEBQ) to determine the convergent validity. Internal consistency (Cronbach alpha coefficient) analysis was used to determine the reliability of the NIAS-PR.

Results: The current study provided evidence for the validity of the translated Turkish version of the NIAS-PR in the pediatric population. The three-factor structure of the NIAS—Picky eating, Appetite, and Fear—was replicated in the Turkish NIAS-PR. The NIAS-PR subscales showed the expected patterns of correlations with the CEBQ subscales. The reliability of the Turkish version of NIAS-PR proved to be satisfactory (total Cronbach's alpha=0.90) in the pediatric population (2-18 years).

Conclusion: This study demonstrated a good internal consistency of the Turkish version of the NIAS-PR. We confirmed the three-factor structure of the Turkish version of NIAS-PR. NIAS-PR is a brief, reliable instrument for ARFID research in Turkish children and adolescents. The NIAS-PR is developed as a screening questionnaire, so health professionals should use it to investigate ARFID-related eating behaviours further. It is worth mentioning that deepening these eating symptoms with clinical interviews is necessary.

Key Words: ARFID, Avoidant/restrictive food intake disorder, NIAS, Reliability, Validation

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ÖZ

Amaç: Bu çalışma, ebeveynler tarafından kaçınan/kısıtlayıcı gıda alım bozukluğu (KKGAB) semptomlarını ölçen Dokuz Maddeli Kaçınan/Kısıtlayıcı Gıda Alım Bozukluğu Tarama Ölçeği'nin (NIAS-EÖ) Türkçe versiyonunun psikometrik özelliklerini değerlendirmeyi amaçlamıştır. NIAS-EÖ, seçici yeme, iştahsızlık/yemeye karşı sınırlı ilgi ve yemek yemenin tiksindirici sonuçlarından korkma olmak üzere üç alt ölçeğe sahiptir. Araştırmanın ikincil amacı ise, KKGAB ile ilişkili yeme davranışları ile çocukların duygusal-davranışsal belirtileri ve ebeveynlerin psikolojik durumları arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntemler: NIAS-EÖ standart prosedürlerle Türkçe'ye çevrilmiştir. Çalışmaya 268 çocuk (133 kız, %49.6; ort. yaş 8.62, yaş aralığı 2-18) ve ebeveynleri (175 anne, %65.2) dahil edilmiştir. Faktör yapısı, doğrulayıcı faktör analizi (DFA) kullanılarak doğrulanmıştır. Sonuçlar, yakınsak geçerliliği belirlemek için geçerli bir ölçek olan Türk Çocuklarının Yeme Davranışı Anketi (ÇYDA) alt testleri ile korelasyon analizleri yapılmıştır. NIAS-PR'nin güvenilirliğini belirlemek için iç tutarlılık (Cronbach alfa katsayısı) analizi kullanılmıştır.

Bulgular: Mevcut çalışma, NIAS-EÖ'nin çevrilmiş Türkçe versiyonunun pediatrik popülasyonda geçerli bir ölçek olduğunu göstermiştir. NIAS'ın üç faktörlü yapısı -Seçici yeme, İştah ve Korku- Türkçe versiyonu NIAS-EÖ için tekrarlanmıştır. NIAS-EÖ alt ölçekleri, CEBQ alt ölçekleri ile beklenen korelasyon modellerini göstermiştir. Pediyatrik popülasyonda (2-18 yaş) NIAS-EÖ Türkçe versiyonunun güvenilirliğinin yüksek olduğu (toplam Cronbach alfa=0.90) saptanmıştır.

Sonuç: Bu çalışma, NIAS-EÖ'nin Türkçe versiyonunun iyi bir iç tutarlılığı olduğunu göstermiştir. NIAS-EÖ'nin Türkçe versiyonunun üç faktörlü yapısı doğrulanmıştır. NIAS-EÖ, Türk çocuk ve ergenlerinde ARFID araştırması için kısa, güvenilir bir araçtır. NIAS-EÖ bir tarama ölçeği olarak geliştirilmiştir, bu nedenle sağlık profesyonelleri bu ölçeği KKGAB ile ilgili yeme davranışlarını daha fazla araştırmak için kullanabilir. Bu kısıtlı/kaçıngan yeme semptomlarının klinik görüşmeler ile derinleştirilmesi gerektiğini belirtmekte fayda vardır.

Anahtar Sözcükler: ARFID, Kaçıngan/kısıtlı yeme bozukluğu, NIAS, Güvenirlik, Geçerlilik

INTRODUCTION

Avoidant/restrictive food intake disorder (ARFID) is an eating/feeding disorder characterised by avoidant/ restrictive eating behaviours. The underlying causes of ARFID are heterogeneous, and it shows three main presentations; selective/neophobic, eating lack of interest in eating, and fear of the aversive consequences of eating, such as vomiting or choking (1). ARFID is a new disorder in DSM-5, an extension of the DSM-IV feeding disorder of early infancy and childhood (2). It can be diagnosed in individuals of any age that is associated with one or more of the following Criterion A symptoms in DSM-5: Significant weight loss (or failure to achieve expected weight gain or faltering growth in children), significant nutritional deficiency, needs for enteral feeding or oral nutritional supplements, impaired psychosocial functioning. These symptoms do not occur during anorexia nervosa or bulimia nervosa, and there is no disturbance related to one's body weight or shape. Additionally, the eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder for ARFID diagnosis (1).

ARFID is common in the community and pediatric clinical samples (3-6). Eating restrictions can occur in only one domain or multiple domains (e.g., both selective eating, appetite, or fear), so they can usually show different presentations (7). Research on ARFID provides important growing data, but more is needed to understand its presentations and prevalence in pediatric populations. In Turkey, there is no measure of ARFID symptoms, neither a self-report nor a parent report. Thus, we aimed to translate the Nine Items Avoidant/Restrictive Food Intake Disorder Screen Parents Report (NIAS-PR) into Turkish and conduct a validity and reliability study of the Turkish version of NIAS-PR. Also, we purposed to assess the relationship between ARFID-related eating behaviours and emotional-behavioural symptoms of children and parents' psychological status.

MATERIALS and METHODS

Participants and Procedure

All parents of children aged 2-18 who were admitted to the General Pediatric Outpatient Clinic in our hospital were invited to the study. The data was collected between June-August 2022. The study did not include children with caregivers other than their mother or father. Parents whose capacities were insufficient to understand and fill in the questionnaires were not included in the study. Parents who agreed to participate were included in the study. Informed consent was obtained from all participants. Approval for the Ankara City Hospital Ethics Committee (08.06.2022/E2-22-1962).

Firstly, demographic characteristics were collected of the child and the family (child's age, gender of the child, presence of psychiatric history admission of child, height and weight of the child, body mass index (BMI) of child, parents' educational levels, feeding history of the child). Children's BMIs (kg/m2) and BMI percentiles were calculated using the gender- and age-dependent Turkish child reference curves. The parent report determined eating problems with yes or no questions: "Do you think your child has eating problems?" Secondly, parents were asked to fill out the Turkish version of the NIAS parent form, Children's Eating Behavior Questionnaire (CEBQ), and Strengths and Difficulties Questionnaire-Parents Form (SDQ) for the children's eating behaviours and emotional and behavioural problems. Additionally, parental psychological status was assessed by Depression Anxiety and Stress Scale (DASS-21).

Measures

The Nine-Item ARFID Screen (NIAS) Parent-Report

The NIAS-PR is a 9-item parent-report questionnaire that assesses avoidant/ restrictive eating patterns. The NIAS is comprised of three subscales: the picky eating subscale measures sensory aversion to food (e.g., "My child is a picky eater"), the appetite subscale measures a lack of interest in eating or food (e.g., "My child does not appear very interested in eating; s/he has a smaller appetite than other kids the same age"), and the fear subscale measures fear of aversive consequences as a consequence of eating (e.g., "My child does not eat enough food because s/he is afraid of discomfort, choking, or vomiting"). Parents respond to each question on a scale from 0 (Strongly Disagree) to 5 (Strongly Agree). Subscales are each scored on a scale from 0 to 15, with higher scores indicating higher levels of each metric (picky eating, lack of interest, and fear). All items may also be summed to calculate a total score, ranging from 0 to 45, with higher scores indicating higher levels of avoidant/restrictive eating broadly (8). Cronbach alphas of the NIAS-PR in the Polish sample were .84, .88, and .99 for the picky eating, lack of interest, and fear subscales, respectively (9).

Written permission was obtained from H. Zickgraf, who developed the questionnaire, to translate and conduct validity and reliability studies of the NIAS parent form in Turkish children. Two authors first translated the NIAS parent form from English to Turkish, resulting in a single version after the consensus meeting. Then an independent native speaker back-translated the scale into English. After a pilot study with ten patients, minor adaptations were made for cultural suitability, and the final Turkish version of the NIAS parent form was obtained. English and Turkish versions of NIAS-PR are presented in Table I.

Children's Eating Behavior Questionnaire (CEBQ)

The CEBQ was developed by Wardle et al.(10) and translated and adapted into Turkish (11). It includes questions to be answered by the parents that evaluate the children's eating behaviour habits. The Cronbach alpha value of the adapted Turkish version of the study was .69 (11). The CEBQ is a Likert-type questionnaire answered by the parents and includes 35 items, each assessed on a scale of five points (1 = never, 5 = always). Eight subdimensions were determined to measure child eating behaviour from the scale as follows: Food responsiveness (FR), Emotional overeating (EOE), Enjoyment of food (EF), Desire to drink (DD), Satiety responsiveness (SR), Slowness in eating (SE), Emotional undereating (EUA) and Food fussiness (FF).

Strengths and Difficulties Questionnaire-Parents Form (SDQ)

The SDQ was developed by Robert Goodman to evaluate the emotional and behavioural problems in children and adolescents.(12) The SDQ has been adapted to the Turkish language (13). There are two Turkish forms of SDQ parent for the 2-4 age and the 4-17 age period. We used two versions of the Turkish SDQ parent form in our study. Both versions of the SDQ parent form have 25 items that question positive and negative behaviour characteristics. They contain five subscales: hyperactivity–inattention, emotional symptoms, peer problems, conduct problems, and prosocial behaviour. Each subscale consists of five items, and the sum of the first four subscales produces a total difficulties score. A higher score indicates

Table I: NIAS-PR: English and Turkish versions.

	English Version of the NIAS-PR	Turkish Version of the NIAS-PR
1	My child is a picky eater	Çocuğum yemek seçen biridir.
2	My child doesn't like many of the foods that other kids his or her age eat easily	Çocuğum, yaşıtı diğer çocukların kolayca yediği çoğu yiyeceği sevmez.
3	My child refuses to eat everything but a short list of preferred foods	Çocuğum, tercih ettiği yemeklerin olduğu kısa bir liste dışındaki her şeyi yemeyi reddeder.
4	My child does not appear very interested in eating; s/he has a smaller appetite than other kids the same age	Çocuğum yemek yemeye pek ilgili görünmüyor; aynı yaştaki diğer çocuklara göre daha az iştahlıdır.
5	Left to his/her own devices, my child would not eat a large enough volume of food	Kendi haline bırakıldığında, çocuğum yeterince fazla miktarda yemek yemez.
6	It is difficult to get my child to eat a large enough volume, even when I offer foods that s/he really likes	Çocuğuma gerçekten sevdiği yiyecekleri sunduğumda bile yeterince fazla miktarda yemesini sağlamak zordur.
7	My child refuses to eat because s/he is afraid of discomfort, choking, or vomiting	Çocuğum yemek yemeyi reddeder çünkü rahatsızlık hissinden, boğulmaktan veya kusmaktan korkar.
8	My child restricts him/herself to certain foods because s/he is afraid that other foods will cause discomfort, choking, or vomiting	Çocuğum kendisini belirli yiyeceklerle sınırlandırır çünkü diğer yiyeceklerin rahatsızlık hissine, boğulmaya veya kusmaya neden olacağından korkar.
9	My child does not eat enough food because s/he is afraid of discomfort, choking, or vomiting.	Çocuğum yeterince yemek yemez, çünkü rahatsızlık hissinden, boğulmaktan veya kusmaktan korkar.

NIAS-PR: *Nine Items Avoidant/Restrictive Food Intake Disorder Screen-Parent Report.*

a greater likelihood of significant problems for the first four subscales and the total difficulties score. Higher scores on the prosocial behaviour subscale reflect strengths.

Depression Anxiety and Stress Scale

Depression Anxiety and Stress Scale (DASS-21) was used to determine the parents' current psychological status. It is a self-report questionnaire that consists of three subscales (Depression, Anxiety, and Stress) which include seven items per subscale (14). The reliability and validity of the DASS-21 were confirmed for the Turkish population (15). Higher scores indicate higher levels of each symptom (depression, anxiety, and stress).

Statistical analysis

The psychometric properties of the NIAS-PR were evaluated through tests for validity and reliability. Data analyses were carried out using RStudio version 1.3.1093 (R Studio, PBC) (16). Using the lavaan package, we conducted confirmatory factor analysis (CFA) with the "diagonally weighted least squares (DWLS)" estimator (17). Items with factor loadings above 0.40 were examined as salient. Model fit was evaluated using the comparative fit index (CFI; > 0.90 acceptable, > 0.95 excellent), Tucker–Lewis index (TLI; > 0.90 acceptable, > 0.95 excellent), root mean square error of approximation (RMSEA; < 0.08 good, < 0.05 excellent) (18). For the evaluation of convergent validity, Spearman's correlation coefficient was calculated between the NIAS-PR scores and subdimensions of CEBQ. Reliability was examined in terms of internal consistency, tested by Cronbach's alpha coefficient. Item-total correlation and Cronbach alpha coefficient when the item deleted were calculated for item analysis of the reliability.

The relationships between demographic variables and the subdimension scores of the NIAS were analysed via SPSS 11.5 (SPSS, Chicago, IL, USA). The differences between demographic variables in NIAS sub-dimension scores were examined using the Mann-Whitney U Test. Associations between continuous variables and NIAS-PR subdimensions scores were determined by Spearman correlation analysis. A value of $p < 0.050$ was considered statistically significant.

RESULTS

Sample characteristics

Two hundred sixty-eight children (133 girls, 49.62%; mean age 8.62, age range from 2 to 18 years) and parents (175 mothers, 65.29%) were included in the study. Our sample consisted of 30.22% preschool children (aged 2 to 5 years; n=81), 41.41% school-age (aged 6 to 11 years; n=111) children and 28.35% adolescents (aged 12 to 18 years, n=76). The parents were all literate and at least a primary education graduate. The demographic features of the participants are presented in Table II. BMI, derived from self-reported height and weight, ranged from 10.65 to 52.0 kg/m^2 (Median = 17.43 kg/m^2). Moreover, the BMI percentile ranged from 0.02 to 99.98 (Median = 69.15). Based on the recommended cutoff points of BMI for Turkish children (< 5th percentile=Underweight, 5th to 84th percentile= healthy weight, 85th to 95th percentile = overweight, and > 95% percentile = obese) (19), 19 (7.08%) had a BMI in the underweight range, 158 (58.95%) in the healthy weight range, 28 (10.44%) in the overweight range, and 63 (23.50%) in the obese range. Eating problems in children were reported by 33.58 % of parents (n=90). In 16.79 per cent of the sample (n=45), there was a history of psychiatric admission and follow-up for any reason. Parents reported that 95.89 per cent of the children (n=257) have a history of breastfeeding, and the median age of introducing new food is six months (min:0-max:30 months). In 20.14 per cent of the sample (n=54), parents reported difficulties introducing solid foods to their children. Parents reported (13.43%, n=36) concerns about their child's physical development being worse than their peers.

Table II: Demographic features of the sample (n = 268)

	Results
Age of child (years)*	8 (2-18)
Gender of the child (girl)†	133 (49.62)
BMI of the child (kg/m^2)*	17.43 (10.65-52)
Percentile BMI of the child	69.15 (0.02-99.98)
Parents (mother)†	175 (65.29)
Age of mother (years)*	37 (22-57)
Age of father (years)*	40 (27-68)
Education status of the mother†	
Primary School-Secondary School	53 (19.77)
High School	71 (26.49)
University	144 (53.73)
Education status of the father†	
Primary School-Secondary School	44 (16.41)
High School	84 (31.34)
University	140 (52.23)

****:** Median and minimum–maximum values are presented, **†:** n(%), **BMI:** Body mass index*

Validity of NIAS-PR

The items and factor loadings are given in Table III. All nine items loaded higher than 0.40. The factor loading values at the subscales level ranged between 0.78 and 0.90 for the Picky eating subscale, between 0.86 and 0.92 for the Appetite subscale, and between 0.89 and 0.94 for the Fear subscale. Also, the total contribution of three factors to the variance was 78.4%. The fit indices calculated as a result of the CFA were determined to be RMSEA = 0.092 (95%CI:0.070-0.115), CFI = 0.996 and TLI = 0.995).

For the present study, all CEBQ subscales were analysed for convergent validity of NIAS-PR. Eight subscales of CEBQ include food-approach behaviours (food responsiveness, enjoyment of food, emotional overeating, desire to drink) and

Table III: Confirmatory factor analysis results of Turkish NIAS-PR (n = 268)

Items		Picky Eating (F1)	Appetite (F2)	Fear (F3)
1.	My child is a picky eater	0.781		
2.	My child doesn't like many of the foods that other kids his or her age eat easily	0.887		
3.	My child refuses to eat everything but a short list of preferred foods	0.901		
4.	My child does not appear very interested in eating; s/he has a smaller appetite than other kids the same age		0.915	
5.	Left to his/her own devices, my child would not eat a large enough volume of food		0.858	
6.	It is difficult to get my child to eat a large enough volume, even when I offer foods that s/he really likes		0.864	
7.	My child refuses to eat because s/he is afraid of discomfort, choking, or vomiting			0.892
8.	My child restricts him/herself to certain foods because s/he is afraid that other foods will cause discomfort, choking, or vomiting			0.924
9.	My child does not eat enough food because s/he is afraid of discomfort, choking, or vomiting.			0.940
	Eigenvalue	2.209	2.320	2.533
	Variance Explanation Percentage	0.245	0.258	0.281

NIAS-PR: *Nine Items Avoidant/Restrictive Food Intake Disorder Screen-Parent Report*

Table IV: Correlations subscales for NIAS-PR with CEBQ (Convergent validity)

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1.	1										
2.	0.682***	1									
3.	0.292***	0.446***	1								
4.	-0.154*	-0.357***	-0.132*	1							
5.	-0.132*	-0.242***	-0.115	0.700***	1						
6.	-0.442***	-0.622***	-0.295***	0.552***	0.441***	1					
7.	0.132*	0.065	0.134*	0.413***	0.382***	0.164*	1				
8.	0.545***	0.643***	0.226***	-0.215**	-0.134*	-0.562***	0.157*	1			
9.	0.347***	0.522***	0.307***	-0.133*	-0.111	-0.561***	0.134*	0.632***	1		
10.	0.243***	0.300***	0.104	0.100	0.177**	-0.224***	0.275***	0.522***	0.443***	1	
11.	-0.381***	-0.382***	-0.102	0.409***	0.383***	0.522***	0.174**	-0.411***	-0.152*	-0.001	1

1: *NIAS-PR Picky eating,* ***2:*** *NIAS-PR Appetite,* ***3:*** *NIAS-PR Fear,* ***4:*** *CEBQ-FR,* ***5:*** *CEBQ-OEO,* ***6:*** *CEBQ-EF,* ***7:*** *CEBQ-DD,* ***8:*** *CEBQ-SR,* ***9:*** *CEBQ-SE,* ***10:*** *CEBQ-EUA,* ***11:*** *CEBQ-FF, Spearman correlation analysis with rho coefficient;* ***NIAS-PR:*** *Nine Items Avoidant/Restrictive Food Intake Disorder Screen—Parent Report,* ***CEBQ=*** *Children's Eating Behavior Questionnaire,* ***FR=*** *Food responsiveness,* ***EOE=*** *Emotional overeating,* ***EF=*** *Enjoyment of food,* ***DD=****Desire to drink,* ***SR=*** *Satiety responsiveness,* ***SE=****Slowness in eating,* ***EUA=*** *Emotional undereating,* ***FF=*** *Food fussiness*

food-avoidance behaviours (satiety responsiveness, slowness in eating, food fussiness, and emotional undereating). It was hypothesised that CEBQ food-avoidance subscales would positively correlate with NIAS-PR subscales, and CEBQ food-approach subscales would negatively correlate with NIAS-PR subscales. There is a moderately negative correlation between CEBQ enjoyment food subscale scores and NIAS-PR picky eating scores and NIAS-PR appetite scores (r= -0.448, p<0.001; r=-0.627, p<0.001, respectively). However, CEBQ enjoyment food subscale scores negatively correlated weakly with NIAS-PR fear subscale scores (r= -0.297, p<0.001). There is a moderately positive correlation between CEBQ satiety responsiveness subscale scores and NIAS-PR picky eating scores and NIAS-PR appetite scores (r= 0.546, p<0.001; r= 0.640 p<0.001, respectively). Additionally, CEBQ slow eating scores correlated moderately with NIAS-PR appetite subscale scores (r= 0.529, p<0.001). Results of the correlation analysis of NIAS-PR subscales with CEBQ subdimensions (Convergent validity) have been shown in Table IV.

Reliability of NIAS-PR

Internal consistency (Cronbach alpha coefficient) analysis was used to determine the reliability of the NIAS-PR. The median (min–max) was 5.91 (0.00-12.84) for the Picky Eating score,

Table V: Analysis of the reliability of the Turkish NIAS-parent form (n=268)

Factor	Item Total Correlation	Alpha If Item Deleted
Picky Eating Cronbach's Alpha=0.862		
My child is a picky eater	0.702	0.838
My child doesn't like many of the foods that other kids his or her age eat easily	0.766	0.779
My child refuses to eat everything but a short list of preferred foods	0.746	0.798
Appetite Cronbach's Alpha=0.872		
My child does not appear very interested in eating; s/he has a smaller appetite than other kids the same age	0.809	0.768
Left to his/her own devices, my child would not eat a large enough volume of food	0.752	0.823
It is difficult to get my child to eat a large enough volume, even when I offer foods that s/he really likes	0.708	0.861
Fear Cronbach's Alpha=0.914		
My child refuses to eat because s/he is afraid of discomfort, choking, or vomiting	0.801	0.896
My child restricts him/herself to certain foods because s/he is afraid that other foods will cause discomfort, choking, or vomiting	0.840	0.865
My child does not eat enough food because s/he is afraid of discomfort, choking, or vomiting	0.838	0.866

NIAS-PR: Nine Items Avoidant/Restrictive Food Intake Disorder Screen-Parent Report

Table VI: Correlations subscales for NIAS-PR with SDQ, DASS-21 and other clinical variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1.	1										
2.	0.683***	1									
3.	0.291***	0.441***	1								
4.	0.213**	0.198**	0.225**	1							
5.	0.212**	0.245***	0.177**	0.557***	1						
6.	-0.017	-0.081	-0.091	-0.244***	-0.371***	1					
7.	0.290***	0.250***	0.164*	0.363***	0.442**	-0.187**	1				
8.	0.264***	0.224**	0.090	0.381***	0.464***	-0.230**	0.871***	1			
9.	0.311***	0.243***	0.153*	0.323***	0.410***	-0.222**	0.800***	0.832***	1		
10.	-0.081	-0.272***	-0.132*	0.071	-0.142*	.214**	-0.024	-0.063	-0.074	1	
11.	-0.054	-0.273***	-0.061	-0.042	-0.085	0.073	0.023	0.014	0.106	0.122*	1

1: *NIAS-PR Picky eating,* ***2:*** *NIAS-PR Appetite,* ***3:*** *NIAS-PR Fear,* ***4:*** *SDQ-internalizing,* ***5:*** *SDQ-externalizing,* ***6:*** *SDQ-prosocial,* ***7:*** *DASS-21 depression,* ***8:*** *DASS-21 anxiety,* ***9:*** *DASS-21 stress,* ***10:*** *Age,* ***11:*** *BMI percentile. Spearman correlation analysis with rho coefficient;* ***NIAS-PR:*** *Nine Items Avoidant/Restrictive Food Intake Disorder Screen—Parent Report,* ***SDQ:*** *Strengths and Difficulties Questionnaire-Parents Form,* ***DASS-21=*** *Depression Anxiety and Stress Scale,* ***BMI:*** *Body mass index,* ****** $p < 0.050$; ******* $p < 0.010$; ******** $p < 0.001$

4.32 (0.00–13.19) for the Appetite score and 1.86 (0.00-13.78) for the Fear score. In the analyses conducted for the subscales, the Cronbach alpha coefficient was found to be 0.86 for the Picky Eating subscale, 0.87 for the Appetite subscale, and 0.91 for the Fear subscale. The total Cronbach alpha coefficient was found to be 0.90. In the NIAS-PR, the total item correlation was adequate for all items. Removing any item from the scale did not cause an important change in Cronbach's alpha coefficient of the relevant sub-dimension. Results of the analysis of the reliability of the Turkish NIAS-parent form have been shown in Table V.

Relationships between NIAS-PR and other clinical measurements

There is a significant difference in NIAS-PR picky eating (U ($N_{difficulty\ solid\ food}$ = 54, $N_{no\ difficulty\ solid\ food}$ = 214) = 3755, z = -3.821, p <0.001), appetite (U ($N_{difficulty\ solid\ food}$ = 54, $N_{no\ difficulty\ solid\ food}$ = 214) = 3561, z = -4.223, p <0.001, and fear scores (U ($N_{difficulty\ solid\ food}$ = 54, $N_{no\ difficulty\ solid\ food}$ = 214) = 3977, z = -3.550, p <0.001) between those who reported difficulty initiating solid food and those who did not. All NIAS subscales scores were higher in the group with reported difficulty initiating solid food than no difficulty with solid food. There is no significant difference in NIAS-PR picky eating scores between parents with and without concerns about children's physical development (U ($N_{physical\ development\ concern}$ = 36, $N_{no\ physical\ development\ concern}$ = 232) = 3321, z = -1.910, p=0.056). However, in these groups, there is a significant difference in NIAS-PR appetite scores (U ($N_{physical\ development\ concern}$ = 36, $N_{no\ physical\ development\ concern}$ = 232) = 2626, z= -3.531, p <0.001) and NIAS-PR fear scores U ($N_{physical\ development\ concern}$ = 36, $N_{no\ physical\ development\ concern}$ = 232) = 3052, z= -2.649, p=0.008). Spearman correlation results of NIAS-PR and other clinical measurements were presented in Table VI.

DISCUSSION

The current study provided evidence for the validity of the translated Turkish version of the NIAS-PR in the pediatric population in Turkey. The three-factor structure of the NIAS—Picky eating, Appetite, and fear—was replicated in the Turkish NIAS-PR. Our findings were consistent with previous studies supporting the three-factor structure and the addition of ARFID subtypes to DSM-5 (1,8,9,20,21). The three NIAS-PR subscales are intercorrelated; however, they represent different constructs. To better understand the underlying mechanisms that caused avoiding and restricting food intake and to provide more effective therapeutic intervention, it is necessary to reveal these different constructs and presentations of ARFID (8, 9).

The Turkish NIAS-PR subscales were associated with other clinical measures, including age, BMI, children's behavioural problems, parents' psychological distress. Age was negatively associated with Appetite and Fear subscales but unexpectedly not with Picky Eating. Studies in picky eating trajectories indicated that picky eating is predominantly present in preschool children, and picky eating is usually a transient behaviour and part of normal development in preschool children (22-24). Prevalence of picky eating was highest at three years of age (27.6%) and lowest at six years of age (13.2%) in the population-based cohort (23). However, a prospective study reported that picky eating was often a chronic problem affecting 40% of children for more than two years (25). Mascola et al. (25) demonstrated that the incidence of picky eating decreases after preschool, but the prevalence remained relatively stable. We found no association between age and picky eating, which seems consistent with picky eating being a stable trait reflecting individual eating style. Only Appetite subscale of the Turkish NIAS-PR was related to BMI. Unexpectedly, there was no relationship between picky eating and BMI percentile in our study. Findings regarding the relationship between picky eating and children's weight status are conflicting but indicate a lower BMI in picky eaters (26-29). Children with picky eating eat a selective number of foods, which may result in an inadequate intake of necessary nutrients (30). These picky eaters may compensate for their restricted intake of disliked food with much more palatable energy-dense food and favourite food (31). Thus, these picky eating behaviours may not affect their weight status or BMI. We may have found no relationship between BMI percentile and picky eating because of these compensatory eating behaviours.

All subscales of the Turkish NIAS-PR were associated with comorbid behavioural and emotional problems. Picky eating is associated with emotional and behavioural problems, including internalising and externalising problems (32-34). Moreover, a population-based study indicated that internalising and externalising problems predicted picky eating in children from 6 to 18 years old (34). Children's avoidance and restrictive eating pattern might impair their overall psychosocial functioning, resulting in behavioural and emotional problems (35). In our study, NIAS-PR subdimensions were related to behavioural problems, but there was a low correlation. Our sample consisted of the general pediatric population, and 16.8 per cent of the sample had a history of psychiatric admission for any reason. The heterogeneity of the sample may be related to this low level of correlation. The association between ARFID-related eating and behavioural problems may be more evident in a group with a clinically significant ARFID eating disorder. Our study showed that picky eating and appetite subscales were associated with all parental psychopathology symptoms; however, fear subscales were positively related to only depression and stress levels. Picky eating has been associated with mealtime conflict and increased family stress (25, 32). Studies have suggested that negative parental feeding practices may be related to parents' anxiety about their children eating too little and low parental self-efficacy (36-38). Their children's picky eating and insufficient intake can cause stress to parents. Higher stress may negatively impact family relationships and parental feeding practices, so parents' pressure to eat may increase picky eating and food avoidance. It has been demonstrated that there is a bidirectional relationship between parental pressure to eat and picky eating (39).

The three subscales of the NIAS-PR—Picky eating, Appetite, and Fear—were differentially related to other CEBQ eating behaviours, supporting the convergent validity of NIAS-PR and CEBQ. As expected, the Appetite and Picky eating subscales were negatively associated with food-approach subscales of CEBQ (Food responsiveness, Enjoyment of food, Emotional overeating) and were positively correlated with food avoidance subscales of CEBQ (satiety responsiveness and slowness). Unexpectedly, CEBQ food fussiness and NIAS-picky eating were correlated weakly. The different terminology of selective eating could cause this result. The definitions of picky/fussy eating are varied in the literature (30). Food fussiness of CEBQ includes food neophobia-related items, which refers to the unwillingness to eat new foods (10). However, NIAS-PR picky eating items are more related to the consumption of an insufficient amount or inadequate variety of food. Picky eaters may have no problem trying new foods but refuse to eat them every time they are presented (40). In our study, there was a low relationship between the NIAS-Fear subscale which shows fear of aversive consequences from eating and CEBQ-Desire to drink, CEBQ-Satiety responsiveness, and CEBQ-Slowness in eating. However, there was no relationship between CEBQ-Emotional undereating and emotional overeating and NIAS-Fear. A significant part of our sample (28.3 %) was adolescents. Since our assessment was based on only the parent report, the impacts of adolescents' internal emotional states on eating behaviour may not have been recognised by their parents.

The reliability of the Turkish version of NIAS-PR proved to be satisfactory (total Cronbach's alpha=0.90) in the pediatric population (2-18 years). The general Cronbach's alpha coefficient of the Turkish version of the NIAS-PR was quite similar to that of

the Polish version of NIAS-PR in children (9). The results of this study demonstrated a good internal consistency of the Turkish version of the NIAS-PR; thus, we recommend that healthcare providers utilise this instrument as a screening tool for ARFID-related eating behaviours in Turkish children and adolescents.

The current study has several limitations. First, eating and feeding behaviours were based on only parent reporting. Our study did not use any psychiatric clinic interview for eating disorder symptomatology since there is no Turkish version of the clinical interview. Thus, we could not determine the rates of eating disorders in the sample. Second, our study's cross-sectional design did not allow us to evaluate the test–retest reliability of the Turkish NIAS-PR. Third, the children's weight and height were reported by parents, and researchers did not carry out anthropometric measures, so this may cause biased reporting due to parental concerns about their child's weight. Finally, knowledge about our sample features (e.g. chronic diseases and medical drug use) that may impact eating behaviours was limited. NIAS-PR validity should be re-evaluated within specific pediatric samples with detailed information in future studies.

CONCLUSION

The current study demonstrated a good internal consistency of the Turkish version of the NIAS-PR. Moreover, we confirmed the three-factor structure of the Turkish version of NIAS-PR. To our knowledge, the NIAS-PR is the first specific measurement tool to measure ARFID symptoms in Turkey. This study results provide an instrument for ARFID research in Turkish children and adolescents. It is worth mentioning that the NIAS-PR is developed as a screening questionnaire, so mental health professionals should deepen these eating symptoms with clinical interviews. We recommend that the NIAS-PR be validated in different clinical samples.

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Non-invasive Evaluation of Liver Involvement of Children with Cystic Fibrosis by Shear-Wave Elastography

Kistik Fibrozisli Çocuklarda Karaciğer Tutulumunun Shear-Wave Elastografi ile Non-invaziv Değerlendirilmesi

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ABSTRACT

Objective: Hepatobiliary complications commonly occur in cystic fibrosis with increasing prevalence due to longer life expectancies and widespread screening efforts. Shear-wave elastography is a novel noninvasive method that involves application of local mechanical compression on soft tissue using focused ultrasonography and acquiring strain images that show tissue response. We aimed to compare abdominal ultrasonography and Shear-wave elastography and also clinical and laboratory findings of children with cystic fibrosis prospectively.

Material and Methods: This study is a prospective study conducted in thirteen cystic fibrosis patients followed between February 2018 and March 2019. The severity of cystic fibrosis-related liver disease was categorized according to international criteria. Elastography measurement was performed in the same session with the evaluation of the liver by abdominal ultrasonography in the patients. The liver stiffness measurements were compared with clinical data, biochemistry parameters and ultrasound findings.

Results: Measurements were performed in thirteen cystic fibrosis children (three boys, ten girls). The median kiloPascal value of liver stiffness measurements with shear-wave elastography is 6.36 (IQR 5.40-10.80). The median liver stiffness measurement in subjects without cystic fibrosis-related liver disease was 6.30 (IQR 5.26-16.18) kiloPascals (n=5); The median liver stiffness measurement in subjects with cystic fibrosis-related liver disease was 6.46 (IQR 5.43-10.80) kiloPascals. While no significant correlation was found between kiloPascal values and age, gender, AST, ALT, hemoglobin A1c values, a strong positive correlation was found between cystic fibrosis-related liver disease and hemoglobin A1c and ALT values (r=0.702, p=0.007; r=0.761, p=0.003, respectively).

Conclusion: Cystic fibrosis-related liver disease has a significantly varying disease burden, its prevalence is increasing, and its early recognition is crucial for treatment and follow-up. Although there are no clear range values determined for children in tissue stiffness measurements in Shear-wave elastography, clinical and other laboratory and imaging methods and follow-up and evaluation are important.

Key Words: Children, Cystic Fibrosis, Liver, Shear-Wave Elastography

ÖZ

Amaç: Kistik fibrozis dünyada beyaz ırkın en sık görülen genetik hastalığıdır. Kistik fibroziste ortalama yaşam beklentisi arttığından komplikasyonlar ve yönetimi daha önem kazanmıştır. Shear-wave elastografi, odaklanmış ultrasonografi kullanılarak yumuşak doku üzerinde lokal mekanik kompresyon uygulanmasını ve doku tepkisini gösteren gerinim

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görüntülerinin elde edilmesini içeren yeni, invaziv olmayan bir yöntemdir. Bu çalışmada kistik fibrozisli çocukların abdominal ultrasonografi ve Shear-wave elastografi ile klinik ve laboratuvar bulgularını prospektif olarak karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Bu çalışma, Şubat 2018 ile Mart 2019 tarihleri arasında takip edilen on üç kistik fibrozis hastasında gerçekleştirilen prospektif bir çalışmadır. Kistik fibrozis ile ilişkili karaciğer hastalığının şiddeti uluslararası kriterlere göre kategorize edildi. Hastalarda karın ultrasonografisi ile karaciğerin değerlendirilmesi ile aynı seansta elastografi ölçümü yapıldı.

Bulgular: Toplam on üç kistik fibrozisli çocuk değerlendirildi. Shear-wave elastografi ile karaciğer sertliği ölçümlerinin median değeri 6.36 (IQR 5.40-10.80) kiloPaskal'dı. Kistik fibrozise bağlı karaciğer hastalığı olmayan deneklerde medyan karaciğer sertliği ölçümü 6.30 (IQR 5.26-16.18) kiloPaskal (n=5)'di; Kistik fibrozis ilişkili karaciğer hastalığı olan kişilerde medyan karaciğer sertliği ölçümü 6.46 (IQR 5.43-10.80) kiloPaskal olmuştur. kiloPascal değerleri ile yaş, cinsiyet, AST, ALT, HbA1c değerleri arasında anlamlı bir ilişki bulunmazken, kistik fibrozis ilişkili karaciğer hastalığı ile hemoglobin A1c ve ALT değerleri arasında güçlü bir pozitif korelasyon bulundu (sırasıyla r=0.702, p=0.007; r=0.761, p=0.003).

Sonuç: Kistik fibrozis ile ilişkili karaciğer hastalığı, önemli ölçüde değişen bir hastalık yüküne sahiptir, prevalansı artmaktadır ve erken tanınması tedavi ve takip için çok önemlidir. Shear-wave elastografide doku sertliği ölçümlerinde çocuklar için belirlenmiş net bir aralık değerleri olmamakla birlikte klinik ve diğer laboratuvar ve görüntüleme yöntemleri ile takip ve değerlendirme önemlidir.

Anahtar Sözcükler: Çocuklar, Kistik fibrozis, Karaciğer, Shear-wave elastografi

INTRODUCTION

Cystic fibrosis (CF) is a monogenic disease thought to affect at least 100,000 people worldwide. Mutations in cystic fibrosis transmembrane conductance regulator (CFTR), the gene encoding the epithelial ion channel that normally transports chloride and bicarbonate, lead to impaired mucus hydration and clearance. Since the discovery of the most common CFTR mutation (Phe508del), more than 2000 mutations have been identified in CFTR (1). Clinical information is available on an increasing number of detected CFTR mutations, variants with variable clinical outcomes, and variants that cause CF that are not definitively disease-causing. The prognosis in CF has improved markedly with modern multidisciplinary care, improvement of respiratory complications, and modulatory therapies. As a result, non-pulmonary complications are becoming increasingly important. Cystic fibrosis liver disease (CFLD) is the third leading cause of death in people with cystic fibrosis. It is estimated that between 20 and 40% of all CF patients have cystic fibrosis-related diabetes (CFRD) (2). CFLD generally has two phenotypes: focal biliary cirrhosis, which begins early in life and leads to multilobular cirrhosis, or obliterative portal venopathy, which occurs later in life (1-3). In an international study on severe CFLD (cirrhosis and portal hypertension (PHT)), the prevalence was reported as 3-5%; 94% of patients were diagnosed before the age of 20 (3). Early detection of CFLD is difficult due to the lack of a reliable screening tool; liver function tests and ultrasonographic changes may not be sufficient. Non-invasive diagnostic methods are needed to identify those at higher risk of developing liver disease in children with CF and to predict which of these patients will develop CFLD. Ultrasound (US) elastography is a non-invasive imaging modality that has been used to assess tissue stiffness (TS) in the clinical setting for approximately 3 decades. Two-dimensional shear wave elastography (2D-SWE) is a new technique. In the US device, acoustic radiation force is automatically generated by the probe and applied to the tissue at certain frequencies and intensities. In this way, it allows the evaluation of TS both quantitatively and qualitatively (4). Today, life expectancy has increased with the newly developed diagnosis and treatment methods in CF. Since it is a chronic disease that requires long-term follow-up, there is an important need to develop easy-to-apply and non-invasive methods that predict liver complications. It has been found that elastography can significantly predict liver fibrosis in adult patients, but there are not enough studies on elastography in pediatric patients. The aim of this study is to measure liver parenchymal changes with shear wave elastography (SWE) in pediatric patients with CF and to evaluate them together with clinical, laboratory and US results.

MATERIALS and METHODS

Prospective analysis of liver stiffness measurements (LSM) with SWE and abdominal US of liver findings of patients diagnosed and followed up with CF between February 2018 and March 2019 in the Pediatrics Hematology Oncology Training and Research Hospital, Ankara Health Sciences University, Department of Pediatric Pulmonology were performed. Approval was obtained for the study from Ankara Pediatrics Hematology Oncology Training and Research Hospital, Clinical Research Ethics Committee (26.02.2018- 2018-031). The patients' SWE and abdominal US results were compared to their clinical, laboratory and microbiological results. Medical records were used to acquire demographic, clinical, laboratory, and radiological information on the patients. Blood was drawn from all patients prior to imaging and a routine liver panel was analyzed. The panel included, among others: Alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), alkaline phosphatase (ALP), bilirubin, gamma-glutamyl transpeptidase (GGT), international normalized ratio (INR). All patients gave written informed consent. The cystic fibrosis-related liver involvements of the patients were classified according to international guidelines (5,6). Patients without CFLD were defined by no evidence of liver disease on examination, imaging, or laboratory evaluations, and non-prescribed ursodeoxycholic acid (UDCA). Patients classified as CFLD without portal hypertension met at least one

of the following criteria: persistent AST, ALT, GGT 2 times the upper limit of normal or intermittent elevations of these values, or steatosis (histological determination) or fibrosis (histological determination); cirrhosis without cholangiopathy and portal hypertension, with ultrasonographic abnormalities incompatible with cirrhosis/liver involvement; or the use of UDCA. CFLD with cirrhosis/PHT was defined as demonstration of cirrhosis and PHT based on clinical examination/imaging, histology, and laparoscopy. SWE performance was evaluated by a pediatric radiologist with 6-MHz and 9-MHZ point SWE and 9-MHz 2D-SWE. LSM results in the cases were reported in kiloPascal (kPa). The validity of the measurements was evaluated by the device. Simultaneous abdominal US evaluations of the patients were performed by the same pediatric radiologist. The descriptive statistics of the study were shown as number, percentage, median and interquartile range (IQR). Statistical analysis was evaluated in SPSS 23 package program.

RESULTS

Thirteen pediatric CF patients were included in the study and patient characteristics are shown in Table I. 10 patients were female (76.9%) and 3 were male (23%). The mean age of the patients was 5.4 (0.7-16). Patients had a mean body weight of 18.6 (6.4–35.5) kg, mean height of 105.2 (55–143) cm and a mean body mass index (BMI) of 16 (12.9–19.2) kg/m^2. All patients had CFTR genetic test results, Phe508del mutation was the most common (n=8, 61.5%). In the abdominal US of the patients, hepatomegaly was found in 1 patient (7.6%), hepatosteatosis and hepatomegaly were found in 2 patients (15.3%), while the others were evaluated as normal (76.9%). ALT and AST were >1.3 times the upper limit of normal range in 4 (30.7%) and 5 (38.5%) of subjects, respectively. Total and direct bilirubin values of all patients were within normal ranges. Five (38.5%) patients were classified as without CFLD and 8 (61.5%) subjects as CFLD without PHT. There was no patient with CFLD with PHT. Twelve patients (92%) had pancreatic insufficiency and were receiving pancreatic enzyme replacement therapy. None of the patients with CF had endocrine pancreatic insufficiency. Three patients had a history of meconium ileum. Due to the small age of the sample group, pulmonary function tests could be performed in 4 (30%) patients. The mean pulmonary function forced expiratory volume in 1 second (FEV1) of the patients was 53% (n=4). None of the patients had cirrhosis US criteria or ascites.

The median kPa value of the patients was 6.36 (IQR 5.40-10.80). In comparisons between patients, there was no statistically significant difference between kPa values in patients with Phe508del mutation, liver involvement, elevated AST/ALT, and patients with and without elevated hemoglobin A1c (HBA1c) (p=0.222; p=0.833; p=0.284; p=0.940, respectively). While no significant correlation was found between kPa values and age, gender, AST, ALT, HbA1c values, a strong positive correlation was found between CFLD and hemoglobin A1c (HbA1c) and ALT values (r=0.702, p=0.007; r=0.761, p=0.003, respectively). One patient has hepatomegaly and normal liver function tests and the patient's Kpa value was 6,36; two patients with elevated liver function tests and hepatosteatosis had Kpa values of 5.15 and 19.3; 1 patient with elevated liver function tests had a Kpa of 6.38. Abdominal US and liver function tests of other patients were normal.

Table I: Summary of the distribution of demographic and clinical variables of patients (n=13).

Clinical Variable	Number (n), (%), Mean +/- SD
Age at LSM (year)	5.4±2.5 years
Sex	
Male	76.9
Female	23
Laboratory Findings	
ALT	34.2 U/L (10–67)
>1.3 times the ULN ALT	30.7
AST	44.6 U/L (21–87)
>1.3 times the ULN AST	38.4
GGT	23.8 U/L (7–110)
HBA1c	5.4 (4.4-6.5)
BMI	16 kg/m^2 (12.9–19.2)
CF-related diabetes	n= 4, (30.7)
Ursodeoxycholic acid therapy	n= 7, (53.8)
Chronic *P. aeruginosa* infection	n= 7, (53.8)
deltaF508 mutation	n= 8, (61.5)
Stage of liver disease	
CFnoLD	n= 5, (38.4)
CFLD	n= 8, (61.5)
Hepatic steatosis	n= 2, (15.3)
Hepatomegaly	n= 3, (23)
kPa values	
CFnoLD	n=5, 7.79 (5.2-13.53)
CFLD	n=8, 9.23 (4.1-20.2)

ALT: *alanine aminotransferase,* ***AST:*** *aspartate aminotransferase,* ***BMI:*** *body mass index,* ***CFLD:*** *cystic fibrosis liver disease,* ***CFnoLD:*** *cystic fibrosis with no evidence of liver disease,* ***GGT:*** *gamma-glutamyl transferase,* ***HBA1c:*** *hemoglobin A1c,* ***kPa:*** *kiloPascal,* ***LSM:*** *liver stiffness measurement,* ***P. aeruginosa:*** *Pseudomonas aeruginosa,* ***SD:*** *standard deviation,* ***UNL:*** *upper limit of normal range.*

DISCUSSION

Hepatic involvement is an important cause of mortality and morbidity in patients with CF. Many factors play a role in the etiology of CFLD. Detection and staging of CFLD poses challenges in clinical practice due to the lack of specific diagnostic tools, but identifying children at risk of developing CFLD is of clinical importance for CF patient management. CFLD is usually asymptomatic and CFLD screening includes physical examination, biochemical evaluations and US, with further studies added as needed (7). The guidelines recommend

annual monitoring of liver enzymes in all patients with CF. If abnormal and there are persistent unexplained elevations in liver enzymes, US and liver biopsy may be considered (8). Liver biopsy is still used as the most valid standard for the evaluation of liver fibrosis. However, it is an invasive procedure that can cause serious complications (9). Non-invasive diagnostic methods are needed to identify and evaluate patients at risk of developing liver disease (10). Therefore, researchers focused on the evaluation of non-invasive methods for the evaluation of liver fibrosis. One of these methods is elastography, which measures TS or elasticity. These include transient elastography (TE or FibroScan) and 2D-SWE. 2D-SWE is an integrated US method that provides a color map of liver elasticity values simultaneously with real-time visual imaging (4). This study evaluated the ability of 2D-SWE to detect CFLD in pediatric CF patients. In our clinical practice, we needed more sensitive noninvasive methods to detect and evaluate CFLD in children, and we used and evaluated SWE as a screening method for CFLD in our patients to gain more experience.

US detection of CFLD is difficult and non-specific unless it is at an advanced stage (11). 2D-SWE is a promising new tool to detect hepatic fibrosis indirectly by measuring liver stiffness and has been shown to be useful in adult CF patients and different chronic liver diseases (11,12). In a study of 125 children with CF with SWE, the LSM was 8.1 kPa (IQR = 6.7–11.9) in CFLD; It was found to be 6.2 kPa (IQR = 5.6–7.0; $p<0.0001$) in CFnoLD and 5.3 kPa (IQR = 4.9–5.8; $p<0.0001$) in healthy controls. LSM was significantly higher in CFLD and cystic fibrosis with no evidence of liver disease (CFnoLD) than in controls (11). Other studies have evaluated LSM using SWE in healthy control children and have shown median values ranging from 5.5 kPa to 7.4 kPa (13-15). Several TE studies have reported higher LSM in CFLD compared to CFnoLD children (8, 16, 17). A meta-analysis of TE suggested a cut-off point of 5.95 kPa for increased liver stiffness (18). A meta-analysis of 12 studies evaluated 550 children with chronic liver disease and established a cut-off point of 9.4 kPa to predict significant liver disease (11,19). In our study, the median LSM in patients with CFnoLD was 6.30 (IQR 5.26-16.18); was similar to that reported for CFnoLD by other groups using TE. In our study, the median LSM for CFLD was 6.46 (IQR 5.43-10.80) kPa, and it was lower than the studies using TE (11,17,19). Other studies with TE have reported much higher median LSM values between 14 and 15.1 kPa. These differences between measurements may be due to differences in patients' CFLD severity and study designs (8,16). In our study, there was no statistically significant difference in kPa values between patients without CFLD and patients with CFLD, but the study sample was small. Also, none of the subjects with CFLD in our study had PHT or cirrhosis. Monitoring serial LSM for changes over time may be a more useful strategy for detecting early fibrosis and categorizing LSM values in CFLD. More data and studies are needed to predict accurate thresholds that are disease specific, according to age and BMI. A study in children and young adults with CF showed a correlation between liver stiffness measurement (LSM) and the presence and severity of liver disease (8). Taken together, all these results confirm that SWE is a reliable and reproducible non-invasive method to detect advanced fibrosis in children with CFLD, and that advanced liver disease with cirrhosis shares common LSM features across different diagnostic groups.

One of the advantages of LSM over biopsy is that it allows monitoring of liver disease progression. This study could not evaluate the progression of liver disease using SWE, as CFLD development and progression to fibrosis are variable in patients with CF. Relatively less data are available on 2D-SWE and pediatric references are lacking. Although the specificity of TE was good (87%), its sensitivity was found to be quite low (55%) (18).

No specific biomarker was convincingly associated with kPa values in our study, but the fact that some children have already been treated with UDCA may explain the lack of evidence in this regard. Despite the lack of validated reference ranges, numerical results in kPa may be useful on an individual basis in monitoring disease progression. One study showed that liver stiffness increased over time and that the worsening slope detected by elastography and longitudinal measurements could predict CFLD (20). This is an important aspect of the potential of these methods in patient-based clinical evaluation. With non-invasive elastography methods, a clear distinction cannot be made between PHT and liver fibrosis. Limitations include the lack of reference values for children for the 2D SWE method and the lack of validation and standardization for different techniques.

Many factors play a role in the etiology of CFLD. Studies have linked CFLD with genotype, history of meconium ileus, malnutrition, CFRD, and male gender (21-24). Fluctuations in transaminase levels may occur in CF patients due to respiratory tract infections, multiple drug use, nutrition and complications (5). Studies have shown that male gender, Pseudomonas aeruginosa, Phe508del homozygosity, history of meconium ileus, and CFRD are important independent risk factors for cirrhosis in CF patients (2). Hemodynamic changes as a result of advanced cirrhosis can exacerbate ventilation-perfusion mismatch and cause hypoxia. One study showed that hypoxic conditions favored the growth of resistant Pseudomonas aeruginosa strains (25, 26). The role of UDCA in the treatment of CFLD is controversial; In a recent cohort study and systematic review by the Cochrane collaboration, it was found that the use of UDCA did not change the incidence of severe CFLD (24, 27). In a retrospective study of a large group of patients with CF, previous use of UDCA in the last 20 years did not change the incidence of severe CFLD (24). CFRD is a common and serious complication of CF that usually occurs after the second decade of life. One study showed that patients with CFLD have a more than 11-fold increased risk of developing CFRD compared with individuals without CFLD (28). In our study, a strong positive correlation was found between CFLD and HbA1c values,

which is consistent with the literature (r=0.761). Other studies have also shown this relationship (7,24,28,29). Therefore, earlier screening of patients with CFLD for CFRD should be considered. In addition, longitudinal follow-up of these patients with the 2D SWE method will be important.

The most important limitation of the study is the small sample size due to the small number of patients. However, the study design reflects a population of subjects reflecting clinical practice and patient distributions in a CF center. Another limitation is the lack of histological evaluations of CFLD patients. However, there was no CFLD with cirrhosis/PHT in the patient group. kPa and FEV1 values could not be compared since most of the patients were under 6 years of age.

As with other liver diseases and systemic diseases with liver involvement, there is a need for markers that allow accurate assessment of the severity of liver disease as well as the detection of fibrosis in CF. Noninvasive differentiation and recognition of necroinflammation from fibrosis plays an important role in this area. In addition, disease-specific cut-off values need to be applied for all diagnostic tools presented.

More research involving different chronic liver diseases is needed for a better understanding of SWE. This is particularly important for CF because the clinical course of the disease and liver involvement are not the same for all mutations. Because this method is not established, comparison of published studies and interpretation of measured values is difficult.

CONCLUSION

This study provides evidence that SWE may be a useful, non-invasive tool for assessing liver disease in patients with CF. Measurement of SWE with TS in patients with CF may guide further management regarding the timing of assessment of CFLD development in patients. Prospective studies with a larger population are needed to detect liver involvement in the early period in patients with CF and to calculate the cut-off values of SWE in this patient group. Longitudinal follow-up of the patients will be more meaningful to evaluate the effectiveness of SWE.

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The Other Side of the Coin: Uveitis in Patients with Juvenile Idiopathic Arthritis

Madalyonun Diğer Yüzü: Juvenil İdiyopatik Artritli Hastalarda Üveit

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ABSTRACT

Objective: Juvenile idiopathic arthritis (JIA) is a childhood rheumatic disease that causes joint inflammation and tissue damage. Non-infectious uveitis is the most common extra-articular manifestation of JIA.The aim of this study is to evaluate the risk factors that play a role in occurrence and recurrence of uveitis and, to determine the relationship between arthritis and uveitis activity in patients with JIA.

Material and Methods: This retrospective, cross sectional study included JIA patients with/without uveitis from a referral center in Turkey. The Juvenile Arthritis Disease Activity Score was used to evaluate the disease activity and calculated for arthritis and uveitis separately.

Results: Uveitis was seen in 26 (13.3%) of 195 JIA patients. Of 26 JIA associated uveitis (JIA-U) patients, 19 (73%) had an oligoarticular subtype. The median age at diagnosis of JIA with uveitis was younger than without uveitis (p=0.015). Oligoarticular JIA was found to be associated with recurrence of uveitis (p=0.021). The occurrence age of arthritis and uveitis was significantly younger in patients with recurrent uveitis (p=0.041, p=0.002, respectively). The median JADAS27 score at the onset of uveitis was lower in the recurrent group (p=0.038).

Conclusion: Early age is a significant risk factor for occurrence and recurrence of uveitis. It is important to remember that, during the disease course, patients with low disease activity may also develop uveitis.

Key Words: Age, Disease activity, Juvenile idiopathic arthritis, Pediatrics, Recurrence, Uveitis

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Contribution of the Authors / Yazarların katkısı*: *TEKGÖZ N: Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/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. ***ÇELİKEL E:*** Planning methodology to reach the Conclusions. ***AYDIN F:*** Constructing the hypothesis or idea of research and/or article. ***TEKİN Z:*** Taking responsibility in logical interpretation and conclusion of the results. ***KURT T:*** Constructing the hypothesis or idea of research and/or article. ***SEZER M:*** Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study. ***GÜNGÖRER V:*** Taking responsibility in necessary literature review for the study. ***KARAGÖL C:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***COSKUN S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***KAPLAN MM:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***ÖNER N:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***POLAT MC:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***ÖZMEN S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***SEZER S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***ÇELİKEL ACAR B:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar.

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ÖZ

Amaç: Juvenil idiyopatik artrit (JİA), eklem iltihabı ve doku hasarına neden olan çocukluk çağı romatizmal bir hastalıktır. Enfeksiyöz olmayan üveit, JİA'nın en sık görülen eklem dışı belirtisidir. Bu çalışmanın amacı, JIA'lı hastalarda üveit oluşumunda ve tekrarlamasında rol oynayan risk faktörlerini değerlendirmek ve artrit ile üveit aktivitesi arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntemler: Bu retrospektif, kesitsel çalışmaya Türkiye'deki bir sevk merkezinden üveiti olan/olmayan JIA hastaları dahil edildi. Hastalık aktivitesini değerlendirmek için Juvenil Artrit Hastalık Aktivite Skoru kullanıldı ve artrit ve üveit için ayrı ayrı hesaplandı.

Bulgular: Üveit 195 JIA hastasının 26'sında (%13.3) görüldü. 26 JIA-U hastasının 19'unda (%73) oligoartiküler alt tip vardı. Üveitli JİA'nın tanı ortanca yaşı üveitsiz JİA'ya göre daha gençti (p=0.015). Oligoartiküler JİA üveit nüksü ile ilişkili bulunmuştur (p=0.021). Tekrarlayan üveiti olan hastalarda artrit ve üveitin ortaya çıkış yaşı anlamlı olarak daha gençti (sırasıyla p=0.041, p=0.002). Üveit başlangıcındaki medyan JADAS27 skoru tekrarlayan grupta daha düşüktü (p=0.038).

Sonuç: Erken yaş, üveit oluşumu ve nüksü için önemli bir risk faktörüdür. Hastalık seyri sırasında, düşük hastalık aktivitesine sahip hastalarda da üveit gelişebileceğini unutmamak önemlidir.

Anahtar Sözcükler: Yaş, Hastalık Aktivitesi, Juvenil Idiyopatik Artrit, Pediatri, Nüks, Üveit

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a childhood rheumatic disease that causes joint inflammation and tissue damage. Non-infectious uveitis is the most common extra-articular manifestation of JIA. Uveitis developed during the disease course due to uveal inflammation. Although the cause of uveal inflammation is not known precisely, several risk factors identified in the occurrence of uveitis. These are JIA-subtype, presence of antinuclear antibody (ANA) and human leukocyte antigen (HLA) B-27, gender, and younger age at disease onset (1,2). Chronic anterior uveitis is the most common JIA associated uveitis (JIA-U) form, and female gender, early age at arthritis onset (<6 years), positive ANA status, and oligoarticular subtype are risk factors that increase its occurrence (3).

JIA-U often has a silent and insidious onset and is most commonly independent of arthritis activity (4). However, recent studies reported relationship between arthritis and uveitis activity (5,6). Zak et al. (7) reported that 20% of patients with JIA who developed uveitis in childhood had ocular complications in adulthood. This result indicates that JIA-U issues such as recurrence persist beyond childhood and highlights the importance of identifying risk factors associated with JIA-U.

The aim of this study is to evaluate the risk factors that play a role in the occurrence and recurrence of uveitis in patients with JIA. Additionally, it is also planned to determine the relationship between arthritis and uveitis activity.

MATERIALS and METHODS

Study design, data collection, definition

This observational study included the patients who were diagnosed and followed up with JIA and JIA-U, between April 2005 and May 2020.

Systemic findings, normal ESR/CRP, and physician's global assessment of disease activity) (11).

The study was approved by Ankara City Hospital, No. 2 Clinical Research Ethics Committee (E2-21-714/ 21.04.2021).

Statistical Analysis

IBM SPSS Statistics for Windows, version 26.0 (SPSS Inc, Chicago, IL, USA) was used to perform statistical analysis. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Continuous variables that do not have normal distribution were expressed as median (IQR). Categorical variables were summarized as counts (percentages). The Chi-square test was used to compare categorical variables, and Mann-Whitney U-test was used to compare non-normally distributed continuous variables. For the multivariate analysis, the possible factors identified with univariate analyses ($p<0.1$) were further entered into the logistic regression analysis to determine independent predictors of uveitis. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. The odds ratio (OR) and their 95% confidence interval (CI) obtained in the adjusted regression analysis were calculated. The statistical significance level was accepted as a p-value <0.050.

RESULTS

Characteristics of JIA patients:

A total of 195 patients with JIA were enrolled in the study and 122 patients (62.5%) were female. The median age was 7.8 (4.4-12.2) years. A hundred and seven patients (55%) were oligoarticular JIA, 13 patients (6.6%) were polyarticular JIA, 23 (12%) patients were ERA, and 52 (26.6%) patients were systemic JIA.

Characteristics of JIA-U patients:

Twenty-six patients (13.3%) developed uveitis during the study period. Seventeen (65.4%) of the patients with JIA-U were female. The median duration between JIA diagnosis

and uveitis was 4.5 months. Of 26 JIA-U patients, 19 (73.3%) had oligoarticular, 3 (11.5%) had polyarticular, and 4 (15.3%) had ERA subtype. Presence of ANA was present in 9 patients (34.6%). Uveitis occurred in 2 patients (7.7%) before arthritis and in 10 patients (38.4%) after arthritis. Uveitis and arthritis were coexisting in 10 patients (38.4%) at disease onset. Four patients (15.3%) developed uveitis after withdrawal of treatment. Anterior uveitis was present in 24 patients (92.3%) and granulomatous uveitis in 2 patients. Seven patients (27%) had bilateral, 19 patients (73%) had unilateral disease. The characteristics of the patients were summarized in Table I. Treatment at diagnosis of uveitis was methotrexate (MTX) in 9 patients, NSAID in 1 patients, biological DMARDs in 2 patients, and MTX + biological DMARDs in one patient. Thirteen patients were received only topical therapy for ocular inflammation. Thirteen patients (50%) had uveitis under JIA treatment.

Table I: Characteristics of JIA patients with uveitis

	Uveitis (n=26)
Female gender*	17 (65.4)
Arthritis at the onset of the disease*	24 (92.3)
Uveitis at the onset of the disease*	12 (46.2)
Age at JIA onset, year†	5.1 (3-7.8)
Age at uveitis onset, year†	6.9 (4.4-9.6)
Duration between JIA and uveitis onset, months†	4.5 (0-29.8)
JIA subtype	
Oligoarticular*	19 (73.1)
Others*	7 (26.9)
Active joint count†	2 (1-3)
Uveitis type*	
Anterior uveitis	24 (92.3)
Granulomatous uveitis	2 (7.7)
ESR (mm/hour)†	28.5 (14.8-36)
CRP (mg/dl)†	2.4 (1-12.8)
ANA positivity*	9 (34.6)
HLA-B27 positivity*, n=16	4 (25)
JADAS27 at JIA onset†	19 (14-23)
JADAS27 at uveitis onset†	11 (9-17)
Treatment	
Treatment at uveitis onset*	
No treatment	13 (50)
NSAID	2 (7.6)
MTX	9 (34.6)
Biologic DMARDs	3 (11.5)
Treatment during active uveitis*	
MTX	25 (96.2)
Biologic DMARDs	13 (50)
Total duration of MTX, months†	50.5 (24-72.5)
Duration of MTX before starting biologic DMARDs, months,†, n=12	24 (4-40.5)
Total duration of biologic DMARDs, months†, n=12	33 (23.3-39.5)
Uveitis relapse episode†, n=15	1 (1-3)
Remission on medication, months†	18 (12-37.5)
Remission off medication, months†, n=5	40 (16.5-60)

:** *n (%),* **†**: *median (IQR, %25-75),* ***JIA: *Juvenile idiopathic arthritis,* ***IQR:*** *Interquartile range,* ***ANA:*** *Antinuclear antibody,* ***JADAS:*** *The Juvenile Arthritis Disease Activity Score,* ***HLA:*** *Human Leukocyte Antigen,* ***ESR:*** *Erythrocyte sedimentation rate,* ***MTX:*** *Methotrexate,* ***DMARDs:*** *Disease modifying anti-rheumatic drugs*

Comparison of JIA patients with and without uveitis:

The age of disease onset was significantly younger in patients with uveitis than without uveitis (p=0.015). There was no significant difference between the two groups in sex, JIA subtype, presence of ANA, JADAS27 at diagnosis. Rates of MTX and biologic DMARD use for arthritis were higher in patients with JIA-U than in those without uveitis (p<0.001, p=0.038 respectively). The comparison of JIA patients with and without uveitis was summarized in Table II.

Predicting risk factors of uveitis:

We performed multivariate analysis to determine the risk factors of JIA-U. This model included possible risk factors such as presence of ANA, female gender, and JIA subtype. This present study showed that patients with early age at JIA onset had higher odds of occurring uveitis (Table III).

Comparison of JIA-U patients with none-recurrent and recurrent uveitis:

Of the 26 JIA-U patients, 15 had recurrent episodes, and 11 had a single episode. The median episode during the follow-up period was 1 (1-3). The demographic and baseline characteristics of these two groups were shown in Table IV. There was no significant difference in gender, clinical presentation, positive ANA status, JADAS27 at time of JIA diagnosis between two groups. Oligoarticular JIA was found associated with recurrence of uveitis (p=0.021). Patients with the recurrent uveitis were significantly younger at disease onset than the none-recurrent group (p=0.041, p=0.002, respectively). The median JADAS27 at the onset of uveitis was lower in the recurrent group (p=0.038). Topical cycloplegics and steroids were initially used in all patients with uveitis. The median duration of MTX usage and the median time to initiation of biologic DMARDs after MTX were significantly longer in the relapse group (p=0.013, p=0.045). There was no significant difference in the median duration of biological DMARDs usage between the two groups.

Uveitis-related complications:

Of 26 patients, 15 patients had ocular complications at follow-up. Posterior synechiae (66.6%) was the most frequent complication in our study. Other complications were cataract in two patients, glaucoma in one patient, and iris atrophy in one patient.

Table II: Characteristics of JIA patients with and without uveitis.

	Patients without Uveitis (n=169)	Patients with Uveitis (n=26)	p
Gender, female*	105 (62.1)	17 (65.4)	0.750
Age at JIA onset, year†	8.7 (5.1-12.4)	5.1 (3-7.8)	0.015
Age at uveitis onset, year†		6.9 (4.4-9.6)	
Duration between JIA and uveitis onset, month†		4.5 (0-29.8)	
JIA subtype Oligoarticular* Others*	 100 (59.2) 69 (40.8)	 19 (73.1) 7 (26.9)	0.176
ESR (mm/hour)†	34 (14-62)	28.5 (14.8-36)	0.279
ANA positivity	33 (19.5)	9 (34.6)	0.081
JADAS27 at JIA onset†	19.4 (17-22.2)	19 (14-23)	0.323
JADAS27 at uveitis onset†		11 (9-17)	
Active joint count†	2 (1-3)	2 (1-3)	0.459
MTX treatment*	101 (59.8)	25 (96.2)	<0.001
Biologic DMARDs*	50 (29.6)	13 (50)	0.038

:** *n(%),* **†:** *median (IQR, %25-75),* ***JIA: *Juvenile idiopathic arthritis,* ***IQR:*** *Interquartile range,* ***ANA:*** *Antinuclear antibody,* ***JADAS:*** *The Juvenile Arthritis, Disease Activity Score,* ***ESR:*** *Erythrocyte sedimentation rate,* ***MTX:*** *Methotrexate,* ***DMARDs:*** *Disease modifying anti-rheumatic drugs*

Table III: Risk factors for the development of uveitis

	Patients without Uveitis (n=169)	Patients with Uveitis (n=26)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p	OR (95% CI)	p
Female gender	105 (62.1)	17 (65.4)	1.15 (0.48-2.74)	0.750	1.02 (0.41-2.56)	0.961
Diagnosis age<8	78 (46.2)	20 (76.9)	3.89 (1.49-10.17)	0.006	3.58 (1.35-9.47)	0.010
Oligoarticular JIA	100 (59.2)	19 (73.1)	1.87 (0.75-4.70)	0.181	1.40 (0.52-3.75)	0.501
ANA positivity	33 (19.5)	9 (34.6)	2.18 (0.89-5.33)	0.087	1.82 (0.71-4.65)	0.212

Hosmer and Lemeshow Test p value 0.350, ***JIA:*** *Juvenile idiopathic arthritis,* ***OR:*** *Odds Ratio,* ***ANA:*** *Antinuclear antibody*

Table IV: Characteristics of JIA-U patients with and without recurrent uveitis

	Non-recurrent, n=11	Recurrent, n=15	p
Female gender*	5 (45.5)	12 (80)	0.103
Arthritis at disease onset	10 (90.9)	14 (93.3)	1.000
Uveitis at disease onset	4 (36.4)	8 (53.3)	0.391
Age at JIA onset, year†	6.7 (4.2-13.4)	4.4 (2.8-6)	0.041
Age at uveitis onset, year†	9.3 (7-15.3)	5.6 (3-7.4)	0.002
Duration between JIA and uveitis onset, month†	4 (0-62)	0 (0-12)	0.180
JIA subtype Oligoarticular* Others*	 5 (45.5) 6 (54.5)	 14 (93.3) 1 (6.7)	0.021
ANA positivity*	4 (36.4)	5 (33.3)	1.000
JADAS27 at JIA onset†	15 (14-28)	19 (13-22)	0.357
JADAS27 at uveitis onset†	17 (10-22.3)	9 (2.3-11.5)	0.038
Arthritis relapse episode†	1 (1-2)	1 (0-2)	0.726
Total duration of MTX, month†	24 (18-58)	72 (40-108)	0.013
Duration of MTX before starting biologic DMARDs, month†	3 (3-26.5)	27.5 (12.8-68.3)	0.045
Total duration of biologic DMARDs, month†	35 (17.5-58)	33 (24-34)	0.639

:** *n(%),* **†:** *median (IQR, %25-75),* ***JIA: *Juvenile idiopathic arthritis,* ***IQR:*** *Interquartile range,* ***ANA:*** *Antinuclear antibody,* ***JADAS:*** *The Juvenile Arthritis Disease Activity Score,* ***MTX:*** *Methotrexate,* ***DMARDs:*** *Disease modifying anti-rheumatic drugs*

DISCUSSION

Uveitis is a crucial complication of JIA. Risk factors associated with the occurrence of uveitis should be known to guide specialists in the follow-up of patients. According to our findings, "early onset age at diagnosis" was a risk factor for occurrence and recurrence of uveitis in JIA. However, JADAS27 at uveitis onset was significantly lower in recurrent uveitis than in non-recurrent uveitis.

Ocular inflammation is an insidious condition that affects quality of life. JIA is the most frequent systemic disease that causes noninfectious uveitis. Yalçındağ et al. (12) reported that 25% of non-infectious pediatric uveitis was associated with JIA. In a multicenter study from Turkey, Sahin et al. (13) reported the rate of uveitis development as 6.8% among 500 patients with JIA. In the current study, 26 patients (13.3%) developed JIA-U.

There is a stronger association between inflammatory arthritis and uveitis in childhood than in adults. The various risk factors such as early age at disease onset, female gender, oligoarticular subtype, and positive ANA status increase the odds of developing uveitis (14). In a prospective study that included 1497 Canadian JIA patients, the young age (<7 years) at diagnosis and ANA positivity were independent risk factors for uveitis (15). Calandra et al. (16) reported that JIA-U was strongly related with arthritis at younger age and presence of ANA. However, female gender and oligoarticular subtype were not showed as independent risk factors for uveitis. Similarly, our study showed that there was no difference between JIA and JIA-U groups in parameters gender and oligoarticular subtype. However, the oligoarticular disease was significantly common in recurrent JIA-U group. We observed a higher positive ANA status in the JIA-U group compared to the JIA group, although not statistically significant (34.5% vs. 19.5%). Tappeiner et al. (17) showed that ANA positivity was strongly associated with JIA-U in multivariate analysis .

In a prospective study, uveitis reactivation was associated with age at disease onset (uveitis <5 years, arthritis <4 years) and active disease (18). Similarly, in our study, the median age at arthritis in JIA-U patients was significantly younger than in JIA patients (5.1 years vs 8.7 years). In addition, younger age at onset of the disease increased the recurrence rate of uveitis. The median age at uveitis onset was significantly lower in recurrent patients than in non-recurrent patients (5.6 years vs 9.3 years).

JIA-U is usually of the non-granulomatous type (19). In a retrospective study of 125 JIA-U patients, granulomatous type of uveitis was reported 27.2% (20). Another study reported that, granulomatous subtype could be probably due to the intense inflammation (21). Granulomatous uveitis was defined in two patients in our study. These two patients had uncontrolled inflammation due to treatment non-compliance.

The disease activity of JIA is variable due to its heterogeneous nature. Optimal control of inflammation prevents long-term disability. Many authors reported that arthritis and uveitis activity might parallel each other (6,22,23). In a recent multicenter study, the JADAS27 at disease onset was significantly higher in patients with uveitis than those without uveitis (24). Heiligenhaus et al. found the disease activity of JIA to be similar in the group with and without uveitis. In addition, moderate and high disease activity was associated with reactivation of uveitis (18). According to our findings, JADAS27 was not different between patients with JIA-U and JIA without uveitis. However, the JADAS27 was significantly lower in the recurrent uveitis group than the non-recurrent group. These critical findings highlight that the JADAS27 is may be insufficient in evaluating the disease activity in the presence of uveitis. Otherwise, it can be considered that arthritis activation and uveitis recurrence in JIA may be independent of each other, and in this case, due to the insidious course of uveitis, eye examinations should be performed regularly in patients who are in remission for arthritis.

Patients diagnosed with JIA in the last 15 years in our center were included in our study. In 15 years there have been significant advances in the treatment approach of JIA-U. In addition to MTX and topical corticosteroids, the use of biological DMARDs has become widespread over the years. Papadopoulou et al. (25) reported that JIA patients treated with MTX had a lower rate of developing uveitis during the disease than those who were not treated. Heiligenhaus et al. (18) showed that topical corticosteroid use was associated with a significantly higher risk of uveitis recurrence. In our study, the median duration of MTX usage was longer in the recurrent group. Furthermore, the median time interval before initiating biological DMARDs after the MTX usage was longer in the recurrent group. Early and effective treatment prevents recurrence of uveitis. In recent years, biological DMARDs are recommended to achieve clinical remission in a short time interval (26).

The major limitations of our study were the retrospective design, the small number of patients. In addition, the outcomes of JIA patients in the last 15 years were evaluated in this study. During this period, the use of biologic agents has increased with updates in the treatment approach. It is inevitable that this change will have an effect on uveitis recurrence over the years, but the effect of the changing treatment modality over the years was not analyzed in this study.

In conclusion, the treatment of JIA should be planned according to both joint and ocular involvement. Sometimes uveitis can be more difficult to treat than arthritis. We emphasize that "early age" is a significant risk factor for developing and recurrence of uveitis. However, it is to keep in mind that patients with low disease activity may also develop uveitis. Since the risk of recurrence of uveitis is increased in oligoarticular JIA, these patients should be carefully follow-up for uveitis. Therefore, treatment and follow-up should be planned with a multi-

disciplinary approach, including a pediatric rheumatologist and ophthalmologist.

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The Coexistence of Postpartum Depression with Infantile Colic and Sleep Problems

Doğum Sonrası Depresyon ile Bebeklik Koliği ve Uyku Sorunlarının Birlikteliği

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ABSTRACT

Objective: This study aims to examine the frequency and the factors that can cause postpartum depression (PPD) in the mothers who gave birth at Şan Med Hospital in Şanlıurfa.

Material and Methods: The study was performed on volunteer mother-baby couples who were born in Şanlıurfa Şan Med Hospital and were admitted to Şan Med Hospital Pediatrics Polyclinic between September 2017 and December 2017. Participants were asked to provide some information about themselves and their babies, as well as their babies' crying and sleeping patterns. The Edinburgh postpartum depression scale (EPDS) was administered to the mothers.

Results: It was determined that the frequency of PPD increased by 2.73-folds for mothers whose babies cried excessively, and by 2.79-folds for the mothers whose babies had unconsolable crying/restlessness lasting 2-3 hours a day. The results indicated that the risk of PPD was 6.86-folds higher in mothers of infants who awoke frequently, as compared to the mothers of infants who had regular sleep patterns.

Conclusion: Infantile colic and prolonged crying are associated with higher maternal depression scores.

Key Words: Infantile colic, Postpartum depression, Prolonged crying

ÖZ

Amaç: Çalışmamızda Şanlıurfa'da Şan Med Hastanesinde doğum yapan annelerde doğum sonrası depresyon (PPD) sıklığı ve etki eden faktörlerin incelenmesini amaçladık.

Gereç ve Yöntemler: Şanlıurfa Şan Med Hastanesinde doğumu gerçekleştirilen ve Şan Med Hastanesi Çocuk Sağlığı ve Hastalıkları polikliniğine Eylül 2017 ve Aralık 2017 tarihleri arasında gelen ve çalışmaya katılmak isteyen anne bebek çiftleri çalışmaya alındı. Anne ve bebek özellikleri, bebeklerin ağlama ve uyku düzenleri sorgulandı. Annelere Edinburg postpartum depresyon ölçeği (EPDS) uygulandı.

Bulgular: Aşırı ağlaması olan bebeklerin annelerinde PPD sıklığının 2.7 kat, 2-3 saat ağlayan bebeklerin annelerinde 2.8 kat arttığı saptandı. Ayrıca sık uyanması olan bebeklerin annelerinde, düzenli uykusu olan bebek annelerine göre 6.9 kat arttığını saptadık.

Sonuç: İnfantil kolik ve uzun süreli ağlama yüksek anne depresyon puanları ile ilişkilidir.

Anahtar Sözcükler: İnfantil kolik, Doğum sonrası depresyon, Uzun süreli ağlama

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The protocol of the study was approved by Hacettepe University's Non-Interventional Research Ethics Committee (Project Number: GO 17/687).

Contribution of the Authors / Yazarların katkısı*: *GÜNEŞ B: 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. ***YALÇIN 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, 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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INTRODUCTION

Postpartum depression (PPD) is a significant health problem and the most common psychological condition encountered by mothers and others around them, it occurs in almost a third of women (1). A study by Poçan et al.(1) found that the incidence of PPD was 28.9%, according to Edinburgh Postpartum Depression Scale (EPDS) scores, with EPDS > 12 values defined as indicating PPD. In a meta-analysis by Keser Özcan et al. (2), the prevalence of PPD in Turkey overall was reported as being 23.8% (21.2% in developed cities and 25% in developing cities). In a study by Wang et al., (3) which included 565 studies from 80 different countries or regions, PPD was detected in 17.2% of the global population. While significant differences were seen between countries according to the level of development, it was reported that the risk of PPD was lower in developed countries (3). Postpartum period is when a new mother is most likely to develop postpartum depression. It frequently has serious detrimental effects on the infant (4). Mostly, PPD can begin within four weeks of birth and last up to 1 year (5). Multiple conditions and circumstances were seen as increasing the risk of PPD, including: socioeconomic difficulties, a lack of social support, a sense of loneliness, marital problems, exposure to physical violence, unplanned pregnancies, first pregnancy, being pregnant at an early age, a fear of childbirth, multiple pregnancies, being depressed in previous pregnancies, inability to breastfeed, a history of pregnancy and birth that ended in loss, early mother-infant separation (often due to the baby receiving neonatal intensive care treatment due to illness or divorce),and a family history of mental illness. It has also been found that depression in mothers during and after pregnancy negatively affects the health and development of the fetus and the baby, with subsequent negative effects on the physical and mental development of the baby after birth (6,7). It is normally the case that the baby of a depressed mother has sleep problems and a compulsive temperament, which only serves to increase the mother's depression (8-10).

The symptoms of infantile colic in an otherwise healthy baby are unexplained and inconsolable crying attacks, drawing the legs to the abdomen, reddening of the face, bloating and gas. Infantile colic occurs with 10-30% of infants, with crying attacks beginning in the second week after birth and normally disappearing by the third month. It is known that infantile colic can be a cause of maternal PPD. Furthermore, the parental frustration caused by incessant crying can result in child abuse and even infanticide (11).

It is for these reasons that the early management of PPD is important for maternal and infant health. This study therefore contributes to this goal of effective management by examining the relationship between PPD frequency, as well as maternal and infant characteristics, in mothers who have given birth at Şan Med Hospital in Şanlıurfa.

MATERIALS and METHODS

In this study, Mother-baby pairs born at the Şanlıurfa Şan Med Hospital, and who came to the Pediatric Health and Diseases Outpatient Clinic between September 2017 and December 2017, and wished to participate in the study were included. The mothers were first informed about the study and a written consent form was obtained from all participants. The protocol of the study was approved by Hacettepe University's Non-Interventional Research Ethics Committee (Project Number: GO 17/687).

In this cohort type study, anthropometric measurements of the mother-infant couple were taken at birth, after one week, and after one month. Information on the tracking form includes the age of the parents, the mother's working and the parents' educational status, mode of pregnancy, if the parents smoke or not, incidence of health problems during pregnancy, time of birth, birth weight, type of birth, order of birth, gender, incidence of health problems in the baby, initiation of breastfeeding within the first hour, breastfeeding characteristics such as pre-feeding nutritional status, and crying and sleep characteristics. In addition, EPDS was applied in the first month after birth, with the mother providing her impressions of her baby's crying, sleeping patterns and frequent waking.

Edinburgh Postpartum Depression Scale is a 10-item evaluation scale that is completed solely by the mother in which she is asked to consider the emotions she has experienced during the last 7 days (12). Each question of EPDS is assigned a score between 0 and 3, with a result of over 13 indicating a clear risk of depression. The scale takes around 5 minutes to complete (13-16), with the validity and reliability study of EPDS for Turkey being conducted by Engindeniz et al. (17).

Statistical Analysis

Data were analyzed with the SPSS v.22 program and presented as mean, standard deviation (SD), or percentage ratio. The effect of the parameters on the incidence of depression was examined with the Chi-square test. The effects of maternal and infant factors on depression were analyzed using multiple logistic regression analysis. Odds ratio and 95% confidence intervals (CI) were calculated by logistic regression analysis. A value of $p<0.050$ was considered significant.

RESULTS

The study comprised of a total of 126 mother-infant couples who completed both the baby follow-up and the one-month follow-up components. Mean maternal age was 27.9 (SD =5.4) years, and paternal age was 31.6 (SD =5.4) years. It was found that 9.5% of mothers smoked during pregnancy and 43.7% of them had contact with cigarettes in the environment. A total of 46% of the infants were found to have had exposure to smoking

Table I: The effects of family and infant characteristics and mother on the EPDS

Variables Groups	Total n (%)*	EPDS >12 n %**	OR (95% CI)
Maternal age, years			
<25	34 (27)	12 (35.3)	ref
25-34	76 (60.3)	17 (22.4)	0.53 (0.22-1.28)
≥35	16 (12.7)	2 (12.5)	0.26 (0.05-1.35)
Paternal age, years			
<25	9 (7.1)	4 (44.4)	ref
25-34	83 (65.9)	22 (26.5)	0.45 (0.11-1.83)
≥35	34 (27)	5 (14.7)	0.22 (0.04-1.09)
Maternal employment status			
Housewife	113 (89.7)	27 (23.9)	ref
Employed	13 (10.3)	4 (30.8)	1.42 (0.40-4.96)
Maternal education status			
<8 years	54 (42.9)	11 (20.4)	ref
≥8 years	72 (57.1)	20 (27.8)	1.50 (0.65-3.48)
Paternal education status			
<8 years	23 (18.3)	5 (21.7)	ref
≥8 years	103 (81.7)	26 (25.2)	1.22 (0.41-3.60)
Pregnancy type			
Spontaneously	113 (89.7)	27 (23.9)	ref
with treatment	13 (10.3)	4 (30.8)	1.42 (0.40-4.96)
Smoking exposure during the antenatal period			
No	68 (54.0)	12 (17.6)	ref
Yes	58 (46.0)	19 (32.8)	2.27 (0.99-5.22)
Health problem in pregnancy			
No	109 (86.5)	26 (23.9)	ref
Yes	17 (13.5)	5 (29.4)	1.33 (0.43-4.13)
Delivery mode			
Normal	39 (31.0)	13 (33.3)	ref
Cesarean section	87 (69.0)	18 (20.7)	0.52 (0.22-1.21)
Gestational week			
<37	15 (11.9)	3 (20.0)	ref
≥37	111 (88.1)	28 (25.2)	1.35 (0.35-5.13)
Low birth weight			
<2500 g	13 (10.3)	4 (30.8)	ref
≥2500 g	113 (89.7)	27 (23.9)	0.71 (0.20-2.48)
Birth order			
First child	45 (35.7)	11 (24.4)	ref
2nd child	38 (30.2)	13 (34.2)	1.61 (0.62-4.18)
≥3 childs	43 (34.1)	7 (16.3)	0.60 (0.21-1.73)
Infant's gender			
Boy	64 (50.8)	18 (28.1)	ref
Girl	62 (49.2)	13 (21.0)	0.68(0.30-1.54)
Breastfeeding within the first hour			
No	57 (45.2)	15 (26.3)	ref
Yes	69 (54.8)	16 (23.2)	0.85 (0.38-1.90)
Infants feeding before breastfeeding			
No	82 (65.1)	23 (28.0)	ref
Yes	44 (34.9)	8 (18.2)	0.57(0.23-1.41)
Excessive crying of the baby, which exhausts the mother			
No	76 (60.3)	13 (17.1)	ref
Yes	50 (39.7)	18 (36.0)	2.73(1.19-6.26)
Baby's inconsolable crying/restlessness lasting 2-3 hours/day			
No	83 (66.4)	15 (18.1)	ref
Yes	42 (33.6)	16 (38.1)	2.79 (1.21-6.44)
Baby's sleep patterns			ref
Regular	49 (39.5)	7 (14.3)	2.18 (0.82-5.83)
Irregular	60 (48.4)	16 (26.7)	6.86 (1.88-
Frequent waking	15 (12.1)	8 (53.3)	24.96)
Total	126 (100)	31 (24.6)	

***** *Percentage of columns,* ****row percent,*** ***ref;*** *Edinburgh Postpartum Depression Scale (EPDS)*

in the prenatal period. 50.8% of the babies were male, 10.3% had low birth weight, and 11.9% were premature. 35.7% of the babies were first child, and 69% of them were delivered by caesarean section. It was determined that 54.8% of the babies began breastfeeding within the first hour. The nutritional status before breastfeeding was detected in 34.9% of the infants. It was recorded that 39.7% of the babies tired their mothers due excessive crying, while 33.6% of babies cried inconsolably or were restless for 2-3 hours a day.

Sleep disorder was detected in 48.4% of the babies, and 12.1% had frequent waking problems. The mean EPDS score of the mothers in the first month was 9.0 (SD=5.7), and this score was seen to be 13 points or higher in 24.6%.

Maternal and paternal age, education, maternal employment status, mode of pregnancy, smoking exposure, health problems during pregnancy, mode of delivery, preterm delivery status, infant birth weight, birth order, sex, infant health problems, and problems with breastfeeding were found to have no effect on the frequency of PPD.

It was determined that the frequency of PPD increased by 2.73-folds (95% CI=1.2-6.3) for mothers whose babies cried excessively, and by 2.79-folds (95% CI=1.2-6.4) for the mothers whose babies had unconsolable crying/restlessness lasting 2-3 hours a day. The results indicated that the risk of PPD was 6.86-folds (95% CI = 1.9-25.0) higher in mothers of infants who awoke frequently, as compared to the mothers of infants who had regular sleep patterns. When other maternal and infant parameters were considered, the incidence of PPD was higher in the mothers of infants with excessive crying or sleep disorders.

DISCUSSION

The current study shows that PPD is detected in one out of every four women, which is similar to the finding of other studies conducted in Turkey (1,2). The worldwide average for PPD is 17.2% (3). One possible reason that a higher rate is reported in the current study may be that EPDS was stringently applied to all mothers. It is also the case that general comparisons are inaccurate due to a lack of global consistency in the tests and limit values being applied to PPD determination.

The frequency of maternal PPD of infants' crying and sleep problems reported according to mother's perception was seen to more than double, with increases of up to 6.9-folds when the sleep problem was in the form of waking frequently. According to a study by Radesky et al. (18), when maternal EPDS was taken as being ≥ 9, crying/restlessness that lasts more than 3 hours a day doubled the risk of depression (95% CI; 1.1-3.7). In cases where inconsolable crying lasted longer than 20 minutes, it was reported that the condition increased by 4-folds (95% CI; 2.0-9-8.1). Being unable to calm a crying baby is a major challenge for many mothers and a significant cause of increased exhaustion. In some cases, the mother may be so tired that they may even neglect their parenting duties and just allow the baby to continue crying. An imbalance between infant and maternal needs increases the risk of adverse outcomes such as PPD and/or infant abuse (19). Another possible result is the mother becoming afraid of being able to provide adequate care, or even harming her baby. In extreme cases, severe depressive symptoms and suicidal thoughts or attempts may occur. Also, PPD also has the potential to have an adverse effect on the mother's life in the future. Although PPD is a common condition, there are several reasons why it is often not diagnosed. These include factors such as the mother experiencing a sense of isolation and so not being able to share her feelings, a reluctance to consult a psychiatrist due to shame, being unable to visit a doctor when called for routine control or not knowing which department to apply to, or a sense of being unable to voice complaints because everyone, including the mother, is solely focused on the newborn baby. It is due to reasons such as these that PPD can often be overlooked. However, it is essential that women who suffer from PPD have extensive follow-up psychiatric consultations (4,5).

Previous studies have reported that sleep problems are more common in children with infantile colic and prolonged crying episodes, with the mothers of such infants more likely to suffer from PPD (11,18-21). Infantile colic and prolonged crying are associated with higher maternal depression scores (21). Due to the increasing evidence that depression affects not only the mother's mental state but also that of the baby, there is increasing interest in prenatal and postnatal depression. A mother's mental health during pregnancy, as well as in the first year after birth, is crucial to her child's mental, social and emotional development (7). In their study, Bang et al. examined 212 pregnant women at 16-20 weeks, and then again at 6 months postpartum, and analyzed studies completed by 97 mothers. Results show that the mother's mood both before and after birth affects the baby. It was suggested that the mother experiencing anxiety and depression during pregnancy can result in bad tempered babies, and such babies were also found to be more prone to infantile colic (22). A study by Netsi et al. (8) showed that there is a significant relationship between the presence of emotional problems with the mother immediately after birth, and crying problems with the baby, as reported by the midwife. In other words, a depressed mother can cause the baby to have crying problems, irregular sleep and a bad temperament, which in turn exacerbates maternal depression (9,10). This conclusion is supported by a number of studies. One by Hanington et al. (23) shows that PPD affects the temperament of infants, while in a work conducted by Bang, 137 mothers were administered EPDS at 1 month after birth and it was found that the babies of mothers with PPD had worse temperaments as compared to babies in a control group (24). A study by Dias et al examined 164 mother-baby couples and compared maternal depression symptoms at the 3rd trimester, the 2nd week postpartum, and the 3rd and 6th months. The study also investigated the effects of prenatal and postnatal anxiety and EPDS scores on infant sleep problems at 6 months. It was found that both prenatal and postnatal early depression symptoms of the mother had a negative effect on the emergence of sleep problems in the baby (25).

Limitations and Strengths

In our study, the progress of the babies during their first 30 days was monitored. While not using a scale for sleep and crying was an important limitation, taking into account the perception of the mother was a strength of the study. It was seen that a mother with PPD may perceive the usual crying time or frequent waking to feed as being a problem.

CONCLUSION

It was determined that the frequency of PPD increased with mothers who considered their babies to be crying excessively or have sleep disorders. It is concluded that the mothers of babies admitted to the outpatient clinic due to excessive crying and sleep disorders should be evaluated for PPD, while the crying and sleep patterns of babies whose mothers have been diagnosed with PPD should be examined.

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Evaluation of Erythrocyte Suspension Usage in Neonates

Yenidoğanlarda Eritrosit Süspansiyonu Kullanımının Değerlendirilmesi

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ABSTRACT

Objective: Erythrocyte suspension (ES) transfusion is frequently used in neonatal intensive care units (NICU). We evaluated the use of ES in hospitalized patients in the NICU of our hospital in terms of transfusion rate, indication, laboratory control, complications, and adherence to the guidelines.

Material and Methods: Patients who were hospitalized at the University of Health Sciences of Turkey, Dr Sami Ulus Maternity and Children Research and Training Hospital, NICU, in 2016, and who received ES were included in this descriptive study.The demographic and clinical characteristics of the patients, the quantity of ES used, and the laboratory tests of the first three transfusions were recorded.The compliance of ES usage indications with the transfusion guidelines published in the Nelson Pediatric Textbook and the Turkish Neonatology (TND) Society Blood Products Transfusion Guidelines was assessed.

Results: One hundred and ninety one of the 1538 admitted patients in the NICU received a total of 633 ES, for a 12.4% ES usage rate. Following an evaluation of the first three transfusions, it was determined that there was 66% compliance with the TND Blood Products Transfusion Guide and 64% compliance with the Nelson Pediatric Textbook transfusion protocol. It was significant that the frequency of retinopathy of prematurity (p=0.015) and intracranial hemorrhage (p=0.001) was high in premature infants who received more than one ES.

Conclusion: Although transfusion is life-saving in crucial circumstances, there may be a cause-effect relationship between the detected morbidity and complications. Each newborn should be carefully evaluated individually and within the framework of the guidelines before having to decide on an erythrocyte transfusion.

Key Words: Complication, Erythrocyte transfusion, Indication, Newborn

ÖZ

Amaç: Yenidoğan yoğun bakım ünitelerinde (YYBÜ) eritrosit süspansiyonu (ES) transfüzyonu sıklıkla kullanılmaktadır. Çalışmamızda hastanemiz YYBÜ'de yatan hastalarda ES kullanımı; transfüzyon sıklığı, endikasyon, laboratuvar kontrolü, komplikasyonlar ve rehberlere uygunluk açısından değerlendirildi.

Gereç ve Yöntemler: Tanımlayıcı nitelikte olan bu çalışmaya Sağlık Bilimleri Üniversitesi, Ankara Dr. Sami Ulus Kadın Doğum, Çocuk Sağlığı ve Hastalıkları SUAM YYBÜ'nde 2016 yılında yatarak izlenen ve yatışı sırasında ES alan hastalar dâhil edildi. Hastaların demografik ve klinik özellikleri, kullanılan ES sayısı ve ilk üç transfüzyona ait laboratuvar testleri

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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. ***ZENCİROĞLU 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, Reviewing the article before submission scientifically besides spelling and grammar.

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kaydedildi. ES kullanım endikasyonlarının Nelson Pediatric Textbook transfüzyon önerileri ve Türk Neonatoloji (TND) Derneği Kan Ürünleri Transfüzyon Rehberi'ne uygunluğu değerlendirildi.

Bulgular: Çalışma süresince YYBÜ'ne yatan 1538 hastadan 191'ine toplam 633 ES transfüzyonu verilmişti, ES kullanım oranı % 12.4'tü. İlk üç transfüzyon incelemesinde TND Kan Ürünleri Transfüzyon Rehberine %66 oranında, Nelson Pediatric Textbook (2016) transfüzyon protokolüne göre ise %64 oranında uygunluk olduğu belirlendi. Birden fazla ES alan prematüre bebeklerde prematüre retinopatisi (p=0.015), intrakranial kanama (p=0.001) sıklığının yüksek olması anlamlıydı.

Sonuç: Transfüzyon uygulaması ciddi ihtiyaç durumunda hayat kurtarıcı olmakla birlikte saptanan morbidite ve komplikasyonlar ile arasında neden sonuç ilişkisi olabilir. Eritrosit süspansiyonu transfüzyonu kararı öncesi her yenidoğan bebeğin bireysel olarak ve rehberler çerçevesinde dikkatle değerlendirilmesi gerekmektedir.

Anahtar Sözcükler: Komplikasyon, Eritrosit transfüzyonu, Endikasyon, Yenidoğan

INTRODUCTION

Neonatal anemia is a frequent issue in neonatal intensive care units (NICUs). In order to improve the oxygen carrying capacity and maintain the functions of vital organs in anemic newborns, erythrocyte suspension (ES) transfusion is a life-saving procedure. Furthermore, long-term anemia has the potential to impact the brain development of both preterm and term infants, as well as other aspects of a pre-existing chronic disease (1). Although data on transfusion practices in late preterm and term newborns is limited, studies have found that 50% of extremely low birth weight (ELBW) infants with a birth weight of 1000 g were transfused within the first two weeks of life and 90% were transfused during their stay in the NICU (2, 3).

In addition to the critical benefits of ES transfusion, it has been linked to a number of complications, including an increased risk of infection, various immunological responses, and particularly in premature infants, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intracranial hemorrhage (ICH), and long-term neurodevelopmental issues (3-6). Along with these risks, Hb values that require transfusions in newborns, challenges evaluating clinical anemia findings, and the hypothesis that current Hb/Hct values in premature and/or ill newborns may not accurately reflect erythrocyte mass may lead to uncertainties in indications for transfusion (2, 7). According to ETTNO (Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants) and TOPS (Transfusion of Premature), two comprehensive studies investigating transfusion threshold values and complication relationships in very low birth weight premature infants, higher transfusion thresholds do not decrease the risk of death or neurodevelopmental retardation. The use of restrictive transfusion approaches (Hb 7–9 g/dl in stable, growing premature infants and 9–11 g/dl in critically ill neonates) has been recommended primarily (8-10).

There is currently no global agreement on this issue, despite criteria such as the severity of anemia, the necessity for respiratory support, clinical symptoms, and laboratory values being similar in different national or international guidelines for neonatal transfusion. Numerous studies have found that implementing and adhering to guidelines is associated with a decrease in the number of transfusions and transfusion complications (11, 12). In our study, the use of ES in patients hospitalized in the NICU of our hospital was examined within the framework of indication, laboratory control, and complications, and its suitability was evaluated according to two guidelines, one of which is national and one of which is international.

MATERIALS and METHODS

This descriptive study was carried out at the University of Health Sciences of Turkey, Dr. Sami Ulus Maternity and Children's Research and Training Hospital, SUAM Neonatal Intensive Care Unit (NICU). The research was approved by the Health Sciences University, Ankara, Pediatrics, Hematology, and Oncology, SUAM Clinical Research Ethics Committee (2018-044). All newborn patients hospitalized in 2016 had their files reviewed retrospectively, and 191 patients who received ES were included in the study. Data on the cases' prenatal, natal, and postnatal histories [maternal age, pregnancy history, chronic disease, gestational week, birth weight, mode of delivery -normal spontaneous vaginal delivery (NSVY) or cesarean section (C/S)-, need for positive pressure ventilation (PBV)/ resuscitation at birth, APGAR scores, genders , laboratory findings -prothrombin time (PT), activated prothrombin time (aPTT), Hb, Hct, platelet count-, accompanying clinical manifestations -ICH, infection, RDS, ROP, congenital anomaly, patent ductus arteriosus (PDA), cyanotic/ severe congenital heart disease, metabolic disease, perinatal asphyxia, indirect hyperbilirubinemia (IHB)-, total hospital stay, transfusion history (number of ES and other transfusions, prior to and following ES, a laboratory control, indication and complication record), and outcome (discharge and death)] were obtained from electronic file records. Labaratuary tests completed no more than 72 hours before and after ES application were evaluated for Hb and Hct values before and after transfusion. The accompanying RDS, ROP, perinatal asphyxia, and apnea conditions were defined using the pertinent sections of the Turkish Neonatology Society's diagnosis and treatment recommendations (13).

The indications (clinical and laboratory findings) listed in the Nelson Pediatric Textbook transfusion protocol and the TND Blood Products Transfusion Guide were considered

for assessments of the use of ES (14, 15). In accordance with these protocols, it was assessed whether the patients received transfusions. Patients were classified as "appropriate transfusion" if they met all laboratory and clinical requirements and "inappropriate transfusion" if they did not meet both requirements. Compliance with any criteria clinically or in the laboratory was determined as "partially appropriate transfusion." For patients who received multiple transfusions, the first three transfusions were taken into account when determining eligibility.

Statistical analyses were performed using the IBM SPSS for Windows Version 22.0 package program. The numerical variables were summarized as mean, standard deviation, median (minimum-maximum), and interquartile range (IQR) values. Numbers and percentages were used to display categorical variables. The Mann-Whitney U test and, when there were more than two groups, the Friedman test were used to determine whether there were differences between the two groups in terms of numerical variables. The Spearman and Pearson correlation coefficients were used to investigate the relationship between various variables. Significance level was accepted as p <0.050. For the purpose of controlling risk factors, odds ratios (OR) and confidence intervals were computed.

RESULTS

ES transfusions were administered to 191 of 1538 patients (997 term and 541 preterm) hospitalized in the NICU during the one-year study period, with an ES use rate of 12.42%. Among these newborns, 69 (36.13%) were preterm and 122 (63.87%) were term (Table I). Infants who were born preterm used ES at a rate of 12.38%, whereas term infants used it at a rate of 12.23%. It was determined that patients received ES at a dose of 10–15 ml/kg.

Patients were admitted for various reasons, such as: 69 (36.13%) have cyanotic or severe cardiopulmonary heart disease, 47 (24.60%) have prematurity, 17 (8.90%) have hypoxic ischemic encephalopathy (HIE), 13 (6.80%) have sepsis, 9 (4.71%) have NEC, 9 (4.71%) have IHB, and 7 (3.70%) have gastrointestinal system anomalies (duodenal atresia, omphalocele, gastroschisis, intestinal obstruction, etc.). 6 (3.14%) have metabolic diseases, 5 (2.62%) have pneumonia, three (1.60%) have acute renal failures, three (1.60%) have anemias, one (0.52%) has a syndromic infant, one (0.52%) has a hypotonic infant, and one (0.52%) has had the umbilical catheter removed by angiography. A summary of the clinical conditions that the patients experienced prior to or following the ES is shown in Table II.

It was determined that a total of 633 ES were given to the 191 patients included in the study, and the number of transfusions/number of transfused patients ratio was found to be 3.31 (±3.33). This rate was 3.22 (±2.12) for preterms and 3.40 (±3.13) for term; and there was no difference between preterm and term newborns (p>0.050). There were identified 121 patients (63.40%) who received ES more than once. ES administered more than once in 62.72% preterm infants and 63.13% of term infants (p>0.050) (Table III). In 2016, 102 of the 541 preterm

Table I: Demographic data and general characteristics of patients.

Variable	n (%) / Median (lower-upper quarter)
Gender (Male/Female)	100 (52.40) / 91(47.60)
Mode of delivery (NSVD*/C/S)	71 (37.17) / 117(61.25)
Term/Preterm	122 (63.87) / 69 (36.13)
Gestational week (n=191)	37 (30-38)
Preterm	29 (27-31)
Term	38 (37-39)
Birth weight (gr)	2450 (1475-3000)
Extremely low birth weight (<1000 gr)	21 (11)
Very low birth weight (1500 gr)	47 (24.60)
Low birth weight (<2500 gr)	92 (48.17)
Normal birth weight (2500-4000 gr)	91 (47.64)
PPV† need at birth (yes/no/unknown)	48 (25.13) / 48 (25.13) / 95 (49.74)
Maternal age	26 (18-34)
Maternal chronic disease (yes/no/unknown)	22 (11.51) / 118 (61.78) / 51 (26.70)

***NSVD:** *Normal spontaneous vaginal delivery* †**PPV:** *Positive pressure ventilation*

Table II: Clinical characteristics of patients

Clinic / Medication*	n (%) / Ortalama (± SD)
RDS	45 (23.56)
ROP	28 (14.65)
Infection/sepsis	161 (84.29)
ICH	55 (28.79)
NEC	27 (14.13)
Perinatal asphyxia	26 (13.61)
Congenital anomaly	133 (69.63)
Cyanotic/severe congenital heart disease	69 (36.12)
PDA	120 (62.82)
Metabolic disease	11 (5.76)
IHB	56 (29.31)
Respiratory support	163 (85.34)
Apnea	34 (17.80)
Caffeine therapy	50 (26.17)
Thrombocytopenia	109 (57.06)
Coagulopathy	106 (55.49)
APGAR score (1. minute)	6.04 (±2.46)
APGAR score (5. minute)	7.75 (±1.82)
Discharge/Exitus	139 (72.80) / 52 (27.20)

** The same patient could have multiple characteristics*

Table III: ES use rates among patients

	Total (n=191) (mean±SD/%)	Term (n=122) (mean±SD/%)	Preterm (n=67) (mean±SD/%)	p
Number of transfusions/number of transfused patients	3.31 (±3.33)	3.40 (±3.13)	3.22 (±2.12)	>0.050
Multiple ES use	63.40	63.13	62.72	>0.050

**p<0.005 is significant*

Table IV: Pre- and post-transfusion Hb/Hct values for the patients

Hb (g/dl)/Hct (mean ± SD)	1. ES transfusion	p	2. ES transfusion	p	3. ES transfusion	p
Pre tx Hb	9.66 ± 1.97		9.41 ± 1.70		9.41 ± 1.49	
Post tx Hb	12.90 ± 2.08	0.000	12.90 ± 2.20	0.000	12.38 ± 1.92	0.000
Hb increase rate	%34		%37		%31	
Pret tx Hct	29.85 ± 6.32		28.79 ± 5.28		28.69 ± 4.40	
Post tx Hct	38.87 ± 6.61	0.000	38.91 ± 6.80	0.000	37.47 ± 5.76	0.000
Hct increase rate	%30		%35		%31	

**p<0.005 is significant*

infants admitted to our hospital had VLBW, 47 of whom were transfused at least once, and the ES transfusion rate was 46%. Twenty of the remaining 439 infants had received at least one transfusion, with a 4.50% ES transfusion rate. In comparison to other preterm infants, preterms with VLBW had a significantly higher rate of ES use (p<0.010).

Prior to transfusion, the laboratory control rate for the Hb and Hct parameters was 100%; however, after transfusion, the rates were 87%–87% and 90%, respectively, and the difference was not statistically significant (p>0.050). Hb increase rates were determined to be 34%, 37%, and 31%, respectively, with Hct increase rates being 30%, 35%, and 31%, respectively, before and after transfusions. All increases were statistically significant (p<0.050) (Table IV). In patients with cyanotic or severe cardiopulmonary heart disease, the mean number of transfusions was 4.12±3.72, compared to 2.83±2.91 in the remaining 122 patients, and this high number of transfusions was significant (p<0.050). Mean pre-transfusion Hb (10.41± 1.16 p =0.000) and Hct (32.14±3.56; p = 0.000) values and post-transfusion Hb (13.50±1.58) (p = 0.021) and Hct (40.73 ±4.85; p = 0.032) mean values were significantly higher in patients with cyanotic or severe cardiopulmonary heart disease.

All three initial ES transfusions were evaluated, and it was found that 250 (66%) of the total 378 transfusions were given with indications of "appropriate" or "partially appropriate" in accordance with the TND Blood Products Transfusion Guide, whereas 128 (34%) were given with an indication of "inappropriate." According to the Nelson Pediatric Textbook transfusion protocol, it was found that 243 (64%) of 378 ES transfusions were administered with "appropriate" or "partially appropriate" indications and 135 (36%) with "inappropriate" indications. Preterm and term infants were compared for use in indications appropriate and inappropriate for the guidelines (as per the recommendations of the TND and the Nelson Pediatric Textbook, respectively) (p= 0.176–0.555 for TX1, TX2, and TX3, and p = 0.566-0.320 for TX3), and no significant distinction was identified in the compliance rates of the two groups.

Regarding all transfusions, 98.40% of the patients had no complications. Two (1.04%) of the 191 patients who received the first ES transfusion had circulatory overload, and one (0.52%) had hypoglycemia; circulatory overload was detected in one (0.84%) of 118 patients who received the second ES transfusion; and circulatory overload was detected in two (2.90%) of 69 patients who received the third ES transfusion. Of the 191 patients evaluated for the study, 139 (72.80%) were discharged, and 52 (27.20%) died during their follow-up (Table II). In 2016, 89.65% (52/58) of patients who died in the NICU received ES at least once. Term infants had a 2.89-fold higher mortality risk than preterm infants (OR:2.89, %95 confidence interval;1.34-6.23) (Supplementary material 1). A comparison of those who used ES once or more revealed that 42 (80.80%) of those who passed away and 79 (56.83%) of those who were discharged used it more than once. It was significant that ES was used frequently in patients who passed away (p=0.002<0.050). Patients who received ES more than once had a 3.19-fold higher mortality risk than those who only received it once (OR:3.19, %95 confidence interval;1.48-6.87) (Supplementary material 1). There was no significant difference between babies who were discharged and those who died in terms of compliance with the guidelines for transfusions (p<0.050).

In preterms who required one or more ES transfusions, it was examined whether there were differences in the rates of premature comorbidities. There was no difference between preterms who received one or more ES transfusions in terms of RDS (p = 0.765), surfactant use (p = 0.523), necrotizing enterocolitis (NEC), or mortality rate (p = 0.055). Premature neonates who received more than one ES, however, had a significantly higher frequency of ROP (p = 0.015) and ICH (p = 0.001).

DISCUSSION

In the cohort study by Patterson et al. (16), they reported information for 16.20% of the transfused newborns in the NICUS Data Collection, while in the study by Portugal et al. (17), of the newborns who were admitted to the NICU, 20.90% received at least one transfusion, and the mean number of transfusions was 2.70±2.16. Another study that examined the 6-year transfusion data of premature infants <32 weeks found that 44% of them received at least one ES, with a mean of 2.30±1.60 transfusions (4). In a study that was conducted in Turkey and examined both term and preterm infants, ES use was 12.60% and the average number of transfusions was 4, whereas another study looking at preterm infants discovered that ES transfusion was used at a rate of 50% (18, 19). The rate of ES use and the number of transfusions/number of transfused patients in our study were comparable to or lower than those reported in the literature. Additionally, the literature supports our findings, which indicated that VLBW newborns had an ES transfusion rate of 46%, which was higher than that of other preterm babies (3, 6, 20). The risk of comorbid diseases like ICH, NEC, sepsis, and RDS, the rise in the survival of preterm infants with low gestational ages, the significant iatrogenic blood loss brought on by phlebotomy, and the lack of adequate evidence-based criteria for transfusion indications may all play a part in this circumstance (20, 21).

According to the Turkish Neonatalogy Association's recommendations, a transfusion of 10–20 ml/kg of ES should increase hemoglobin by 2-3 g/dL and Hct by 7–10%. Furthermore, the targeted Hb/Hct levels following an ES transfusion should be 12 g/dL and 35% (14). Following ES transfusion, the study's increase rates and targeted Hb and Hct levels were all within optimal ranges (14). In an Indian study of newborns born <1500 g and/or <32 weeks the mean pre- and post-transfusion Hb% was 8.1±1.9 g/dl and 10.4±1.8 g/dl, respectively. The mean Hb% improvement was 2.3±2.1 g/dL (22). Pre- and post-transfusion values and rates of increase were comparable to our study in a related study in which transfusion-related file records in the tertiary NICU were examined (23). In response to concerns about longer-term neurodevelopmental outcomes, the TOPS and ETTNO trials paved the way for a wider acceptance of restrictive ES transfusion strategies (e.g., Hb 7-9 g/dl in stable, growing preemies and Hb 9-11 g/dl in critically ill neonates or those needing respiratory support) (8-10). The neonatology clinic at our hospital provides tertiary intensive care services as well as being a center for congenital heart disease and therapeutic hypothermia. It is believed that our unit, which cares for critically ill newborns, is more in line with restrictive transfusion policies given the threshold values and literature-recommended guidelines for ES use.

Mazine et al. (24) conducted a prospective, multicenter study in which the transfusion intakes of 175 patients under the age of 18 (47 of whom were newborns) with cyanotic or acyanotic heart disease were examined in the pediatric intensive care unit. Comparable to our study, it has been reported that the pre-transfusion Hb values of patients with cyanotic heart disease are 11.8±2.1 g/dL, significantly higher and statistically significant than those of patients with acyanotic heart disease (24). The primary goals of transfusions in this high-risk population are to increase the blood's capacity for transport as well as provide tissue oxygenation. The mean post-transfusion Hct values in this study were 40.70±4.85% in the group with cyanotic heart disease, which was significantly higher than the group without cyanotic heart disease. The target Hct value for newborns with cyanotic or severe cardiopulmonary heart disease is recommended at 40%–45% in the TND Blood Products Transfusion Guide (14) In light of the literature on this subject, more research is required to determine the thresholds, risks, and advantages of ES transfusions in children with cyanotic or congenital heart disease (25).

Even though there is no definite Hb value to make a decision for transfusion in preterm and term babies, oxygen requirement, being on a mechanical ventilator, and postnatal age are significant considerations in this decision. The threshold Hb values for ES transfusion in term and preterm newborns have not always been specified with clarity in many guidelines. Newborn transfusions are also given current information as part of the Technical Assistance Project for Improving the Blood Transfusion Management System in Turkey, which is being carried out in our nation (26). Given all of this information, it is obvious that each intensive care unit should adopt and adhere to its own set of transfusion guidelines when deciding whether or not to transfuse ES to patients. In this study, in about two-thirds of cases, transfusion indications were in compliance with the guidelines. In a comprehensive study that covered all NICUs in Switzerland, it was found that 46% of the facilities adopted transfusion practices in accordance with the guidelines, but these guidelines were also very distinct between clinics, and there was no consensus among them (7). In a study with neonatal clinicians in Australia and New Zealand, overall 35% participants and 25% participants working in level 3 neonatal units reported that their local institutions did not have a guideline on blood transfusion for infants with anemia of prematurity. Participants from the tertiary neonatal units were more likely to report that their local institution had a guideline compared with participants from levels 1 or 2 neonatal units (27). In the United States, there was a 65% rate of compliance with the guidelines prior to the organization of electronic programs to increase clinicians' awareness of transfusion, which was comparable to our study (28). In the study by D'Amato et al. (4), it was noted that after six years, the ES transfusion rate had decreased to 31% from 44% when the guidelines were strictly followed. Nevertheless, studies show that adhering to the recommendations decreases the need for transfusions, the risk of mortality, and complications such as ICH and NEC, which are believed to be linked to transfusion (4, 11). It is critical to strictly follow the guidelines in order to reduce heterogeneity

and prevent transfusion risks in clinical practice. Due to the retrospective nature of our study, it was hypothesized that there might be a dearth of clinical data records and that the compliance rates could be lower than they actually are. The low complication rate in our study could also be attributed to adequate information entry into the electronic file system. The very low rate of transfusion-related complications was linked in a study conducted in the tertiary NICU to the lack of long-term follow-up and the examination of file records alone (23).

The higher mortality rate of term infants in this study may be due to common diseases like HIE, congenital heart disease, and metabolic disease, despite the fact that preterm infants are generally thought to have serious health problems. Clinicians may have a tendency to use ES more frequently in newborns who have a clinically high mortality risk, which could clarify the association between the use of multiple ES and mortality rates and risks in this study. It has been demonstrated that there is a correlation between the number of transfusions and the risk of mortality in certain studies examining the transfusion practices of premature newborns (4, 6, 29).

The frequency of ES transfusion and its prematurity-related complications are currently the subject of studies (3, 29). In this study, preterms who received ES transfusions more than once were more likely to experience ROP and ICH. According to a thorough literature review and meta-analysis, ES transfusion is an independent risk factor for ROP in preterm infants (5). Multiple ES transfusions were found to increase the risk of ROP and NEC in a study conducted by Ghirardello et al. (6). The frequency of ES transfusion and the risk of ICH were found to be correlated in a different study examining the transfusion practices of premature infants (4). There have also been studies that claim there is no link between the number of transfusions and prematurity complications (22, 29). Although ES transfusion is not the only cause due to the multifactorial nature of the morbidities commonly encountered in premature babies, given the proven risks of transfusion, this vulnerable group should be handled very selectively before transfusion.

One of the strengths of this study is that the transfusion indication evaluation is thorough, not only in terms of adherence to the guidelines but also by contrasting preterm and term, discharged and exitus, and patient groups that received one or more transfusions. The fact that our unit is a tertiary NICU and admits a variety of patients from the nearby provinces and regions also helps to reduce any potential biases in the patient selection process for our study. One of the limitations of this study was the exclusion of ES transfusions after the third transfusion and the scanning of newborn hospital records only within a year. This retrospective study had additional limitations, such as the inability to assess long-term complications and deficiencies in the observation and recording of symptoms in the documents.

As a result, it was found in this study that ES transfusions carried out in our neonatal clinic were in high compliance with both our national guideline and the recommendations in the Nelson Pediatric Textbook, as well as occurring at rates comparable to studies in the literature. For almost all transfusions, the increases in laboratory values prior to and following the transfusion were within the ranges deemed suitable by the TND Blood Products Transfusion Guidelines. The relationship between the frequency of ROP and ICH and the number of transfusions given to preterm infants was remarkable. Preventing unnecessary transfusions, particularly in premature infants, may reduce morbidity. It is critical to carefully assess each newborn baby individually and within the criteria of the guidelines in order to reduce ES transfusions that can be regarded as tissue transplants; this will be a more rational approach.

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Supplementary material 1: Investigation of mortality risk in newborns and use of multiple ES in different groups

Variables	p	OR	95 % CI
Mortality risk (term/preterm)	0.003	2.89	1.34-6.23
Use of multiple ES (discharge/exitus)	0.002	3.19	1.48-6.87

***OR:** Odds ratios, †**CI:** Confidence intervals*

Attitudes and Beliefs of Parents About Human Papilloma Virus Vaccination in Their Daughters During COVID-19 Pandemic: A Cross Sectional Study

Ebeveynlerin COVİD-19 Pandemisi Sırasında Kız Çocuklarına İnsan Papilloma Virüs Aşısı Yaptırılmasına İlişkin Tutum ve İnançları: Kesitsel Bir Çalışma

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ABSTRACT

Objective: This study aimed to determine parents' current attitudes and beliefs using a standardised scale towards Human Papilloma Virus and its vaccine during COVID-19 Pandemic.

Material and Methods: This is a descriptive cross sectional study including a total of 303 parents who applied to a training and research hospital pediatric clinic with a daughter aged 9-18 years old. A demographic variable questionnaire and The Turkish version of the Carolina Human Papilloma Virus Immunization Attitudes Scale (CHIAS) were assessed.

Results: The Turkish version of the Carolina Human Papilloma Virus Immunization Attitudes Scale mean± SD scores of harms/barriers/effectiveness/uncertainty factors subgroup were calculated as 2.2±0.6, 2.5±0.7, 2.3±0.7, 2.9±0.8, respectively. 19.8% of parents were aware of Human Papilloma Virus and 22.5% of them declared to be willing to vaccinate their daughters against the infection. Human Papilloma Virus acceptance rate was still modest and lower than for vaccines in general during COVID-19 Pandemic.

Conclusion: According to the result of this study, during COVID-19 Pandemic, the both female and male awareness and intention to vaccinate their daughters against Human Papilloma Virus is low. This is the first study analyzing parents' current attitudes and beliefs using a standardised scale towards Human Papilloma Virus in Turkey and also is the first analyzing this subject during COVID-19 pandemic in the literature. Health education programs given by family doctors, pediatricians and community health professionals to parents is critically important in accepting this vaccine.

Key Words: Awareness, COVID-19, Human Papilloma Virus, Parents, Vaccination

ÖZ

Amaç: Bu çalışma, COVİD-19 Pandemisi sırasında ebeveynlerin Human Papilloma Virüsü ve aşısına yönelik standart bir ölçek kullanarak mevcut tutum ve inançlarını belirlemeyi amaçlamıştır.

Gereç ve Yöntemler: Bu çalışma, bir eğitim ve araştırma hastanesi çocuk kliniğine 9-18 yaşlarında kız çocuğu ile başvuran toplam 303 ebeveynin dahil edildiği tanımlayıcı kesitsel bir çalışmadır. Bir demografik veri anketi ve Carolina Human Papilloma Virüsü Bağışıklama Tutumları Ölçeğinin (CHIAS) Türkçe versiyonu ile değerlendirme yapılmıştır.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was conducted after the approval from the Ethical Committee of Ankara Training and Research Hospital (15.06.2020/241).

Contribution of the Authors / Yazarların katkısı*: *GÜVEN AG: 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. ***ABSEYİ SN:*** 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. ***SEVİM M:*** 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, Reviewing the article before submission scientifically besides spelling and grammar. ***TAŞAR MA:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar.

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Bulgular: Zararlar/engeller/etkililik/belirsizlik faktörleri alt grubunun Carolina Human Papilloma Virüsü Bağışıklama Tutumları Ölçeği'nin ortalama±SS puanları sırasıyla 2.2±0.6, 2.5±0.7, 2.3±0.7, 2.9±0.8 olarak hesaplandı. Ebeveynlerin %19.8'i Human Papilloma Virüsün'den haberdardı ve %22.5'i kızlarını enfeksiyona karşı aşılamak istediğini bildirdi. Human Papilloma Virüsü kabulü, COVİD-19 Pandemisi sırasında hala yetersiz ve rutinde uygulanan aşılardan daha düşüktü.

Sonuç: Bu çalışmanın sonucuna göre, COVİD-19 Pandemisi sırasında hem kadınların hem de erkeklerin kız çocuklarını Human Papilloma Virüsü'ne karşı aşılama konusundaki farkındalıkları ve istekleri düşüktür. Bu çalışma, Türkiye'de ebeveynlerin Human Papilloma Virüsü'ne yönelik mevcut tutum ve inançlarını standart bir ölçek kullanarak analiz eden ilk çalışmadır ve aynı zamanda literatürde bu konuyu COVİD-19 Pandemisi sırasında analiz eden ilk çalışmadır. Aile hekimleri, çocuk doktorları ve toplum sağlığı uzmanları tarafından ebeveynlere verilen sağlık eğitim programları, bu aşının kabul edilmesinde kritik öneme sahiptir.

Anahtar Sözcükler: Farkındalık, COVİD-19, İnsan Papilloma Virüsü, Ebeveynler, Aşılama

INTRODUCTION

Human Papilloma Virus (HPV) is one of the most common sexually transmitted infections. To date, more than 200 HPV genotypes were identified some of which mainly infect cutaneous tissues and induce warts. Other types which are known as oncogenic is related with cervical, anal, neck and head cancers (1). By the age of 45 years, more than 80% of sexually active women and men are expected to be infected (2). With 549.847 cases (13.1% of all cancer in women) and 311.365 deaths (6.9% of all cancer deaths in women), cervical cancer was accepted to be the third most common cancer among women worldwide in 2018 (3). All cases of cervical cancer are estimated to be attributable to an HPV infection, therefore cervical cancer is the most preventable cancer globally (4).

The priority target audience of HPV vaccination are the 9-14 aged girls according to World Health Organization (WHO) (5). Centers for Disease Control and Prevention (CDC) has recommended routine HPV vaccination for both boys and girls at age 11 or 12 years but it can also be started from 9 years old. According to CDC estimates, by the use of vaccines, most HPV cancers and genital warts associated with different HPV types have diminished 71% among adolescent girls and 61% among young adult women (6). When vaccination rate is achieved more than >80% in girls, the risk of HPV infection decreases in boys. For increasing vaccine uptake, the importance of health care providers' clear recommendation has been established by previous research (7). General communication principles must include information about the benefits of vaccination and cancer prevention, but also avoid expressions of vaccine urgency when addressing parents' questions or concerns (8).

There are three forms of HPV vaccine currently. Bivalent form targets genotypes 16 and 18 which is accepted as high risk. Quadrivalent form includes also genotypes HPV 6 and 11, which is accepted as low-risk causing generally genital warts. Ninevalent vaccine which is the last form is effective on HPV 6,11,16,18,31,33,45,52,58 genotypes (7).

Parents' consent is essential for the vaccination of children and adolescents, therefore, parental attitude and belief is very important for vaccination success. Previous studies that examine socio-demographic features and religious beliefs show that there were associations between parents' knowledge, beliefs, and acceptance of the HPV vaccination for their daughters (9-11). Mothers are the most effective people for their daughter's vaccination decision and fathers have less information about HPV and its importance (10,11).

In systematic reviews analysing community-based studies regarding HPV vaccine attitudes of parents, it was also mentioned that there is a limitation in the studies in terms of using standard measurement instruments in Turkey (12). As in many countries, in Turkey, because of the parents' vaccine refusal, there has been an increase in the incidence of vaccine preventable diseases (13). In 2017, reported number of parents who signed vaccine rejection form reached 23.000 (which was 183 in 2011 and 12.000 in 2016 respectively) according to the Ministry of Health's public health data by The Turkish Medical Association (14).

During the COVID-19 Pandemic, lack of access to routine healthcare resulted in missed HPV vaccinations and leave children unprotected (15). There is no study regarding the parents' attitudes and beliefs about HPV vaccine during pandemic. The aim of this study was to analyze parents' current attitudes and beliefs using a standardised scale towards HPV and its vaccine in Turkey and to bring out whether this burden had changed awareness in Turkey.

MATERIALS and METHODS

A total of 303 parents with a daughter aged 9-18 years old who applied to a training and research hospital pediatric clinic for her children were included in the study. The study was conducted in the adolescent health, social pediatrics and general pediatrics outpatient clinics between June and October 2021. It was designed according to the ethical rules of Declaration of Helsinki. All participants were given detailed information before signing the consent form. The participants were informed that participation was on voluntary basis and that they could withdraw from the study at any time. The study was conducted after the approval from the Ethical Committee of Ankara Training and Research Hospital (Approval Number: 241).

A descriptive cross sectional study method was used to gather information on parents' knowledge, attitudes about HPV, and

decision-making process regarding HPV vaccination. After detailed literature review, a demographic variable questionnaire was performed by authors including mothers age, educational level, marital and employment status, children's age and number of children, household income, parents' employment status, and also child's vaccine status. Vaccine status were evaluated with the following questions: 1. Does your child have a vaccination card? 2. Do you regularly vaccinate your child? 3. Can you get your child an annual flu vaccine? 4. Have you had your child vaccinated for a fee other than the Ministry of Health Vaccination Schedule?

All of the parents were informed about the aim and the methodology of the study by the researchers. Three questions regarding HPV were also asked to mothers: 1. Have you ever heard HPV vaccine? 2. Do you know what causes cervical cancer/genital warts? 3.Do you have any idea about human papilloma viruses? After answering the questions, an information brochure about HPV vaccine was given to each parent.

The Carolina HPV Immunization Attitudes and Beliefs Scale (CHIAS) was created by McRee et al. (16) to investigate HPV vaccine decision making in a region where cervical cancer is high in women. It enables the researchers compact, standard measurement of parents' attitudes and beliefs about HPV vaccine. It includes 16 questions about HPV vaccine attitude and belief items and has 4 factors (harms, barriers, effects and uncertainty). Factor 1: "Harms" consists of six items related to perceived potential harms from the vaccine, including health problems, and an increased likelihood of girls being sexually active. Factor 2: "Barriers" consists of five items about perceived barriers to HPV vaccination including cost and access to a healthcare provider. Factor 3: "Effects" includes two items related to the perceived effectiveness of the HPV vaccine in protecting against genital warts and cervical cancer. Factor 4: "Uncertainty" consists of three items to evaluate whether it contains sufficient information about the HPV vaccine and the perception of community vaccination norms. The Turkish version of CHIAS developed by Sunar and et al. (17) is a valid and reliable measurement tool for Turkish society (Cronbach alfa is 0.62). CHIAS was applied to each parent finally. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement recommendations were followed during this cross-sectional study (18).

Statistical Analyses

Statistical Package for the Social Sciences version 19.0 were used when performing all statistical analysis. The distribution of continuous numeric variables was examined by Kolmogorov Smirnov test. Descriptive statistics were shown in the mean or median form for the continuous variables and in the percentage form for the categorical variables. The Independent Samples T Test, One-Way Anova was used when researching the importance of the difference in terms of mean values between the groups. The Chi-Square test was used when evaluating the categorical variables. p value< 0.050 was considered to be statistically significant.

RESULTS

A total of 303 parents with a daughter aged 9-18 (median=14) years old were included in the study. The study group's demographic variables are seen in Table I.

Means and factor loadings of parents' CHIAS HPV Vaccine Attitude and Belief are seen in Table II.

The mean±SD of harms/barriers/effectiveness/uncertainty factors subgroup were calculated as 2.2±0.6, 2.5±0.7, 2.3±0.7, 2.9±0.8, respectively. In the harms subgroup, the highest

Table I: Demographic Variables of the Study Group

Demographic Variables of the Study Group (n=303)	
Parent's gender*	
Women	292 (96.4)
Men	11 (3.6)
Parent's age (years)†	40 (28-60)
Child's age (years)†	14 (9-18)
Marital status*	
Married	285 (94.1)
Divorced/widow	18 (5.9)
Family type*	
Core family	233 (76.9)
Extended family	70 (23.1)
Number of children*	
One	21 (6.9)
Two	122 (40.3)
≥ Three	160 (52.8)
Household income*	
Below minimum wage	102 (33.7)
Minimum wage	157 (51.8)
Above minimum wage	44 (14.5)
Parent educational status*	
Primary school and below	107 (35.3)
Secondary school	71 (23.4)
High school and above	125 (41.3)
Parent's working status*	
Mother	
Unemployed	22 (7.6)
Housewife	212 (70.0)
Working	69 (22.8)
Father	
Unemployed	51 (16.8)
Working	227 (74.9)
Retired	25 (8.3)
Information about the child's vaccination (Yes)*	
Have you had your child vaccinated regularly?	283 (93.4)
Is there a vaccination card available?	188 (62.0)
Dou you get the annual flu vaccine?	26 (8.6)
Have you had any vaccinations other than the Ministry of Health vaccination schedule?	41 (13.5)

** n (%), † median (min- max)*

Table II: The Carolina HPV Immunization Attitudes Scale HPV Vaccine Attitude and Belief Means and Factor Loadings

	Mean±SD	Median (Min-Max)
Harms		
The HPV vaccine might cause short term problems, like fever or discomfort	2.6±0.9	3 (1-4)
The HPV vaccine is being pushed to make money for drug companies.	2.0±0.9	2 (1-4)
The HPV vaccine might cause lasting health problems.	2.2±0.9	2 (1-4)
If a teenage girl gets the HPV vaccine, she may be more likely to have sex.	2.4±0.9	2.5 (1-4)
I think the HPV vaccine is unsafe.	2.3±0.9	2.5 (1-4)
Child's name is too young to get a vaccine for a sexually transmitted infection like HPV.	2.8±1.2	3 (1-4)
Barriers		
How hard do you think it would be to find a provider or clinic where you can afford the vaccine?	2.5±0.9	2.5 (1-4)
How hard do you think it would be to find a provider or clinic that is easy to get to?	2.4±0.9	2.5 (1-4)
How hard do you think it would be to find a provider or clinic that has the vaccine available?	2.4±0.9	2.5 (1-4)
I am concerned that the HPV vaccine costs more than I can pay.	2.8±1.0	3 (1-4)
How hard do you think it would be to find a provider or clinic where you don't have to wait long to get an appointment?	2.5±0.90	2.5 (1-4)
Effectiveness		
How effective do you think the HPV vaccine is in preventing genital warts?	2.2±0.7	2 (1-4)
How effective do you think the HPV vaccine is in preventing cervical cancer?	2.3±0.80	2 (1-4)
Uncertainty		
I don't have enough information about the HPV vaccine to decide whether to give it to child's name.	2.9±1.1	3 (1-4)
The HPV vaccine is so new that I want to wait a while before deciding if my daughter should get it.	3.2±1.0	4 (1-4)
Other parents in my community are getting their daughters the HPV vaccine.	2.5±1.2	2 (1-4)

Table III: Participant's Responses to HPV-Related Questions

	n (%)
Do you know what Human Papilloma Virus is?	60 (19.8)
Do you know what causes cervical cancer/genital warts?	63 (20.8)
Have you heard of the cervical cancer/genital warts vaccine?	116 (38.3)
Are you considering getting your child vaccinated against Human Papilloma Virus?	68 (22.5)

mean score (2.8±1.2) was received for the answer given to the question "I think my daughter is too young to be vaccinated against a sexually transmitted infection such as HPV". In the barriers subgroup, the highest mean score (2.8±1.0) was received for the answer given to the question "I am concerned that the HPV vaccine costs more than I can pay". Also, in the effectiveness subgroup, the highest mean score (2.3±0.8) was received for the answer given to the question "How effective do you think the HPV vaccine is in preventing cervical cancer?". As the last in the uncertainty subgroup, the highest mean score (3.2±1.0) was received for the answer given to the question "The HPV vaccine is so new that I want to wait a while before deciding if my daughter should get it".

Only 19.8% of the participants stated that they knew what HPV was (Table III). The rate of those who thought to have their child vaccinated with HPV was only 22.5%. Also, 21.2% of mothers and 9.1% of fathers stated that they knew what HPV was (p=0.322). The percentage of parents who had heard HPV vaccination was 38.4% in mothers and 36.4% in fathers group (p=0.893).

No correlation was found between parent-child age and factor score means (p=0.085). The means of the harms and barrier factor scores of the parents whose children had a vaccination card were 2.2±0.6 and 2.5±0.7, and the means of harm and barrier factor scores of the parents whose children did not have a vaccination card were 2.3±0.6 and 2.6±0.7; this difference was statistically significant (p= 0.032; 0.045, respectively)

The means of harms factor scores of parents who have their children vaccinated outside of the Ministry of Health's vaccination schedule was 2.1±0.6, the barriers factor score mean was 2.3±0.6; the mean of the harms factor scores of parents who do not have their child vaccinated outside the vaccination schedule was 2.3±0.6, the mean of the barriers factor score was determined as 2.6±0.7 (p= 0.034; 0.020, respectively).

There was no relationship between the child's having a vaccination card and the parents' vaccinating their child that is not included in the Ministry of Health vaccination schedule and the effectiveness and uncertainty factor mean scores (p=0.072).

The means of harms factor scores of parents of those who earn above the minimum wage were found to be lower than

Table IV: The Relationship Between the Socioeconomic Variables of the Study Group and the Factor Score Means

	Harms		Barriers		Effectiveness		Uncertainty	
	mean±SD	p	mean±SD	p	mean±SD	p	mean±SD	p
Parent's gender		p=0.295		p=0.117		p=0.801		p=0.993
Women	2.2±0.6		2.5±0.7		2.5±0.7		2.9±0.8	
Men	2.4±0.6		2.9±0.7		2.2±0.6		2.9±0.9	
Marital Status		p=0.546		p=0.008		p=0.213		p=0.127
Married	2.2±0.6		2.6±0.6		2.3±0.7		2.9±0.8	
Divorced/widow	2.2±0.6		2.1±0.6		2.5±0.8		3.1±0.7	
Family Type		p=0.590		p=0.796		p=0.759		p=0.852
Nuclear	2.2±0.6		2.5±0.7		2.3±0.7		2.9±0.8	
Extended	2.3±0.6		2.6±0.7		2.3±0.7		2.9±0.8	
Number of Children		p=0.052		p=0.167		p=0.796		p=0.435
One	2.0±0.7		2.6±0.7		2.3±0.6		2.7±0.9	
Two	2.2±0.6		2.5±0.7		2.2±0.7		2.9±0.7	
≥Three	2.3±0.6		2.6±0.7		2.3±0.7		2.9±0.8	
Family Income		p=0.006		p=0.052		p=0.797		p=0.353
Under Minimum Wage	2.3±0.6		2.7±0.7		2.3±0.7		2.9±0.7	
Minimum Wage	2.2±0.6		2.5±0.7		2.3±0.7		2.9±0.8	
Above Minimum Wage	1.9±0.6		2.4±0.8		2.3±0.7		2.7±0.8	
Parent Education Level		p=0.072		p=0.074		p=0.505		p=0.783
Primary Education and below	2.3±0.6		2.6±0.6		2.2±0.6		2.9±0.8	
Secondary Education	2.2±0.6		2.6±0.7		2.3±0.7		2.9±0.8	
High School and over	2.2±0.6		2.4±0.7		2.3±0.7		2.9±0.8	
Working Status		p=0.031		p=0.110		p=0.175		p=0.763
Mother Unemployed	2.2±0.6		2.5±0.8		2.2±0.8		2.8±0.6	
Housewife	2.3±0.6		2.6±0.7		2.2±0.7		2.9±0.8	
Working	2.1±0.6		2.4±0.7		2.4±0.7		2.8±0.8	
Father								
Unemployed	2.2±0.5	p=0.677	2.5±0.6	p=0.558	2.3±0.7	p=0.266	2.8±0.7	p=0.616
Working	2.6±0.6		2.6±0.7		2.3±0.7		2.9±0.8	
Retired	2.2±0.6		2.4±0.7		2.5±0.8		2.7±0.9	

Table V: The Relationship Between the Participant's Responses to HPV*-Related Questions and the Factor Score Means

	Harms		Barriers		Effectiveness		Uncertainty	
	mean±SD	p	mean±SD	p	mean±SD	p	mean±SD	p
Do you know what Human Papilloma Virus is?		p=0.059		p=0.024		p=0.001		p=0.003
Yes	2.1±0.6		2.4±0.8		2.5±0.7		2.6±0.8	
No	2.3±0.6		2.6±0.7		2.2±0.7		2.9±0.8	
Do you know what causes cervical cancer/genital warts?		p=0.001		p=0.036		p=0.147		p=0.001
Yes								
No	2.0±0.6		2.4±0.7		2.4±0.7		2.5±0.8	
	2.3±0.6		2.6±0.7		2.2±0.7		2.9±0.8	
Have you heard of the cervical cancer/genital warts vaccine?		p=0.004		p=0.090		p=0.005		p=0.025
Yes								
No	2.1±0.6		2.5±0.7		2.4±0.8		2.8±0.8	
	2.3±0.6		2.6±0.7		2.2±0.6		2.9±0.8	
Are you considering getting your child vaccinated against Human Papilloma Virus?		p=0.001		p=0.181		p=0.001		p=0.002
Yes	1.9±0.6		2.4±0.7		2.6±0.7		2.6±0.8	
No	2.3±0.6		2.6±0.7		2.2±0.7		2.9±0.7	

***HPV:** Human Papilloma Virus*

those who received the minimum wage and those below the minimum wage (p= 0.003;0.005, respectively) (Table IV).

Housewives' means of harms factor scores were found higher than those of working women (p=0.009).

The relationship between the participant's responses to HPV-related questions and the means of factor scores are shown in Table V.

DISCUSSION

In the present study, we aimed to determine the parents of 9-18 aged girls beliefs and attitudes towards HPV vaccine using for the first time a standard scale in Turkey and to compare whether they had changed or not during pandemic. 19.8% of parents were aware of Human Papilloma Virus and 22.5% of them declared to be willing to vaccinate their daughters against the infection. Despite an extraordinary natural event like COVID -19, we observed that the percentage of parents who heard about the HPV vaccine and their desire to have their children vaccinated did not change compared to the previous period. The percentages of HPV vaccine acceptance were still lower than other childhood vaccines in general during COVID-19 Pandemic.

In a different study designed in Turkey before pandemic, Seven et al. showed that only 26.9% of mothers and 25.0% of fathers had claimed to be aware of HPV(19). In the same study, 14.4% of mothers and 15.5% of fathers also reported that they would have been willing to vaccinate their daughter if the vaccine had been available in Turkey. Kılıç et al. (20) in their descriptive study, designed to identify the opinions of Turkish adolescent girls and their parents about HPV vaccination and the consistency, found that 44.9% of fathers and also 45.5% of mothers wanted their daughters to be vaccinated against HPV. Similar to these results, in different European countries before COVID-19 Pandemic, it was shown that HPV knowledge and vaccine acceptance vary between studies and are also still modest. In systematic literature reviews, it was reported that 64.4% of parents (range 1.7 to 99.3) had known about HPV infection (21). In our study 20.2% of mothers and 9.1% of fathers had known about HPV infection. These different findings may be due to different methodological approaches in different study populations. The hospital region where the study was conducted consists of a low socioeconomic population. Contrary to our expectations for increased HPV vaccine acceptance, our results were lower than HPV vaccine acceptance data of pre-pandemic parents. This decline can be explained by COVID-19 vaccines being on the agenda, HPV vaccine information's being remained in the background and due to the impact of ongoing vaccine refusal.

In this study, the harm factor scores of parents were significantly lower in high in-come families and in families with a mother's occupation. Also, the harm factor scores were also significantly lower in the group who had known cervical cancer, heard about the HPV vaccine and thought to have their child vaccinated. In a different study in Thailand, one of the countries with the highest cervical cancer prevalence in the world, using a theoretical framework called Health Belief Model, similar to our results it was shown that HPV and cervical cancer knowledge were significantly higher in participants coming from high-income level (9).

Most studies published in Turkey reported that awareness, knowledge, and positive attitude on HPV and vaccine increased as the mother's education level increased (11). Contrary to the results of many previous studies, we did not find any factor score differences according to parents' gender and education level. Zhu et al. (22) also designed a study in Chinese-American parents to examine factors associated with willingness to vaccinate their children. Similar to our results, they found that parents generally lacked knowledge on HPV and the HPV vaccine but education level and gender were not related to parental intention of HPV vaccination for their children.

In this study, barrier scores of parents were significantly lower in the group knowing HPV and its associated morbidities. Liebermann et al. (23) using Thematic Content Analysis designed a study in the Dominican Republic where cervical cancer is the second most common cause of cancer death in women. They observed, like our results, that one of the barriers of HPV vaccination implementation were low to moderate knowledge of HPV and cervical cancer, especially in the rural and suburban groups. Although two studies were representing diverse geographic settings, similar socioeconomic groups may clarify these similar study data. Our study's mean barrier scores were also higher than studies designed in different countries (16).

We could not find any significant differences in effectiveness scores of parents according to family income, but Grandahl et al. reported that in contrast to their hypothesis, parents who had a lower income, perceived more benefits compared to parents having a higher income (9) . Authors attributed it to the difficulty of almost 40% of the participating mothers accessing basic health services such as cervical cancer screening tests. In Turkey, health services are available to many individuals and are provided free of charge.

This study has some limitations. The participants were selected only from one hospital and its results cannot be generalized to Turkey. Studies that include different socioeconomic and cultural group of parents could have yielded more reliable results to the literature. Due to the negative social influence of the pandemic, and as a result of the decrease in admission to hospitals due to fear of contamination we were able to reach such a population. Also, it was not conducted on parents' attitudes towards vaccination on their boys. Another restriction of the study was that, data collection was made self-report, not by interview. Due to the fact that physicians had to work in different positions in hospitals during the pandemic, the parents could have not been informed or educated face-to-face by a physician. If approximately for 10 minutes information had been

provided instead of giving an information form, different results could be reached in the study. Despite these limitations, in this study the assessments were made by a valid and reliable instrument for the first time in Turkey. It is the first study providing important results about attitudes and beliefs of parents about HPV vaccination during COVID-19 Pandemic.

CONCLUSION

The awareness and be willing to vaccinate their daughters of parents against HPV infection is still low in Turkey during COVID-19 Pandemic. To the best of our knowledge, this study is the first analyzing parents' current attitudes and beliefs using a standardised scales towards HPV and its vaccine during COVID-19 Pandemic. We would have hoped that the concern of being infected by a novel fatal virus would increase the parents' desire to have their child vaccinated against other vaccine-preventable diseases. The fact that COVID-19 vaccines are more on the agenda and the vaccine refusal may have caused these results. Provider-oriented public health interventions from physicians and other healthcare providers, including family doctors, pediatricians and community health professionals is very important towards vaccination. Effective answers about safety and emphasizing benefits such as cancer prevention must be given as a brief message when giving information about HPV vaccination. Health education programs aiming at both sexes and including both mothers/fathers would increase knowledge and awareness on HPV and HPV vaccine. In countries where HPV vaccines is not included in national vaccination schedules, inclusion of HPV vaccines in their immunization programs would reduce indecision. Future studies must be designed paying attention to these informational techniques by the health worker.

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Psychiatric Symptoms in Children with Neurogenic Bladder

Nörojen Mesane Tanılı Çocuklarda Psikiyatrik Belirtiler

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ABSTRACT

Objective: This study aimed to evaluate children with ''neurogenic bladder" diagnosis in terms of anxiety and depression.

Material and Methods: Thirty-three pediatric patients with neurogenic bladder followed in Adana City Training and Research Hospital Pediatric Urology and Nephrology outpatient clinics from May 2023 to July 2023 and 20 healthy controls who were age and sex-matched, from public schools located in the same geographic area were included in the study. All participants were requested to complete the Hospital Anxiety and Depression Scale, Conners' Parent Rating Scale and Turgay DSM-IV Disruptive Behavior Disorders Rating Scale.

Results: Global score of the CPRS reported by parents, was higher in patients than controls (p=0.012). CPRS Hyperactivity/Impulsivity and Anxiety subscale scores of the patients were significantly higher than controls. Global score of the CPRS reported by parents, was higher in patients with CKD than without (p=0.033). CPRS- Learning problems subscale of the patients with CKD was also higher than the patients without (p=0.023). DSM-IV Total score and the DSM-IV inattention score was higher in patients with CKD than without. Hospital Anxiety and Depression Scale-anxiety subscale reported by children was higher in patients without wheelchair dependence than the patients with (p=0.002). CPRS-conduct disorder and CPRS-Hyperactivity/ Impulsivity subscale scores of the patients without wheelchair dependence was higher than the patient with (p=0.016, p=0.009). DSM-IV hyperactive/impulsive subscale score of the patients without wheelchair dependence was higher than the patients with (p=0.043).

Conclusion: Children with NB are at risk for physical, neurocognitive, psychosocial, and family challenges. Anxiety and depression symptoms should not be underestimated. For long-term appropriate management of such vulnerable patients psychological support is required.

Key Words: Anxiety, Depression, Neurogenic bladder, Pediatrics, Psychiatry

ÖZ

Amaç: Bu çalışmada "nörojenik mesane" tanılı çocukların anksiyete ve depresyon açısından değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Adana Şehir Eğitim ve Araştırma Hastanesi Çocuk Ürolojisi ve Nefroloji polikliniklerinde Mayıs 2023-Temmuz 2023 tarihleri arasında takip edilen 33 nörojen mesaneli çocuk hasta ve aynı coğrafi bölgede bulunan devlet okullarından yaş/cinsiyet olarak eşleştirilmiş 20 sağlıklı kontrol çalışmaya dahil edilmiştir. Tüm katılımcılardan Hastane Anksiyete ve Depresyon Ölçeği, Conners Ebeveyn Derecelendirme Ölçeği ve Turgay DSM-IV Yıkıcı Davranış Bozuklukları Derecelendirme Ölçeği'ni doldurmaları istendi.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Ethics committee approval was obtained from the Local Ethics Committee of Adana City Training and Research Hospital for the study (Approval Date:06.04.2023; Approval Number:2431).

Contribution of the Authors / Yazarların katkısı: EKBERLİ G: Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar. ***TANER S:*** 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, Reviewing the article before submission scientifically besides spelling and grammar. ***GÜNEŞ S:*** Planning methodology to reach the conclusions.

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Bulgular: Ebeveynlerin bildirdiği CPRS global skoru, hastalarda kontrollere göre daha yüksek olarak tespit edildi (p=0.012). Hastaların CPRS Hiperaktivite/Dürtüsellik ve Anksiyete alt ölçek puanları kontrollerden anlamlı olarak yüksekti. Ebeveynler tarafından bildirilen CPRS global puanı, KBH olan hastalarda olmayanlara göre daha yüksekti (p=0.033). KBH olan hastaların CPRS- Öğrenme sorunları alt ölçek puanı da olmayanlara göre daha yüksekti (p=0.023). DSM-IV Toplam puanı ve DSM-IV dikkatsizlik puanı KBH olan hastalarda olmayanlara göre daha yüksekti. Hastane Anksiyete ve Depresyon Ölçeği-çocukların bildirdiği anksiyete alt ölçeği, tekerlekli sandalye bağımlılığı olmayan hastalarda, olanlara göre daha yüksekti (p=0.002). Tekerlekli sandalye bağımlılığı olmayan hastaların CPRS-davranım bozukluğu, CPRS-Hiperaktivite/Dürtüsellik alt ölçek puanları, DSM-IV hiperaktif/dürtüsel alt ölçek puanı tekerlekli sandalye bağımlılığı olan hastalara göre daha yüksekti (p=0.016, p=0.009, p=0.043).

Sonuç: Nörojen mesaneli çocuklar fiziksel, nörobilişsel, psikososyal ve ailevi zorluklar açısından risk altındadır. Anksiyete ve depresyon belirtileri hafife alınmamalıdır. Bu tür savunmasız hastaların uzun vadeli uygun yönetimi için psikolojik destek gereklidir.

Anahtar Sözcükler: Anksiyete, Depresyon, Nörojen mesane, Pediatri, Psikiyatri

INTRODUCTION

Neurogenic bladder (NB) may develop as a result of a lesion at any level in the nervous system. Main consequences of this condition are urinary incontinence, stool incontinence recurrent urinary tract infection (UTI), vesicoureteral reflux (VUR) and renal failure requiring dialysis and/or transplantation (1). The main goals of treatment regarding urinary tract are prevention of UTI, prevention of upper urinary tract deterioration and achievement of continence (2). An ongoing multidisciplinary approach, close follow-up and cooperation of both caregiver and patient are paramount for proper management and achievement of the best-possible quality of life (QoL) in this patient population (3). Early administration of antibiotic prophylaxis, anticholinergics and clean intermittent catheterization (CIC) after closure is main part of treatment and has shown to decrease renal complications (4). Like patients with other chronic diseases, anxiety and depression (A/D) among children with NB could contribute to non-adherence in treatment regimens which may result with severe consequences (5). Lower urinary tract storage and emptying problems is reported to be associated with behavioral and emotional symptoms such as anxiety and depression (6). Depressed patients reported to be noncompliant to treatment recommendations compared with nondepressed patients (7).

Considering the importance of treatment compliance and the early exposure children with NB to multiple clinical procedures lead us to conduct this study. Presence of A/D in NB population and comparison with healthy controls aimed to be evaluated in this study.

MATERIALS and METHODS

Study Design

This cross-sectional study was conducted to evaluate the presence of attention deficit and hyperactivity disorder (ADHD), A/D in patients with a diagnosis of NB and to compare it with healthy control group. Thirty-three pediatric patients with NB followed in Adana City Training and Research Hospital Pediatric Urology and Nephrology outpatient clinics from May 2023 to July 2023 and 20 healthy controls who were age and sex-matched, from public schools located in the same geographic area were included in the study. Diagnostic criteria for NB was defined as presence of emptying or storage defect of urine and stool secondary to neural tube defects or other congenital malformations (1). Clinical and laboratory data were already available as a part of the routine protocol for managing. The patients' differentiated kidney functions and scarring were evaluated with Tc 99m dimercaptosuccinic acid (DMSA) scan. Presence of more than 10% decrease in differentiated kidney functions in scintigraphic evaluation was considered as loss of function. The definition and classification of chronic kidney disease (CKD) was evaluated according to Kidney Disease: Improving Global Outcomes guidelines (8). Glomerular filtration rate (GFR) was estimated (eGFR) adopting the original Schwartz formula (9).

After informed consent had been provided all participants were requested to complete the Hospital Anxiety and Depression Scale (HADS). Parents of all participants were requested to fill in Conners' Parent Rating Scale (CPRS) and Turgay DSM-IV Disruptive Behavior Disorders Rating Scale (T-DSM-IV-S).

Inclusion and exclusion criteria

The study included pediatric patients 6-18 years of age who are being treated with diagnosis of NB. In selection of patients diagnosed with NB, the inclusion criteria were absence of any mental disabilities or mobilization problems. All children were mobile either with a wheelchair or spontaneously. Patients with acute illness (e. g. infections, clinical instabilities) were not scheduled for interviews.

Exclusion criteria were; patients <6 years old, patients who do not want to fill in the scales, illiterate patients, and patients with mental retardation.

Controls

The control group consisted of healthy sex and age-matched children from public schools who gave informed consent to take part in the study. All controls were healthy and had no medical or family history of renal diseases. Healthy status was determined through a review of the medical history and either a parental report or self-report to rule out the presence of chronic or acute diseases.

Clinical and laboratory measurements

Clinical characteristics, anthropometric measurements, laboratory test, radiological test results were evaluated during the clinic visit and by reviewing medical records at the time of interview. Clinical data included gender, age, height, weight, primary etiology of NB, stage of CKD, wheelchair status, treatment compliance, CIC compliance, experienced surgical procedures were recorded. Laboratory tests included serum levels of BUN, creatinine, hemoglobin were recorded.

Sociodemographic Characteristics Data Form

The authors created a questionnaire including information on sociodemographic features of children and caregivers. The form applied to all caregivers and children.

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale is a reliable and valid questionnaire for hospitalized populations, consisting of seven questions (rated 0, 1, 2 and 3) related to anxiety (subscale A) and seven others to depression (subscale D), thus providing two scores (10). The HADS has been adapted and used in various studies to assess anxiety and depression symptoms in children and adolescents (11). Turkish validity and reliability study was carried out by Aydemir et al. (12).

Conner's Parent Rating Scale (CPRS)

Conners' Rating Scales 2 (CRS), which were developed primarily for use in drug studies of children with hyperkinesias (13). The items in the Conners scales are rated on a Likert-type scale, typically ranging from "not at all" to "very much." The Conners scale includes different versions, such as the Conners' Rating Scales-Revised (CRS-R) and the Conners 3rd Edition (Conners 3). These scales are typically completed by parents, teachers, and sometimes the child or adolescent themselves. They consist of a series of items that assess various domains, including inattention, hyperactivity/impulsivity, aggression, oppositional behavior, and other behavioral and emotional problems (14). The scores obtained from the scales help in quantifying the severity of symptoms and identifying areas of concern. The scales provide standardized scores that allow for comparisons to be made with normative data from the general population. Turkish validity and realiability study eas conducted by Dereboy et al (15).

Turgay DSM-IV Disruptive Behavior Disorders Rating Scale parent form (T-DSM-IV-S)

The Turgay DSM-IV Disruptive Behavior Disorders Rating Scale parent form was developed by Turgay (16) and translated into Turkish by Ercan et al (17). The T-DSM-IV-S is based on DSM-IV diagnostic criteria and evaluates hyperactivity–impulsivity, inattention, opposition-defiance, and conduct disorder. Symptoms are scored on a 4-point Likert scale (0 = not at all; 1 = just a little; 2 = quite a bit; and 3 = very much). The T-DSM-IV-S was shown reliable and valid for Turkish children (17). All psychometric instruments used for psychological assessment were read to the participants to reduce differences due to educational levels and performance.

Ethical Considerations

Ethics committee approval was obtained from the Local Ethics Committee of Adana City Training and Research Hospital for the study (Approval Date:06.04.2023; Approval Number:2431). Verbal and written consent was received from caregivers who agreed to participate in the study.

Statistical Analysis

All statistical analyses were analyzed by SPSS version 25 software package. 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 (minimum-maximum) under the nonparametric conditions. Independent sample t test was used for the comparison of normally distributed numeric variables; the Mann-Whitney U test for non-normal distributions. P values less than 0.050 were considered to be statistically significant.

RESULTS

The patient group consisted of 20 girls and 13 boys, and the control group consisted of 11 girls and 10 boys. The mean age of the patients was 10.8±3.7 years, and the mean age of the control group was 12.0±3.3 years. The patient and control groups were similar in terms of age and gender (p=0.201, p=0.551). Demographical and clinical characteristics of the patients were shown in Table I.

Patients and the Controls

Hospital Anxiety and Depression Scale reported by children and adolescents were similar in patient and control group in terms of HADS-depression and HADS-anxiety scores. Global

Table I: Demographical and clinical characteristics of the patients with neurogenic bladder

Patients Characteristics	n=33 (%)
Gender (male/female)	13/20
Mean age (years)	10.8±3.7
Neurogenic bladder etiology	
Meningomyelocele	23 (69.7)
Spina bifida	5 (15.2)
Cerebral palsy	2 (6.1)
Non-neurogenic neurogenic bladder	1 (3.0)
Posterior urethral valve	1 (3.0)
Postoperative	1 (3.0)
Wheelchair dependence	24 (72.7)
Presence of kidney function loss	9 (24.3)
Presence of CKD	12 (36.4)
Need for urological surgery	3 (9.1)
CIC therapy	24 (72.7)

Table II: Comparison of the Hospital Anxiety and Depression Scale, Conners' Parent Rating Scale and T-DSM-IV-S scale scores of the patient and control groups

	Patients (n=33)	Controls (n=23)	p
Hospital Anxiety and Depression Scale*			
HADS-depression	4.7± 3.2	4.5± 4.4	0.899‡
HADS-anxiety	5.3± 3.9	5.0±3.5	0.847‡
Conners' Parent Rating Scale †			
CPRS- Conduct disorder	1 (0-13)	1 (0-5)	0.272‖
CPRS- Hyperactivity/ Impulsivity	2 (0-10)	1 (0-4)	0.006‖
CPRS- Learning problems	3 (0-9)	1 (0-7)	0.542‖
CPRS- Anxiety	4 (0-16)	2 (0-15)	0.033‖
CPRS- Psychosomatic subscale	2 (0-12)	0 (0-4)	0.057‖
CPRS- Global score	19 (4-45)	8 (0-30)	0.012‖
T-DSM-IV-S Scale †			
DSM-IV inattention	3 (0-24)	4 (0-17)	0.653‖
DSM-IV hyperactive/impulsive	2 (0-12)	3 (0-17)	0.416‖
DSM- IV Total	6 (0-28)	7 (0-34)	0.640‖

*****Mean± SD, †Median (Min-Max), ‡Independent t-test, ‖Mann-Whitney U test, **HADS:** Hospital Anxiety and Depression Scale, **CPRS:** Conners' Parent Rating Scale, **T-DSM-IV-S Scale:** Turgay DSM-IV Disruptive Behavior Disorders Rating Scale*

Table III: Comparison of the Hospital Anxiety and Depression Scale, Conners' Parent Rating Scale and DSM-IV AD/ADHD scale scores of the patients with and without CKD.

	Patients with CKD (n=12) Median (Min-Max)	Patients without CKD (n=21) Median (Min-Max)	p
Hospital Anxiety and Depression Scale			
HADS-depression	5 (1-12)	5 (1-15)	0.890
HADS-anxiety	5 (3-17)	3 (0-13)	0.095
Conners' Parent Rating Scale			
CPRS- conduct disorder	2 (0-3)	1 (0-13)	0.332
CPRS- Hyperactivity/ Impulsivity	2 (1-4)	3 (0-10)	0.830
CPRS- Learning problems	4 (1-9)	2 (0-5)	0.023
CPRS- Anxiety	4 (2-16)	4 (1-11)	0.395
CPRS- Psychosomatic subscale	2 (0-5)	1 (0-8)	0.294
CPRS- Global score	23 (11-44)	13 (4-45)	0.033
T-DSM-IV-S Scale			
DSM-IV inattention	9 (0-24)	3 (0-13)	0.003
DSM-IV hyperactive/impulsive	4 (1-9)	2 (0-12)	0.186
DSM- IV Total	15 (1-28)	4 (0-19)	0.013

*****Mann-Whitney U test, **HADS:** Hospital Anxiety and Depression Scale, **CPRS:** Conners' Parent Rating Scale, **T-DSM-IV-S Scale:** Turgay DSM-IV Disruptive Behavior Disorders Rating Scale*

Table IV: Comparison of the Hospital Anxiety and Depression Scale, Conners' Parent Rating Scale and DSM-IV AD/ADHD scale scores of the patients with and without wheelchair dependence

	Patients with wheelchair dependence (n=24)	Patients without wheelchair dependence (n=9)	p
Hospital Anxiety and Depression Scale*			
HADS-depression	4.6±3.2	5±3.3	0.463‡
HADS-anxiety	3.8±2.8	8.4±4.7	0.002‡
Conners' Parent Rating Scale†			
CPRS- conduct disorder	1 (0-8)	3 (1-13)	0.016§
CPRS- Hyperactivity/ Impulsivity	2 (0-7)	4 (1-10)	0.009§
CPRS- Learning problems	3 (0-9)	1 (0-5)	0.965§
CPRS- Anxiety	4 (1-16)	6 (2-11)	0.069§
CPRS- Psychosomatic subscale	1 (0-8)	3 (0-5)	0.392§
CPRS- Global score	16 (4-44)	24 (10-50)	0.058§
T-DSM-IV-S Scale†			
DSM-IV inattention	3 (0-13)	5 (0-24)	0.275§
DSM-IV hyperactive/impulsive	2 (0-12)	5 (1-9)	0.043§
DSM- IV Total	5 (0-22)	12 (1-28)	0.094§

*****Mean± SD, †Median (Min-Max) ‡Independent t-test, §Mann-Whitney U test, **HADS:** Hospital Anxiety and Depression Scale, **CPRS:** Conners' Parent Rating Scale, **T-DSM-IV-S Scale:** Turgay DSM-IV Disruptive Behavior Disorders Rating Scale*

score of the CPRS reported by parents, was higher in patients than controls (p=0.012). CPRS Hyperactivity/Impulsivity and Anxiety subscale scores of the patients were significantly higher than controls, respectively (p=0.006, p=0.033). The T-DSM-IV-S was reported by parents. T-DSM-IV-S inattention, T-DSM-IV-S hyperactive/impulsive and T-DSM-IV-S total scores were similar in patient and control groups. Comparison of the scores between patient and control group were shown in Table II.

Patients with CKD

Hospital Anxiety and Depression Scale scores were similar in patients with and without CKD. Global score of the CPRS reported by parents, was higher in patients with CKD than without (p=0.033). CPRS- Learning problems subscale of the patients with CKD was also higher than the patients without (p=0.023). T-DSM-IV-S total score and the T-DSM-IV-S inattention score was higher in patients with CKD than without, respectively (p=0.013, p=0.003). Comparison of the scales of the patients with and without CKD was shown in Table III.

Patients with/without Wheelchair Dependence

Hospital Anxiety and Depression Scale-anxiety subscale reported by children was higher in patients without wheelchair dependence than the patients with (p=0.002). CPRS-conduct disorder and CPRS-Hyperactivity/ Impulsivity subscale scores of the patients without wheelchair dependence was higher than the patient with (p=0.016, p=0.009). T-DSM-IV-S hyperactive/impulsive subscale score of the patients without wheelchair dependence was higher than the patients with (p=0.043). Comparison of the scales of the patients according to their wheelchair dependence was shown in Table III.

DISCUSSION

Presented study detected CPRS Hyperactivity/ Impulsivity and Anxiety subscale scores of the patients to be significantly higher than controls. World Health Organization reported around 10% of children and adolescents suffer from mental disorders, and of those 3% develop a depressive disorder (18). Depression is often comorbid with anxiety (up to 30%) (19). Comorbidity is important because both of the conditions contribute to significant impairment in the daily functioning of the child (20). Depression is reported to be more common among those with chronic somatic health problems. Concomitance of depression with chronic condition influences adherence of patient to medical recommendations, pharmacotherapy and control visits beside emotional and cognitive functioning (21). Kabra et al. (22) screened A/D among pediatric patients of NB and their caregivers. They found considerable anxiety in adolescents with NB and both A/D in caregivers. Lopes et al. (23) in their cross-sectional study evaluated QoL of pediatric patients with lower urinary tract malformations managed with incontinent or continent urinary stomas or by urethral CIC and compared them with heathy controls. The patients reported to have negative perceptions regarding necessity of undergoing CIC and to the occurrence of daytime urinary losses, however, the feeling associated to the CIC procedure itself resulted in a positive perception which is explained by the possibility to be diaper-free. In our study contrary to the literature HADS, CPRS and T-DSM-IV-S scores were similar in patients with and without CIC. These not expected results can be explained by the fact that the patients and caregivers are incompatible with CIC treatment due to the socio-cultural structure and belief structure of the population. Small number of study group or discordance between in numbers of compared groups may be another reason.

Another interesting result of this sturdy difference regarding HADS-anxiety scores, CPRS-conduct disorder and CPRS-Hyperactivity/ Impulsivity subscale scores, T-DSM-IV-S hyperactive/impulsive subscale score between those with and without wheelchair dependence. Those without wheelchair dependence detected to have higher scores compared with wheelchair dependent patients. Although we have no data on the cause of this finding in this preliminary study with small sample size the explanations can be as follows; the fact that the small number of patients who have the same pathology and are not wheelchair dependent in their surroundings may be a source of concern for the future. The patient's unwillingness to adapt to the requirements of the condition or, perhaps high expectations may be the reason also.

NB patients with CKD or ESRD can experience multiple hospital visits, examinations, wide ranged treatment modalities like medications, CIC, surgical procedures or renal replacement therapies. The exact prevalence of psychiatric disorder in pediatric CKD patients varies (10–35%) depending on the progression of CKD and the age of the child (young children or adolescents). In the study conducted by Kogon et al. (24) 7% of children and adolescents with CKD met the study criteria for depression and 5% reported elevated depressive symptoms. Moreira et al.(25) in their study conducted of 28 children and adolescents with pre-dialysis CKD and 28 healthy sex/age-matched controls concluded that CKD negatively impact the QoL of pediatric patients, contributing to a higher frequency of depression and separation anxiety. Multicenter study enrolled with CKD patients on hemodialysis, peritoneal dialysis and on conservative treatment concluded that the level of anxiety among the researched group, with the exception of hemodialysis patients, was not significantly different than the level of anxiety among healthy subjects (26). Demir et al.(27) reported presence of psychiatric disease to be most important factor affecting Qol in transplanted children. Consistent with the literature, global score of the CPRS, DSM-IV total score and the DSM-IV inattention score was higher in patients with CKD than without. Limited mobilization capacity with wheelchair, multiple hospital visits, long hospitalizations due to acute illness, complicated management therapies are obliges patients to live in isolation from their school and social environment. Family and

close relatives are only social network of these patients. This isolation may be source of A/D in these patients group.

Impairments in cognitive abilities including impaired intellectual abilities and difficulties in executive functioning, such as attention, memory in CKD patients have been frequently reported in the literature (28-30).

Moreira et al. (25) found a significant difference in the frequency of grade retention, delayed educational attainment and interruption of studies between CKD patients and matched controls. Elorza et al. (31) explained worse scores for psychosocial health and school dimensions in CKD patients compared to healthy controls and claimed this condition to be secondary to medical interventions inherent to the treatment and due to disease development. Educational status of mother is reported to be highly related with cognitive status of patient possibility due to the mother's undeniable role in the treatment and follow-up (32). However, studies have shown that despite these challenges, improvements in cognitive functioning are probable with improvements in renal function (33).

Remarkable and consistent with the literature finding of our study is statistically significant difference between CKD and non-CKD patients regarding CPRS- Learning problems subscale. In addition to the fact that the known effect of the disease and treatment process on learning difficulties manifests itself severely in our society, the education and awareness level of the caregivers is an ongoing challenge for clinicians. Beside proper management and follow-up awareness should be created among family members, caregivers and schools regarding these children.

CONCLUSION

In accordance with the protocol we applied in NB patient group, we prefer to begin CIC and medical treatment at an early age. We think that subjecting patients in the adolescent age group to NB examinations and treatments is a source of anxiety for the patient and caregiver. As a result of improvement in medical care opportunities long life expectation is grooving in NB patient population. We think that, beside management and follow-up of primary disease, monitoring and referring of patients regarding A/D symptoms may develop QoL.

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Evaluation of Pediatric Cases Followed in Burn Center

Yanık Merkezinde Takibi Yapılan Pediatrik Olguların Değerlendirilmesi

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ABSTRACT

Objective: Burn injuries are among the most important causes of unintentional death in young children. Although most pediatric burns do not cause serious clinical problems, severe burns have a higher mortality rate than adult patients with similar burns. In this study, we aimed to discuss the clinical features of pediatric burn patients hospitalized in the Burn Center of Eskisehir City Hospital.

Material and Methods: This study evaluated pediatric patients between the ages of 0 -18 years who were hospitalized and followed up between June 1, 2019 and August 1, 2023 at the Burn Center of Eskişehir City Hospital were evaluated retrospectively. Patients were evaluated according to age, gender, presence of chronic diseases, parenteral treatment rates, types of burns, total body surface area and the area affected by the burn.

Results: The most common burn type was scald burn with 89.5% (n=246). According to the types of burns, especially scalding and flame burns were found to have a longer hospitalization period than electrical burns. While there was a significant correlation between the percentage of burns and the duration of intensive care unit stay and hospitalization (p=0.001), the number of operations increased as the percentage of burns increased (p=0.072).

Conclusion: Exposure to burns was mostly observed in children aged 0-24 months. Burns may cause more serious consequences in pediatric cases. By looking at the types of burns in pediatric patients according to age groups, we think that burn cases in this age group can be reduced by raising awareness of families and taking precautions.

Key Words: Burn, Burn Unit, Children, Electrical Burn

ÖZ

Amaç: Yanık yaralanmaları, küçük çocuklarda, istem dışı ölümlerin en önemli nedenleri arasında yer almaktadır. Pediatrik yanıkların çoğu ciddi klinik sorunlara yol açmamakla birlikte, ciddi yanıklarda benzer yanıklara sahip erişkin yaş grubu olgulara göre göre daha yüksek mortaliteye sahiptir. Bu çalışmada, Eskişehir Şehir Hastanesi Yanık Merkezi'nde yatan çocuk yanık hastalarının klinik özelliklerini tartışmayı amaçladık.

Gereç ve Yöntemler: Bu çalışmada Eskişehir Şehir Hastanesi Yanık Merkezi'nde 1 Haziran 2019 - 1 Ağustos 2023 tarihleri arasında yatırılarak takip edilen 0-18 yaş arası çocuk hastalar retrospektif olarak değerlendirildi. Hastalar yaş, cinsiyet, kronik hastalık varlığı, parenteral tedavi oranları, yanık tipleri, toplam vücut yüzey alanı ve yanıktan etkilenen alana göre sınıflandırıldı.

Bulgular: En sık yanık türü %89.5 (n= 246) ile haşlanma yanığıydı. Yanık türlerine göre özellikle haşlanma ve alev yanıklarında elektrik yanıklarına göre yatış süresinin daha uzun olduğu saptandı. Yanık yüzdesi ile yoğun bakım yatış süresi ve hastane yatış süresi arasında anlamlı ilişki saptanırken (p=0.001), yanık yüzdesi arttıkça operasyon sayısının da artış gösterdiği belirlendi (p=0.072).

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Contribution of the Authors / Yazarların katkısı*: *BİLDİRİCİ Y: 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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Sonuç: Yanık maruziyeti en çok 0-24 ay arası çocuklarda görülmektedir. Yanıklar pediatrik olgularda daha ciddi sonuçlara yol açabilmektedir. Çocuk hastalarda yanık tiplerine ve yaş gruplarına göre bakıldığında ailelerin bilinçlendirilmesi ve önlem alınması ile bu yaş grubundaki yanık vakalarının azaltılabileceğini düşünmekteyiz.

Anahtar Sözcükler: Yanık, Yanık Ünitesi, Elektrik Yanığı, Çocuk

INTRODUCTION

The skin is the largest organ in the body and consists of the epidermis and dermis. The skin acts as a barrier to infection and radiation, maintains fluid-electrolyte balance and provides thermal regulation. A burn is a trauma with high mortality and morbidity that results in necrosis of part or all of the epidermis and dermis, usually due to thermal contact. Causes of burns include thermal burns, burns caused by electrical current, flame and inhalation injuries, chemical burns, contact burns and scalding burns. Age, sex, cause of burn, percentage and degree of burn are determinants of mortality and morbidity (1). Burn injuries are among the leading causes of unintentional death in young children. Although most pediatric burns do not result in serious clinical problems, severe burns have a higher mortality rate compared to adult patients with similar burns (2,3).

The most common burns in pediatric patients are thermal burns caused by scalding or contact with hot food (2). Non-food thermal burns can be caused by fireworks, irons or campfires. Chemical burns can be caused by many common cleaning products or topical or mucosal contact with various acidic or alkaline products (2,4,5). Although electrical burns are most common in adults, exposures can also occur in children. Electrical burns cause little visible damage to the body because most of the damage occurs in deeper tissues. However, electrical burns can also cause nerve and muscle damage and arrhythmias (2,6).

In this study, we aimed to discuss the clinical characteristics of pediatric patients admitted to the burn centre of Eskişehir City Hospital, the only burn centre in Eskişehir province, in the literature.

MATERIALS and METHODS

This study evaluated pediatric patients between the ages of 0 and 18 years who were hospitalized and followed up between June 1, 2019 and August 1, 2023 at the Burn Center of Eskişehir City Hospital were evaluated retrospectively. Patients were evaluated according to age, gender, presence of chronic diseases, burn types, percentage of total body surface area (TBSA) and area affected by the burn, number of surgeries performed, and length of stay in the ward and intensive care unit were recorded. Discharge, parental request and death were recorded. Data were obtained retrospectively from the hospital information system and patient records.

This study was approved by the Eskişehir City Hospital Non-Interventional Ethics Committee with the decision of ESH/GOEK-2023/43 dated August 17, 2023 and was conducted in accordance with the principles of the Declaration of Helsinki and all relevant legislation.

Statistical method:

All data were analysed using the Statistical Package for the Social Sciences (SPSS) 21.0 (IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp). Continuous variables were analysed using Independent sample T-test or Mann-Whitney U-test, considering data distribution and homogeneity. Data were expressed as the mean ± standard deviation (SD) when they were normally distributed and as the median when they were not normally distributed. Categorical variables are expressed as percentages. The Pearson chi-square test was used for the relationship between two categorical variables. The Shapiro-Wilk test was used to determine whether the data were normally distributed. The normality assumption of the variability between the medians of the independent groups was assessed using the Kruskal-Wallis test. Groups were compared within themselves. The results were evaluated at the 95% confidence interval and significance was evaluated at the $p<0.050$ level.

RESULTS

Of the 275 patients who participated in the study, 58.5% (n=161) were male. The age of the patients ranged from 0 to 16 years, with a median age of 2 years (min: 0, max: 16). The most common type of burn was scalding with 89.5% (n=246). Some characteristics of the patients that may be associated with burns are shown in Table I.

Scald burns were more common in the younger age group and electrical and flame burns were more common in the school age group. Table II provides information on the type of burn and age of onset.

In the study, the total body area burn percentage ranged from 1-60, and the median percentage was 8. Table III shows the relationship between the median values of burn percentage, mean number of surgeries, and length of hospital stay according to burn type. There was no significant difference in the number of operations according to burn type. When the relationship between burn type and length of hospital stay was evaluated, it was found that the length of hospital stay was longer for scalding and flame burns compared to electrical burns.

Table I: Burn-related characteristics of the patients

Features associated with burns	n (%)
Sex	
Female	114(41.5)
Male	161(58.5)
Age Groups	
0-12 months	35 (12.7)
>12-24 months	86 (31.3)
>2-6 years	78 (28.4)
> 6-12 years	51 (18.5)
>12-18 years	25 (9.1)
Burn site	
Head and neck	35 (12.7)
Body	40 (14.5)
Upper extremity	85 (30.9)
Lower extremity	59 (21.5)
In more than one field	56 (20.4)
Type of burn	
Scalding	246 (89.5)
Electricity	7 (2.5)
Flame	21 (7.6)
Chemical	1 (0.4)

Table II: Information on burn type and age at onset

Type of burn	Mean Age ± SD (year)
Scalding	3.47± 0.24
Electricity	7.14±2.38
Flame	10.61±0.92

Table III: The relationship between burn type and burn percentage, mean number of operations, and total length of stay in ward or intensive care unit

	Scalding	Electricity	Flame	Total	p
TBSA Percentage*	8 (1-40)[a]	1 (1-3)[b]	9 (2-60)[a]	8 (1-60)	0.001
Number of Operations*	0 (0-16)	0 (0-5)	0 (0-14)	0 (0-16)	>0.050
Hospitalization Period (day)*	7 (1-38)[a]	3 (1-7)[b]	9 (1-40)[a]	7 (0-40)	<0.050
Intensive Care Duration (days)*	0 (0-42)[a]	0 (0-1)[ab]	0 (0-57)[b]	0 (0-57)	0.001
Total Hospital Stay (days)*	8 (1-58)[a]	4 (1-7)[b]	9 (1-86)[c]	8 (1-86)	<0.050

*****Median(min-max), **TBSA:** Total Body Surface Area*

While there was a significant correlation between the percentage of TBSA and the duration of intensive care unit stay and hospitalization (p=0.001), the number of surgeries increased as the percentage of burns increased (p=0.072).

One of the children who participated in the study was a 13-year-old child with epilepsy and mental retardation, and the TBSA was scalding with a rate of 23%. The patient was followed for 4 days in the ward and 22 days in the intensive care unit and underwent 3 operations. A 24-month-old child diagnosed with haemophilia who had a scalding burn with a TBSA of 2% was discharged after two days in hospital without the need for surgery. Apart from these two children, there were no patients with chronic diseases.

Pearson correlation analysis between total length of hospitalization and total body surface area affected by burns showed a positive correlation (r: 0.683, p < 0.001).

The median length of hospital stay was 7 (min-max:1-86) days for boys and 8 (min-max:1-58) days for girls. The median length of hospital stay was not statistically different between the sexes (p=0.283), according to the Mann-Whitney U-test. When examining the discharge patterns, it was found that 1 (0.4%) patient died, 261 (94.9%) patients were discharged and 13 (4.7%) patients left the hospital at the parents' request.

DISCUSSION

Burns in the pediatric age group represent a significant proportion of all burn cases. Accurate assessment of burn patients is both life-saving and important in determining treatment or surgical intervention. Although most burn cases can be treated outpatient, 5% are severe burns and require hospitalization (5,7-10). Burns involving more than 10% of the body surface area, burns to the hand, foot, face or perineum, electrical burns or chemical burns require hospitalisation (9).

Eskişehir City Hospital is one of the most important burn centres in the region, which also serves the surrounding provinces and has received the title of a burn centre in 2019. It is a center with 12 beds, 4 intensive care beds, 1 operating room, 1 hydrotherapy room and 2 dressing rooms, 1 outpatient polyclinic room, specialized personnel, a general surgeon who has received burn training and a pediatric surgeon who monitors pediatric cases.

When gender is considered in pediatric burns, several studies have shown that boys are more likely to suffer burns than girls(11-13). In our study, 58.5% of cases were male, which is consistent with the literature.

Pediatric burns usually occur in the home and the most common cause is scalding in Turkey (14-17). After scald burns, flame burns and electrical burns are the next most common types of burns in the pediatric age group (5,18,19). In our study, similar to the literature, scalds were the most common cause of burns, followed by flame and electrical burns.

Children are more susceptible to flame and electrical burns than other age groups. This is due to exposure during industrial work or play. In our study, scalding burns were observed in the younger age group, whereas electrical and flame burns were observed in the school-age group. This situation was similar to data from developing countries (9,20). Rapid growth and development and excessive mobility in infants aged 0-12 months are common causes of scalds (21). Again, between the ages of 1 and 3, as motor skills develop, scalds from hot water and scalds from other foods can cause burns to the hands, feet

and trunk. In school-age children, flame and electrical burns are more common (22). During adolescence, flame, electrical and scalding burns are also seen as a result of starting to work in the home or as a result of increased physical activity and the young person's efforts to become independent (6).

In pediatric burn cases, the body surface area affected by burns varies, and it is known that mortality and hospital length of stay increase as the body surface area affected by burns increases (5,23-25). In our study, the mean body surface area of the patients was found to be 8%, and it was found that the length of hospital stay increased as the body surface area ratio increased. In our study, the length of hospital stay and the number of surgeries increased as the percentage of TBSA increased.

Studies have reported burn mortality rates in pediatric patients ranging from 0.65% to 15.4%. Mortality increases with flame burns (5,26). The most common causes of mortality are acute renal failure, sepsis, shock and disseminated intravascular coagulation (5,17-19, 27-30). In our study, 1 patient (0.4%) died, which is lower than the rates reported in the literature. The mortality rate was so low in our study because there were not many burn patients with a large body surface area affected by burns and not many patients who required intubation.

In conclusion, similar to the literature, burns were more common in males and the most common cause was scalding. In this study, burns were mostly observed in children aged 0-24 months, and these burns can be reduced by ensuring that parents pay more attention to this issue for this age group and by organising the home environment and living spaces. Electrical burns were more common in the school age group and were low voltage injuries. Flame burns are seen in older age groups. Burns can have more serious consequences in pediatric cases. By examining the categories of burns in pediatric patients by age group, we believe that burn cases in this age group can be reduced by raising parental awareness and instituting preventative measures.

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Comparison of Biologic Monotherapy Versus Biologic and Disease-Modifying Anti-Rheumatic Drug Combination in the Treatment of Non-Systemic Juvenile Idiopathic Arthritis

Sistemik Olmayan Juvenil İdiyopatik Artrit Tedavisinde Biyolojik Monoterapi ile Biyolojik ve Hastalık Modifiye Edici Anti-Romatizmal İlaç Kombinasyonunun Karşılaştırılması

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ABSTRACT

Objective: To explore the efficacy of biologics as mono- or combination therapy with conventional disease modifying anti-rheumatic drugs (cDMARDs) in the treatment of juvenile idiopathic arthritis (JIA).

Material and Methods: Medical records of patients with JIA followed-up from January 2020 to 2023 who were treated either with biologic drugs as monotherapy or with combination of cDMARD were reviewed retrospectively. Data of demographic features, clinical scores and treatments were assessed.

Results: Two hundred five cases received etanercept, adalimumab, or tocilizumab alone or in combination with a cDMARD for JIA were included. The male to female ratio of the cohort was almost equal. Oligoarticular was the most common subtype of JIA.

Majority (n=128, 62.4%) of the group received biologic drugs as monotherapy, while the remaining third (n=77, 37.6%) used a combination of biologic and a cDMARD. Nearly half of the group (57.1%) were treated with etanercept and etanercept monotherapy was the most commonly used one among all JIA subtypes except juvenile psoriatic arthritis. Adalimumab combination therapy was prescribed in most of the children with juvenile psoriatic arthritis. Adalimumab, alone or in combination with methotrexate, was preferred for all 8 patients with uveitis at the onset of the disease. Adalimumab combined (n=9) and tocilizumab monotherapy (n=4) were the most common biologics in those who developed uveitis during follow-up.

Conclusion: Etanercept, adalimumab, or tocilizumab are effective and safe biologics in treatment of JIA. Prescribing biologic drugs timely as combined or monotherapy in certain cases is effective in preventing early and late sequelae of JIA.

Key Words: Biologics, Disease-modifying anti-rheumatic drugs, Juvenile idiopathic arthritis

ÖZ

Amaç: Jüvenil idiyopatik artrit (JİA) tedavisinde konvansiyonel hastalık modifiye edici anti-romatizmal ilaçlar (cDMARD'lar) ile mono veya kombinasyon tedavisi olarak biyolojiklerin etkinliğini karşılaştırmak.

Gereç ve Yöntemler: Ocak 2020- 2023 arasında kadar izlenen monoterapi olarak biyolojik ilaçlarla veya cDMARD kombinasyonuyla tedavi edilen hastaların tıbbi kayıtları retrospektif olarak incelendi. Demografik özellikler, klinik skorlar ve tedavi verileri değerlendirildi.

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Contribution of the Authors / Yazarların katkısı*: DEMİRKAN FG:** 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. ***AKTAY AYAZ N: 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: Tek başına veya JIA için bir cDMARD ile kombinasyon halinde etanersept, adalimumab veya tosilizumab alan 205 vaka dahil edildi. Grubun kadın erkek oranı hemen hemen eşitti. Oligoartiküler JİA'nın en yaygın alt tipiydi.

Grubun büyük çoğunluğu (n=128, %62.4) biyolojik ilaçları monoterapi olarak alırken, geri kalan üçte birlik kısım (n=77, %37.6) biyolojik ve bir cDMARD kombinasyonu kullanmıştı. Grubun yaklaşık yarısı (%57.1) etanersept ile tedavi edilmişti ve jüvenil psoriatik artrit dışında tüm JİA alt tipleri arasında en sık kullanılan etanersept monoterapisiydi. Jüvenil psoriatik artritli çocukların çoğuna adalimumab kombinasyon tedavisi verildi. Hastalığın başlangıcında üveitli 8 hastanın hepsinde tek başına veya metotreksat ile kombinasyon halinde adalimumab tercih edildi. Takip sırasında üveit gelişenlerde adalimumab kombine (n=9) ve tosilizumab monoterapisi (n=4) en yaygın biyolojik ilaçlardı.

Sonuç: Etanersept, adalimumab ve tosilizumab JİA tedavisinde etkili ve güvenli biyolojik ilaçlardır. Biyolojik ilaçların zamanında ve uygun hastalarda kombine veya monoterapi olarak seçilmesi, JİA'nın erken ve geç sekellerini önlemede etkilidir.

Anahtar Sözcükler: Biyolojikler, Hastalık modifiye edici anti-romatizmal ilaçlar, Juvenil idiyopatik artrit

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common cause of chronic inflammatory arthritis seen under the age of 16 and can cause severe disability. The incidence of the disease has been reported as 19.8 per 100,000 children (1, 2).

Currently, treatment strategies of JIA includes non-steroidal anti-inflammatory drugs (NSAIDs) as the first-line therapy. Corticosteroids and conventional disease-modifying anti-rheumatic drugs (cDMARDs) are required in nonresponsive cases. Treatment response may vary according to the subtype of the disease and accompanying complications.

The introduction of biologic drugs have revolutionized improving patients' quality of life as they reduces the Juvenile Arthritis Disease Activity Score (JADAS) and the number of joints affected. In addition, with the widespread use of biologics in the treatment of JIA, the dose of other conventional medications used together with biologics drugs can be reduced and the harmful effects of those with long-term side effects such as corticosteroids can be prevented (3, 4).

In Türkiye, etanercept (ETA), adalimumab (ADA), and tocilizumab (TCZ) are the main licensed biologics and recommended for children with systemic and non-systemic JIA subtypes in case of inadequate response or intolerance to DMARDs. Previous reports have revealed that 80% of children with JIA are treated by combination of biologics and methotrexate rather than replacing methotrexate with biologics (3,5,6). According to the literature, depending on the molecular structure of biologic drugs, JIA subtype or complications of the disease such as uveitis, monotherapy of biologics or combination with DMARDs can be preferred. However, centers continue to determine their preferences according to their own experiences and the rules of healthcare systems of countries (7, 8).

The aim of this observational study is to evaluate the efficacy of combination versus mono-therapy of biologics licensed in Türkiye for children with non-systemic JIA.

MATERIALS and METHODS

The study was approved by the Istanbul Faculty of Medicine, Clinical Research Ethics Committee (17.05.2022-871316). All patients and their parents gave written informed consent in accordance with the Declaration of Helsinki.

The medical charts of 205 patients treated with biologic agents out of 856 JIA patients with JIA were reviewed retrospectively. Patients who were followed-up between January 2019 and January 2023 enrolled to the study according to being eligible for the following criteria: 1) Meeting the International Association of Rheumatology Societies (ILAR) criteria for JIA, 2) No history of comorbid rheumatologic disease, 3) Negative scanning results for tuberculosis, and 4) Absence of a systemic symptom leading to systemic JIA (sJIA). Because sJIA is the only subtype recognized as an autoinflammatory disease rather than an autoimmune disease, it is distinguished from other subtypes by its more severe disease course, different and challenging treatment strategies. For these reasons, patients with a diagnosis of sJIA, which is often considered a separate disease, were excluded from this study. 5) Patients receiving abatacept, etc., which are relatively less preferred in the treatment of JIA, were excluded from the study.

Demographic and clinical features, laboratory variables, family history, received medications, and periodic outcome measures were collected retrospectively.

Intermittent recording of the juvenile arthritis disease activity score-27 (JADAS-27) assessed the efficacy of the main treatment (9). The Wallace criteria was accepted for the definition of inactive disease. Components of this criteria were as follows: No active arthritis or uveitis; a physician's global assessment indicating no disease activity; no fever, rash, serositis, splenomegaly, or lymphadenopathy; and no elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level (10).

The cohort was divided into 2 groups: Those who received biologic monotherapy (ETA, ADA, or TCZ) and those who received biologic and cDMARDs combination therapy. All groups involve patients who had the respective treatments for at least 3 months and follow-up of >6 months. Firstly, the main comparison was between TCZ and tumor necrosis factor (TNF)-alpha inhibitors (TNFi) used as monotherapy or in combination with a DMARD. Secondly, patients received TNFi were categorised by concomitant conventional (methotrexate, sulfasalazine, or leflunomide) therapy. The period of drug

exposure terminated either at the recorded discontinuation date, the final available visit, or when switching to another DMARD or biologic, whichever took place earlier.

Reasons for discontinuation of treatment or resumption of the discontinued drug were recorded. The corticosteroid sparing effect of the main treatment was determined by recording discontinuation data and the duration of steroid use.

Statistical Analysis

Descriptive statistics were expressed as frequencies or percentages for categorical variables. Continuous variables are stated with mean±standard deviation (SD) or median with interquartile range (IQR) according to the normality of the data. To compare groups Pearson's chi-squared test, Fisher's exact test, independent-samples t-test and Mann– Whitney U test were used depending on type of the data processed. The p-values less than 0.05 were considered as statistically significant. Statistical analyses were performed utilizing SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Overall, 205 of 856 children with non-systemic JIA aged 2 to 18 years and receiving biologic drugs were enrolled to the study. The male to female ratio of the cohort was almost equal. Oligoarticular was the most common subtype of JIA. Patient characteristics and the distribution of patients by JIA subtype according to ILAR criteria is summarized in Table I.

As a complication of JIA, uveitis developed in 24 patients during the course of the disease. Eight (3.9%) of them were diagnosed incidentally at the onset of JIA, and 16 (7.8%) of them were diagnosed with uveitis during periodic visits for JIA. ADA alone or in combination with methotrexate was preferred for all patients with uveitis at the onset of the disease. ADA combined therapy (n=9) was the most common, and TCZ monotherapy (n=4) was the second most common in those who developed uveitis during follow-up.

Majority (n=128, 62.4%) of the group received biologic drugs as monotherapy, while the remaining third (n=77, 37.6%) used a combination of biologic and cDMARD. Nearly half of the group (57.1%) were treated with ETA in the entire cohort and ETA monotherapy was the most commonly used drug among all JIA subtypes except juvenile psoriatic arthritis. ADA combination therapy was prescribed in most of children with juvenile psoriatic arthritis. At the last visit, while 20 (9.8%) patients had discontinued biologic therapy, 185 (90.2%) were still under biologic therapy. Among the whole group baseline disease characteristics (median VAS, PGA, CRP, and ESR values) were slightly more severe in children received either TCZ mono or TCZ combination therapy than the other groups. Comparison of the groups by index drugs at study enrolment can be seen table II.

Fifteen patients were under systemic corticosteroid therapy at the time of biologic initiation and at the last visit one case with juvenile psoriatic arthritis required corticosteroid therapy with adalimumab and leflunomide.

Methotrexate was the major cDMARD most preferred when combination of biologics was required. In TCZ combination group leflunomide and methotrexate were prescribed at similar rates.

When comparing the medications for discontinuation, the most common cause was achieving inactive disease (19, 9.3%) for

Table I: The demographic features and the distribution of disease subgroups

Features	
Gender (female/male)*	101/104 (49.3 / 50.7)
Age, years†	14.2 (10.6-18)
Age at diagnosis, years†	9 (4.2-12.6)
The delay in diagnosis, months†	2.4 (1-8.5)
Follow-up period, years†	3.8 (2-6.3)
Age at biologic onset, years†	11 (6.7-14.5)
The disease duration at initiation of biologic therapy, months†	23.7 (10.5-40.5)
The duration of biologic therapy usage, months†	20.7 (10.2-40.7)
Family history of rheumatologic disease*	
Rheumatoid arthritis	21 (10.2)
Psoriazis	5 (2.4)
JIA	3 (1.4)
JIA subtypes	
Oligoarticular JIA*	115 (56.1)
Persistent*	107 (52.2)
Extended*	8 (3.9)
RF-negative polyarticular JIA*	35 (17.1)
Enthesitis-related arthritis JIA*	35 (17.1)
Psoriatic arthritis*	11 (5.4)
RF-positive polyarticular JIA*	9 (4.4)

:** *n(%),* **†:** *(median, IQR),* ***JIA: *juvenile idiopathic arthritis,* ***RF:*** *rheumatoid factor,* ***IQR:*** *interquartile range*

Table II: Comparison of the groups by index drugs at study enrolment

	Index drug at study enrolment					
	ETA mono (n=81)	**ETA combo (n=36)**	**ADA mono (n=31)**	**ADA combo (n=35)**	**TCZ mono (n=16)**	**TCZ combo (n=6)**
JIA category*						
Oligoarticular						
Persistent	46 (43)	22 (20.6)	16 (15)	17 (15.9)	5 (4.7)	1 (0.9)
Extended	3 (37.5)	2 (25)	0	1 (12.5)	2 (25)	0
RF-negative polyarticular	16 (45.7)	2 (5.7)	4 (11.4)	4 (11.4)	6 (17.1)	3 (8.6)
Enthesitis-related	11 (31.4)	7 (20)	8 (22.9)	7 (20)	1 (2.9)	1 (2.9)
Psoriatic	2 (18.2)	1 (9.1)	2 (18.2)	4 (36.4)	1 (9.1)	1 (9.1)
RF-positive polyarticular	3 (33.3)	2 (22.2)	1 (11.1)	2 (22.2)	1 (11.1)	0
ANA positivity*	28 (41.2)	11 (34.4)	12 (41.4)	17 (54.8)	3 (20)	2 (33.3)
Seropositivity (RF and/or anti-CCP)*	3 (3.7)	3 (8.3)	2 (6.4)	3 (8.5)	1 (6.2)	1 (16.6)
HLA-B27 positivity*	6 (7.4)	3 (8.3)	5 (16)	4 (11.4)	0	1 (16.6)
ESR (mm/hour)†	10 (23)	8 (19)	18 (19)	10 (24)	20 (40)	7.5 (30)
CRP (mg/L)†	1.7 (6.4)	1.8 (6.4)	3.7 (18.5)	2 (13.6)	7.4 (57.5)	6.6 (23.1)
Patient/parent global assessment†	6 (2)	5 (3)	6 (3)	5 (4)	8 (3)	6.5 (3)
Physician global assessment†	5 (2)	5 (2)	5 (3)	5 (3)	6 (3)	6 (5)
Concomitant cDMARD*						
MTX		27 (75)		27 (77.1)		3 (50)
SAZ	-	5 (13.8)	-	3 (8.5)	-	0
LEF		2 (5.5)		4 (11.4)		3 (50)

***:** *n(%),* **†:** *median (IQR),* ***DMARDs:** Disease-modifying antirheumatic drugs, **JIA:** juvenile idiopathic arthritis, **RF:** rheumatoid factor, **IQR:** interquartile range, **ETA:** Etanercept, **ADA:** Adalimumab, **TCZ:** Tocilizumab, **ANA:** Antinuclear antibody, **CCP:** Cyclic citrullinated peptide, **HLA:** Human leukocyte antigen, **ESR:** Erythrocyte sedimentation rate, **CRP:** C-reactive protein, **MTX**: Methotrexate, **SAZ:** Sulfasalizne, **LEF:** Leflunomide*

all groups. TCZ-mono (31.3%) and ETA-monotherapy (11.1%) groups were the two in which treatments were stopped most frequently due to inactive disease. Patients' failure to comply with follow-up periods and drug administration (10, 4.9%) were among the other reasons for discontinuation. Discontinuation was usually noted for adverse events in children treated with TCZ mono- and ADA combination therapy (4% vs. 3%). Shorter disease duration, RF- polyarticular JIA subtype, concomitant steroid treatment and higher JADAS-27 levels at baseline were significantly associated with greater risk of discontinuation.

Ineffectiveness (29, 14.1%) and uveitis (8, 3.9%) were the leading causes of switching biologic therapies. TCZ mono- (7%, 43.8%) and combination (5%, 83.3%) treatments were switched significantly more often than other groups due to poor efficacy (p=0.01).

At the first year evaluation, significant improvement in disease activity parameters was observed in patients in all groups. Remission in JADAS-27 was achieved in 65%, 61.2%, and 50.7% in the ETA, ADA, and TCZ combination cohorts, respectively. In monotherapy cohorts JADAS-27 remission rates were 60%, 58%, and 41.7% for ETA, ADA, and TCZ groups, respectively. Although less improvement was observed in the JADAS-27 scores of the patients who received TCZ monotherapy, there was no significant difference between groups (p=0.7).

DISCUSSION

This is a comprehensive retrospective observational study comparing ETA, ADA, and TCZ, which are currently used in the treatment of JIA. Previous reports are mostly associated with effectiveness of cDMARD monotherapy and combination of them with biologic medications in JIA. Our study stands out for comprehensively comparing the use of the most commonly used biologics as monotherapy and in combination with cDMARDs.

Within a span of decade, biologic medications became widespread in treatment of JIA. In cases where cDMARDs are insufficient to provide remission, bDMARDs are preferred as both mono- and combination therapy. In clinical practice, TNFi such as ETA are the first-line biologics that are the most frequently used in JIA (11,12). Data of the German registry regarding ETA use in JIA revealed that ETA is safe and effective for treatment of JIA (13). A prospective, open-label, multicenter registry evaluating the long-term safety and efficacy of ETA mono- or in combination with methotrexate reported that all these drugs might be preferred in JIA because they are effective (14). In another study comparing combination versus monotherapy of ETA, cases receiving combination therapy with methotrexate showed greater ACR Pedi 70 response at the end of the first year, than patients receiving ETA alone (62% vs 45%; $p < 0.010$) (15). In the present study, there was no significant

difference between ETA mono- and combination therapies in terms of median JADAS-27 scores, PGA, or VAS. Patients who received ETA and methotrexate concomitantly and ETA monotherapy showed significant improvement in JADAS-27 scores at the end of first year ($p<0.001$). However, there is still insufficient evidence about the accurate time of discontinuation of ETA in JIA.

ADA, a fully human monoclonal anti-TNFi, is accepted for being effective and safe in the treatment of JIA. In German BIKER registry, long-term data was reported regarding ADA versus ADA and methotrexate for JIA management. In patients with ADA monotherapy, ERA ($p = 0.004$) was documented more often. No differences in treatment response or adherence to treatment between groups were declared (16). ADA is frequently preferred in JIA associated uveitis. A study determining the role of ADA in the treatment of JIA-uveitis in children showed that the combination of ADA with methotrexate is safe and effective (17). ADA was the second most common bDMARD prescribed in all groups of our cohort following ETA. It was the most important choice in our cases that develop uveitis during the course of the disease and at the onset of the disease. All uveitis subjects were in remission under ADA mono- and combination therapy in our study at the first year of biologic initiation.

It is known that the neutralizing antibody against bDMARDs may have a negative effect on the functional drug level indirectly by increasing drug clearance through the formation of immune complexes (18, 19). Secondary failure and adverse events of bDMARDs can be related to the anti-drug antibodies. ETA is a non-immunogenic anti-TNFi. Although antibodies are produced in the immune system against ETA, they are not neutralizing and do not affect drug efficacy or safety. However, the use of ADA carries the risk of developing anti-drug antibodies leading to neutralization and related effects (19). Studies have shown that methotrexate has a protective effect on the formation of anti-drug antibodies, which is a major challenge especially for the use of anti-TNFi. In our study, methotrexate was the most common cDMARD prescribed for combination with biologics. Although we did not evaluate anti-drug antibody levels, our study shows that the combination of bDMARDS with methotrexate is as effective as monotherapy and is often preferred by rheumatologists in clinical practice.

TCZ is a recombinant humanized monoclonal antibody whose mechanism of action is an interleukin-6 receptor antagonist. It has been frequently prescribed for the treatment of systemic and polyarticular forms of JIA (20). Moreover, recent literature provides promising outcomes regarding the efficacy of intravenous and subcutaneous TCZ in the management of JIA associated uveitis (21, 22). In previous studies, in contrast with anti-TNFi, no improvement in outcome has been observed by combining TCZ with cDMARD. So, TCZ was identified as being highly effective as a monotherapy (6, 23). In this study, TCZ mono- and combination therapies were most commonly preferred for the treatment of RF-polyarticular JIA and JIA-associated uveitis, and were effective and well tolerated. Because our data included a small number of cases receiving TCZ, it was difficult to make comparisons for the TCZ alone and the combined treatment groups.

This study also has some limitations. Clinical data were collected retrospectively from patient records and this was not an inception cohort. At the same time, it was very difficult to make an optimal evaluation because there was not a homogeneous number of patients in all groups. However, such data are valuable for clinicians as they are real-life data.

In conclusion, bDMARDs, which can be used in combination or alone, are critically important drugs in the treatment of JIA. Considering their cost-effective properties, choosing them as combined or monotherapy timely is effective in preventing early and late sequelae of JIA. Prospective, controlled randomized studies based on real-life data with larger patient groups on these drugs would be of great value.

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Awareness of Endoscopy Nurses About Anesthesia Management in the Pediatric Gastrointestinal Endoscopy Unit; A Survey Study

Pediatrik Gastrointestinal Endoskopi Ünitesinde Çalışan Endoskopi Hemşirelerinin Anestezi Yönetimi Konusundaki Farkındalığı; Bir Anket Çalışması

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ABSTRACT

Objective: We aimed to determine the awareness of endoscopy nurses working in pediatric gastrointestinal endoscopy units on anesthesia applications they encountered in clinical practice.

Material and Methods: Endoscopy nurses that work in pediatric gastrointestinal endoscopy units in Turkey were invited to this study. Among the 33 questions, seven were in the section questioning the endoscopy nurses' demographics and occupational working time (Section 1). In the other part, 16 questions were asked about what should be known during the anesthesia administration and recovery process (Section 2). The remaining 10 questions were statements that determined the level of awareness regarding anesthesia practices in pediatric gastrointestinal endoscopy units. (Section 3).

Results: The total of 80 participants' mean age was 40.3±9.1 years, and 91.3% were female. Seventy seven percent of the participants replied "yes" to the statement of "The endoscopy nurse should be able to evaluate possible complications by considering the American Society of Anesthesiology (ASA) classification of the patients." Thirty five percent of participants knew about the Modified Aldrete Scoring System. The mean age, total working time, and working time in the pediatric gastrointestinal endoscopy unit were found to be lower in those who agreed with the statement "Patients can be discharged with their parents/caregiver without any scoring or criteria evaluation two hours after the procedure".

Conclusion: In conclusion, although the pediatric endoscopy nurse is not responsible for anesthesia management practices, their awareness and knowledge about anesthesia management play a key role for the endoscopy and the anesthesia team in ensuring patient safety.

Key Words: Anesthesia, Children, Endoscopy, Nurse

ÖZ

Amaç: Bu çalışmada, endoskopi hemşirelerinin klinik uygulamada karşılaştıkları anestezi uygulamaları konusundaki farkındalık düzeylerini belirlemeyi amaçladık.

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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 the Second Ethics Committee of Ankara Bilkent City Hospital. (02.06.2021/E2-21-472).

Contribution of the Authors / Yazarların katkısı*: *SEVER F: 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. 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. ***HIZLI Ş:*** 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, Reviewing the article before submission scientifically besides spelling and grammar.

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Gereç ve Yöntemler: Bu çalışmaya Türkiye'deki pediatrik gastrointestinal endoskopi ünitelerinde çalışan endoskopi hemşireleri davet edildi. Toplam 33 sorudan oluşan anketin yedi sorusu, endoskopi hemşirelerinin demografik bilgilerini ve mesleki çalışma sürelerini sorgulayan bölümde yer aldı (Bölüm 1). Diğer bölümde, anestezi uygulaması ve postoperatif derlenme süreci sırasında bilinmesi gereken konularla ilgili 16 soru soruldu (Bölüm 2). Kalan on soru, pediatrik gastrointestinal endoskopi ünitelerinde anestezi uygulamaları konusundaki farkındalık düzeyini belirleyen ifadelerdi (Bölüm 3).

Bulgular: Toplam 80 katılımcının yaş ortalaması 40.3±9.1 yıl olup %91.3'ü kadındı. Katılımcıların %77'si, "Endoskopi hemşiresi, hastaların Amerikan Anestezi Topluluğu (ASA) sınıflamasını dikkate alarak olası komplikasyonları değerlendirebilmelidir" ifadesine "evet" yanıtını verdi. Katılımcıların %35'i Modifiye Aldrete Skoru Sistemi hakkında bilgi sahibiydi. Ortalama yaş, toplam çalışma süresi ve pediatrik gastrointestinal endoskopi ünitesindeki çalışma süresi, "Hastalar endoskopi ünitesindeki işleminden iki saat sonra ebeveyn/yardımcılarıyla herhangi bir skor veya kriter değerlendirmesi olmaksızın taburcu edilebilir" ifadesine katılanlarda daha düşük bulundu.

Sonuç: Pediatrik endoskopi hemşiresi anestezi yönetimi uygulamalarından sorumlu olmasa da, anestezi yönetimi hakkındaki edineceği bilgi ve farkındalık ile hastanın güvenliğini sağlamak adına endoskopi ve anestezi ekibi için kilit bir rol oynayacaktır.

Anahtar Sözcükler: Anestezi, Çocuk, Endoskopi, Hemşire

INTRODUCTION

Pediatric gastrointestinal (GI) endoscopy is a common procedure increasingly used to investigate and diagnose gastrointestinal disorders in children (1,2). Adequate sedation for all types of endoscopy procedures is a necessity in pediatric patients for diagnostic and therapeutic procedures (3,4).

The awareness of the endoscopy nurses working in pediatric endoscopy units about the application of anesthesia is important in terms of nursing service. The Society of Gastroenterology Nurses and Associates (SGNA) recommends that a registered nurse (RN) be present to assist the endoscopy team during the administration of anesthesia to increase patient safety (5). It has been stated that having an RN in the room with the anesthesiologist increases patient safety (6). Few studies on the clinical experiences and awareness levels of nurses collaborating with anesthesia teams in pediatric endoscopy units have been published.

In this survey study, we aimed to determine the awareness of endoscopy nurses working in pediatric endoscopy units on anesthesia applications they encountered in clinical practice.

MATERIALS and METHODS

Following approval of Ankara Bilkent City Hospital Second Ethical committee (02.06.2021/E2-21-472), this survey study was conducted in the Pediatric Gastroenterology, Hepatology and Nutrition Clinic of Ankara Bilkent City Hospital between 1-30 June 2021. The study included endoscopy nurses working in pediatric GI endoscopy units in Turkey, and contact was made with the endoscopy units of fifty hospitals in Turkey that perform pediatric GI endoscopic procedures for this survey study. Pediatric endoscopy nurses who were not working in the pediatric GI endoscopy units and those who were unwilling to participate in the survey were excluded from the study. The questionnaires were delivered to the voluntarily participating nurses via hospital visits or electronic media. The questionnaire consisted of 33 items evaluating demographic data and nursing practice of pediatric endoscopy nurses about sedation in their units. Among the 33 questions, seven were in the section questioning the endoscopy nurses' demographics and occupational working time (Section 1). In the other part, even if the endoscopy nurse is not a practitioner, 16 questions were asked about what should be known during the anesthesia administration and recovery process (Section 2). The remaining ten questions were statements that determined the level of awareness regarding anesthesia practices in pediatric GI endoscopy units. (Section 3). This study was registered with ClinicalTrials.gov (ref. NCT 05032443).

Statistical analysis

Data were analyzed using the IBM SPSS 25.0 (Armonk, NY, IBM Corp.) statistical software package. In addition to descriptive statistical methods (frequency, percentage, mean, standard deviation, median, minimum and maximum), the Pearson Chi-square or Fisher's exact test was used to compare qualitative variables. When differences among more than two groups were determined, pairwise comparisons were made to identify the source of the difference. Conformity of data with normal distribution was evaluated with the Kolmogorov-Smirnow test, skewness-kurtosis, and graphical methods (histogram, Q-Q Plot, Stem and Leaf, and Boxplot). The One-Way ANOVA test evaluated the quantitative variables with a normal distribution. When a difference was determined, the posthoc Tukey HSD test was used to identify the source of the difference. The level of statistical significance was considered $p<0.050$. The power of the study was determined using the G*Power 3.1.9.7 statistical software package. The study's power was 89% when n=80, groups=3, $\alpha=0.05$, and effect size (f) was 0.4.

RESULTS

Eighty volunteers from forty endoscopy units that met our study's criteria replied to our questionnaire, covering over 85% of Turkey in general. Medical centers performing endoscopies in the operating room and not in a separate endoscopy unit were excluded from the study.

Table I: Demographic Characteristics of Participants

	Mean ± SD (n=80)
Age (Years)*	40.3 ± 8.1
Gender†	
Female	73 (91.25)
Male	7 (8.75)
The Institution Employed†	
City Hospital	27 (33.75)
University Hospital	26 (32.5)
Training and Research Hospital	18 (22.5)
Private Hospital	9 (11.25)
TotalEmployment Duration (months)*	209.2 ± 111
3-12 Months†	3 (3.75)
>12 Months†	77 (96.25)
Duration of Employment in the pediatric GI endoscopy unit (months)*	79.6 ± 74.1
3-12 Months†	16 (20)
>12 Months†	64 (80)
Is the pediatric GI endoscopy unit Located as a Separate Unit in Your Current Institution?†	
Yes	48 (60)
No	32 (40)

***:** *Mean ± SD,* **†:** *n (%),* ***GI:** Gastrointestinal*

Table II: Comparison of demographic characteristics of participants in question about time of discharge

	The patients can be discharged accompanied by their parents/patient caregiver two hours after the procedure without any scoring or criteria assessment in pediatric GI endoscopy units performing sedation."			p*
	I agree (n=29)	I am indecisive (n=33)	I disagree (n=18)	
Age (years)†	36.1 ± 8.8	42.6 ± 6.8	42.9 ± 6.3	0.001 *
Gender‡				
Female§	25 (86.2)	30 (90.9)	18 (100)	0.248 **
Male§	4 (13.79)	3 (9.1)	-	
The Institution Employed§				
University Hospital	8 (27.58)	15 (45.45)	3 (16.66)	0.279 ***
Research and Training Hospital	8 (27.58)	5 (15.15)	5 (27.77)	
City Hospital	11 (37.93)	10 (30.3)	6 (33.33)	
Private Hospital	2 (6.89)	3 (9.1)	4 (22.22)	
Total Employment Duration‡†	156.8 ± 104.8	251.1 ± 100.5	216.7 ± 109.4	0.003 *
3-12 (months)§	2 (6.89)	1 (3)	--	0.296 **
>12 (months)§	27 (93.11)	32 (97)	18 (100)	
Duration of Employment in the Present Institution†	53.0 ± 50.9	91.7 ± 81.2	100.3 ± 83.3	0.047 *
3-12 (months)§	7 (24.14)	8 (24.24)	1 (5.5)	0.220 ***
>12 (months)§	22 (75.86)	25 (75.76)	17 (94.45)	
Is the pediatric GI endoscopy unit located as a separate unit in your current institution?				
Yes§	16 (55.17)	22 (66.7)	10 (55.6)	0.594 ***

:** *One-Way Anova Test (Mean ± SD),* **†:** *Mean ± SD,* **‡:** *The comparison was made by combining the groups "I am indecisive" and "I disagree",* **§:** *n (%),:** *Fisher's exact test (n (%)),* ***:** *Pearson Chi-Square Test (n (%)),* ***GI:** Gastrointestinal*

Section 1: Questions involving demographic characteristics

The participants' mean age was 40.3±9.1 years, and 91.3% were female. The education level of most of them (81.2%) was bachelor's degree or higher. Almost 34% of them worked in a City Hospital, 32.5% in a University Hospital, 22.5%in a Training and Research Hospital, and 11.3%in a Private Hospital. Twenty percent of the nurses worked in a pediatric GI endoscopy unit for less than 12 months. Sixty percent of the nurses noted their pediatric GI endoscopy unit was located as separate units from the operating room. The remaining participants expressed that pediatric endoscopic procedures had been performed in the adult endoscopy unit. Demographic data are outlined in Table I.

Section 2: Questions about knowledge of pediatric endoscopy nurses for anesthesia management and recovery process

In this section, for the question "Does the endoscopy nurse have an obligation to inform the patient and parents that the procedure will be performed under anesthesia?", Forty seven percent of the participants expressed that such an obligation was not present. The ratio of participants stating that checking and recording the patient's preprocedural vital signs is unnecessary was 41.3%. The rate of those who did not think that it was necessary to inform the patient/parent and stated that the patient's vital signs did not need to be taken before the procedure was found to be statistically significantly higher in those with a working time of > 12 months in the pediatric GI endoscopy unit (p=0.044, and p=0.027, respectively). Seventy seven percent of the participants replied "yes" to the statement of "The endoscopy nurse should be able to evaluate possible complications by considering the American Society of Anesthesiologists (ASA) classification of the patients." Thirty five percent of participants knew about the Modified Aldrete Scoring system; 75% of these nurses stated that the patients' sedation scores were evaluated and recorded in the recovery room. In the recovery room, 61.3% of the participants expressed that they evaluated their patients with a sedation scoring system and recorded the postprocedural results. Regarding the question of "Had you received training for pre and post-anesthesia nursing services before you started working in the pediatric GI endoscopy unit?" only 38.8% of the participants answered as "yes." This study found that a higher ratio of the participants who answered "yes" to this question was knowledgeable of and used the Modified Aldrete Scoring System (7). Also, these participants recorded the results, evaluated probable complications and considering the patients' ASA classification (p=0.014, 0.046, and p=0.002, respectively).

Section 3: Questions to evaluate participants' awareness

The third section of the survey involved ten statements to evaluate participants' awareness, which were replied as "I agree," "I am indecisive," and "I disagree." Eighty two percent of the participants expressed that they agreed with the statement "Anesthesia should be administered in all patients in pediatric GI endoscopy units." The ratio of participants thinking that an anesthesiologist should perform anesthesia applications in these units was 96.3%. The mean age, total working time, and working time in the pediatric GI endoscopy unit were found to be lower in those who agreed with the statement "Patients can be discharged with their parents/caregiver without any scoring or criteria evaluation two hours after the procedure" compared to those who answered "I am indecisive" and "I disagree" and this result was statistically significant. (p=0.001, p=0.003, and p=0.047, respectively-the mean age, total working time, and working time in the pediatric GI endoscopy unit) (Table II).

No statistically significant differences were observed among participants' responses to the questions in this section pertaining to educational status, employing institution, and durations of employment (p>0.050).

DISCUSSIONS

Pediatric endoscopic gastrointestinal procedures are performed in pediatric GI endoscopy units with deep sedation or general anesthesia (8). In our pediatric GI endoscopy unit approximately 2200 procedures are performed annually. Due to the substantial volume of procedures involved, we believe that endoscopy nurses should possess awareness regarding anesthetic procedures and management. Enhanced knowledge among endoscopy nurses could contribute to an improved patient safety monitoring process. The endoscopy nurses participating in this study are not included in the anesthesia team, but the procedure is performed by anesthesia to every pediatric patient they encounter. The duties and responsibilities of the endoscopy nurse include maintenance and cleaning of endoscopic accessories, documenting/labeling of pathology samples, assisting the endoscopist, etc (9,10). Furthermore, alongside these duties, we posit that the endoscopy nurses working in the pediatric GI endoscopy units have critical role in preoperatively reviewing documentation before the procedure (eg, signed consent), informing the patient and the parent that the procedure will be performed under anesthesia, monitoring the vital signs of the patients in the postanesthetic period, along with using a sedation scale to guide practice, understand potential postoperative complications, and ensuring that patients are discharged according to discharge criteria. In a survey study conducted with responses from 65 endoscopy units, it was stated that endoscopy nurses had additional responsibilities such as checking consents before the procedures and completing discharge instructions after discussing with the endoscopist (6). Endoscopy nurse should make sure the physician (endoscopist, surgeon, anesthesia provider) did the right thing during the consent process (ie, the patient knows who is doing the procedure, what the procedure is, its risks and benefits, etc).

Invasive gastrointestinal endoscopic procedures should be performed under anesthesia in pediatric patients. Preoperative evaluation and consent forms should be obtained, documented, and placed into the patient's chart to determine the pre-anesthesia risk classification in patients undergoing sedation and for preoperative review by the physicians and the endoscopy nurse (11). In our research, approximately fifty percent of the participants held the perspective that endoscopic procedures should not be conducted in the absence of anesthesia consent, while the remaining fifty percent exhibited uncertainty or indicated that the procedure could proceed without explicit anesthesia consent. This situation indicates a significant deficiency in the legal requirements and oversight pertaining to anesthesia consent and the registration system. Moreover, a slightly lesser percentage, just under 50%, of endoscopy nurses have expressed that there is no necessity

to inform or educate patients or their family members about the endoscopic procedure that is to be performed under anesthesia. In recent a study, it was reported that patients who gave informed consent for endoscopy were better informed by nurses about the procedure (12). Informing the patients and parents also with the endoscopy nurse is very valuable and alleviates the workload of the whole team.

Most of our patients in our clinic are ASA 1 or 2, although patients with ASA 3 or 4 could be having a band ligation due to esophageal varices or a percutaneous endoscopic gastrostomy. The risk of a development of a postoperative complication is higher in patients with ASA 3 or 4 (13-16). Potential complication developments should be kept in mind during the procedure as well as during recovery and nursing applications should be planned. Patients and family members should be informed about potential complications such as nausea and vomiting, hypo-hypertension, desaturation, respiratory failure, respiratory arrest, cardiac arrest, etc. that may occur in the recovery department after anesthesia, and the patients should be monitored and followed closely. Our investigation has unveiled that just under 50% of endoscopy nurses held the perspective that their patients were not susceptible to risks during this specific period. While it is true that the anesthesia team assumes responsibility for the postoperative recovery room in our nation, it remains of paramount importance for pediatric endoscopy nurses to possess an acute awareness of potential complication development during this critical juncture, directly correlating with the assurance of patient safety. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) suggests at least one nurse is necessary to monitor patients in the post-anesthetic recovery room until the patient is stabilized, to provide adequate space for privacy, and to evaluate side effects related to endoscopic procedures (17). Unlike the operating room environment, there is not always a fixed nurse in the recovery room in endoscopy units. In this case, the endoscopy nurse can undertake the task of patient follow-up. We think that the endoscopy nurse should be trained with this awareness.

Scoring systems should be included in quality standarts to maintain patient safety in the post-anesthesia recovery unit such as the Modified Aldrete Scoring System (7). Modified Aldrete Scoring System is routinely used for patient follow-up in the post-anesthesia period in our hospital. In this study, the ratio of participants who thought that sedation scoring and hospital discharge criteria should be applied in the postop period in patients who underwent anesthesia was 81.3%. Sixty five percent of the participants stated they were unaware of the Modified Aldrete Scoring system but only 61.3% of the participants expressed that a sedation scoring system was used and documented in the post-anesthesia recovery room of the pediatric GI endoscopy unit where they worked. In summary, the majority of pediatric endoscopy nurses stated that a scoring system was necessary to determine the sedation level of patients in the recovery room, yet there was a knowledge deficit. On the other hand, their knowledge deficiency related to the scoring system used and its content was determined.

Discharge criteria should also be assessed prior to patient release. In this survey, 36% of participants indicated that an anesthetized patient could be discharged from the recovery unit after two hours, regardless of whether they met any scoring criteria. This finding is unsurprising given that fewer than 40% of pediatric endoscopy nurses reported receiving training upon initial employment. Establishing guidelines for competent and standardized nursing practices within pediatric GI endoscopy units is imperative.

Limitation

According to the current laws in our country, sedation and/or general anesthesia applications are only performed by an anesthesiologist. At least one endoscopy nurse assists the gastroenterologist during the procedure. The endoscopy nurses in our study group had never applied sedation and were in the position of external observers in this regard. Therefore, there was no similar survey study conducted with endoscopy nurses in the same situation in the literature, and we had difficulty in making comparison of findings.

CONCLUSION

The endoscopy nurse is a valuable staff member. The endoscopy nurses' knowledge and expertise can be utilized in more important ways both for the endoscopy and the anesthesia team for ensuring patient safety. In conclusion, our study results emphasizes that; although the pediatric endoscopy nurse is not responsible for anesthesia management practices, they should be aware of anesthesia management before, during, and after the procedure. In addition each institution needs to create it's own internal policies and procedures based on guidelines.

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Hyponatremia and Its Effects on Prognosis in A Tertiary Pediatric Intensive Care Unit

Hiponatremi ve Etkilerinin Üçüncü Basamak Pediatri Yoğun Bakım Hastalarında Değerlendirilmesi

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ABSTRACT

Objective: Hyponatremia is accepted as an independent risk factor in pediatric intensive care units. Many comorbidities such as infectious diseases, central nervous system problems and incorrect replacement solutions are blamed in the pathogenesis of hyponatremia. In this study, we aimed to investigate the etiology and prognosis of hyponatremia in a tertiary pediatric intensive care unit.

Material and Methods: We retrospectively analyzed 342 pediatric patients hospitalized in the pediatric intensive care unit of Kayseri City Hospital. Patients with a serum sodium level below 135 mEq/L were considered hyponatremia. Critical hyponatremia was defined as serum sodium less than 125 mEq/L. Data on length of hospital stay, mortality and comorbidities were analyzed.

Results: The data of 342 pediatric patients were evaluated. The male/female ratio was 192/150 (56.1% vs. 43.9%). The mean age of the patients was 41.78 months (±57.7) (min-max 1-212). Twenty-five patients had serum sodium below 125 mEq/L, which could be defined as critical hyponatremia. The mean sodium was 131 (±3.3) mEq/L (min-max: 109-134). The levels of serum creatinine significantly differs before and after treatment ($p<0.001$). The mean resolution time of hyponatremia was 2.1 days (±1.29) (min-max: 1-12) Serum sodium was 125 mEq/L and below in a total of 23 patients. The mortality rate was 23% in all patients at the end of their follow-up.

Conclusion: Hyponatremia is a common problem in pediatric intensive care unit. Especially severe hyponatremia can be related with increased mortality. Close monitoring of sodium is needed in especially trauma patients and central pathologies as well as bronchopneumonia patients.

Key Words: Child, Hyponatremia, Sodium

ÖZ

Amaç: Çocuk yoğun bakım ünitelerinde hiponatremi bağımsız bir risk faktörü olarak kabul edilmektedir. Hiponatreminin patogenezinde enfeksiyon hastalıkları, merkezi sinir sistemi sorunları ve yanlış replasman sıvılarının kullanımı gibi birçok faktör bulunmaktadır. Bu çalışmada üçüncü basamak bir pediatrik yoğun bakım ünitesinde hiponatreminin etiyolojisini ve prognozunu araştırmayı amaçladık.

Gereç ve Yöntemler: Kayseri Şehir Hastanesi 3. Basamak Çocuk Yoğun Bakım Ünitesi'nde yatan 342 çocuk hastayı retrospektif olarak inceledik. Serum sodyum düzeyi 135 mEq/L'nin altında olan hastalar hiponatremi olarak kabul edildi.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was carried out with the approval of Kayseri City Hospital Ethics Committee, dated 18.03.2021 and project number 332.

Contribution of the Authors / Yazarların katkısı: AKSOY OY: Is major contributor in writing the manuscript. Was involved in the design of the study, and analysis of the data. All authors read and approved the final manuscript. ***KESKİN Ş and MOD:*** Were involved in the collection of the data. ***DURSUN A, ÖZSOYLU S, ÇELİK B, DOĞAN M:*** Were involved in the clinical follow-up of the patients. ***BAŞTUĞ F:*** Was involved in the design of the study, and analysis of the data. All authors read and approved the final manuscript.

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Kritik hiponatremi, serum sodyumunun 125 mEq/L'den az olması olarak tanımlandı. Hastanede kalış süresi, mortalite ve komorbiditelere ilişkin veriler analiz edildi.

Bulgular: 342 pediatrik hastanın verileri değerlendirildi. Erkek/kadın oranı 192/150 (%56.1'e karşı %43.9)'du. Hastaların yaş ortalaması 41.78 ay (±57.7) (min-maks 1-212)'di. 25 hastada kritik hiponatremi olarak tanımlanabilecek 125 mEq/L'nin altında serum sodyumu vardı. Ortalama sodyum 131 (±3.3) mEq/L (min-maks: 109-134)'dü. Serum kreatinin düzeyleri tedavi öncesi ve tedavi sonrası anlamlı farklılık gösterdi (p<0.001). Hiponatreminin ortalama düzelme süresi 2.1 gün (±1.29) (min-maks: 1-12)'di. Toplam 23 hastada serum sodyumu 125 mEq/L ve altındaydı. Takipleri sonunda tüm hastalarda mortalite oranı %23'tü.

Sonuç: Hiponatremi çocuk yoğun bakım ünitelerinde sık görülen bir sorundur. Özellikle ciddi hiponatremi artmış mortalite ile ilişkilendirilebilir. Akciğer enfeksiyonlarında, travma hastalarında ve santral sinir sistemi patolojilerinde serum sodyumunun yakından izlenmesi gerekmektedir.

Anahtar Sözcükler: Çocuk, Hiponatremi, Sodyum

INTRODUCTION

Hyponatremia is defined as having a serum sodium level below 135 mEq/L, and a serum level below 125 mEq/L is generally considered serious. It is one of the most common electrolyte disorders, and is associated with increased morbidity and mortality especially in critically ill patients. Underlying medical conditions may worsen the prognosis (1).

Hyponatremia is accepted as an independent risk factor in pediatric intensive care units. Many factors such as dehydration, gastrointestinal losses, central nervous system pathologies, acute or chronic kidney injury, syndrome of inappropriate antidiuretic hormone secretion (SIADH) and incorrect replacement solutions are blamed in the pathogenesis of hyponatremia (2).

Hyponatremia may cause cerebral edema and neurologic symptoms. If correction is made too quickly, osmotic demyelination syndrome (formerly known as central pontine myelinolysis) will occur. Fluid resuscitation is very important in critically ill patients, as sudden increases or decreases in serum sodium levels can cause severe changes in the central nervous system (3).

Early diagnosis and prompt treatment are essential to prevent morbidity and mortality. In order to treat hyponatremia properly, the patient's volume status, etiology of hyponatremia and underlying problems should be known. In this study, we aimed to investigate the etiology and prognosis of hyponatremia in a tertiary pediatric intensive care unit.

MATERIALS and METHODS

Study Population and Collection of The Data

We retrospectively evaluated pediatric patients with hyponatremia in the tertiary pediatric intensive care unit at Kayseri City Hospital between June 2018 and December 2020. Hyponatremia was accepted as having serum sodium less than 135 mEq/L. Critical hyponatremia was defined as having serum sodium less than 125 mEq/L. Resolution of hyponatremia was defined as a rise in serum sodium above 135 mEq/L. If there was hyponatremia in repeated hospitalizations, the last hospitalization of the patient was included. The available data of 342 patients were recoded. Data on primary diagnoses, treatment options, length of hospital stay, and mortality were analyzed. Annual mortality rate of the tertiary pediatric intensive care unit was obtained from the hospital's records.

Statistical analysis

Analysis of data from 342 pediatric patients with hyponatremia performed with IBM SPSS for Windows version 17. The normality of numerical variable distributions was evaluated with the Shapiro-Wilk test. Student's t-test was performed in normally distributed data. The Mann-Whitney U test was used to compare data with skewed distributions. Frequency and percentages were used as descriptive values in categorical data. Arithmetic mean ± standard deviation was used for normally distributed data, median and interquartile range were used for non-normally distributed data. p-value <0.050 was considered significant.

The study was carried out with the approval of Kayseri City Hospital Ethics Committee, dated 18.03.2021 and project number 332.

RESULTS

We reviewed the records of 342 patients. The male/female ratio was 192/150 (56.1% vs. 43.9%). The mean age of the patients was 41.78 months (±57.7) (min-max 1-212). Twenty-five patients had serum sodium below 125 mEq/L, which could be defined as critical hyponatremia. The mean sodium was 131 (±3.3) mEq/L (min-max: 109-134). The lowest serum sodium was 109 mEq/L. The mean post-treatment serum sodium was 137.9 (±2.8) (min-max: 127-163). There was a significant difference between serum sodium levels before and after treatment (p<0.001).

At the time of detection of hyponatremia, the mean serum creatinine was 0.56 mg/dL (±1.07) (min-max: 0.02-13.15). After treatment, mean serum creatinine was 0.45 mg/dL (±0.6) (min-max: 0.01-4.82). The levels of serum creatinine significantly differs before and after treatment (p<0.001).The highest serum creatinine value of 13.15 mg/dL was found in a patient with chronic kidney disease due to bilateral kidney dysplasia, the

patient underwent peritoneal dialysis and the control serum creatinine value was 3.3 mg/dL. The lowest serum sodium (109 mEq/L) in this cohort belonged to the same patient.

The mean serum potassium level at the time of hyponatremia is 4.3 mEq/L (Min-max: 2.3-8.2). Twenty-four patients had hyperkalemia (serum potassium was above 5.5 mEq/L).

Severe hyperkalemia (serum potassium ≥6.5 mEq/L) was present in 4 patients. One of these patients had pseudohypoaldosteronism, serum sodium was 126 mEq/L and serum potassium was 6.8 mEq/L. Electrolyte values returned to normal in the follow-up with treatment. Two patients had acute renal failure and one patient was being followed up after sudden arrest.

There were 4 patients with severe hypokalemia (serum potassium ≤2.5 mEq/L). Two of them had been diagnosed with cystic fibrosis, one with neurometabolic disease, and one with maple syrup urine disease.

There were 5 patients with serum chloride below 80 mEq/L. Two of these patients had cystic fibrosis (patients with severe hypokalemia), one had undergone necrotizing enterocolitis operation and the other had surgery for perforated appendicitis. The other was the chronic kidney disease patient requiring dialysis, who had the lowest sodium and highest creatinine values in the cohort. When the urine densities were examined, there were 10 patients with a urine density of 1040 and above. Five had trauma. Fluid restriction was performed in two of these ten patients, considering SIADH in the follow-up.

When the primary diseases of the patients and the underlying diagnoses were evaluated, it was documented that the most common ones are infectious diseases (bronchopneumonia in 60 patients, bronchiolitis in 25 patients, acute gastroenteritis in 16 patients, etc.). Neurological problems are the next common one. Cerebral palsy was seen in 12 patients, epilepsy in 13 patients, and status epilepticus in another 12 patients. Eighteen patients had an established diagnosis of hereditary and metabolic disease. Intoxication was the reason of hospitalization in 16 patients, whereas 14 patients had trauma. 16 patients with diabetic ketoacidosis had hyponatremia. Cardiac problems were seen in 12 patients. Hematologic malignancies were the reason of hospitalization in 11 patients. Kidney diseases were the primary diagnosis in 10 patients including 5 hemolytic uremic syndrome patients (Table I).

The reasons for admission to the pediatric intensive care unit were respiratory distress in 142 patients (41.5%), shock in 42 patients (12.3%), severe dehydration in 24 patients (7%), acute kidney injury in 8 patients (2.4%), and trauma in 14 patients (4.1%) (Table II). In most of the cases, the exact cause of hyponatremia cannot be detected from the medical records of the patients. Hyponatremia was associated with dehydration in 69 patients (20.2%), acute kidney injury in 22 patients (6.4%), SIADH in 10 patients (2.9%), central salt wasting in 3 patients

Table I: Diagnoses of the patients

Disease	Patient number (n)
Infectious diseases	
Bronchopneumonia	60
Bronchiolitis	25
Acute gastroenteritis	16
Rash&erythema	3
Sepsis	2
Meningitis	1
Meningoencephalitis	1
Neurological diseases	
Cerebral palsy	12
Epilepsy	13
Status epilepticus	12
Spinal muscular atrophy	2
Hypoxic ischemic encephalopathy	3
Guillain-Barre Syndrome	1
Kidney diseases	
aHUS	1
HUS	4
Acute renal failure	2
Chronic kidney disease	2
Posterior urethral valve	1
Hematological malignancies	
ALL	9
AML	2
Diabetic ketoacidosis	16
Cardiac issues	
Aortic coarctation	2
Dilated cardiomyopathy	4
Fallot tetralogy	3
Arrythmia	3
Post-arrest	7
Trauma	14
Intoxication	16
Hereditary and Metabolic Diseases	18
Other	89
Total	342

aHUS: *Atypical hemolytic uremic syndrome,* ***HUS:*** *Hemolytic uremic syndrome,* ***ALL:*** *Acute lymphoblastic leukemia,* ***AML:*** *Acute myeloid leukemia*

(0.9%), and incorrect replacement solution in one patient (Table III). Five among ten patients with SIADH had bronchiolitis/bronchopneumonia, and two patients had neurologic problems.

The treatment options were intravenous electrolyte replacement in 313 patients (91.5%), fluid restriction in 10 patients (with SIADH) (2.9%), oral sodium chloride administration in 19 patients (5.6%). Electrolyte replacement were made according to the patients' clinical status and age. Deficit treatments were administered when necessary.

The mean resolution time of hyponatremia was 2.1 days (±1.29) (min-max: 1-12). The median recovery time from hyponatremia was 2 days. The mean resolution time of hyponatremia in patients with serum sodium above 130 was 1.9 (±1.1) (min-max: 1-9) days. Recovery time of hyponatremia was significantly

Table II: The reason of the need for pediatric intensive care unit hospitalization

Cause	Frequency	Percent
Respiratory problems	142	41.5%
Shock	42	12.3%
Severe dehydration	24	7%
Acute kidney injury	8	2.4%
Trauma	14	4.1%
Others	112	32.7%
Total	342	100.0

Table III: Detected cause of hyponatremia

Cause	Frequency	Percent
None	237	69.3
Dehydration	69	20.2
Acute kidney injury	22	6.4
SIADH	10	2.9
Central salt loss	3	0.9
Wrong solution	1	0.3
Total	342	100.0

shorter in patients with serum sodium closer to normal range (p<0.010).

Serum sodium was 125 mEq/L and below in a total of 23 patients. Mortality was recorded in 4 of 23 patients whose serum sodium level was below 125 mEq/L. When we excluded other obvious causes of mortality (such as serious neurometabolic diseases, post-arrest patients, severe cardiac anomalies), there was a correlation between low serum sodium and increased mortality risk (p=0.050). Recovery time was longer in patients with critical hyponatremia (p<0.001). No correlation was found between serum sodium level below 125 mEq/L and length of hospital stay.

Average length of intensive care unit stay is 30.3 days (±65) (min-max: 1-480). The median hospital stay was 7 days. There were 13 patients with a hospital stay of 180 days or more. Mortality was recorded in 6 of them at follow-up. Mortality was found to be higher in patients with a long hospital stay and this was statistically significant. The mean sodium level of these patients was 132 mEq/L, and two had chronic lung disease (one with tracheostomy), one had spinal muscular atrophy, one had hydrocephalus, one had epilepsy, two had a diagnosed syndromic condition, and two had hypoxic ischemic encephalopathy. Most of the patients with long hospitalizations had genetic, neurological or metabolic disease.

It was recorded that 81 of 342 patients died due to various reasons at the end of the hospitalization period. The mortality rate was determined as 23% in patients who were found to have hyponatremia during one period of intensive care hospitalization. According to the data obtained from the medical records of the hospital, the annual mortality rate in the tertiary intensive care unit at the time of the study was 60 in 766 patients and the mortality rate was 8%.The mortality rate in patients with hyponatremia during intensive care hospitalization was found to be significantly higher than general intensive care mortality.

Table IV: Treatment choices for hyponatremia

Treatment	Frequency	Percent
Intravenous electrolyte replacement	313	91.5
Fluid restriction	10	2.9
Oral sodium chloride administration	19	5.6
Total	342	100.0

A correlation could not be established between the admission sodium value, the total length of hospital stay and the rate of mortality (p>0.050). However, there was a relationship between critical hyponatremia (serum sodium ≤125mEq/L) and mortality (p=0.050). It was noted that critical hyponatremia prolonged the recovery day of hyponatremia but did not affect the total hospitalization time.

DISCUSSION

Hyponatremia is a common problem in pediatric intensive care units, and is associated with increased mortality (4,5). Although the main outcome of prognosis can be attributed to the primary disease; hyponatremia and electrolyte imbalances may contribute to increased mortality (1).

In a study, it was stated that 32.4% of patients with serum electrolyte disorders in the pediatric emergency department needed an admission to the pediatric intensive care unit (6). Fluid resuscitation is very important in critically ill patients because an abrupt increase or decrease in serum sodium levels can cause severe changes in the central nervous system (2).

Children are more prone to hyponatremia, especially when hospitalized for respiratory and central nervous system infections such as pneumonia or meningitis. Lung diseases such as bronchopneumonia and bronchiolitis can lead to SIADH by unclear mechanisms, and nervous system abnormalities can cause antidiuretic hormone secretion from the pituitary. SIADH is also more common in hospitalized, post-operative patients due to administration of hypotonic fluids, medications, and the body's response to stress (7,8). Ten patients with SIADH in our cohort, responded well to fluid restriction. Tolvaptan may be indicated in cases which do not respond to fluid restriction (9).

Hyponatremia is a common finding in patients with intracranial problems such as trauma or hemorrhage and is associated with increased mortality, and length of stay in intensive care units. Its diagnosis and treatment are essential for prompt neurocritical care (3). In addition to trauma patients and central pathologies, sodium should be closely monitored, especially in patients

with bronchopneumonia (10,11). Luu et al. (12) concluded that hyponatremia may worsen the prognosis in children with bronchiolitis in the pediatric intensive care unit.

The most common cause of serum sodium abnormality in neurocritical patients is SIADH, a clinical entity that can be underestimated and therefore poorly treated, early diagnosis is essential to prevent complications (1). In our cohort most of the patients with hyponatremia had bronchopneumonia/bronchiolitis (24.8%). Besides, half of ten patients with SIADH had bronchopneumonia/bronchiolitis.

Acute gastrointestinal losses due to acute gastroenteritis, as well as diarrhea and vomiting, are another important cause of hyponatremia and one of the leading diagnoses in our cohort. Dehydration can occur not only from gastrointestinal losses, but also from failure of oral nutrition in a severely injured or sick child. When we tried to figure out the cause of hyponatremia, we found dehydration in about 20% of the patients.

Most of the patients in our study had serious chronic comorbidities including metabolic diseases and neurological diseases. This might explain the high mortality rate in our cohort. Among 16 patients with diabetic ketoacidosis hyponatremia was detected. Since hyperglycemia and hypertriglyceridemia can cause pseudohyponatremia, this may be a false low sodium result.

Kidney diseases can cause hyponatremia. Especially in dialysis patients, fluid overload may occur and dilutional hyponatremia may be encountered. Additionally, pseudohypoaldosteronism is a serious problem, manifested by low serum sodium and high serum potassium despite normal to high aldosterone levels. One of the important causes of pseudohypoaldosteronism is congenital anomalies of the kidney and urinary tract such as hydronephrosis.

In addition to hyponatremia, if the patient has hypokalemia and hypochloremia with metabolic alkalosis the physician should be careful about renal tubular diseases such as Bartter's Disease, or a case of pseudobartter, which is usually seen in cystic fibrosis. Two of our patients with hypokalemia and hypochloremia accompanying hyponatremia had cystic fibrosis.

The significant decrease in the serum creatinine value of our patients can be explained by the fact that some of the patients were dehydrated at admission and had prerenal acute renal failure that subsequently recovered rapidly with volume replacement.

Serum electrolyte abnormalities were demonstrated to be associated with longer stay in pediatric intensive care unit, however we could not show such correlation (13). We showed that mortality rate was higher in patients with a long hospital stay.

Mortality of hyponatremia in pediatric intensive care unit is reported up to 37.7% (14). In our study, we found the mortality rate to be 23% in hyponatremia patients hospitalized in the tertiary pediatric intensive care unit, and this mortality rate is obviously high when compared to the annual death rate of the pediatric intensive care unit.

The limitations of our study arise from its retrospective nature. Since we selected the study group only as hyponatremic patients with available data in the medical records, we could not give an exact prevalence of hyponatremia in general hospitalizations in pediatric intensive care unit. Also we could not determine which infusion solutions were given to the patients in the first applications. Furthermore, the true prevalence of hyponatremia in such critically ill patients is difficult to document, as most of the patients receive intravenous infusion (especially saline) in the emergency room or inpatient clinic before being admitted to intensive care (15,16). In most of the patients, information about the cause of hyponatremia could not be obtained from the system notes and laboratory records. Keeping proper records is also very important.

CONCLUSIONS

The patients with hyponatremia needs a cautious approach. Etiology and exact causes should be documented in order to ameliorate the electrolyte imbalances, in especially hyponatremia. Since hyponatremia is associated with increased mortality, prompt treatment is important. The treatment should be planned carefully and precisely in order to prevent central nervous system complications. Further prospective studies were necessary to document the effects of sodium imbalances in critically ill children.

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A Case of DIHSS/DRESS Syndrome-Related Acute Hepatic Failure

Akut Hepatik Yetmezliğin Eşlik Ettiği DiHSS/ DRESS Sendromu Olgusu

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ABSTRACT

'Drug Induced Hypersensitivity Syndrome' (DiHS) or 'Drug Rash with Eosinophilia and Systemic Symptoms' (DRESS) syndrome is a life threatening, delayed type drug hypersensitivity reaction. This syndrome is characterized by fever, skin rash, lymphadenopathy, hematological abnormalities and visceral involvement and liver is the most frequently involved visceral organ. Liver involvement is mostly presented as acute anicteric hepatitis with elevated liver enzymes. Rarely, it can be presented as cholestasis which indicates a worse prognosis. In this article, a case of valproic acid induced-DRESS syndrome who presented with acute hepatic failure is presented. Diagnosis of DRESS syndrome may delay due to the long interval between drug intake and the onset of symptoms. The variety of symptoms can also be challenging. Early diagnosis is important in terms of reducing morbidity and mortality.

Key Words: Drug Induced Hypersensitivity Syndrome, DRESS, Drug allergy, Hepatic failure

ÖZ

"Drug Induced Hypersensitivity Syndrome" (DIHS) ya da diğer adı ile "Drug Rash with Eosinophilia and Systemic Symptoms" (DRESS) sendromu, yaşamı tehdit edebilen gecikmiş tip ilaç hipersensitivite reaksiyonudur. Ateş, deri döküntüsü, lenfadenopati, hematolojik anormallikler ve çoklu organ tutulumu ile karakterizedir. Karaciğer en sık tutulan organ olup, çoğunlukla karaciğer enzim yüksekliği ve akut anikterik hepatit şeklinde karşımıza çıkmaktadır. Çok daha nadir olarak kolestaz eşlik edebilir ve bu durum kötü prognoza işaret etmektedir. Bu yazıda valproik asit ilişkili hepatik yetmezlik ve ağır kolestazın görüldüğü DRESS sendromlu bir olgu sunulmuştur. İlaç kullanımı ile semptomların başlangıcı arasındaki sürenin uzun olması ve semptomların çeşitliliği nedeniyle DRESS sendromunun tanısında gecikmeler olabilmektedir. Hastalığın erken tanınması, morbidite ve mortaliteyi azaltmak açısından oldukça önem taşımaktadır.

Anahtar Sözcükler: Drug Induced Hypersensitivity Syndrome, DRESS, İlaç alerjisi, Hepatik yetmezlik

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INTRODUCTION

Drug-induced hypersensitivity syndrome (DIHS), also known as drug rash with Eosinophilia and Systemic Symptoms (DRESS), is a delayed type of drug-sensitive reaction that may be life-threatening, first identified by Bocquet et al. (1) in 1996. Diagnostic criteria were then determined by the Japanese drug study group and the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) respectively (2,3). Total score according to the RegiSCAR scoring system <2 points: not DRESS, 2-3 points: likely DRESS; 4-5 points: possible DRESS and >5 points as certain DRESS (3).

The incidence of this picture, characterized by fever, skin rash, lymphadenopathy, hematological abnormalities (eosinophilia, atypical lymphocytes), multi-organ involvement is estimated to be between 1/1000 and 1/10.000, although the exact incidence is unknown (4). It is more rare in childhood than in the adult age group. In etiology, aromatic anticonvulsants such as phenitoin, phenobarbital, carbamazepine and lamotrigin, sulfonamides, allopurinol, dapson, gold salts, and minocycline are among the most commonly considered drugs responsible (4,5). Although the pathogenesis is not fully understood, the deficiency of the epoxy hydroxylase enzyme, which eliminates the toxins that are the destruction products of aromatic anticonvulsants, is one of the most commonly considered mechanisms responsible (6). The genetic predisposition to some HLA alleles has been suggested, and studies are ongoing. In addition, the reactivation of especially the human herpes virus (HHV) 6, Ebstein Barr Virus (EBV), cytomegalovirus (CMV), and Herpesviruses like HHV 7 is also thought to play a role in DRESS syndrome (6,7)

The most frequently accompanying organ involvement in DRESS is liver, with most patients experiencing anicteric hepatitis with elevated serum alanine aminotransferase (ALT) enzyme (4). Much more rarely, it can become icteric and accompany cholestasis, and this often indicates a worse prognosis(4). A DRESS syndrome case is presented who with acute hepatic insufficiency and has been successfully treated, a very heavy picture to raise awareness about this severe drug reaction, which is thought to have been less diagnosed because it did not come to mind.

CASE REPORT

An 11-year-old male patient applied to our hospitals emergency clinic with fever lasting for 3 days and with a widespread rash all over the body. In the patient's history, he was diagnosed with epilepsy 36 days ago and started valproic acid therapy, and a week ago he was again medical exam and examined in the centre for fever complaints, levatirecetam was replaced with the valproate acid treatment due to elevated aspartate aminotransferase (AST) and alanine aminotránsferaze (ALT) values.

In the physical examination that took place at our hospital, the overall condition was good, he was conscious, his body temperature was 38.7°C, his breathing rate was 23/min, his heart rate was 108/min and his blood pressure was 100/60 mmHg. In the physical examination, there were maculopapular rashes that were to be visible on both sides of cheeks, widespread throughout the body, some with a tendency to merge, including icteric sclerosis. the liver was about two centimeters below the costa (Figure 1A). Other system inspections are normal.

In laboratory studies; haemoglobin 10.8 g/dL, leukocyte count 11.4x103/µL (peripheral proliferation; 60% partial, 30% lymphocytes, 9% monocytes and 1% eosinophilic), thrombocyt count 143x103/µL, AST 1372 U/L (<51) ALT 782 U/ L (<37), lactate dehydrogenase (LDH) 785 IU/ L(<332), gamma glutamil transferase (GGT) 224 U/ l(<61), total bilirubin 4.46 mg/ dL(<1.2), direct bilirubine 4.3 mg/dl(<0.3), INR 1.28 (0.8-1.2) alkaline phosphatase (ALP) 417 U/l (129-417), fibrinogen 78 mg/dl (180-350), C-reactive protein (CRP) 3 mg/L(<5) were found. The serologies of EBV, CMV, Parvovirus, Rubella, Toxoplasma, anti-HIV, Hepatitis A, B and C were negative. Reproduction was not detected in blood and urine cultures taken under sterile conditions. In the patient's abdomen ultrasound examination, the liver's craniocodular length was estimated to be 139 mm above the upper limit of normal for age, while the dorsal craniocaudal length increased by 141 mm for age. The lumen of the gallbladder was observed in contractual appearance, its thickness increased, and an effusion of 4.5 cm was detected in the pelvis.

The patient was initiated intravenous fluid therapy, sefotaxim, pantoprozole, and continued oral levetiracetam therapy. Due to high liver function tests, intravenous infusion of n-acetylsysteine (NAC) was initiated to benefit from its cytoprotective effect. In patients with hyperbilirubinemia dominated by direct bilirubin and elevated GGT, oral ursodeoxycholic acid (UDKA) was initiated due to cholestasis. Treatment with 2 mg/kg methyl prednisolone was initiated after a skin biopsy with DRESS pre-diagnosis. After three days of systemic steroid therapy, the patient with fever and rashes decreased in AST, ALT, GGT and bilirubin, but received 5 mg of vitamin K for 2 days because of INR: 1. 52. On the 7th day of service recovery, a patient with recurrent fever, developing consciousness fainting and elevated liver enzymes (AST: 866 U/L, ALT: 694 U/l, total bilirubin:16.06 mg/ dL, direct bilirubine: 14.04 mg/dL, INR: 1.8) was monitored in pediatric intensive care unit for acute hepatic insufficiency. In addition to intravenous therapy with 2 mg/kg/day of methyl prednisolone, 2 g/day intravenous immunglobulin (IVIG) (with a duration of 2 days) and once fresh frozen plasma of 15 cc/ kg/dose were given. After two days of intensive care follow-up, the patient's overall condition improved, fever decreased, rashes reduced, and liver enzymes gradually declined, and the INR returned to normal. For cardiovascular involvement troponin T (tropT) was 0.006 ng/mL (<0.014), and creatine kinase (CKMB) was 23 U/l (<247). No pathology was detected

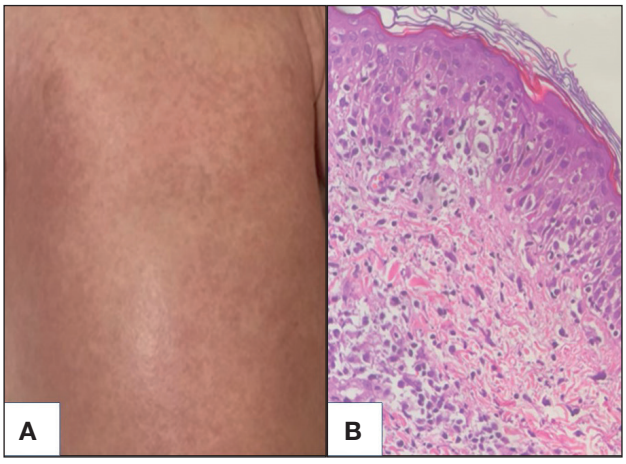

Figure 1: (A) Maculopapular rashes, commonly found in the patient's body, with a tendency to merge. **(B)** The hematoxylene-eosin-painted section of the skin punch biopsy shows focal spongiosis, lymphocyte exocytosis and basal vacuoleal changes in the epidermis.

in echocardiography. The differential diagnosis of alpha-1 antitripsin, alphafetoprotein, hepatic autoimmune antibodies, seruloplasmine was examined and the results showed no pathology. Microscopic examinations of the punch biopsy sample of the hematoxylene-eosin-painted cuts from the inguinal rash region showed focal spongiosis in the epidermis, lymphocyte exocytosis, and basal vacuoleal changes. Perivascular mononuclear inflammation infiltration observed in superficial and medium dermis (Figure 1B). The lymphocytes subgroups were CD45 %95, CD3+CD4+ %36.2, CD3 +CD8+ %48.6, CD3-CD16/56+ %1.4, CD19+ %11.2 and CD4/CD8 ratio 0.7. The number of CD8+ cytotoxic T lymphocytes was also increased. The patient's RegiSCAR score was 4 (possible DRESS) with fever, rash, biopsy DRESS-compatible findings, liver involvement more than 15 days of rash and excluding other findings.

The patient with a decrease in liver enzymes and a return to normal INR was discontinued with NAC infusion after 6 days On the 15th day of hospitalization, the patient, who was generally in good condition, with no fever and acute phase reagents negative, was discontinued from the current antibiotics, with AST: 69 U/L ALT: 116 I/L GGT:264 IU/L INR:0.84 on the 20th day, and with direct bilirubin reduced to 3.7 mg/dL The patient was discharged with a plan to discontinue systemic steroid therapy at 6 weeks by reducing the dosage from 2 mg/kg/day. The patient's skin appearances began to decrease from the 12th day of hospitalization, and was completely recovered in control a month later. It was not done because the patient's provocation test with the drug was contraindicated. Skin patch tests and intradermal tests could not be done because the family didn't approve because of the severity of the clinical picture.

The patient's ursodeoxycholic acid treatment was discontinued in the second month of follow-up, when liver enzymes returned to normal. The patient, who had been monitored with intermittent poliklinical controls for a year, had no recurrence of rash, and liver enzymes were observed within the normal range, with anti-nuclear antibodies (ANA), celiac and autoantibodies of the thyroid negative for autoimmune diseases.

DISCUSSION

DIHSS/DRESS is a very serious and life-threatening late-type systemic drug hypersensitivity reaction. Clinical symptoms usually occur after 2-6 weeks of starting use of the drug, and the rash is usually in the form of maculopapular erythematosus skin rash, and sometimes the lesions can progress to vesicles, ulcers, atypical target lesions, purpura, sterile small pustules, and even exfoliative dermatitis or erythrodermia (3,5). In our patient, the widespread, fusion-prone maculopapular rash appeared one month after starting valproic acid therapy. Diagnostic criteria of the Japan Allergy Association or RegiSCAR are widely used in DIHSS/DRESS diagnosis (3,4). In laboratory evidence, leukocytosis and eosinophilia are often present in patients, while the absence of eosinophilia does not rule out the diagnosis. Literature reports eosinophilia rates ranging from 60-70% in various studies (8). Even some patients, especially in the early stages, may experience leukopenia or lymphopenia (8). One or both CD4+ and CD8+ T cells have increased together, and CD19+ B cells and CD16-56+ NK cells are decreased. CD4+ T cells are high in the early stages, gradually decreasing, returning to normal after about 2 months, and their numbers correlate with the severity of the clinical symptoms (9). Again, the detection of CD4+ and CD8+ T lymphocytes in skin lesions reveals the role of these cells in the pathogenesis of the disease. Our patient was not diagnosed with eosiofilia at the time of diagnosis, but the lymphocytes subgroup analysis showed that CD8+T cells were high and NK cells low.

Fever accompanying skin signs, lymphadenopathy, flu-like symptoms, eosinophilia, and internal organ involvement such as hepatitis, myocarditis, pericardiitis, nephritis and colitis being seen in DIHSS/DRESS and the prognosis is usually determined by internal organ involvement (5,10). The most commonly involvement organ is the liver and is mostly in the form of acute anicteric hepatitis. When the picture becomes icteric and accompanied by cholestasis, this usually indicates a worse prognosis (4). Coagulopathy and sepsis associated with hepatic necrosis, which is primarily responsible for mortality in DIHS/DRESS, with mortality ranging from 5 to 10% (3,5,11). In our patient in addition to steroid therapy, IVIG has been given, predicting high mortality due to severe cholestasis and acute hepatic insufficiency. In literature, the widely accepted treatment for DIHS/DRESS is the discontinuation of the drug responsible and systemic corticosteroid therapy. Treatment with a minimum dose of 1 mg/kg of prednisolone equivalent to a steroid is recommended to be discontinued and reduced at 6-8 weeks after clinical remission (6). High doses (1gr/

kg) of IVIG for 2-5 days are recommended for patients who do not respond to steroid therapy, and therapies such as valgansiclovir or plasmaferese are indicated for patients with herpes virus reactivation (12). There is evidence that NAC treatment also prevents the progression of liver damage (13). The NAC was initiated early in order to benefit our patient from its cytoprotective effect.

With the development of fever, lymphadenopathy or atypical lymphocytosis, DRESS syndrome can be confused with acute viral infections or hematological malignancies. Reactivation of human immunodeficiency virus (HIV), Epstein Barr virus (EBV) and HHV-6 can occur as mononucleosis-like diseases along with rash and systemic symptoms. When it comes to liver involvement, viral serological tests should be performed for hepatotropic viruses such as hepatitis viruses and influenza. Peripheral spread should be carefully examined for hematological malignancies, and bone marrow should be assessed if suspected. For the distinctive diagnosis, it is important to have drug use in the story that may be responsible for DRESS.

The risk of life-threatening reactions in the long-term follow-up of patients requires that drug use and drug provocation tests, such as drugs responsible for the drug or cross-reaction aromatic anticonvulsants, should be avoided, and patients and their relatives should be informed in detail. If necessary, skin patch tests may be used to detect a suspect drug or find a safe alternative drug. (14). The skin patch test could not be carried out because the family did not approve because of the weight of the clinical Picture.

11.5% of patients with DRESS syndrome can develop long-term symptoms such as organ failure and autoimmune diseases autoimmune thyroid disease is most frequently in adolescents and kidney failure in the elderly (4). Long-term monitoring of patients is important for autoimmune diseases. Our patient's liver enzymes and kidney function tests, which have been monitored for a year with periodic poliklinical controls, have been observed within the normal range, and no autoantibody positive has been detected.

Clinical characteristics DRESS syndrome may be diagnosed with delays due to its wide range and the length of time between drug use and the onset of symptoms (6). Early detection of the disease, immediate discontinuation of the relevant drug or drugs, and initiation of necessary supportive therapies are essential for reducing morbidity and mortality.

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This is My COVID-19 History During Pregnancy and Breastfeeding Period: Maternal and Neonatal Outcomes

Gebelik ve Emzirme Dönemime Ait COVİD-19 Hikayem: Anne ve Yenidoğan Verileri

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ABSTRACT

The novel type coronoviruses cause the Coronovirus disease-19 as global health problem around the world since 2019. The number of pregnant women infected by new type of coronoviruses are on the rise.

COVID-19 infection in pregnancy ranges from asymptomatic infection to mild disease (no evidence of pneumonia or hypoxia) to moderate disease (viral pneumonia) until severe disease (severe pneumonia) and critical illness (acute respiratory distress syndrome, sepsis, septic shock, or complications such pulmonary embolism or acute coronary syndrome). But most pregnant women infected with SARS-CoV-2 are asymptomatic and most symptomatic women experience only mild or moderate cold/flu-like symptoms.

The effect of these viruses on the fetus, virus transmission from mother to baby and the protective role of antibodies are not clear yet. However, the majority of newborns were asymptomatic, tachypnea most likely secondary to transient tachypnea observed as the most common symptom.

Additionally, late complications after the Coronovirus disease-19 can be presented in some organs and/or systems like heart, brain, lung, gastrointestinal system.

Here described a case whose got Coronovirus disease-19 during third trimester of the pregnancy with transient and intermittant cardiac dysrhythmia after Coronovirus disease-19.

Key Words: Breastfeeding, Cardiac Dysrhythmia, COVID-19, Pregnancy

ÖZ

Yeni tip Koronovirus bağlı olan Koronovirus 19 hastalığı, 2019'dan beri tüm dünyanın sağlık problemi haline gelmiştir. Gebelik sürecinde de enfeksiyonun görülme sıklığı artmaktadır.

Gebelikte enfeksiyonun seyri asemptomatik, hafif bulgular (hipoksi ve pnömoni olmaksızın), viral pnömoni ve en nihayet ağır hastalık (akut solunumsal stres sendromu, sepsis, septik şok, pulmoner emboli veya akut koroner sendrom) şeklinde olmakla birlikte çoğunlukla asemptomatik bir seyir görülmektedir.

Enfekte anneden fetusa geçen virusun, fetusta nasıl bir etkiye yol açtığı ve antikorların koruyucu etkisi tam olarak netlik kazanmamıştır. Her ne kadar pek çok yenidoğan asemptomatik olsa da, yenidoğanın geçici takipnesi şeklinde bulgular görülebilmektedir.

Ek olarak, Koronovirus 19 hastalığının, kalp, beyin, akciğer, gastrointestinal sistem gibi bazı organ ve/veya sistemlere ait geç dönemde komplikasyonları da olabilmektedir.

Burada, gebeliğin son döneminde Koronovirus 19 hastalığı geçiren, sonrasında geçici ve aralıklı kardiyak disritmi bulguları olan bir vaka tartışılmıştır.

Anahtar Kelimeler: Emzirme, Kardiyak disritmi, COVİD-19, Gebelik

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INTRODUCTION

The novel type coronoviruses (SARS-COV-2) cause the Coronovirus disease-19 (COVID-19) as global health problem around the world since 2019 (1). The numbers of pregnant and breastfed women with COVID-19 are on the rise.

It has been suggested that the overall risk of vertical transmission and clinical symptoms in newborns of women with COVID-19 is small, although risks of neonatal complications are higher compared to infants of non-infected mothers (2,3). It is expected that infection by the SARS-CoV2 virus during pregnancy may increase the risk of maternal and fetal health complications and evolve to severe pneumonia, causing admissions to intensive care units (4).

Here, reported a COVID-19 experience during pregnancy and lactation period, without fetal complication and with possible late maternal complication.

CASE REPORT

A 42 years old healty woman had sore throat, malaise and severe myalgia in week 34 of pregnancy. Then she lived anosmia and ageusia. After five days she felt better, but anosmia and ageusia has continued three weeks. The patient had no other known health problems. One month later detection of the presence of anti-SARS-CoV-2 immunglobulin G (IgG) and immunglobulin A (IgA) in the serum were performed by ELISA method (EUROIMMUN, Germany). The levels of antibodies were positive, then the COVID-19 disease was confirmed. This test detected antibodies against the receptor binding domain of the SARS-CoV-2 spike protein. The results are given semiquantitave. The optical density reference value of the calibrator is 0.372, 0.302 for IgG and IgA respectively and the valid reference range >0.140 optical density. For the calculated value <0.8 negative, ≥0.8 to <1.1 limit value, ≥1.1 is considered positive. The specificities are 99.6% and 92.5% for IgG and IgA respectively. IgG and IgA were found positive, their semiquantitative values are 10.015 and 4.165 respectively.

At 39th week of pregnancy the delivery has occurred without complication. The baby was healty, her birth weight was 2820 gram. Umblical cord blood, placenta, amniotic fluid, nasopharyngeal swabs both of woman and her baby and colostrum were collected to analyse the SARS-COV-2 and antibodies. Breast milk sample was collected after the first lactation.

The samples were studied with the SARS-CoV-2 Real Time-q polimerase chain reaction (PCR) method. Nucleic acid isolation from nasopharyngeal swab and amniotic fluid samples was performed on the EZ1 Advanced (Qiagen, Germany) device using the EZ1® Virus Mini Kit v2.0 (Qiagen, Germany). Nucleic acid isolation from placenta tissue sample was performed using the QIAamp® Viral ribonucleic acid Mini Kit (Qiagen,Germany).

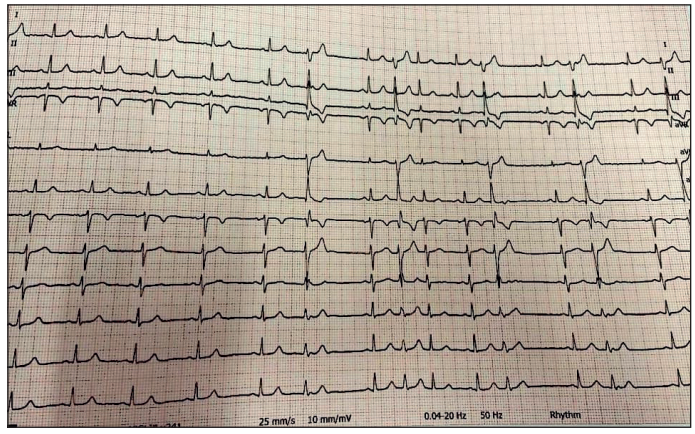

Figure 1: The electrocardiogram (ECG) showed ventricular extrasystoles. On ECG, the amplitudes and durations of P, QRS, T waves were normal.

The Real Time-qPCR was studied with the genesig® COVID-19 kit (PRIMER DESIGN, UK). The kit targets the ORF1ab gene region and the lower limit of detection is 0.33 copies/µl. The kit has been validated for the detection of SARS-CoV-2 human respiratory tract specimens. This was taken into account when evaluating the result of the placenta tissue sample and the amniotic fluid sample. The results were negative in all samples.

Antibodies were negative in samples other than breast milk. Breast milk IgG was negative, IgA was positive. IgA semiquantitative value was found 7.645, but control antibody tests result was negative one month later. PCR tests of nasopharyngeal swabs both of woman and her baby were ngative.

Anti-covid-IgG was still positive in the blood even a year later of COVID-19 without vaccination. Now the baby is 27 months old, she is healty. The antibody test was performed once after the birth when the baby was 12 months old and her control antibody was negative. Her growth parameters (weight, height, head circumference) and neurodevelopmental status are normal, according for her age.

Furthermore, the woman lived cardiac arrhythmia on second month of postpartum. The electrocardiogram showed ventricular extrasystoles (VES) (Figure). On ECG, the amplitudes and durations of P, QRS, T waves were normal. There were narrow VES examples with right axis. It was found 9773 VES on 24-hour cardiac rhythm holter monitorization. Hemogram, renal function tests, liver function tests, electrolytes, thyroid function tests, lipid profiles, cardiac biomarkers (troponine 1, creatinine kinase MB) were performed. The results were normal in range except lipid profiles. The levels of total cholesterol, low density lipoprotein were 255.163 miligram/deciliter respectively. Ecocardiography revealed no abnormality. The cardiologists adviced to start beta-blocker medicine. But the woman refused due to breastfeeding. She was feeling three days lasting palpitation once a week. She didn't feel arrhytmia for several. Control rhythm holter monitorization was normal. Her body mass index was 22.6 and she hadn't any other health problem.

DISCUSSION

Breastfeeding protects infants against infections mainly via secretory IgA antibodies. The anti-covid IgA was positive in the breastmilk when SARS-COV-2 PCR test of this case was negative. Control value was negative one month later in the breast milk even the anti-covid-IgG antibodies higly positive in the blood. The antibody levels are negative in umblical cord blood also. Although it is known that antibodies transmitted transplacental from the mother have protection in the baby up to six months, Both of these results showed that the effects of transplacental anti-Covid-IgG and breast milk anti-Covid-IgA antibodies did not last long. There is similar case in the litherature (5). Furthermore, both virus PCR and antibodies analyses are negative in other samples, like placenta, umlical cord blood. It is not yet known how SARS-CoV-2 shedding occurs in breast tissue, and whether this viral ribonucleic acid represents infectious viral particles. It seems that, this virus and/or its particles can arrive to the breast tissue, causes inflammation and anti-inflammatory effect, although it is transient response. There is limited information on potential transmission of the infection from mother to child, particularly through breast milk. Generally there were no detected SARS-COV-2 in breast milk of the cases informed in the litherature, like this case (6,7). The benefits of breastfeeding is known well, therefore breastfeeding should be advised always, also during COVID-19 (8).

SARS-CoV-2 infects individuals by binding the spike protein on angiotensin-2 converting enzymes receptors and using the proteolytic host serine protease, transmembrane protease serine 2, for entry into the cell. Multiple tissue types in the placenta, including placental syncytiotrophoblast and cytotrophoblast, express these proteins starting at 7 weeks gestation, allowing for SARS-CoV-2 placental infection. These receptors are not highly expressed in fetal lung tissue, and are not present in fetal brain tissue. Despite the presence of the cellular machinery to facilitate placental and transplacental infection, such infection is rare (9). Mechanisms that protect from invasion of fetal tissue by SARS-CoV-2 are yet to be elucidated. Neverthless, neonatal complications can occur such as admission to neonatal intensive care units, preterm birth, cesarean section and low birth weight due to exposure in the thirth trimester of pregnacy (10). Fortunately, the health situation of the current baby was still normal. Therefore, we concluded that, SARS-COV-2 hadn't teratogenic effect on this baby and there weren't any fetal complications. Of course, we need more reports about the possibility of teratogenic effect of SARS-COV-2.

It's well known that, immunglobuline G antibodies can be transferred from mother to baby. In a study conducted that 76% of neonates from seropositive mothers had antibodies against SARS-CoV-2 in cord blood, of whom 56% had a SARS-CoV-2 negative test result at birth (11). Although, a positive association between maternal IgG levels with neonatal IgG levels was observed in that study, the IgG level in this current baby was negative while the IgG level positive in the mother.

We know that myocardial injury is the most common reported cardiovascular event in patients with COVID-19 (12). In terms of arrhythmia, atrial arrhythmias and bradyarrhythmia are the most common in the acute setting of COVID-19, with an incidence of 13 % and 12.8 % respectively. Furthermore, the atrioventricular block has been observed with an incidence of 8.6%, while ventricular arrhythmia was reported in 5.9% of cases, being the less predominant form (13). There is limited data about the effect of SARS-COV-2 on myocardial injury in pregnant women. A study showed that, COVID-19 induced myocardial injury and left ventricular dysfunction in pregnant women (14). Hovewer, study pointed that, it is not clear if the rate of cardiac injury in the study population was due to COVID-19 or pregnancy itself or systemic illness. To our knowledge, there is no information about post-Covid cardiac complication depended on COVID-19 during pregnancy. Most likely the VES etiology of this case was idiopatic but it may depend on post-covid complication.

In summary, there is limited knowledges related to vertical transmission of SARS-CoV-2 via breastfeeding, and intrauterin infection with SARS-CoV-2. Fortunately this case didn't have any problem during delivery and the baby was healthy. This report describes exposed fetus by SARS-COV-2 during third trimester of pregnancy and the situation regarding immunity to this virus in human milk. The number of reports are on the rise and we are learning better the COVID-19, but many questions still require answers, as clinical outcomes of pregnant women with COVID-19 infection and long-term follow-up of the baby born to a mother with COVID-19 disease.

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