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

Original Articles / *Özgün Araştırmalar*

Case Reports / *Olgu Sunumları*

Volume / *Cilt* 17 Number / *Sayı* 2 March/*Mart* 2023

ANKARA BİLKENT ŞEHİR HASTANESİ ÇOCUK HASTANESİ

Turkish J Pediatr Dis
Türkiye Çocuk Hast Derg

ISSN 1307-4490
E-ISSN 2148-3566

Turkish Journal of Pediatric Disease

Türkiye Çocuk Hastalıkları Dergisi

Vol/*Cilt* 17 • Number/*Sayı* 2 • March/*Mart* 2023

https://dergipark.org.tr/tr/pub/tchd

ISSN: 1307-4490 E-ISSN 2148-3566
Vol./*Cilt*. 17, No.2, **March**/*Mart*, 2023

Turkish Journal of Pediatic Disease
Türkiye Çocuk Hastalıkları Dergisi

Official Journal of Ankara Bilkent City Hospital, Children's Hospital
Ankara Bilkent Şehir Hastanesi, Çocuk Hastanesi Yayını

ANKARA BİLKENT ŞEHİR HASTANESİ
ÇOCUK HASTANESİ

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Turkish Journal of Pediatic Disease
Türkiye Çocuk Hastalıkları Dergisi

ANKARA BİLKENT ŞEHİR HASTANESİ
ÇOCUK HASTANESİ

Owner on Behalf of the Ankara Bilkent City Hospital Children's Hospital *Ankara Bilkent Şehir Hastanesi Çocuk Hastanesi Adına Sahibi*	**Emrah ŞENEL** Ankara Bilkent City Hospital Children's Hospital, Turkey
Publishing Manager/*Yazı İşleri Müdürü*	**Metin YİĞİT** Ankara Bilkent City Hospital Children's Hospital, Turkey
Head Office/*Yönetim Ofisi*	Ankara Bilkent City Hospital Children's Hospital, Turkey Tel: +90 (312) 552 60 00 / 401506
Editor/*Editör*	**İbrahim İlker ÇETİN** Ankara Bilkent City Hospital Children's Hospital, Turkey
Press Office/*Baskı Ofisi*	Üçüncü Kitap© is a brand of Remres Research Advertising Consulting Software Trade Limited Company Kavaklıdere Mah. Güfte Cad. No:12/4 Kızılay, Çank aya, *Ankara*, Türkiye Tel: +90 (312) 419 01 53
Publication Type/*Yayın Türü*	Common periodical / Yaygın süreli Published four issues per year: January, March, May, July, September, November *Yılda altı kez yayımlanır: Ocak, Mart, Mayıs, Temmuz, Eylül, Kasım*
Publishing Frequency/*Yayın Aralığı*	Bimonthly / *2 Ayda Bir*
Publication Language/*Yayın Dili*	English
This journal printed on acid-free paper *Dergimiz asitsiz kağıda basılmaktadır*	Printing Date / *Basım Tarihi* : 22.03. 2023

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.

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Bu dergi geri dönüştürülebilir, imha etmek istediğinizde lütfen geri dönüşüm kutularına atınız.

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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.

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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.

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

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

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

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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

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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 $p<0.001$.

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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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Kaynak dergi ise;

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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.

Kaynak kitaptan bölüm ise;

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Baskı yılı:Bölümün ilk ve son sayfa numarası.

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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Sodium and Potassium Imbalances in the Pediatric Emergency Department: Single-Center Experience

Çocuk Acil Kliniğinde Sodyum ve Potasyum Bozuklukları: Tek Merkez Deneyimi

Dilek KONUKSEVER[1], Sevinc PUREN YUCEL[2]

[1]Department of Pediatrics, Ankara City Hospital Children Hospital, Bilkent, Ankara, Turkey
[2]Department of Biostatistics, Cukurova University, Adana, Turkey

ABSTRACT

Objective: In this study, it was aimed to examine the spectrum of sodium and potassium disorders in a pediatric emergency department.

Material and Methods: Our study was cross-sectional and single-center. Patients under the age of 18, who were admitted to the pediatric emergency clinic for any reason except trauma, between 2017 and 2020 and were found to have sodium and/or potassium disorders in their examinations were included in the study. The admission diagnoses and electrolyte levels of the patients were recorded. Electrolyte disturbances were grouped as mild, moderate, and severe.

Results: A total of 757 patients were included in the study. Of these, 358 (47.3%) were female and 399 (52.7%) were male. Single electrolyte disturbance was detected in 649 (85.8%) of the participants, while mixed type electrolyte disturbance was detected in 108 (14.2%). The most common electrolyte disturbance in the patients was hyponatremia (56%). This was followed by hyperkalemia (27.5%), hypokalemia (19.9%) and hypernatremia (10.8%). Acute gastroenteritis was the most common underlying disease in both the single and mixed electrolyte disorder groups.

Conclusion: Our study detects that the most common electrolyte disturbances in pediatric emergency services occur in patients with gastroenteritis. These disorders were often of mild severity. Mild electrolyte disturbances may be subclinical, so routine electrolyte measurement in the pediatric emergency room is important for early diagnosis.

Key Words: Electrolyte Imbalance, Pediatric Emergency, Potassium, Sodium

ÖZ

Amaç: Bu çalışmada çocuk acil servis başvurularında sodyum ve potasyum bozuklukları spektrumunun incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Araştırmamız kesitsel ve tek merkezlidir. 2017-2020 yılları arasında çocuk acil kliniğine herhangi bir nedenle başvurup tetkiklerinde sodyum ve/veya potasyum bozukluğu tespit edilen, 18 yaşından küçük hastalar çalışmaya dahil edildi. Hastaların başvuru tanıları ve elektrolit düzeyleri kaydedildi. Elektrolit bozuklukları hafif, orta ve şiddetli olarak gruplandırıldı.

Bulgular: Çalışmaya toplam 757 hasta dahil edildi. Bunların 358 (%47.3)'i kız ve 399 (%52.7)'u erkekti. Katılımcıların 649 (85.8%)'nda tekli elektrolit bozukluğu saptanırken 108 (%14.2)'nde mikst tipte elektrolit bozukluğu saptandı. Hastalarda

0000-0003-2334-9590 : KONUKSEVER D
0000-0002-5768-3549 : PUREN YUCEL S

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*: Ankara Training and Research Hospital Clinical Research Ethics Committee, 10 July 2020, No: E-20/305

***Contribution of the Authors / Yazarların katkısı*: KONUKSEVER D:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in 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.**PUREN YUCEL S:** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / *Atıf yazım şekli* : Konuksever D and Puren Yucel S. Sodium and Potassium Imbalances in the Pediatric Emergency Department: Single-Center Experience. Turkish J Pediatr Dis 2023;17:85-90.

Correspondence Address / Yazışma Adresi:
Dilek KONUKSEVER
Department of Pediatrics, Ankara City Hospital Children Hospital, Bilkent, Ankara, Turkey
E-posta: dilekkonuksever@hotmail.com

Received / Geliş tarihi : 13.03.2022
Accepted / Kabul tarihi : 22.04.2022
Online published : 27.06.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.1086983

en sık rastlanan elektrolit bozukluğu hiponatremiydi (%56). Bunu sırasıyla hiperkalemi (%27.5), hipokalemi (%19.9) ve hipernatremi (%10.8) izledi. Akut gastroenterit, hem tek hem de mikst elektrolit bozukluğu gruplarında en sık altta yatan hastalıktı.

Sonuç: Çalışmamız, çocuk acil servislerinde en sık elektrolit bozukluklarının gastroenteritli hastalarda meydana geldiğini saptamıştır. Bu bozukluklar genellikle hafif şiddetteydi. Hafif elektrolit bozuklukları subklinik olabilir, bu nedenle pediatrik acil serviste rutin elektrolit ölçümü erken tanı için önemlidir.

Anahtar Sözcükler: Elektrolit Bozuklukları, Çocuk Acil, Potasyum, Sodyum

INTRODUCTION

Electrolyte balance is vital for the human body as it is essential for the proper functioning of organs and numerous metabolic processes (1). These electrolytes are kept in balance in the body within a very narrow range, consequently, disruption of this balance can cause a wide range of symptoms and diseases.

Electrolyte imbalance has many causes. Fever, liver or kidney problems, infections, certain medications, and many other clinical conditions can cause electrolyte imbalance. Furthermore, dehydration frequently upsets the delicate balance of electrolytes in children (2).

It has been revealed that children are more vulnerable to dehydration due to their small body size and high metabolic rate, resulting in faster replacement of water and electrolytes compared to adults (3).

Sodium, the main cation of the extracellular fluid is responsible for the balance of fluid in the human body (4, 5). Sodium also influences the function of muscles and plays a critıical role in the central nervous system. Sodium imbalances are common electrolyte disorders in children (6).

Another common electrolyte disturbance is potassium imbalance (6,7). Potassium, the most important intracellular cation plays a critical role in cellular osmolarity and nerve impulse transmission. Disturbances in potassium homeostasis can cause potentially life-threatening consequences such as cardiac arrhythmias, muscle paralysis, and respiratory failure (4).

Sodium and potassium imbalances are quite common in both hospitalized patients and emergency clinical presentations (8). Electrolyte disturbances can result in serious morbidity and mortality, depending on their severity and rate of occurrence. As these abnormalities are very common in clinical practice, immediate detection of electrolyte disturbances and determining the underlying problems are very crucial to ensure appropriate treatment.

This study mainly focuses on understanding the frequency of severity of different types of sodium and potassium imbalance among children diagnosed with dysnatremia and dyskalemia in the pediatric emergency department and determining their association with underlying diseases.

MATERIAL and METHODS

This retrospective study was conducted in the pediatric emergency department of a tertiary care hospital after obtaining ethics committee approval (Ministry of Health Ankara Training and Research Hospital Clinical Research Ethics Committee, 10 July 2020, No: E-20/305). All non-traumatic emergency applications under the age of 18 are accepted here. For this study, the electronic records of all patients who applied to the pediatric emergency department during the three years were examined and those with dysnatremia and/or dyskalemia were identified. Children with a history of intravenous serum supplementation before biochemical testing were excluded from the study. All patients' gender, age, and diagnosis according to ICD 10 were recorded.

Hyponatremia was defined as <135 mEq/L, with subcategories of mild (130-134 mEq/L), moderate (120-129 mEq/L) and severe (<120 mEq/L) (9). Hypernatremia was defined as >145 mEq/L, with subcategories of mild (146-150 mEq/L), moderate (151-170 mEq/L) and severe (>170 mEq/L) (10, 11).

Plasma potassium less than 3.5 mEq/L was considered hypokalemia. A potassium level of 3-3.4 mEq/L mild, 2.5-2.9 mEq/L moderate, and < 2.5 mEq/L was defined as severe hypokalemia (12). Plasma potassium higher than 5 mEq/L was considered hyperkalemia. 5.5-6 mEq/L were defined as mild, 6.1-7 mEq/L as moderate, and > 7 mEq/L as severe (12).

Since the number of patients with severe electrolyte disorders was low, those with moderate and severe electrolyte disorders were classified as a single group in statistical evaluations.

Statistical Analysis

Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate. The Chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Kolmogorov-Smirnov test. For comparison of continuous variables between two groups, the Student's t-test or Mann-Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

During the study period, 757 patients were diagnosed dysnatremia and/ or dyskalemia in the pediatric emergency department. Among those 358 (47.3%) were female and 399 (52.7%) were male. The most frequently detected abnormality was hyponatremia seen in 424 (56%) patients. Among those, mild hyponatremia was detected in 327 (77.1%), moderate hyponatremia in 95 (22.4), and severe hyponatremia in 2 (0.5) patients. Secondly, the predominant abnormality was hyperkalemia seen in 208 (27.5%) cases and the most frequently was mild form (n:198, 95.2%). While hypokalemia was observed in the third frequency (n:151, 19.9%), hypernatremia was detected the least (n:82, 10.8%).

The most frequent diseases found were acute gastroenteritis (n:265, %35), followed by asthma /acute bronchiolitis (n:126, %16.6) and convulsion (n:98, %12.9). Descriptive statistics for demographic and patient characteristics are presented in Table I. We reported acute gastroenteritis was the most common

Table I: Demographic features and incidence of electrolyte imbalance in relation to the primary illness (n=757).

Age (years) mean ± standard deviation median (min-max)	3.9±4.8 2.0 (0.0-18.0)
Gender*	
Female	358 (47.3)
Male	399 (52.7)
Primary illness*	
Acute gastroenteritis	265 (35.0)
Asthma and Acute bronchiolitis	126 (16.6)
Convulsion	98 (12.9)
Upper respiratory tract infection	93 (12.3)
Pneumonia	82 (10.8)
Poisoning	42 (5.5)
Meningitis	14 (1.8)
Carbonmonoxide exposure	12 (1.6)
Syncope	7 (0.9)
Others	18 (2.4)
Sodium*	
Hyponatremia	424 (56.0)
Mild	327 (77.1)
Moderate	95 (22.4)
Severe	2 (0.5)
Hypernatremia	82 (10.8)
Mild	41 (50.0)
Moderate	38 (46.3)
Severe	3 (3.7)
Potassium*	
Hypokalemia	151 (19.9)
Mild	134 (88.7)
Moderate	14 (9.3)
Severe	3 (2.0)
Hyperkalemia	208 (27.5)
Mild	198 (95.2)
Moderate	10 (4.8)
Severe	-

***** *n(%)*

Table II: Primary diseases of the patients according to the severity of dysnatremia and dyskalemia.

	Hyponatremia (n=424)		Hypernatremia (n=82)		Hypokalemia (n=151)		Hyperkalemia(n=208)	
	Mild (n=327)	Moderate+Severe (n=97)	Mild (n=41)	Moderate+Severe (n=41)	Mild (n=134)	Moderate+Severe (n=17)	Mild (n=198)	Moderate+Severe (n=10)
Acute gastroenteritis	123 (37.6)	38 (39.2)	23 (56.1)	18 (43.9)	53 (39.6)	8 (47.1)	42 (21.2)	-
Asthma/Acute bronchiolitis	42 (12.8)	16 (16.5)	1 (2.4)	2 (4.9)	34 (25.4)	-	50 (25.3)	3 (30)
Convulsion	50 (15.3)	9 (9.3)	7 (17.1)	11 (26.8)	10 (7.5)	4 (23.5)	20 (10.1)	1 (10)
Upper respiratory tract infection	42 (12.8)	18 (18.6)	2 (4.9)		11 (8.2)	1 (5.9)	30 (15.2)	1(10)
Pneumonia	28 (8.6)	4 (4.1)	5 (12.2)	5 (12.2)	7 (5.2)	2 (11.8)	36 (18.2)	-
Poisoning	20 (6.1)	5 (5.2)	2 (4.9)	1 (2.4)	11 (8.2)	1 (5.9)	3 (1.5)	1 (10)
Meningitis	3 (0.9)	1 (1.0)	-	4 (9.8)	3 (2.2)	-	5 (2.5)	-
Carbonmonoxide exposure	4 (1.2)	1 (1.0)	-	-	2 (1.5)	1 (5.9)	5 (2.5)	-
Syncope	5 (1.5)	-	1 (2.4)	-	1 (0.7)	-	1 (0.5)	4 (40)
Others	10 (3.1)	5 (5.2)		-	2 (1.5)	-	6 (3.0)	-

Data are expressed as n (%)

Table III: Demographic Characteristics and Urea, Creatinin Levels of the Patients According to the Severity of Dysnatremia and Dyskalemia.

Characteristics	Hyponatremia (n=424)		p	Hypernatremia (n=82)		p	Hypokalemia (n=151)		p	Hyperkalemia (n=208)		p
	Mild (n=327)	Moderate + Severe (n=97)		Mild (n=41)	Moderate + Severe (n=41)		Mild (n=134)	Moderate + Severe (n=17)		Mild (n=198)	Moderate + Severe (n=10	
Age(years)	4.4±4.7 2.0 (0.0-18.0)	5.2±5.3 3 (0.0-17)	0.523[a]	4.2±5.6 2.0 (0.0-17.0)	1.5±4.9 1.0 (0.0-17)	0.001[a]	5.2±5.6 2.0 (0.0-18.0)	5.8±6.4 2.0 (0.0-18)	0.775[a]	1.9±3.5 1.0 (0.0-17.0)	1.2±1.2 1.0 (0.0-3.0)	0.838[a]
Gender,n(%) Female Male	147 (45.0) 180 (55.0)	45(46.4) 52 (53.6)	0.803[b]	26 (63.4) 15 (36.6)	31 (75.6) 10 (24.4)	0.337[b]	63 (47.0) 71 (53.0)	6 (35.3) 11 (64.7)	0.512[b]	86 (43.4) 112 (56.6)	5 (50.0) 5 (50.0)	0.751[b]
Urea (mg/dL)	25.1±16.2 23.0 (4.0-177)	26.1±20.6 22 (5-183)	0.935[a]	26.5±16.6 20.5 (5.0-92.7)	50.9±38.6 38.5 (10-173)	0.001[a]	23.5±19.1 21.0 (1.0-177.0)	26.1±40.5 14.0 (4.0-173)	0.077[a]	21.4±17.5 16.0 (2 -137)	33.0±42.7 17.0 (1-121)	0.984[a]
Creatinin (mg/dL)	0.3±0.1 0.1 (0.3-1.2)	0.4±0.2 0.3 (0.1-1.3)	0.267[a]	0.4±0.3 0.3 (0.1-1.9)	0.5±0.2 0.4 (0.1-1.2)	0.043[a]	0.4±0.2 0.3 (0.1-1.1)	0.3±0.3 0.2 (0.1-1.4)	0.020[a]	0.3±0.1 0.2 (0.1-1.1)	0.4±0.3 0.2 (0.1-1.1)	0.144[a]

Unless otherwise specified data are expressed as mean ± standard deviation, median (min-max). [a]: Chi-squared test, [b]: Mann Whitney U test

Table IV: Demographic features and incidence of combined electrolyte imbalance in relation to the primary illness (n=108).

	n=108
Age(years) mean ± standard deviation	4.0±5.4
median (min-max)	1.0 (0.0-17.0)
Gender*	
Female	51 (47.2)
Male	57 (52.8)
Primary illness*	
Acute gastroenteritis	41 (38.0)
Asthma/ Acute bronchiolitis	22 (20.4)
Convulsion	14 (13.0)
Upper respiratory tract infection	12 (11.1)
Pneumonia	9 (8.3)
Meningitis	2 (1.9)
Senkop	1 (0.9)
Poisoning	1 (0.9)
Carbonmonoxide exposure	1 (0.9)
Others	5 (4.6)
Electrolyte Imbalance*	
Hyponatremia + hypokalemia	46 (42.5)
Hyponatremia + hyperkalemia	43 (40)
Hypernatremia + hypokalemia	14 (12.9)
Hypernatremia + hyperkalemia	5 (4.6)

***** *n(%)*

disease in hyponatremia, hypernatremia, and hypokalemia groups. Otherwise, asthma /acute bronchiolitis were the most common diagnosis in hyperkalemia disorders. The primary diseases of the patients according to the severity of hypokalemia and hyperkalemia are detailed in Table II.

When we evaluated electrolyte disorders according to their subcategories, it was determined that patients with moderate+severe hypernatremia were younger than patients with mild hypernatremia (p=0.001). Also, mean urea and creatinine levels were higher in the moderate+severe hypernatremia group (p=0.001 and p=0.043, respectively). In those with hypokalemia, creatinine levels were found to be significantly higher in the mild group than in the moderate + severe group (p=0.020). A comparison of demographic and clinical characteristics according to dysnatremia and dyskalemia is presented in Table III .

The mixed electrolytes imbalances were in 108 (14.3%) patients and 57 (47.2%) were male. Acute gastroenteritis was the most frequently seen in diagnosis and the most frequently mixed abnormality was the combination of hyponatremia with hypokalemia (n:46, 42.6%) (Table IV).

DISCUSSION

Children are prone to electrolyte disturbances due to their hemodynamic instability (3). Studies on electrolyte disturbances have been mainly focused on children with specific diseases or children in intensive care units. Only Rothrock et al. (13)

conducted a study on electrolyte disorders in the pediatric emergency clinic, however, the main focus of the study was the clinical findings of electrolyte disorders rather than their severity and frequency of them. To our knowledge, our study is the first to examine the severity of electrolyte disturbances and ıts relation to underlying diseases in the pediatric emergency clinic.

The most common electrolyte imbalance was hyponatremia(n: 424, 56%) and the second was hyperkalemia (n: 208, 27.5%). In both hyponatremia and hyperkalemia, imbalances were most often of mild severity (77.1%, 95.5%, respectively). Mild disorders were found to be common (88.7%) in patients with hypokalemia, while mild and moderate/severe disorders were found at a similar rate in patients with hypernatremia (50%, 50%, respectively).

Hyponatremia was the most common electrolyte abnormality in our study (56%). Several previous studies also showed that hyponatremia was the most common (4,13,14). Agarwal et al. (4) found hyponatremia in 84.2% of cases in their study in the pediatric intensive care unit. Elala et al. (14) evaluated the admitted to pediatric emergency and intensive care units patients and they showed the incidence of hyponatremia at 51.4%. Rothrock et al. (13) showed in their multicenter study that hyponatremia is the most common electrolyte disorder in pediatric emergency clinics (39.1%) and the most common underlying disease was acute gastroenteritis. Similarly, we detected a high incidence of acute gastroenteritis in children with hyponatremia. Agarwal et al. (4) reported that the most common underlying disease in patients with hyponatremia was central nervous system pathologies. However, it is important to note that children with gastroenteritis were not included in this study.

In our study, the most common electrolyte disorder was hyponatremia, while the least common was hypernatremia (9,5%). On the other hand, Naseem et al. (15) found the most common electrolyte disorder was hypernatremia after hypocalcemia in their study. Similarly, Haider et al. (18) reported hypernatremia more than hyponatremia in their study. Nevertheless, hyponatremia has been reported more commonly than hypernatremia in many studies in the literatüre (4,6,13, 14,16,17). We believe that this may be due to the diversity of the underlying disease and the intravenous fluid content given to the patients.

In this study, we detected that hyperkalemia was the second most common serum electrolyte abnormality next to hyponatremia (27.5%). Previous studies have reported the incidence of hyperkalemia as 26.8%, 26.6%, 24.8%, 14%, 18.8%, 15.3% (4,6,13-15,18). In our study, the most common underlying disease of those with hyperkalemia was asthma/acute bronchiolitis. We think that the high detection of hyperkalemia in this disease group may be associated with a critical illness (poor perfusion, lactic acidosis, etc) or age-related difficulty obtaining blood samples (hemolysis) in our study group.

The incidence of hypokalemia was detected in 19.9% of cases. The most common underlying disease in these cases was acute gastroenteritis. In different studies this incidence was reported 64%, 57.4%, 49%, 28%, 30.58%, 9.6% (4,6,13-15, 18) .The incidence of hypokalemia was higher than our results in all studies except Rothrock et al. (13).

In our study, mixed electrolyte disorders were found in 108 children. The most frequent underlying disease was acute gastroenteritis (n:41, 38%). This disease was also the most common in single electrolyte imbalances. In previous studies, the incidence of mixed acid-base disorder was reported as 69.5%(15), 57.3%(18), and 42.2%(14). These rates are higher than in our study. Since these studies were conducted in the intensive care unit, we think that the difference in the patient profile and the treatments used may cause the incidence difference.

Limitation

Our study has several limitations. First was its retrospective design. Therefore the diagnoses were based on the ICD-10 coding which the different physicians found relevant. Secondly, although blood samples were taken from the patients before treatment we could not exclude that some patients might have had medical treatment before coming to our hospital. Thirdly our study did not aim at which electrolyte disorders have contributed to the higher morbidity and mortality. The fourth our study was a single center. Therefore our results may not truly reflect the general population

CONCLUSION

Electrolyte imbalances accompany many diseases. However, no study has been reported on the frequency of electrolyte disturbances in the pediatric emergency department. To our knowledge, this study is the first the frequency of severity of different types of sodium and potassium imbalance among children diagnosed with dysnatremia and dyskalemia in the pediatric emergency department and examine their association with underlying diseases. In the current study, we demonstrated the most common electrolyte disorder was hyponatremia. This disorder was most frequently detected in cases diagnosed with acute gastroenteritis. Our study reveals a high prevalence of mild electrolyte disturbances in the pediatric emergency department. Mild electrolyte disorders may be subclinical and this may cause a delay in diagnosis. Early detection and management of these cases are important because the timely intervention is essential in the proper treatment of electrolyte disorders.

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Fractional Excretion of Urea in Pediatric Patients with Acute Kidney Injury

Pediatrik Akut Böbrek Hasarında Fraksiyone Üre Ekskresyonu

Ozlem Yuksel AKSOY, Zehra AYDIN, Mihriban INOZU, Begum AVCI, Fatma Semsa CAYCI, Umut Selda BAYRAKCI

Department of Pediatric Nephrology, Ankara City Hospital, Ankara, Turkey

ABSTRACT

Objective: Fractional excretion of sodium (FeNa) and fractional excretion of urea (FeU) are used to differentiate prerenal and renal injuries in acute kidney injury (AKI). In this study, we aimed to compare the discriminative power of FeU with FeNa between prerenal and renal azotemia groups as well as among AKI stages according to pRIFLE criteria.

Material and Methods: Laboratory and medical records of 55 pediatric AKI patients who had the measurements of random urine excretions of urea, creatinine and sodium as well as serum urea, creatinine and sodium levels in order to calculate FeU and FeNa values at the time of AKI diagnosis were evaluated retrospectively. Patients were divided into prerenal and renal injury groups according to the clinical findings and laboratory data. Sensitivities and specifities of FeNa and FeU in differentiating prerenal versus renal injury were determined. FeNa and FeU values were compared in patients with different RIFLE stages.

Results: Among 55 pediatric AKI patients 31 were boys, 24 were girls. The mean age at the time of diagnosis was 71.1 ± 83.5 months (min-max: 1-216). When we grouped the patients as having FeU<35% and FeU≥35%, the difference between the numbers of the patients in prerenal and renal groups was significant (p=0.039). The sensitivity and specificity of FeU to determine prerenal vs renal injury were calculated as 50% and 77.1% respectively. When FeNa and FeU were used together (FeNa>1% and FeU>35%) in order to distinguish prerenal and renal injuries the specificity increased to 81% (p=0.020). Mean FeU was significantly different between AKI stages (p=0.022), and was higher in Injury and Failure stages when compared with the Risk stage.

Conclusion: Fractional urea excretion is as important as FeNa in evaluating children with AKI. We recommend to obtain FeU in pediatric AKI in order to differentiate prerenal and renal etiology and to differentiate the severity of the injury according to the AKI stages in order to arrange the treatment.

Key Words: Acute kidney injury, Children, Fractional urea excretion, pRIFLE

ÖZ

Amaç: Fraksiyone sodyum ekskresyonu (FeNa) ile fraksiyone üre ekskresyonu (FeU) akut böbrek hasarında prerenal ve renal hasarı ayırt etmek için kullanılmaktadır. Bu çalışmada, FeNa ve FeU değerlerinin prerenal ve renal azotemi grupları ile pRIFLE kriterlerine göre akut böbek hasarı evrelerini ayırdetmedeki gücünü kıyaslamayı amaçladık.

0000-0001-7905-3524 : AKSOY OY
0000-0002-9605-725X : AYDIN Z
0000-0003-1574-1971 : INOZU M
0000-0002-5136-1995 : AVCI B
0000-0001-6779-275X : CAYCI FS
0000-0002-5301-2617 : BAYRAKCI US

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 Local Ethics Committee (Ankara City Hospital, Clinical Studies E2-21-330).

Contribution of the Authors / Yazarların katkısı*: *AKSOY OY: 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 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. ***AYDIN Z:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***INOZU M:*** 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. ***AVCI B:*** 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. ***CAYCI FS:*** 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. ***BAYRAKCI US:*** 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 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.

How to cite / *Atıf yazım şekli* : Aksoy OY, Aydin Z, Inozu M, Avci B, Cayci FS and Bayrakcı US. Fractional Excretion of Urea in Pediatric Patients with Acute Kidney Injury. Turkish J Pediatr Dis 2023;17:91-95.

Correspondence Address / Yazışma Adresi:

Ozlem Yuksel AKSOY
Department of Pediatric Nephrology, Ankara City Hospital, Ankara, Turkey
E-posta: ozlem_yurtsever@yahoo.com

Received / Geliş tarihi : 14.12.2021
Accepted / Kabul tarihi : 23.05.2022
Online published : 19.08.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.1036384

Gereç ve Yöntemler: Akut böbrek hasarı tanısı sırasındaki FeU ve FeNa değerlerini hesaplamak amacıyla spot idrar üre, kreatinin ve sodyum ekskresyonları ile serum üre, kreatinin ve sodyum değerleri elde olunan 55 pediatrik akut böbrek hasarı hastasının laboratuvar ve klinik verileri retrospektif olarak değerlendirildi. Hastalar klinik ve laboratuvar bilgiler ışığında prerenal ve renal hasar grupları olarak ikiye ayrıldı. Prerenal ve renal hasarı ayırt etmede FeNa ve FeU testlerinin sensitivite ve spesifisiteleri hesaplandı. Farklı RIFLE evreleri olan hastalar arasında FeNa ve FeU yüzdeleri kıyaslandı.

Bulgular: Elli beş pediatrik akut böbrek hasarı hastasının 31'i erkek, 24'ü kızdı. Tanı anında ortalama yaş 71.1±83.5 ay (min-max: 1-216)'di. Hastaları FeU değerlerine göre FeU<%35 ve FeU ≥35% olarak iki gruba ayırdığımızda prerenal ve renal gruplardaki hasta sayıları arasındaki fark anlamlıydı (p=0.039). Prerenal ve renal hasar ayırımını belirlemede FeU testinin sensitivitesi %50, spesifisitesi %77.1 olarak hesaplandı. FeNa ve FeU birlikte kullanıldığında (FeNa >%1 ve FeU >%35) spesifisite %81'e yükseldi (p=0.020). FeU ortalaması akut böbrek hasarı evreleri arasında anlamlı olarak farklıydı (p=0.022) ve Risk evresiyle kıyaslandığında Injury ve Failure evrelerinde daha yüksekti.

Sonuç: Fraksiyone üre ekskresyonu, pediatrik akut böbrek hasarı olan çocukların değerlendirilmesinde FeNa kadar önemlidir. Prerenal ve renal hasarı ayırt etmede ve akut böbrek hasarı evrelerine göre böbrek hasarının şiddetinin belirlenmesinde FeU değerinin elde edilmesini öneriyoruz.

Anahtar Sözcükler: Akut böbrek hasarı, Fraksiyone üre ekskresyonu, pRIFLE

INTRODUCTION

Acute kidney injury (AKI), is characterized by an abrupt increase in serum urea and creatinine concentrations, a decrease in glomerular filtration rate (GFR) and the disability of the kidneys to regulate acid-base, water, and electrolyte balance (1-3). AKI is an important problem to assess. Mortality in patients with AKI increases along with the increase in serum creatinine (4). The Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) classification determines the grade of AKI based on serum creatinine level or glomerular filtration rate (GFR) and urine output (5). Pediatric RIFLE (pRIFLE) is a modified version for the setting of AKI in children (6).

AKI is usually multifactorial, and it is a diagnostic challenge to differentiate prerenal insult from acute tubular necrosis (ATN) (5,7). Distinguishing these two entities is important in order to manage the patient properly and to assess the outcome (5). Prompt diagnosis of intrinsic renal injury and exclusion of other causes might enhance better outcome (1,8). There is a lack of a clinical gold standard used for that purpose. The blood urea nitrogen-to-creatinine ratio (BUN/Cre), urinary/plasma creatinine and urinary/plasma osmolarity ratios, urinary sodium concentration, and fractional excretion of sodium (FeNa) are used to differentiate prerenal AKI from intrinsic injury (5,9,10).

Fractional excretion of sodium, is the most reliable and available test that is widely used to differentiate prerenal and intrinsic renal failure, particularly ATN (1). A value less than 1% suggests transient or prerenal AKI, whereas FeNa greater than 1% supports acute tubular necrosis or persistent AKI. However FeNa has some limitations in various conditions such as diuretic administration, contrast nephropathy, sepsis, bilateral renal artery stenosis, acute glomerulonephritis, acute interstitial nephritis, acute rejection, glucosuric states, metabolic alkalosis, and ATN superimposed upon chronic effective volume depletion (heart failure, nephrotic syndrome) (1,2,5,11-14). Fractional excretions of other substances such as chloride, urea, uric acid, and lithium were studied to differentiate these conditions (1,15-17). Together with FeNa, fractional excretion of urea (FeU) has been studied by many investigators (18,19).

Proximal segment of the nephron is the major site for the reabsorption of urea and the reabsorption is not directly affected by diuretics, therefore FeU is thought to be a better diagnostic measure than FeNa (5).

In this study we evaluated the utilization of FeU in the setting of pediatric AKI. We aimed to show the advantages of using FeU together with FeNa in differentiating prerenal vs renal injury, and in addition to that, we wanted to show if FeU and FeNa are different among AKI stages.

MATERIAL and METHODS

From the database of our hospital, we retrospectively analyzed the medical records of the pediatric patients with the diagnosis of acute kidney injury. We included 55 patients who had random plasma and urine urea, creatinine, sodium results (at the time of diagnosis of acute kidney injury) in order to calculate fractional excretions of urea and sodium, respectively. Newborns were excluded due to the immaturity of their renal tubular functions.

Demographic data, age, serum urea, creatinine, sodium, potassium levels, FeNa, FeU and AKI stages determined according to pediatric RIFLE criteria were recorded. Patients at the Loss stage and the End-stage renal disease stages were not included in the study since most of these patients were anuric. Patients were divided into prerenal and renal injury groups according to the history of the disease, BUN/Cre ratio (>20 is supportive of prerenal causes), and presence or absence of rapid amelioration of renal function with volume repletion. Patients were further divided into four subgroups according to their fractional excretion results as FeNa<1%, FeNa≥1% and FeU<35%, FeU≥35%, and the patient numbers were compared (in order to calculate sensitivities and specificities of the tests) between prerenal/renal injury groups and among RIFLE stages.

The study was approved by the Local Ethics Committee (Ankara City Hospital, Clinical Studies E2-21-330) and the study was conducted by the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using IBM SPSS for Windows (SPSS version 17.0). Student t test was performed for normally distributed data, and Mann-Whitney U test for non-normally distributed data. To evaluate the difference between FeU and FeNa among different AKI stages (Risk-Injury-Failure), one-way analysis of variance and Tukey's post hoc tests were used. Pearson Chi-Square test was used to evaluate the difference between FeU and FeNa in between prerenal and renal injury groups.

Frequencies and percentages were used as descriptive values in the categorical data. Arithmetical mean±standard deviation was used for the normally distributed data, and median and interquartile range (IQR) were used for the non-normally distributed data.

Statistical significance was accepted as 0.05.

RESULTS

The study included 55 (female/male:24/31) pediatric AKI patients. Mean age at diagnosis was 71.1±83.5 months (min-max:1-216). Twenty patients were classified as having prerenal AKI and 35 patients as having renal injury. In the prerenal azotemia group, the etiology of prerenal AKI was acute gastroenteritis and dehydration in most of the cases, whereas in renal injury group acute glomerulonephritis and acute tubulointersitial nephritis were common. According to pediatric RIFLE criteria 24 patients were classified as the Risk stage, 16 patients as the Injury stage and 15 patients as the Failure stage.

Mean serum urea, creatinine, sodium, potassium levels were similar in prerenal and renal groups (Table I). Mean serum urea is 58.5±31.5 mg/dL at the Risk stage, 55.7±27.8 mg/dL at the Injury stage, 90.2±51.1 mg/dL at the Failure stage. Mean serum urea was significantly different between AKI stages (p=0.018). Mean serum creatinine is 0.99±0.31 mg/dL at the Risk stage, 0.95±0.17 mg/dL at the Injury stage, 1.88±0.55 mg/dL at the Failure stage. Mean serum creatinine was significantly different between AKI stages (p<0.001).

Table I: The clinical and the laboratory data of prerenal and renal injury groups.

	Prerenal	Renal	p
Number of the patients	20	35	
Age (months)	97±86	55±78	0.072
BUN (mg/dL)	35±14	28±20	0.198
Serum Urea (mg/dL)	75±30	61±42	0.198
Serum creatinine (mg/dL)	1.12±0.39	1.28±0.61	0.291
Serum sodium (mmol/L)	136±12	137±8	0.721
Serum potassium (mmol/L)	4.4±0.8	4.0±0.8	0.153
FeNa (%)	1.5±2.9	4.4±3.6	0.004
FeU (%)	8.2±18	56±21	0.003
FeNa<1% (n)	15/20	3/35	<0.001
FeU<35% (n)	10/20	8/35	0.039

Table II: FeNa and FeU values between different stages of pRIFLE.

RIFLE	n	Mean±Std. Dev.	Median (Min-Max)	p*
FeNa (%)				
Risk Stage	24	1.90±1.78	1.45 (0.06- 6.98)	0.004
Injury Stage	16	2.25±3.48	1.38 (0.19-13.09)	
Failure Stage	15	6.35±4.5	6.11 (0.82-13.39)	
FeU (%)				
Risk Stage	24	40.31±17.31	35.12 (15.88-80.06)	0.022
Injury Stage	16	55.5±22.8	56.16 (18.75-96.44)	
Failure Stage	15	58.5±23.16	62.8 (17.17-91.78)	

**Kruskal Wallis test*

Among 18 patients with FeNa<1%, 15 (83.4%) of them had prerenal causes, and among patients with FeNa≥1%, 32 (86.4%) of them had renal causes. When we compared FeNa<1% group with FeNa≥%1 group, prerenal etiology was significantly predominant in FeNa<1% group (p<0.001). This is consistent with the fact that FeNa less than 1% supports prerenal etiology. The sensitivity and specificity of FeNa to determine prerenal vs renal injury were calculated as 75% and 91.4 % respectively.

The fractional excretion of urea less than 35% is supportive of prerenal etiology. When we grouped the patients according to their FeU levels as FeU<35% and FeU≥35, the difference in patients' numbers in prerenal and renal groups was significant (p=0.039). The sensitivity and specificity of FeU to determine prerenal vs renal injury were calculated as 50% and 77.1% respectively. When FeNa and FeU were used together, the difference in patients' numbers between prerenal and renal groups was significant (p=0.02), and the specificity of the tests to differentiate prerenal vs renal injury was calculated as 81%.

Mean FeNa was 1.9% at the Risk stage, 2.25% at the Injury stage, and 6.35% at the Failure stage. Mean FeNa was significantly different between AKI stages (p=0.004). Mean FeU was 40.31% at the Risk stage, 55.5% at the Injury stage, and 58.5% at the Failure stage. Mean FeU is significantly different between AKI stages (p=0.022) (Table II).

The possibility of FeU being less than 35% at the Risk stage was 2.901 times higher than that of Injury and Failure stages (Odds ratio 2.901 CI: 95%, 0.906-9.286). The possibility of FeU being more than 35% at the Failure stage was 4.333 times higher than the Risk stage (Odds ratio 4.333 CI: 95%, 0.86-21.843).

DISCUSSIONS

The present study supports that the utilization of FeU, as well as FeNa, is useful to differentiate prerenal azotemia from renal injury. Prerenal azotemia is a more common condition than

intrinsic renal failure (18,20). Contrary to the literature, the number of our subjects in the prerenal injury group seems to be less when compared with the renal injury group, this is due to the retrospective nature of our study, and to the fact that prerenal azotemia is usually corrected quickly with adequate hydration, and further evaluation is usually preserved for the suspicion of renal injury.

Differentiating prerenal and intrinsic renal injury is extremely important, since correcting the volume status of the patient will ameliorate the ongoing problem. The FeNa and FeU are both useful tests used to discriminate these two entities. The primary use of FeNa which mainly reflects the function of distal nephron is that low levels of it (<1%) suggests prerenal failure whereas a high level (2%) favors intrinsic renal failure (1,13,21). However active transport of sodium chloride can be affected by diuretic usage leading to an alteration in FeNa, and this affects the utilization of FeNa in patients who were administered diuretics (9).

Urea is a lipid-soluble molecule that can cross the membranes of the cell easily by passive diffusion (1,21). In the glomerulus urea is freely filtered, and then reabsorbed mainly in the proximal tubule, finally 50-60% of the filtered urea is excreted (1,21). Urea is also actively transported in the renal tubules. When there is a decrease in perfusion, urea reabsorption increases, and as a result of this, the excretion of urea decreases (usually <35%). If the patient has an intrinsic renal failure due to the tubular insult, urea reabsorption decreases and FeU exceeds 50% (1,13). However, many conditions such as sepsis, gender, aging, protein infusion, liver disease, certain drugs interfere with the active transport of urea affecting the result of FeU (18,22).

It is shown that endotoxemia causes cytokines to downregulate urea transporters (18,23). In other words, among cases with endotoxemia or sepsis FeU results may erroneously suggest a prerenal etiology in the presence of an intrinsic renal injury. When compared with the literature, in our study we found slightly lower sensitivity and specificity of FeU to differentiate prerenal azotemia from intrinsic renal injury (50% and 77.1% respectively). The most common possible etiology of prerenal AKI was acute gastroenteritis in children enrolled in this study. We can speculate that, the possible infectious etiology in our patients might have affected the excretion of urea therefore leading to the lower sensitivity and specificity of FeU found in our study. Infectious diarrhea might have also caused an increase in intestinal urea loss, and as a consequence of that, even in prerenal azotemia cases elevated FeU results might have been found contrary to expectations (4).

Fractional excretions of certain substances such as uric acid and urea are difficult to quantify in newborns especially in premature babies due to the immaturity of tubular function (24). Fractional excretion of uric acid is shown to be very high at birth and declines over the first month of life (25). Therefore, we excluded the newborns from our study.

Fahimi et al. (1) showed that FeU was a better index than FeNa to differentiate prerenal from intrinsic renal failure. Although both indices were higher in patients with intrinsic renal failure, FeU <35% better discriminated prerenal patients than did FeNa<1%. They also found that FeU <30% had a higher sensitivity than previously reported FeU<35% in the adult population to discriminate prerenal failure patients. In our study FeNa<1% had higher sensitivity and specificity to discriminate prerenal from renal injury when compared with FeU. Since our study is retrospectively designed, we cannot detect the patients with diuretic administration.

Carvounis et al. (13) in their cohort, analyzed the data of 50 subjects with prerenal azotemia, 27 subjects with prerenal azotemia treated with diuretic administration, and 25 subjects with acute tubular necrosis. They reported the sensitivity and specificity of Feu<35% to differentiate prerenal azotemia were 90% and 96%, respectively.

Pepin et al.(5) concluded that, in patients not receiving diuretics, FeNa is more able to distinguish transient from persistent AKI, whereas in patients treated with diuretics, neither FeNa nor FeU can be used. Diskin et al.(18) evaluated FeNa and FeU in 100 azotemic oliguria patients and concluded that both tests accurately differentiate prerenal from intrinsic renal injury and FeU appears to be more accurate in patients receiving diuretics.

Our results support that FeU together with FeNa is a useful marker to differentiate prerenal azotemia from renal injury. We showed the utilization of FeNa and FeU together differentiates prerenal from renal injury with a specificity of 81%.

We also found that both FeU and FeNa are both significantly lower at the Risk stage when compared with the Injury and Failure stages. Tubular function is much better in especially early stages of AKI, in other words, renal capacity to reabsorb certain molecules is better at the beginning of the insult (1). The low FeU and FeNa results at the Risk stage could be explained by this fact. When the damage advances, kidney's ability of reabsorption diminishes, and FeNa and FeU increase (1). To the best of our knowledge, this is the first study evaluating both FeNa and FeU in different stages of AKI.

The restrictions of our study are its small size and retrospective nature. Furthermore we were not able define the patients with diarrhea or sepsis, and/or receiving diuretics.

Acute kidney injury is associated with a high mortality rate, therefore early interventions are important to avoid the renal damage. In a patient with suspected acute kidney injury, FeU together with FeNa should be obtained in order to differentiate prerenal injury from renal insult, and also to distinguish an early stage of AKI from advanced stages.

CONCLUSION

The fractional excretion of urea is an important tool similar to FeNa in evaluating children with AKI. We recommend to obtain FeU together with FeNa in children with AKI to differentiate

prerenal azotemia from intrinsic renal failure excluding the patients with sepsis or diuretic administration. FeU and FeNa are both found to be significantly lower at the early stages of AKI than advanced stages, and might be helpful for the arrangement of treatment strategies.

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The Relationship Between Oxidative Stress and Adenotonsillar Hypertrophy in Children

Çocuklarda Oksidatif Stres ile Adenotonsiller Hipertrofi Arasındaki İlişki

Gulşah ALYAR[1], Nurinnisa OZTURK[2], Ozgur YORUK[3], Ozge Nur TURKERI[4], Nuri BAKAN[5]

[1]Vocational School of Health Services, Atatürk University, Erzurum, Turkey
[2]Faculty of Medicine Medical Biochemistry, Atatürk University, Erzurum, Turkey
[3]Surgical Medical Sciences, Department of Otorhinolaryngology, Ataturk University Faculty of Medicine, Erzurum, Turkey
[4]European University of Lefke Faculty of Health Sciences, Lefkosa, KKTC
[5]Ataturk University Faculty of Medicine, Medical Biochemistry, Erzurum, Turkey

ABSTRACT

Objective: In this study, it was aimed to evaluate the preoperative and postoperative oxidative stress levels of children with obstructive adenotonsillar hypertrophy and to compare the obtained data with healthy children.

Material and Methods: 25 patients and 25 healthy controls were included in the prospective study conducted between March and September 2015. In the study sample, children who were diagnosed with adenotonsillar hypertrophy due to chronic tonsillitis, snoring and mouth breathing and who were planned for adenotonsillectomy were included in the patient group. Control group included 25 healthy volunteers with the same demographic characteristics. Serum and urine samples were collected from the patient group twice, before and after surgery, and once from the control group. 8-hydroxy-2-deoxyguanosine levels of all samples were determined by EIA method, protein carbonyl levels were determined by ELISA method and malondialdehyde levels were determined by manual spectrophotometric method.

Results: In the study, it was found that the serum malondialdehyde levels of children with adenotonsillar hypertrophy were significantly higher than the control group ($p=0.003$) and that there was no difference in terms of other parameters ($p>0.05$). After the operation, it was determined that the levels of all three parameters evaluated significantly decreased compared to before ($p<0.05$). It was determined that there was a statistically significant and weak correlation between malondialdehyde and 8-hydroxy-2-deoxyguanosine values before the operation ($p=0.003$, $r=0.566$).

Conclusion: Hypertrophic adenotonsillar, which is common in the pediatric population, causes many clinical conditions and adversely affects the health and quality of life of children. In line with our findings, we can say that serum and urine MDA levels and tissue PCO levels are useful markers in the evaluation of oxidative damage in children with obstructive ATH and may help to elucidate the etiopathogenesis of the disease. Considering the effects of ATH on health, it is recommended to be considered as an important health problem and to examine the clinical, biochemical and histopathological studies of the disease in a larger sample group.

Key Words: Adenotonsillar hypertrophy, 8-hydroxy-2-deoxyguanosine, Malondialdehyde, Protein carbonyl

ÖZ

Amaç: Bu çalışmada obstrüktif adenotonsiller hipertrofili çocukların ameliyat öncesi ve sonrası oksidatif stres düzeylerinin değerlendirilmesi ve elde edilen verilerin sağlıklı çocuklarla karşılaştırılması amaçlanmıştır.

0000-0003-3628-6664 : ALYAR G
0000-0002-7746-2700 : OZTURK N
0000-0001-5871-2471 : YORUK O
0000-0001-8791-5331 : TURKERI ON
0000-0002-2139-7268 : BAKAN N

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 Atatürk University, Faculty of Medicine, Non-Invasive Clinical Research Ethics Committee (19.02.2015 / B.30.2ATA.0.01.00 / 28).

Contribution of the Authors / Yazarların katkısı*: *ALYAR G: 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. ***OZTURK 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/studyTaking 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. ***YORUK O:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***TURKERI ON:*** Taking responsibility in logical interpretation and conclusion of the results. ***BAKAN N:*** Taking responsibility in logical interpretation and conclusion of the results.

How to cite / *Atıf yazım şekli* : Alyar G, Ozturk N, Yoruk O, Turkeri ON, Bakan N. The Relationship Between Oxidative Stress and Adenotonsillar Hypertrophy in Children. Turkish J Pediatr Dis 2023;17:96-100.

Correspondence Address / Yazışma Adresi:
Gulsah ALYAR
Vocational School of Health Services,
Atatürk University, Erzurum, Turkey
E-posta: gulsah.kiymik@atauni.edu.tr

Received / Geliş tarihi : 06.03.2022
Accepted / Kabul tarihi : 25.05.2022
Online published : 13.06.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.1072563

Gereç ve Yöntemler: 2015 yılı Mart-Eylül ayları arasında yapılan prospektif çalışmaya 25 hasta ve 25 sağlıklı kontrol dahil edilmiştir. Araştırma örnekleminde hasta grubuna kronik tonsillit, horlama ve ağızdan nefes alma şikayeti ile adenotonsiller hipertrofi tanısı alan ve adenotonsillektomi planlanan çocuklar dahil edilmiştir. Serum ve idrar örneği hasta grubundan ameliyat öncesi ve sonrası iki kez, kontrol grubundan bir kez alındı. Tüm numunelerin 8-hidroksi-2-deoksiguanozin düzeyleri EIA yöntem, protein karbonil düzeyleri ELISA yöntem ve malondialdehit düzeyleri manuel spektrofotometrik yöntem kullanılarak belirlenmiştir.

Bulgular: Çalışmada adenotonsiller hipertrofisi olan çocukların serum malondialdehit düzeylerinin kontrol grubuna göre anlamlı olarak yüksek olduğu (p=0.003) ve diğer parametreler açısından fark olmadığı (p>0.050) bulunmuştur. Ameliyattan sonra değerlendirilen her üç parametrenin de öncekine göre anlamlı düzeyde azaldığı tespit edilmiştir (p<0.050). Operasyon öncesi malondialdehit ile 8-hidroksi-2-deoksiguanozin değerleri arasında istatistiksel olarak anlamlı ve zayıf bir korelasyon olduğu belirlenmiştir (p=0.003, r=0.566).

Sonuç: Pediatrik popülasyonda yaygın görülen hipertrofik adenotonsiller birçok klinik duruma neden olarak çocukların sağlığını ve yaşam kalitesini olumsuz etkilemektedir. Bulgularımız doğrultusunda obstrüktif ATH'li çocuklarda serum ve idrar MDA düzeyleri ile doku PCO düzeylerinin oksidatif hasarın değerlendirilmesinde yararlı belirteçler olduğunu ve hastalığın etyopatogenezini aydınlatmaya yardımcı olabileceğini söyleyebiliriz. ATH sağlık üzerindeki olumsuz etkileri sebebiyle hastalığın klinik, biyokimyasal ve histopatolojik çalışmalarının daha geniş bir örneklem grubunda incelenmesi önerilmektedir.

Anahtar Sözcükler: Adenotonsiller hipertrofi, 8-hidroksi-2-deoksiguanozin, Malondialdehit, protein karbonil

INTRODUCTION

Adenoid and tonsillar tissue, which is a component of Waldeyer's ring, has strategic importance due to its anatomical location (1). These tissues, which play a role in mucosal immunity, provide stimulation of immunity against microorganisms and antigens that enter the body through respiration and digestion (2,3). Recurrent and chronic infections of the adenoids and tonsils result in hypertrophy of the lymphoid tissues. Adenotonsillar hypertrophy (ATH) is the enlargement of tonsils and adenoids and often causes partial or complete obstruction of the upper airways as a result of narrowing of the nasopharynx and oropharynx (4). Although the pathophysiology of obstructive ATH has not been fully elucidated, it has been suggested that recurrent episodes of hypoxia/reoxygenation and decreased blood oxygen saturation and increased reactive oxygen species (ROS) with changes in cell metabolism may be effective in the formation of the disease (5). Oxidative stress is defined as the increase in reactive oxygen species (ROS) and ROS can damage DNA's, lipids and proteins by various mechanisms (6,7). Levels of 8-hydroxy-2-deoxyguanosine (8-OHdG), malondialdehyde (MDA) protein carbonyl (PCO) levels are widely used as oxidative stress markers (8,9). We aimed in this study to investigate the relationship between oxidative stress and ATH in children by using 8-OHdG, PCO and MDA levels in plasma and urine samples and PCO and MDA levels in adenoid/tonsillar tissues.

PATIENTS and METHODS

The study was approved by Atatürk University, Faculty of Medicine, Non-Invasive Clinical Research Ethics Committee (19.02.2015/B.30.2ATA.0.01.00/28). The study group consisted of 25 patients with the diagnosis of ATH who subsequently underwent surgical treatment. In the study sample, children who were diagnosed with adenotonsillar hypertrophy due to chronic tonsillitis, snoring and mouth breathing and who were planned for adenotonsillectomy were included in the patient group. Control group included 25 healthy volunteers with the same demographic characteristics. Blood and urine samples were taken from the patients twice, preoperatively and during the 6th month follow-up visits after surgery. To measure 8-OHdG, PCO and MDA levels, single samples of peripheral venous blood (2 mL) and urine (3 mL) were collected from both children with ATH and children without obstructive ATH and maintained at –80°C until analysis. At the same time, the adenoid / tonsillar tissues of patients who underwent adenotonsillectomy were collected in a sterile manner and stored until the study day –80°C.

Statistical Analysis

The suitability of the parameters to the normal distribution was evaluated with the Kolmogrov-Smirnov test. Paired t-test was used in dependent samples to compare the pre- and postoperative values of children with ATH. Independent samples t-test (independent samples t-test or student t-test) was used to compare the values of the patient and control groups. Correlation between parameters was evaluated by pearson correlation analysis. Results are given as mean ± standard deviation (SD). For the significant difference between the groups, p <0.050 was used. Statistical analysis was performed using the SPSS 20.0 program. (SPSS, Chicago, IL, United States)

RESULTS

The demographic characteristics of the patients (study group) and controls are given in Table I.

Table I: Demographic characteristics of participants.

Parameters	Patient group	Control group	p
Age (years)	8.24 ± 2.48	9.20 ± 2.43	0.174
Height (cm)	135.16 ± 19.38	126.76 ± 20.78	0.146
Weight (kg)	29.88 ± 8.11	26.20 ± 4.85	0.058

Table II: Pre-operative serum levels of biomarkers in control group and patients.

Parameters	Patient group (n =25)	Control group (n =25)	p
8-OHdG (ng /mL)	45.84±24.17	41.06±27.50	0.518
MDA (µM)	3.52±1.16	2.49±1.20	0.003*
PCO (nmol / mL)	17.35±4.00	14.32±3.25	0.423

*: *Statistically significant p value.*

Table III: Urinary levels of biomarkers in patients with adenotonsillar hypertrophy and control group.

Parameters	Patient group (n=25)	Control group (n=25)	p
8-OHdG(ng /mL)	318.57 ± 649.19	186.65 ± 168.66	0.330
MDA (µM)	4.34 ± 1.10	1.33 ± 0.87	0.001*

***: *Statistically significant p value.*

Table IV: Pre and postoperative serum levels of biomarkers in patients with adenotonsillar hypertrophy.

Parameters	Preoperative (n=25)	Postoperative (n=25)	p
8-OHdG(ng /mL)	45.84 ± 24.17	26.23 ± 19.54	0.002*
MDA (µM)	3.52 ± 1.16	1.88 ± 0.86	0.001*
PCO (nmol / mL)	17.3 ± 4.00	15.04 ± 2.98	0.001*

***: *Statistically significant p value.*

Table V: MDA, PCO levels of adenoid and tonsillar tissues.

Parameters	Adenoid Tissue (n= 11)	Tonsillary Tissue (n = 20)	p
MDA (µM)	8.95 ± 1.23	8.62 ± 1.71	0.580
PCO(nmol/ mL)	115.10 ± 58.53	67.67 ± 37.21	0.021 *

***: *Statistically significant p value.*

The mean ± standard deviation and p values of serum 8-OHdG, MDA, PCO of the patients and controls are given in table II.

Serum MDA levels of patients were significantly higher than the control group, and there was no difference in terms of other parameters. (Table II).

Urinary MDA levels of patients with ATH were statistically significantly higher (p <0.050) than the control group, and the 8-OHdG levels were not different between the two groups (p <0.050, Table III).

Postoperative 8-OHdG, MDA and PCO levels of the study group were significantly lower than the preoperative values. (p <0.050, Table IV).

There was no significant difference between MDA values of the adenoid and tonsillar tissues removed after surgery, but PCO values were higher in adenoid tissue than the tonsillar tissue (Table V).

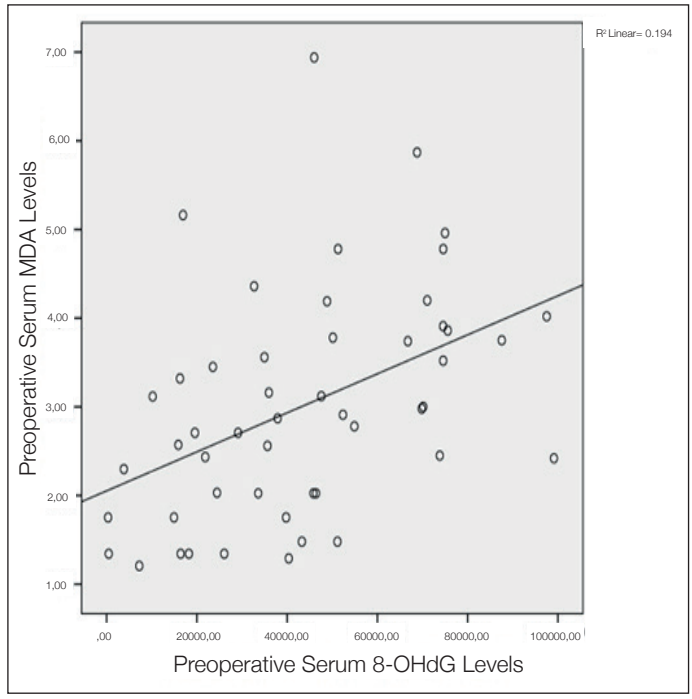

Figure 1: Scatter / Dot Graph Between Pre-Operation MDA and 8-OHdG Values.

There was a weak statistically significant correlation between preoperative MDA and 8-OHdG values at correlation analysis. (p = 0.003, r = 0.566, Figure 1).

DISCUSSION

Acute tonsillitis, adenoiditis and ATH attacks are common in preschool and school-age children and can affect school performance and sleep quality (10). Hypertrophic tonsils and adenoids can cause various degrees of upper respiratory tract obstruction and recurrent respiratory tract infections. In the treatment of these diseases, adenoidectomy and tonsillectomy are frequently applied (11). Oxidative stress is caused by excessive ROS formation as a result of cellular metabolic reactions or exogenous conditions and inability of the antioxidant system to neutralise these excessive ROS (5). ROS causes toxicity by damaging biomolecules in the cell and plays an important role in the pathophysiology of many diseases (5,6,8). It is not exactly clear how ATH causes oxidative stress, but it is assumed that oxidative stress is secondary to hypoxia/ reoxygenation periods in ATH (5). The studies reporting that there is a significant relationship between oxidative stress and obstructive ATH support this information (5,7). Doğruer et al.(12) found excessive ROS production in individuals with obstructive ATH while Abuhandan et al. (5) and Ekinci et al. (13) reported that total oxidant status and oxidative stress index levels were significantly higher in children with ATH. In our study, we investigated the levels of 8-OHdG, MDA and PCO, which are indicators of oxidative stress in adenoid and tonsillar tissues

and body fluids (blood, urine) of children with ATH. One of the important results obtained in the study is that the preoperative serum 8-OHdG, PCO and MDA levels of the patient group were significantly higher than the postoperative period.

8-OHdG levels rise as a result of damage to DNA by ROS during various biochemical reactions (6,14). 8-OHdG is the most frequently studied oxidative stress parameter as a DNA damage indicator (15,16). Under normal circumstances, 8-OHdG is excreted in the urine during DNA repair (17). In our study, we determined that serum 8-OHdG levels decreased significantly after ATH surgery. The decrease in 8-OHdG levels compared to the preoperative period suggests that oxidative stress may play a role in the etiopathogenesis of ATH. Yörük et al. (18) found that serum 8-OHdG and MDA levels in children with adenotonsillar hypertrophy were higher than in the control group. In the same study, they reported that urinary 8-OHdG levels were higher in children with obstructive adenotonsillar hypertrophy compared to the control group. They suggested that the use of 8-OHdG levels in the evaluation of oxidative damage in children with obstructive adenotonsillar hypertrophy may be a useful marker.

Another important finding was that serum MDA levels were higher in children with ATH than in controls. There are similar studies stating that MDA levels decrease after tonsillectomy in children with chronic tonsillitis, acute otitis media and ATH (18-20). Cethana et al. (21) in their study, it was determined that children with chronic tonsillitis had low antioxidant capacity and their superoxide dismutase levels increased relatively after tonsillectomy. In the same study, it was reported that serum MDA levels of the patient group decreased compared to the preoperative period, but could not reach the levels of the control group (21).

In our study, MDA and PCO levels of adenoid/tonsillar tissues were also determined to investigate the role of free radicals in the pathogenesis of ATH. It was determined that adenoid tissue PCO levels of ATH patients were higher than tonsil tissue levels. When the relevant literature is examined, it is the first study in which PCO levels were determined in adenoid/tonsillar tissue samples of children with adenotonsillar hypertrophy and it is important in terms of its results. Repeated exposure of adenoid and tonsillar tissues with pathogenic microorganisms causes intense episodes of hypoxia/reoxygenation and this situation disrupts the balance of ROS production and antioxidant defense. The presence of deep-going mucosal folds larger than the palatine tonsils in the unencapsulated adenoid tissue suggests that this tissue may be more affected by oxidative stress caused by recurrent upper respiratory tract infections (22). Again, our result, the high PCO levels in adenoid tissue, may be due to the fact that the half-life of PCO is longer than that of lipid peroxidation products (23). ROS that increase as a result of oxidative stress cause oxidative modifications on proteins and thus lead to structural and functional changes of proteins (24). PCO is the most widely used marker of protein oxidation and is widely used in the evaluation of oxidative damage (25,26). In our study, it was determined that PCO levels decreased after surgical intervention. In line with these findings, we can say that children with adenotonsillar hypertrophy are under oxidative stress and the increase in oxidative stress may play an important role in the pathogenesis of the disease.

CONCLUSION

The most common cause of upper airway obstruction, which is common in the paediatric population, is the loss of hypertrophic tonsillar muscle tone, as well as many clinical conditions such as difficulty in breathing, mouth breathing, speech and feeding disorders, recurrent respiratory tract infections, and otitis media (27,28). This situation negatively affects the health and quality of life of children (29). In line with our findings, we can say that serum and urine MDA levels and tissue PCO levels are useful markers in the evaluation of oxidative damage in children with obstructive ATH and may help to elucidate the etiopathogenesis of the disease. Considering the additional health problems that ATH may cause, it is recommended to be considered as an important health problem and to examine clinical, biochemical and histopathological studies in a larger sample group.

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Clinical Characteristics of Pediatric Patients with Urea Cycle Disorders

Kliniğimizde Üre Döngüsü Bozukluğu Nedeniyle Takipli Olan Hastaların Klinik Özelliklerinin Değerlendirilmesi

Cigdem Seher KASAPKARA[1], Asburce OLGAC[2], Mustafa KILIC[2], Johannes HAEBERLE[3]

[1]Department of Pediatric Metabolism, Ankara Yıldırım Beyazıt University, Ankara City Hospital, Ankara, Turkey
[2]Department of Pediatric Metabolism, Dr. Sami Ulus Maternity and Child Health Training and Research Hospital, Ankara, Turkey
[3]Department of Metabolism and Children`s Research Center, University Children's Hospital, Zurich, Switzerland.

ABSTRACT

Objective: Urea cycle disorders (UCDs) are inherited deficiencies of the enzymes or transport molecules involved in the cellular excretion of excess ammonia produced during protein metabolism. The aim of this study was to evaluate the clinical characteristics and long-term outcome of pediatric patients with UCDs.

Material and Methods: Our research was conducted between September 2020-March 2021 in Dr. Sami Ulus Maternity and Child Health Training and Research Hospital. Clinical characteristics in 16 patients with UCDs [carbamoyl phosphate synthetase I deficiency (n=1), N-acetylglutamate synthase deficiency(n=1), argininosuccinate lyase deficiency (n=4), argininosuccinate synthetase deficiency (n=4), arginase deficiency (n=2), ornithine transcarbamylase deficiency (n=2), hyperammonemia hyperornithinemia homocitrullinuria syndrome (n=2)] were defined. The term "neonatal-onset" UCD was used if symptoms occurred within 28 days of life, and "late-onset" if symptoms started after the neonatal period.

Results: Eight patients presented with acute metabolic crisis during newborn period. Core clinical phenotype in neonatal-onset UCDs included sepsis-like findings, whereas epilepsy and mental retardation was predominant in late-onset UCDs. For patients with neonatal-onset UCDs, hyperammonemia was more severe at the initial period.

Conclusion: Despite evolving treatment opportunities, still high mortality rates were found in neonatal-onset UCD. UCDs should be suspected in pediatric patients with hyperammonemia and metabolic investigations should be performed immediately to enlighten diagnosis. Neonatal-onset UCD usually present with symptoms of acute hyperammonemia, while moresubtle neurological manifestations are frequent initial findings in the late onset UCD.

Key Words: Hyperammonemia, Neonate, Inborn urea cycle disorders

ÖZ

Amaç: Üre döngüsü bozuklukları (ÜDB'leri), protein metabolizması sonucunda üretilen amonyağın hücresel atılımında yer alan enzimlerin veya taşıyıcı moleküllerinin kalıtsal eksikliklerinden kaynaklanan doğumsal metabolik hastalıklardır. Bu çalışmanın amacı, bölümümüzde takipli olup, ÜDB olan pediatrik yaş grubundaki hastaların klinik özelliklerini ve uzun dönem sonuçlarını değerlendirmektir.

0000-0002-3569-276X : KASAPKARA CS
0000-0002-4989-221X : OLGAC A
0000-0002-6553-9221 : KILIC M
0000-0003-0635-091X : HAEBERLE J

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 ethics commitee of Ankara City Hospital (1099/16.09.2020).

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

How to cite / *Atıf yazım şekli* : Olgac A, Kasapkara CS, Kilic M and Haeberle J. Clinical Characteristics of Pediatric Patients with Urea Cycle Disorders. Turkish J Pediatr Dis 2023;17:101-105.

Correspondence Address / Yazışma Adresi:

Cigdem Seher KASAPKARA
Department of Pediatric Metabolism,
Ankara Yıldırım Beyazıt University, Ankara City Hospital, Ankara, Turkey
E-posta: cskasapkara@gmail.com

Received / Geliş tarihi : 05.04.2022
Accepted / Kabul tarihi : 03.06.2022
Online published : 19.08.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.1098695

Gereç ve Yöntemler: Araştırmamız Eylül 2020-Mart 2021 tarihleri arasında, Dr. Sami Ulus Kadın Doğum ve Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi'nde gerçekleştirildi. ÜDB olan 16 hastada [karbamoilfosfatsentetaz I eksikliği (n=1), N-asetil glutamate sentaz eksikliği(n=1), arginino süksinat liyaz eksikliği (n=4), argininosüksinat sentetaz eksikliği (n=4), arginaz eksikliği (n=2), ornitin transkarbamilaz eksikliği (n=2), hiperamonyemi-hiperornitinemi-homositrülinüri sendromu (n=2)] klinik özellikler geriye yönelik olarak tarandı. Semptomlar yaşamın 28 günü içinde ortaya çıkmış ise "neonatal başlangıçlı ÜDB" terimi, semptomlar yenidoğan döneminden sonra başladı ise "geç başlangıçlı ÜDB" terimi kullanıldı.

Bulgular: Sekiz hasta yenidoğan döneminde akut metabolik kriz ile başvurmuştu. Neonatal başlangıçlı ÜDB'lerde temel klinik fenotip sepsis benzeri bulguları içerirken, geç başlangıçlı ÜDB'lerde epilepsy ve mental retardasyon baskındı. Neonatal başlangıçlı ÜDB olan hastalarda, başlangıç döneminde hiperamonyeminin daha şiddetli olduğu gözlemlendi.

Sonuç: Gelişmekte olan tedavi yöntemlerine rağmen, neonatal başlangıçlı ÜDB'lerde mortalite oranları halen yüksek olarak seyretmektedir. Neonatal başlangıçlı ÜDB'ler genellikle akut hiperamonyemi semptomları ile kendini gösterirken, nörolojik belirtiler geç başlangıçlı ÜDB'de sıklıkla başlangıç belirtisi olarak karşımıza çıkmaktadır. Hiperamonyemisi olan çocuk hastalarda ÜDB'lerden şüphelenilmeli ve tanıyı aydınlatmak için metabolik incelemeler ivedilikle yapılmalıdır.

Anahtar Sözcükler: Hyperammonemia, Yenidoğan, Doğuştan üre döngüsü bozuklukları

INTRODUCTION

Urea cycle disorders (UCDs) are inherited metabolic disorders (IEMs) related with the defects in one of the enzymes or transporters involved in the detoxification of ammonia by conversion to non-toxic urea. UCDs are defects of breakdown of amino acids due to various genetic variations (1,2).

The involved enzymes are carbamoyl phosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) and arginase (ARG1), the mitochondrial ornithine-citrulline antiporter (ORC1) that leads to hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, the enzyme N-acetylglutamate synthase (NAGS) that activates CPS1 and citrin (mitochondrial aspartate-glutamate antiporter) (1,2). The deficiencies of these enzymes cause subtypes of UCDs including CPS1 deficiency, OTC deficiency, ASS deficiency, ASL deficiency, HHH syndrome, NAGS deficiency and citrine deficiency. All UCDs are inherited autosomal recessively, while OTC deficiency is X-linked. Toxic substances, mainly ammonia accumulate in blood in UCDs and may cause serious organ damage, including mainly the nervous system and the liver, or even death. The presentation may be early or late onset, that may determine the prognosis of disease (3,4).

The aim of this study was to document the characteristics and outcome of pediatric patients with UCDs that were diagnosed in our clinic.

MATERIAL and METHODS

Sixteen patients from different families, that were diagnosed and being followed-up Dr. Sami Ulus Maternity and Child Health Training and Research Hospital between September 2020 – March 2021 were included in the study. Data of patients including age, sex, subtype of UCD, age of presentation, genetic variants and clinical findings were collected from patient files. The term "neonatal-onset" UCD defined that symptoms occurred during the first 28 days of life, and "late-onset" defined symptoms starting afterwards.

Informed consent was obtained from parents of each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki The study was approved by the ethics commitee of Ankara City Hospital (1099/16.09.2020).

RESULTS

Clinical characteristics in 16 patients with UCD; including CPS (n=1), NAGS (n=1), ASL (n=4), ASS (n=4), ARG1 (n=2), OTC (n=2) deficiencies, and HHH syndrome (n=2) were defined. Male to female ratio was 8 / 8. Parental consanguinity was present in 13 out of 16 patients. Eight out of 16 patients presented with acute metabolic crisis during newborn period. Age of presentation varied between 2 to 33 days. The main clinical phenotype in neonatal-onset UCD included sepsis-like neonatal crisis revealed in patients within 28 days after birth, and vomiting and coma were frequently reported. For patients with neonatal-onset UCD, hyperammonemia was more prominent during the first presentation of the disease. Initial levels of ammonia varied between 253-2460 µmol/L. Seven out of 8 neonatal onset patients required extracorporeal detoxification, among which 2 patients received peritoneal dialysis (PD), and 5 received continous venovenous hemodiafiltration (CVHH). The mortality rate in neonatal onset cases was 50%. While two patients with neonatal onset UCD showed normal development and were stable, 2 patients had intellectual disability and developmental delay, among the surviving 4 patients (50%) (Table I).

Among late-onset patients, epilepsy and intellectual disability were predominant, emerging more than 28 days after birth. Five out of 8 late-onset patients had parental consanguinity. Age of presentation varied between 33 days to 10 years. Initial symptoms were vomiting, developmental delay, encephalopathy, behavioural changes and hepatic failure. Initial ammonia levels varied between 51 to 273 µmol/l. Only one patient required extracorporeal detoxification that was

Table I: Clinical characteristics of patients involved in the study.

	Patient (Gender)	Diagnosis	Parental consanguinity	Age at admission	Presenting symptoms	Initial ammonia (µmol/L)*	Dialysis mode	Mutation	Outcome
Neonatal onset	1 (M)	ASSD	+	3 d	Vomiting Coma	495	PD	Homozygous ASS1 c.1085G>T	S: 6 y; normal development
	2 (F)	ASSD	+	3 d	Coma	1293	CVVH	NA	D: 21 d
	3 (F)	CPS1D	+	2 d	Vomiting Coma	1371	PD	Homozygous CPS1 c.622_711delExon7	S: 5 y; intellectual disability
	4 (F)	NAGSD	+	6 d	Coma Septic findings	1418	CVVH	Homozygous NAGS c.1450C>T	S: 18 mo; moderate developmental delay
	5 (F)	ASLD	+	6 d	Vomiting Coma	1404	CVVH	Homozygous ASL c.436C>T	D: 15 d
	6 (M)	ASLD	+	4 d	Coma	2460	CVVH	Homozygous ASL c.446+1G>A	D: 20 d
	7 (M)	ASLD	+	3 d	Coma	2551	CVVH	Homozygous ASL c.556C>T	D: 5 d
	8 (M)	HHH	+	2 d	Asymptomatic (Due to family history)	253	PD	Homozygous SLC25A15 c.692A>T	S: 2 y; stable course
Late onset	9 (M)	ASSD	-	33 d	Vomiting	397	PD	Compound heterozygous ASS1 c.814C>T / c.970 + 5G>A	S: 12 mo
	10 (M)	ASSD	+	10 m	Vomiting Developmental delay	74	-	Homozygous ASS1 c.1085G>T	S: 4 y; mild intellectual disability
	11 (F)	OTCD	-	3.5 y	Vomiting	273	-	Heterozygous OTC c.563G>T	S: 5y; normal growth and development
	12 (F)	OTCD	-	5 y	Recurrent encephalopathy	203	-	Heterozygous OTC C:67C>T	S: 7 y; normal growth and development
	13 (F)	ARGD	+	14 y	Epilepsy Mental retardation	154	-	Homozygous ARG1 c.58-3C>G	S: 16 y; stable course
	14 (F)	ARGD	+	2 y	Status epilepticus Hepatic failure	51	-	Homozygous ARG1 c.703_707delGGACTinsAGACTGGACC	S: 3.5; cessation of hepatic failure episodes
	15 (M)	HHH	+	17 y	Epilepsy	155	-	Homozygous SLC25A15 c.535C>T	S: 18 y; stable course
	16 (M)	ASLD	+	11 y	Epilepsy ADHD	120	-	Homozygous ASL c.370 T>A	S: 16 y; stable course

performed by PD. Six out of eight patients showed stable progress and normal development. Only 1 patient among late-onset patients showed mild intellectual disability (Table I).

Diagnoses of all patients were confirmed with molecular genetic analyses. Genetic variants are shown in Table I.

DISCUSSIONS

UCDs are inherited metabolic disorders caused by the defects of one of the enzymes related to urea cycle. The overall incidence of UCDs is nearly 1:35.000 births, and they are all inherited autosomal recessively other than OTC deficiency which is X-linked. Hyperammonemia that is toxic to the central nervous system (CNS) accumulates in bloodstream in UCDs (3,4).

Symptoms of UCDs may occur abruptly, or may manifest in a more chronic way, especially in older ages. Acute symptoms are usually triggered by catabolic events or protein intake. Clinical features are typical in neonatal cases, where enzyme deficiency is complete, which present as hyperammonemic episodes soon after birth with high mortality, and patients experience severe neurological sequela and recurrent hyperammonemic episodes (2). Partial deficiencies present with variable clinical presentations and are later onset, usually present as recurrent attacks of vomiting or encephalopathy. Hepatic and psychiatric findings have been reported. Some specific symptoms may also present, e.g., hair shaft abnormalities (trichorrhexis nodosa) in ASL deficiency and progressive spastic diplegia in ARG1 deficiency and HHH syndrome (5,6).

The initial presentations of our patients were also in accordance with the literature. The neonatal cases mainly presented as hyperammonemic encephalopathy and vomiting, while late-onset patients showed variable manifestations related with the subtype of underlying UCD (e.g. intellectual disability, spasticity, growth retardation) (7). According to the study of Dorum et al. (7), neonatal-onset patients mostly presented as an acute metabolic attack including sespsis like findings, feeding disorder and coma, while later onset patients had chromic symptoms.

Hyperammonemia is an indicator of nitrogen detoxification and is a hallmark for many UCDs. Since the length and quantity of hyperammonemia are related with CNS damage, early diagnosis and treatment is essential. Protein intake should be stopped immediately in a hyperammonemic patient and intravenous dextrose infusion should be given along with nitrogen scavenger drugs (if ammonia level is above 100 umol/L). This is valid for UCDs other than citrin deficiency, as high glucose and protein restriction may worsen the clinical picture (5). Dialysis should be performed when ammonia levels are higher than 500 µmol/L or when there is no decrease in ammonia levels within four hours after initiation of medical therapy. Long-term management of UCDs consists of low protein diet (other than citrin deficiency) and nitrogen scavengers (5). Liver transplantation is also a treatment option for many UCDs, and is curative since it allows cessation of the low-protein diet, but does not improve neurological sequelae (8). Our patients were also treated in accordance with the mentioned guidelines in the literature. Despite appropriate treatment, neonatal-onset cases had mostly poor prognosis.

Dorum et al. (7) have retrospectively analyzed data of 12 patients with UCD and reported that neonatal-onset patients had poor prognosis when compared to later-onset UCD patients. The authors have emphasized the importance of early diagnosis to be the most important measure to improve long term survival. Similiar to findings of Dorum et al. (7), in our patient series, patients with highest ammonia levels also had died in the early course of disease. Within our patient group, ammonia levels ranged between 51 to 2460 µmol/L, and neonatal-onset cases demonstrated higher levels. Due to this condition, 85% of neonatal-onset cases required extracorporeal detoxification.

Bachman has analyzed the outcome of 88 patients with UCDs (9). The author has concluded that, there was an increased risk of intellectual disability in the neonatal-onset group despite extensive treatment, and none of the patients whose plasma ammonia levels were higher than 300 µmol/l initially, had a normal cognitive outcome. Similarly, in our patient group, poor outcome was observed in the neonatal-onset group where ammonia levels were severely increased (above 1000 µmol/L). Our findings also support the fact that hyperammonemia should be detected at the earliest period and treated immediately to prevent irreversible neurological damage and deaths.

Despite the treatment opportunities, mortality rates are still high in neonatal-onset UCDs-around 60%. In our series of patients mortality rate was similar to the rate reported in the literature (%50 among neonatal cases) (8,10). A meta-analysis that has reviewed the observational studies on UCDs, that were published over more than 35 years, has concluded that all UCDs, except female OTCs, have high risks for early onset disease, and neonatal death except for ASLD. It has also been underlined that no improvement of survival was observed over more than three decades (11). In accordance with the findings of this study, our study population also shows that, despite evolving treatment opportunities, mortality among UCD patients is still high, especially among early onset patients, and the underlying subtype of UCD is an important determinant of prognosis.

CONCLUSION

UCDs should be suspected in neonates with hyperammonemia and metabolic tests including ammonia level should be performed immediately to enlighten underlying diagnosis. Although neurological manifestations are reported to be more diagnostic in the late onset UCD, severe hyperammonemia may

cause irreversible neurological damage in the newborn period, and early diagnosis and treatment is essential for prevention.

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Psychological Impacts and Coping Strategies in the Early Period of COVID-19 Pandemic: An Online Self-reported Study in Turkish Child and Adolescent Population

COVİD-19 Pandemisi Erken Döneminde Psikolojik Etkiler ve Başa Çıkma Becerileri: Türk Çocuk ve Ergen Yaş Grubunda Çevrimiçi Bir Ölçek Çalışması

Ayse TOKSOY AKSOY[1], Irem CIHANYURDU[1], Cagla ILBASMIS[1], Hatice UNVER[2], Ayse RODOPMAN ARMAN[1]

[1]Department of Child and Adolescent Psychiatry, Marmara University Medical Faculty, Istanbul, Turkey
[2]Department of Child and Adolescent Psychiatry, Marmara University, Pendik Research and Training Hospital, Istanbul, Turkey

ABSTRACT

Objective: This study determines the psychological problems and coping strategies of children and adolescents during the lockdown applied in the early period of COVID-19 pandemic in Turkey

Material and Methods: The study includes the data of an online self-report questionnaire applied between 12-17th April 2020. The questionnaire consists data about family and peer relationships, online education, psychological responses, activities and newly acquired hobbies during the lockdown.

Results: A total of 717 participants, 278 children (mean age 10.36±1.49 years) and 439 adolescents (15.49±1.72 years) participated in online survey. A statistically significant difference was found in the child and adolescent groups in terms of age ($p < 0.005$). Although girls participated in the survey more in both groups, this rate was significantly higher in the adolescent group ($p = 0.017$). Adolescents significantly more communicated with their friends via social media ($p = 0.000$) than children, children had more attention problems in online education than adolescents ($p = 0.000$). Pandemic caused similar-moderate levels of anxiety in children and adolescents, symptoms such as difficulty falling asleep, reluctance and attention problems were significantly more in adolescents, headache, fatigue and weakness were higher in children. During the lockdown, children and adolescents engaged in activities and had new hobbies at a similar rate to reduce their anxiety or spending time at home ($p = 0.260$, $p = 0.870$). While the children mostly spent time with their family, adolescents spent more time with technology and social media.

Conclusion: The results of this study based on self-report will provide important data on children and adolescents during the lockdown period. The ongoing COVID-19 pandemic will have long-term effects, and the data of this early study may lead new studies, also the results may assist in taking measures in the field of child and adolescent mental health.

Key Words: Adolescent, Children, Coping Strategies, COVID-19 Pandemic, Lockdown, Psychological Effect

0000-0002-4080-9061 : TOKSOY AKSOY A
0000-0001-9141-0379 : CIHANYURDU I
0000-0002-5813-711X : ILBASMIS C
0000-0003-2067-9770 : UNVER H
0000-0002-6884-0706 : RODOPMAN ARMAN A

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, which was planned as a descriptive cross-sectional study, was approved by Marmara University, Faculty of Medicine, Clinical Research Ethics Committee. (20.05.2020/09.2020.558).

Contribution of the Authors / Yazarların katkısı*: *TOKSOY AKSOY A: Constructing the hypothesis or idea of research and/or article, Taking responsibility in patient follow-up, data management and reporting, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***CIHANYURDU I:*** Constructing the hypothesis or idea of research and/or article, Taking responsibility in patient follow-up, data management and Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***ILBASMIS C:*** Constructing the hypothesis or idea of research and/or article, Taking responsibility in patient follow-up, data management and reporting, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***UNVER H:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***RODOPMAN ARMAN A:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / *Atıf yazım şekli* : Toksoy Aksoy A, Cihanyurdu I, Ilbasmiş C, Unver H and Rodopman Arman A. Psychological Impacts and Coping Strategies in the Early Period of COVID-19 Pandemic: An Online Self-reported Study in Turkish Child and Adolescent Population. Turkish J Pediatr Dis 202X;

Correspondence Address / Yazışma Adresi:
Hatice UNVER
Department of Child and Adolescent Psychiatry,
Marmara University Medical Faculty, Istanbul, Turkey
E-posta: drhaticeunver@gmail.com

Received / Geliş tarihi : 26.12.2021
Accepted / Kabul tarihi : 20.06.2022
Online published : 18.08.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.1047592

ÖZ

Amaç: Bu araştırmada COVİD-19 salgını nedeniyle Türkiye'de erken dönemde uygulanan sosyal kısıtlama sürecinde çocuk ve ergenlerin ruhsal durumları ve baş etme becerileri ele alınmıştır.

Gereç ve Yöntemler: Araştırma 12-17 Nisan 2020 tarihleri arasında self-report (öz-raporlama) olarak uygulanan çevrim içi bir anketin verilerini içermektedir. Anket aile ve akran ilişkileri, çevrim içi eğitim, ruhsal yanıtlar, etkinlikler ve yeni edinilen hobilere ilişkin soruları içermektedir.

Bulgular: Anketimize 7-12 yaş grubundan 278 çocuk (yaş ort 10.36±1.49 yıl), 13-18 yaş grubundan 439 ergen (15.49±1.72 yıl) olmak üzere toplam 717 kişi katılmıştır. Yaş açısından çocuk ve ergen grubunda istatistiksel olarak anlamlı farklılık saptanmış ($p < 0.005$). Kızların her iki grupta da ankete daha fazla katıldığı gözlenmekle birlikte bu oran ergen grubunda anlamlı olarak daha yüksek olmuştur ($p = 0.017$). Ergenlerin arkadaşları ile sosyal medya üzerinden anlamlı olarak daha fazla iletişim halinde olduğu saptanmış ($p=0.000$), çocuk yaş grubunun ergenlere göre çevrim içi eğitimde daha fazla dikkat sorunları yaşadığı ($p=0.000$) görülmüştür. Pandemi ve karantinanın çocuk ve ergenlerde benzer düzeyde kaygı oluşturduğu gözlenmiş, uykuya dalma zorluğu, isteksizlik ve dikkat sorunları ergenlerde, baş ağrısı, yorgunluk ve halsizlik gibi belirtiler ise çocuklarda anlamlı olarak daha fazla saptanmıştır. Karantina sürecinde çocuk ve ergenlerin kaygılarını azaltmak ya da vakit geçirmek için benzer oranda etkinliklerde bulunduğu ve hobi edindiği gözlenmiştir ($p= 0.260$, $p=0. 870$). Çocuk yaş grubu en çok ailesi ile vakit geçirirken, ergen yaş grubu daha çok teknoloji ve sosyal medya ile vakit geçirmekteydi.

Sonuç: Özbildirime dayanan çalışmamızın sonuçlarının karantina döneminde çocuk ve ergenlerle ilgili önemli veriler sağlayacağı düşünülmektedir. Halihazırda devam eden COVİD-19 pandemisinin uzun süreçli etkilerinin olacağı akla gelmekte, erken dönemde yapılan bu çalışmanın verilerinin yeni çalışmalara öncülük edebileceği düşünülmektedir.

Anahtar Sözcükler: Ergen, Çocuk, Baş Etme Stratejileri, COVİD-19 Pandemisi, Karantina, Psikolojik Etki

INTRODUCTION

COVID-19 disease was diagnosed first in Wuhan, China on December 31, 2019, and was soon declared as a public health emergency by the World Health Organization (1). After the first COVID-19 case was seen on 13 March 2020 in Turkey, various policies were taken by the government in many areas. In the first place, primary, secondary and high school education was discontinued and online education was started. Social isolation policies were taken to prevent the spread of the virus, so most of the families had to take a break from their work or started remote working at home. In early April 2020; with the start of the curfew under the age of 20 in Turkey, children and adolescents started to spend all their time at home. Although the presence of all family members at home at same time with the curfew may lead to family unity and closer relationships, it is stated that acute isolation, just like hunger, can cause social craving (2). The prolonged isolation, especially such as the lockdown process, may cause difficulties in the family environment and relationships. Factors such as following the new about the epidemic in all social platforms, fear of having or contacting COVID-19, adaptation process to online education at home, change of duties and responsibilities at home, parents working from home, being a healthcare worker among family members, increasing time spent on social media platforms in this process required. Because individuals will be able to develop different adaptation skills or show psychological responses to all these changing conditions (3,4).

Although it is thought that the COVID-19 epidemic will not affect children much at the beginning, the first data reported from China show that children and adolescents are psychologically affected and had behavioral problems (5,6). Childhood and adolescence are vulnerable two age periods, and it is conceivable that the global COVID-19 pandemic may have different psychological effects in these age groups. The epidemic and lockdown will have many effects on the daily lives of children and adolescents; such as acute and chronic stress, concerns for the health of their caregivers, having unexpected losses, closure of schools, increased time spent on the internet and social media, changing routines, worrying about the economic future of their family and country (4). In a study conducted in the early stages of the pandemic in our country, families observed many psychological symptoms in their children (7). Nevertheless, all these mental difficulties will be affected by the individual characteristics of children and adolescents in different age groups and the environment they live in (8).

The increasing use of social media can be the main source for the social interaction of children and adolescents during the curfew and lockdown period, and also children and adolescents closely follow the news about daily agenda in this period. However, the increase in the use of social media has negative effects. The information disseminated on social media can increase threat perception and anxiety, and lead to clinically depression and anxiety disorders (9).

Different behaviors such as increased exercise, sleeping, online sociality, smoking and alcohol use were observed in adults during lockdown period in COVID-19 pandemic and these behaviors were evaluated as functional / non-functional coping strategies to reduce anxiety (10,11). The children and adolescents may also show different adaptation skills during this period, but there was no study on this area. During the lockdown period, while the daily routines of children and adolescents changed, while spending the time they allocated to school or friendships at home, it was aimed to contribute to the literature by learning what they did, their activities or hobbies. In addition, it will be important to address the changing family environment, educational conditions and peer relationships during the lockdown and the psychological responses from the

language of the children and adolescents. It is clear that there is a need for community-based studies to be carried out in such a special period. This study is a community-based study planned with the participation of children and adolescents in all areas mentioned above, and our primary aim was to obtain cross-sectional data for age groups, and the other aim was to compare these data.

MATERIAL and METHODS

This study includes data from an online self-reporting questionnaire prepared by Marmara University School of Medicine, Department of Child and Adolescent Psychiatry. As a study group, researchers tried to reach with online survey children between the ages of 7-12 and adolescents between the ages of 13-18. The questionnaire was first shared with teachers and families via online communication groups, and they were asked to forward it to other groups they were involved in. The study, which was planned as a descriptive cross-sectional study, was approved by Marmara University, Faculty of Medicine, Clinical Research Ethics Committee. (20.05.2020/09.2020.558). Informed consent was obtained from all participants and their parents. The information of the participants was anonymous.

The online survey conducted during the lockdown period (12-17th April). The total of the questionnaire consists of 26 questions about sociodemographics, family, peer relations, psychological responses and activities and new hobbies in lockdown. While preparing the questions of the questionnaire with the Google-forms program, the book of the International Association of Child and Adolescent Psychiatry and Allied Professions was used (12).

Data Analysis

Analyzes were performed with IBM SPSS (Statistical Package Program for Social Sciences) version 22.0. Continuous variables were evaluated with mean ± standard deviation. In the intergroup analysis of continuous variables, normality analyzes were performed with the Kolmogorov-Smirnov Goodness of Fit Test. Mann Whitney U and Student T-tests were used to investigate the difference between the two groups.

RESULTS

Sociodemographic Variables

278 children (10.36±1.49 years) in the 7-12 age group and 439 adolescents (15.49±1.72 years) in the 13-18 age group participated in online survey (for age p<0.005). In the children group, 147 girls and 131 boys completed the questionnaire, while in the adolescent group, this ratio is 272 girls and 167 boys. The girls participated in the questionnaire more in two

Table I: Psychological responses during the COVID-19 outbreak.

Participants	n	Mean±SD	p
Would you rate the anxiety caused by the epidemic?			
Children	276	3.536±1.3384	0.220
Adolescents	436	3.413±1.2573	
Are you having difficulty falling asleep or having nightmares lately?			
Children	276	2.333±1.3769	0.001
Adolescents	435	2.717±1.6251	
How has your appetite changed recently?			
Children	277	2.874±1.0436	0.870
Adolescents	437	3.011±1.0503	
How often do you research about the pandemic?			
Children	273	2.238±1.2478	0.740
Adolescents	427	2.208±1.0989	
Do you ever have headache, fatigue, weakness?			
Children	278	2.43±0.5897	0.000
Adolescents	435	2.147±0.6557	
Do you ever feel reluctant to usual activities and not focus on your homework in the lockdown?			
Children	275	2.455±1.3457	0.000
Adolescents	426	3.164±1.3945	

*1: none, 2: mild, 3: moderate, 4: quite, 5: much, **SD:** Standart deviation, Student T test.*

Table II: Education and peer relations in the lockdown.

Participants	n	Mean±SD	p
How upset you are that schools were closing and being separated from your friends?			
Children	278	3.658±1.3523	0.200
Adolescents	436	3.523±1.3936	
Do you find it difficult focusing on online education?			
Children	275	3.549±1.3777	0.000
Adolescent	433	2.880±1.3538	
Do you regularly do your online homework and follow your teachers' directions?			
Children	276	4.094±1.2023	0.000
Adolescent	432	3.227±1.3382	
How does it feel to meet your friends online or on social media?			
Children	255	3.906±1.2163	0.530
Adolescents	430	3.849±1.1232	

*1: none, 2: mild, 3: moderate, 4: quite, 5: much, **SD:** Standart deviation, Student T test*

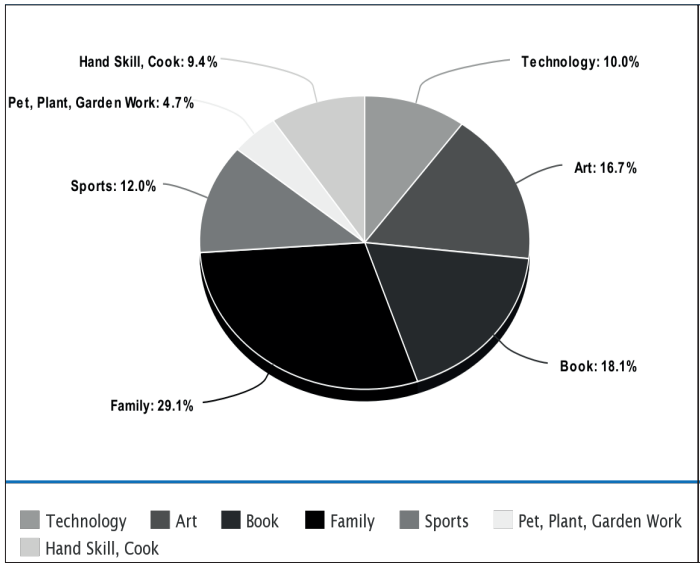

Figure 1: Children's activities in the lockdown.

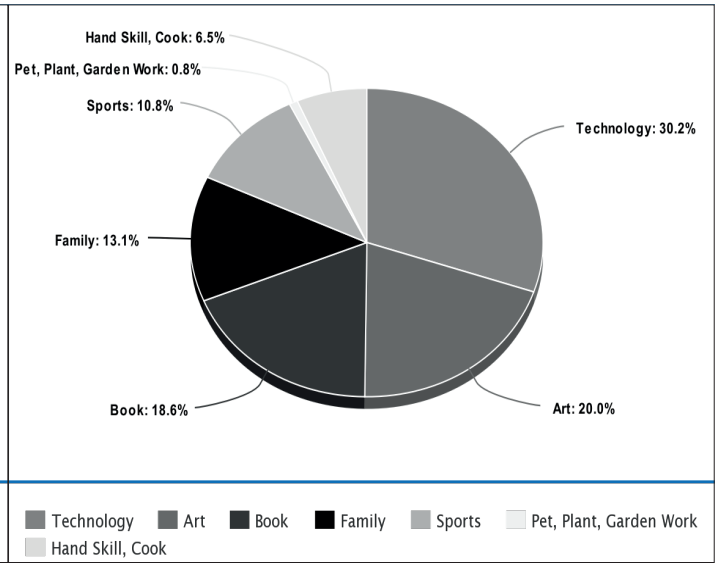

Figure 2: Adolescents' activities in the lockdown.

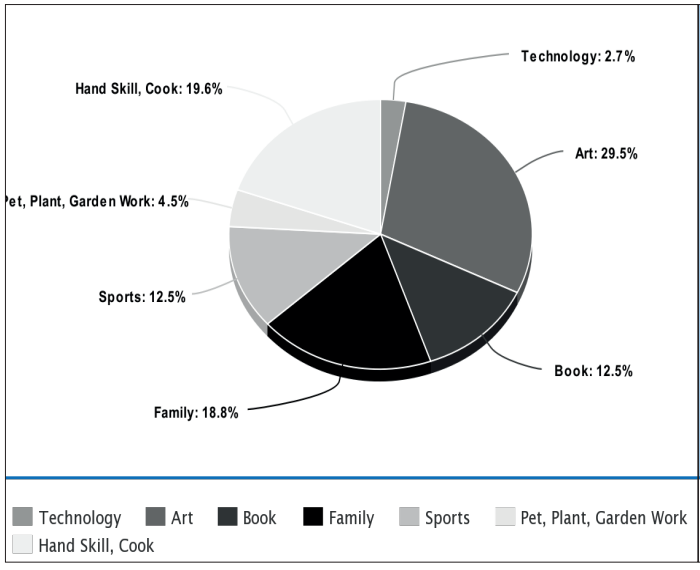

Figure 3: Children's new hobbies in the lockdown.

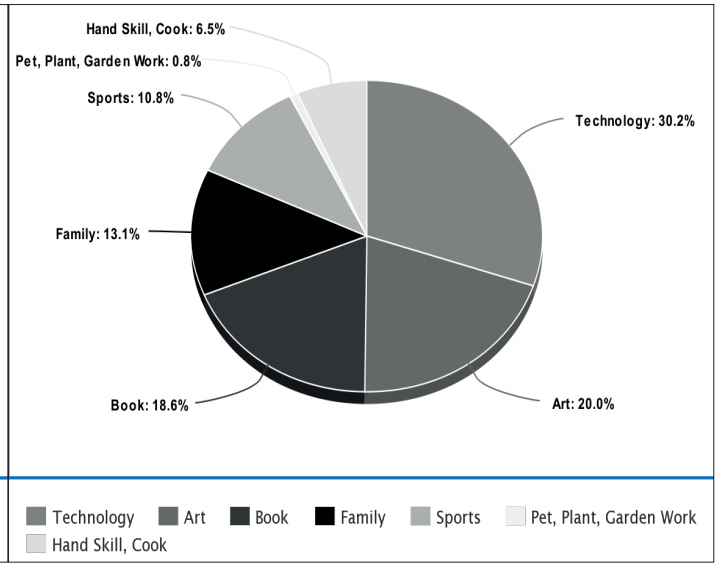

Figure 4: Adolescents' new hobbies in the lockdown.

groups, and a significant difference was observed between the groups in terms of gender (p = 0.017). While the majority of the child participants resided in Istanbul, Ankara or Izmir (3 metropolitan cities in Turkey), the majority of the adolescent participants were living in cities other than Istanbul, Ankara and Izmir (p = 0.000). 62 of the children group and 109 of the adolescent group have healthcare workers in their families (p = 0.430).

Family Environment and Relationships

Regarding the question about whether they were separated from family members during the lockdown, 233 participants in the children group answered 'no', this rate was 382 in the adolescent group, and there was no difference between the groups (p=0.260). The mean of the answers given to fear of having family members' COVID-19 were found to be 3.55± 1.43 in children and 3.44±1.33 in adolescents. It was observed that children had more fear than adolescents (p=0.300). 'Are you spending enough time with your family?' the answers to this question were 'yes' at a high rate in both groups, but no difference was found (p=0.860). The children and adolescents who answered 'no' to this question have been asked to choose one or more of 8 reasons as answers (We are not at the same house because they are healthcare workers, they have to take care of housework, they have to work from home, they are interested in the care of my other siblings, they are constantly following the news about the epidemic on television and the press, communicating with my friends on social media takes time, online education and lessons take my time, they have another). 44% of the children and 47.7% of the adolescents

who think that they cannot spend enough time with their families say that online education and lessons take their time, the rates of following news on television and the press were like 45.9% and 40.3%, take care of housework rates were like 52.3% and 43.8% in the child and adolescent groups, respectively.

Psychological Responses

Pandemic and lockdown cause similar-moderate levels of anxiety in children and adolescents, symptoms such as difficulty falling asleep, reluctance and attention problems were significantly more in adolescents, and headache, fatigue and weakness were found significantly higher in children (Table I). Following the questions about psychological responses, the participants were asked 'Would you like to get psychological professional help at the end of the lockdown?' 85 participants in children group and 111 participants in the adolescent group said 'yes', no significant difference was found between the groups (p=0.140), and psychological help-seeking was less in both groups.

Education and Peer Relations in the Lockdown

During the lockdown, 192 of the children and 419 of the adolescents stated that they communicated with their friends via social media (such as whatsapp, instagram, facebook). The adolescents were in more communication with their friends via social media (p = 0.000) (Table II).

Activities and New Hobbies in the Lockdown

The participants were asked 'Do you have activities to reduce your anxiety or spend time in this process?' the answers to this question (yes / no) were examined, 204 children said 'yes', and 299 adolescents said 'yes', and there was no difference between the groups in terms of activities (p=0.260). The answers to the open-ended question asked to those who answered 'yes' are shown separately in the child and adolescent group in graph form (Figure 1-2). The participants reported more than one answer. While the children group mostly spent time with their family, the adolescent group spent more time with technology.

The participants were asked Have you acquired any new hobbies to reduce your anxiety in lockdown?' the answers to this question (yes / no) were examined, 108 children said 'yes', 165 children said 'no', and 175 adolescents said 'yes' and 260 adolescents said 'no', and there was no difference between the groups in terms of acquiring a new hobby (p=0.870). The answers to the open-ended question asked to those who answered 'yes' are shown separately in the child and adolescent group in graph form (Figure 3-4). The participants reported more than one answer. The answers given are also grouped within themselves. As an example of the answers given; individual and family games such as lego, board-box games, painting (mandala, oil painting), learning to play guitar, violin, dancing, sports, watching movies, growing plants, experiments, learning to cook, book. Both children and adolescents have a low rate of acquiring new hobbies during the lockdown.

DISCUSSION

The results of this online self-reporting study showed that children and adolescents experienced changes in family and friend relationships during the lockdown, had difficulties in online education, changed their daily routines and engaged in many activities to reduce their anxiety and spending time at home. In addition, they expressed that they complained many psychological symptoms. The high number of adolescents participating in this study spent more time on social media and internet, and it was also found that adolescents communicated significantly more with their friends through social media than children. This situation may have been caused by the adolescent group to have their own mobile phones and to be able to access technology and internet platforms more easily as of their age. Also, similar to the results of our study, in a study conducted in our country, researchers found that adolescents spend most of the day in front of the screen during the pandemic period (13). The fact that adolescents spend more time on online platforms may have become a coping strategy or an effort to create personal space for themselves. However, spending too much time on online platforms during the lockdown may increase the perception of threats and level of anxiety and these may cause psychological disorders (14).

The health care workers were few in the families of the participants, and also the participants experienced moderate fear of their families having COVID-19, including more in the child age group. This may have been caused by the online survey being applied about 3 weeks after the lockdown began. According to the results of another online survey conducted during the same period, the level of anxiety of children and adolescents during the lockdown and the frequency of following the news and agenda associated with COVID-19, decreased at the end of lockdown (15). In addition, the resilience levels of the participants, the supportive environment they live in, and their family relationships may have caused their anxiety level to be at a moderate level.

The COVID-19 pandemic and lockdown may lead to many cognitive, emotional, social and physical stress responses in children and adolescents. Symptoms such as attention and memory problems, social withdrawal, somatic symptoms, sleep and appetite problems, behavioral and temperament changes, being more angry can be observed. In addition, stress factors such as the long process of the pandemic, the continued fear of having infection, the spreading information about the epidemic, not being able to communicate face to face with classmates and teachers, lack of personal space at home, economic difficulties and tensions that can lead to domestic violence can make this period different from other stressful life periods. In this study, children and adolescents complained about many psychological symptoms, difficulty getting asleep, reluctance and attention problems were significantly more common in adolescents and symptoms such as pain and weakness were

significantly more common in children. These symptoms may be precursor symptoms of psychiatric diagnoses. Studies have shown that the COVID-19 pandemic leads to symptoms of depression and anxiety, and those who describe these symptoms have a level of clinically diagnosed symptoms (16,17). At the end of the lockdown, psychological professional help-seeking was low in both children and adolescents, and this may have been caused by the fear of contracting COVID-19 in hospital admissions, not paying attention to psychological symptoms as much as physical symptoms, cost factors, lack of awareness and stigma. It is also stated that trusting in medical institutions decreased during these period in all around the world and this pushed individuals not to seek help (18). Although the children group experienced significantly more attention problems in online education than adolescents, but they did more homework in online education and adapted more to the instructions of their teachers. Considering that face-to-face education is more efficient for children, and skills such as school and classroom adjustment, studying, and homework are acquired during primary school, it is clear that children will experience more difficulties in this period than adolescents.

The functional and non-functional coping strategies used when faced with any stressful life events can be different in every child and adolescent. These coping strategies may be affected by the individual, family characteristics and environmental support of children and adolescents (19,20). Decreased peer and teacher support during this period, the change of family relations, increasing tensions may affect coping (11). The burnout in parents increases during the lockdown and this also negatively affects the parent-child/adolescent relationship (21,22). In a multicenter study conducted in our country, the anxiety levels of parents are high in the pandemic, and low education level and being at a young age increase the level of anxiety. (23).

In our study, children and adolescents do many activities to reduce their anxiety or spending time at home, while the children group spent more time with their parents, the adolescent group spent time with technology. At the same time, the majority of participants considered spending enough time with their family. The adolescent group may have preferred to spend more individual time or be in relationships with their peers through technology due to their age period features. In this period, the low rate of hobby acquisition may be related to the difficulty of accessing training and materials for the hobbies researched, or the uncertainty of lockdown and pandemic process may have made it difficult to start a new activity, and more time was spent with routine or usual activities.

This study has some limitations. These limitations include the lack of evaluation of psychological symptoms and coping strategies with a valid self-report measures, the lack of clinically re-evaluation of this data and the lack of information from parents. In addition, the participants generally live in metropolitan cities and the difficulties in the countryside are not addressed, this is preventing the generalisation of the study's data. Nevertheless the results of this study can help to plan early what can be done in similar pandemics. It can contribute to creating new policies in the field of education and mental health. The development and dissemination of services similar to the telemedicine intervention for children with special needs, which were successfully carried out in the early period of the pandemic in Turkey, may help children and adolescent age groups who stay at home during the quarantine period (24). In addition, these results will help clinicians to predict the long-term consequences of symptoms seen in the early stages of pandemic. Long-term follow-up studies are needed in this area.

CONCLUSION

The data obtained through self-reporting would contribute to the literature for children and adolescents living both in Turkey and other countries of the world in the early part of the pandemic and could lead new studies. Also the questions of the online survey may help to develop the awareness of the participants about psychological symptoms and may encourage them to seek psyhological help.

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Vitamin B12 and Folic Acid Levels in Patients with Breath Holding Spells

Katılma Nöbeti Olan Hastalarda B12 Vitamini ve Folik Asit Düzeyleri

Hilal AYDIN[1], Ibrahim Hakan BUCAK[2], Sumeyye ERDOGAN[2]

[1]Department of Pediatrics, Balikesir University, Faculty of Medicine, Balikesir, Turkey
[2]Department of Pediatrics, Faculty of Medicine, Adiyaman University, Adiyaman, Turkey

ABSTRACT

Objective: Breath holding spells are a benign, non-paroxysmal disorder observed in childhood. The pathogenesis of breath holding spells is still unclear. Dysfunction of the autonomic nervous system, iron deficiency, genetic predisposition, interleukin 1, nitric oxide and cerebral erythropoietin have been implicated in the pathogenesis. The purpose of this study was to compare vitamin B12 and folic acid levels between patients diagnosed with breath holding spells and a healthy group.

Material and Methods: Fifty-one cases diagnosed with breath holding spells in the pediatric neurology clinic were included in the study group (Group 1), and 78 healthy patients presenting to the general clinic in the control group (Group 2). Hemoglobin, hematocrit, mean erythrocyte volume, vitamin B12, folic acid, ferritin, iron, and iron binding capacity levels were compared between the study and the control groups.

Results: Mean folate levels were 18.92±12.83 (5.27-91) ng/mL in the study group and 9.95±8.92 (2-37) ng/mL in the control group. Mean B12 levels were 274.13±214.37 (75-1201) pg/mL in the study group and 408.82±194.18 (120-959) pg/mL in the control group. Statistically significant differences in both vitamin B12 and folic acid levels were observed between the groups (p=0.000 and p=0.002, respectively). No significant difference was determined between the attack groups' (<15/month, >15/month) vitamin B12 (p=0.570) or folic acid (p=0.643) levels.

Conclusion: Based on this study, vitamin B12 and folic acid levels should be routinely evaluated in patients diagnosed with breath holding spells.

Key Words: Child, Folic acid, Treatment, Vitamin B12

ÖZ

Amaç: Katılma nöbetleri, çocukluk çağında görülen iyi huylu, paroksismal olmayan bir hastalıktır. Katılma nöbetlerinin patogenezi çok açık değildir. Patogenezde otonom sinir sistemi disfonksiyonu, demir eksikliği, genetik yatkınlık, interlökin 1, nitrik oksit ve serebral eritropoietinin sorumlu olabileceği ileri sürülmektedir. Bu çalışmada katılma nöbeti olan hastalar ile sağlıklı grup arasında B12 vitamini ve folik asit düzeylerinin karşılaştırılması amaçlandı.

Gereç ve Yöntemler: Çocuk nörolojisi kliniğinde katılma nöbeti tanısı konulan 51 olgu çalışma grubuna (Grup 1), genel pediatri kliniğine başvuran 78 sağlıklı hasta kontrol grubuna (Grup 2) alındı. Çalışma ve kontrol gruplarında hemoglobin, hematokrit, ortalama eritrosit hacmi, vitamin B12, folik asit, ferritin, demir ve demir bağlama kapasiteleri karşılaştırıldı.

0000-0002-2448-1270 : AYDIN H
0000-0002-3074-6327 : BUCAK IH
0000-0002-9236-3516 : ERDOGAN S

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 Institutional Ethics Committee of Adiyaman University, Faculty of Medicine, and ethical approvals were obtained prior to initiation of the research work (22.09.2020-2020/8-18).

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

How to cite / *Atıf yazım şekli* : Aydin H, Bucak IH and Erdogan S. Vitamin B12 and Folic Acid Levels in Patients with Breath Holding Spells. Turkish J Pediatr Dis 2023;17:113-117.

Correspondence Address / Yazışma Adresi:
Hilal AYDIN
Department of Pediatrics, Balikesir University,
Faculty of Medicine, Balikesir, Turkey
E-posta: drhilalaydin@gmail.com

Received / Geliş tarihi : 27.03.2022
Accepted / Kabul tarihi : 24.06.2022
Online published : 06.09.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.1094163

Bulgular: Çalışma grubunda ortalama folat düzeyi 18.92±12.83 (5.27-91) ng/mL, kontrol grubunda ortalama folat düzeyi 9.95±8.92 (2-37) ng/mL, ortalama B12 düzeyi çalışma grubu 274.13±214.37 (75-1201) pg/mL, kontrol grubunda ortalama B12 düzeyi 408.82±194.18 (120-959) pg/mL'di. Gruplar arasında B12 vitamini ve folik asit düzeylerinde istatistiksel olarak anlamlı fark bulundu (p=0.000, p=0.002). Atak gruplarının (<15/ay, >15/ay) B12 vitamini (p=0.570) ve folik asit (p=0.643) düzeyleri arasında anlamlı fark saptanmadı.

Sonuç: Bu çalışma sonucunda katılma nöbeti olan hastalarda B12 vitamini ve folik asit düzeylerinin rutin olarak değerlendirilmesi gerektiği kanaatine varıldı.

Anahtar Sözcükler: Çocuk, Folik asit, Tedavi, B12 Vitamini

INTRODUCTION

Breath holding spells are a benign, non-paroxysmal disorder usually observed in childhood. These may occur in children between the ages of six months and six years. Approximately 0.1-4.6% of children younger than two years have been reported to experience one or more breath holding spells (1,2). Such spells are defined as short, involuntary respiratory arrest in children in response to stimuli such as anger, disappointment, fear or injury, although the pathogenesis is not completely understood (3). Factors that precipitate breath holding spells can be prevented by distracting or keeping the child away from those triggers. The attacks usually end within one minute, and no postictal period is observed. Breath holding spells are divided into three types - pale, cyanotic, and mixed, depending on the color changes at the time of attack. Attacks arise from an imbalance between sympathetic and parasympathetic activity (1). Pale-type attacks result from cardiac inhibition mediated by the parasympathetic system, and cyanotic-type attacks mostly develop as a result of respiratory inhibition through the sympathetic system (4,5). The cyanotic type is the most common form, representing 52% of cases (6). Although attacks are frequently observed between the ages of six months and six years, the average reported age at onset is under 18 months (7).

Several studies investigating why and how breath holding spells occur have implicated dysfunction of the autonomic nervous system, iron deficiency, genetics, interleukin 1, nitric oxide, and cerebral erythropoietin (8,9).

The purpose of the present study was to evaluate the role of vitamin B12 and folic acid in the etiopathogenesis of breath holding spells by comparing these between patients diagnosed with breath holding spells and a healthy control group.

MATERIAL and METHODS

Fifty-one patients diagnosed with breath holding spells in the pediatric neurology polyclinic in the Adıyaman University Faculty of Medicine, Turkey, between October 2017 and June 2019 were analyzed retrospectively. Diagnosis was based on the crying period, followed by breathlessness with open mouth, and a history of attack with color change in the face and/or body, loss of consciousness, and change in tone. All diagnosed patients were invited to attend pediatric neurology clinic check-ups at two-month intervals. The study was approved by the Institutional Ethics Committee of Adiyaman University, Faculty of Medicine, and ethical approvals were obtained prior to initiation of the research work (22.09.2020-2020/8-18).

Patients with concomitant neurological diseases such as epilepsy, mental retardation, cerebral palsy or a chronic systemic disease, history of seizures, any neurological disorder, and patients taking medications such as vitamin B12, folic acid, and iron were not included in the study. Patients who presented to the general pediatric clinic during the study period, who were aged between six and 72 months, and for whom the code Z00.1: routine child health examination was entered were included as the control group.

The cases' demographic characteristics (age, gender), attack types, attack frequencies, personal and family histories, hemoglobin (Hb), hematocrit (Hct), mean erythrocyte volume (MCV), iron (Fe), iron binding capacities (IBC), and hormonal parameters (ferritin, vitamin B12, folic acid) were recorded. Permission for the study was obtained from the local ethics committee (decision no. 2020/8-19).

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 23.0 software was used for statistical analysis of the study data. The Independent Sample T test was used for parameters with normal distribution and Fischer's Exact test was applied to evaluate categorical variables. The variables were expressed as mean ± standard deviation, number (n), and percentage (%). Equality of variance in the groups was evaluated using Levene's test. $p < 0.050$ value was assumed for statistical significance.

RESULTS

The study group consisted of 51 patients, 32 (62.7%) male and 19 (37.3%) female, and the control group 78 patients, 51 (65.4%) male and 27 (34.6%) female. Mean ages were 3.32 ±1.01 (1-6) years in the study group and 3.04 ±1.19 (1-6) years

Table I: Demographic features of the study and control groups.

	Study group n (%)	Control group n (%)	p
Male	32 (62.7)	51 (65.4)	0.186
Female	19 (37.3)	27 (34.6)	0.186
Age (years), mean±SD	3.32±1.11	3.04±1.19	0.174

Table II: Laboratory parameters in the study and control groups.

	Study group mean±SD	Control group mean±SD	p
Hb (g/dL)	11.19±1.11	11.85±1.47	0.008
Hct (%)	34.87±3.95	36.04±3.87	0.097
MCV (fL)	69.06±13.57	74.60±6.83	0.003
Ferritin (ng/mL)	16.94±14.52	17.63±12.25	0.808
Iron (ug/dL)	47.43±21.67	55.54±34.07	0.161
Iron binding capacity (ug/dL)	290.39±71.73	295.77±83.30	0.734
Folate (ng/mL)	9.95±8.92	18.92±12.83	0.001
Vitamin B12 (pg/mL)	274.13±214.37	408.82±194.18	0.002

Hb: *Hemoglobin,* ***Hct:*** *Hematocrit,* ***MCV:*** *Mean corpuscular volume,* ***SD:*** *Standard deviation*

Table III: A comparison of the attack groups' vitamin B12 and folic acid levels.

Attack frequency	<15/month mean±SD	>15/month mean±SD	p
Folate (ng/mL)	18.13±7.5	23.69±30.03	0.643
Vitamin B12 (pg/mL)	249.6±206.13	406±223.08	0.570

in the control group. No significant difference was observed between the groups in terms of gender (p=0.186) or age (p=0.174) (Table I). Age at diagnosis in the study group was 1.57±0.76 (0.5-4) years. Examination of the distribution of the different types of breath holding spell revealed pale type in six (11.8%) cases, cyanotic type in 29 (56.9%), and mixed type in 16 (31.4%). A history of breath holding spells was present in the families of 16 (31.4%) patients. The frequency of attacks was <15 attacks/month in 43 (84.3%) cases and >15 attacks/month in eight (15.7%). The mean attack duration was 1.60 ±1.98 (0.15-10) minutes.

Mean Hb levels were 11.19±1.11 (8.80-13.60) g/dL in the study group and 11.85±1.47 (8.72-16.70) g/dL (p=0.008) in the control group, while mean MCV values were 69.06±13.57 (60-88) fL in the study group and 74.60±6.83 (55.11-96.97) fL in the control group (p=0.003). Mean Hct values were 34.87±3.95 (28-51.5) in the study group and 36.04±3.87 (27.97-51.1) (p=0.097) in the control group, while mean ferritin levels were 16.94±14.52 (1.6-75) ng/mL in the study group and 17.63±12.25 (4-66) ng/mL in the control group (p=0.808). Mean iron levels were 47.43±21.67 (20-126) ug/dL in the study group and 55.54±34.07 (5-140) ug/dL in the control group (p=0.161), while mean iron binding capacity (IBC) values were 290.39±71.73 (123-446) ug/dL and 295.77±83.30 (110-499) ug/dL, respectively (p=0.734). No significant difference was observed between the groups' mean Hct, ferritin, Fe, or IBC values.

Mean folate levels were 9.95±8.92 (2-37) ng/mL in the study group and 18.92±12.83 (5.27-91) ng/mL in the control group (p=0.001), while mean B12 levels were 274.13±214.37 (75-1201) pg/mL and 408.82±194.18, respectively (120-959) pg/mL (p=0.002), indicating low statistical significance (Table II).

No significant difference was determined between the attack groups' (<15/month, >15/month) vitamin B12 (p=0.570) or folic acid (p=0.643) levels (Table III).

DISCUSSION

The study data were consistent with the previous literature, with the cyanotic type emerging as the most common form (56%), and a mean age at diagnosis of 18 months.

The pathophysiology of breath holding spells is unclear. Current studies on the subject report an association between iron deficiency (with or without anemia) and breath holding spells, especially since iron supplementation is effective in reducing breath holding spell attacks. This hypothesis focuses on the link between iron deficiency anemia and breath holding spells, cerebral erythropoietin content, nitric oxide production, and interleukin 1. Iron plays a vital role in the formation of the tyrosine hydroxylase enzyme required for the synthesis of catecholamine, as well as for the functioning of enzymes and neurotransmitters in the central nervous system (CNS) (10,11). Iron deficiency causes an increase in serotonin activity and/or a decrease in reductases, and thus an increase in sympathomimetic neurotransmitters (12,13). In their meta-analysis of observational studies, Hetch et al. reported that the use of iron supplements reduced the frequency of attack episodes in patients with iron deficiency together with breath holding spells, with approximately 84% of children experiencing a >50% reduction in attack frequency (14). Anemia causes hypoxia in vital organs including the heart and nervous system, which play an important role in changing the autonomic balance (15). Recurrent breath holding spells cause episodes of hypoxia, including cerebral anoxia, which may in turn give rise

to short-term tonic-clonic seizures in the extremities. Another protective response to cerebral anoxia is increased brain EPO production. A relative depletion of iron occurs since this is consumed in erythropoiesis. The child may gradually become anemic, which may result in more breath holding spells as a result of behavioral 'agitation' (10). A few recent studies have shown that dysfunction of the autonomic nervous system plays a primary role in the occurrence of breath holding spells (16,17). Another study suggested that breath holding spells may be associated with delayed maturation in brain-stem myelination in children (18). While a statistically significant difference was found between the groups in terms of mean Hb and MCV levels in the present study, significant difference was observed in terms of mean iron, iron binding capacity, Hct, or ferritin levels.

Vitamin B12 and folic acid are members of the vitamin B family. Both play a role in various pathways (19). Depending on the neuroanatomical distribution of vitamins in the mammalian brain, it has been suggested that these compounds may have more important activities than their better-known metabolic functions (20,21). Deficiency in vitamin B12 and folic acid may manifest in the form of neurological features or megaloblastic anemia. Physicians should look for signs of dorsal column involvement (such as loss of sense of position and vibration and ataxia), lateral column involvement (including spasticity, hyperreflexia, and Babinski sign positivity), and spinothalamic tract involvement (at the sensory level) in cases of vitamin B12 deficiency (22). Areas of demyelination at cerebral MRI have been reported in patients with vitamin B12 deficiency of with diseases capable affecting the metabolism thereof (23-25). The neurological manifestations of folate deficiency are similar to those of vitamin B12 deficiency, such as cognitive impairment, dementia, depression, and, less frequently, peripheral neuropathy and subacute combined spinal cord degeneration (26). The functional and specific functions of folic acid in the child brainstem are currently unknown. Duque-Díaz and Coveñas described the presence and distribution of cell bodies (fusiform, small/medium, with one short dendrite) containing folic acid in child brainstem. It appears that the number of cell bodies diminishes in an age-dependent manner (27).

Vitamin B12 and folic acid levels play an important role in homocysteine metabolism, and hyperhomocysteinemia is observed in case of folic acid and vitamin B12 deficiency (28). Hyperhomocysteinemia leads to the production of hydrogen peroxide and superoxide free radicals. This condition causes oxidative damage in vascular endothelial cells. Nitric oxide (NO) release by endothelial cells has been shown to decrease with high homocysteine levels (29). NO consists of the semi-essential amino acid L arginine created by the endothelial nitric oxide synthetase enzyme, on condition that vitamin B6, folic acid and vitamin B12 are present at sufficient levels (30). NO is also a powerful endogenous vasodilator (31). Studies have shown that vitamin B12 and folic acid deficiency cause various hematological, neurological, and psychiatric disorders (19). Hyperhomocysteinemia is observed in case of deficiency of both vitamin B1 and folic acid, resulting in decreased NO release from the endothelium and diminished NO synthesis. Vasoconstriction occurs a result of this decrease in NO, and hypoxic attacks may occur. A limited number of studies have investigated vitamin B12 levels in patients with breath holding spells. Arslan et al. (32) compared vitamin B12 levels between 30 patients with breath holding spells and a healthy group, with no significant difference being found between the two. In the present study, vitamin B12 and folic acid levels were significantly lower in the study group compared to the control group. However, no significant difference was observed between the attack groups in terms of vitamin B12 or folic acid levels. This study is the first to examine the folic acid level in breath holding spells, and also the first to examine the relationship between vitamin B12 and folic acid in breath holding spells.

The main limitation of this study is that homocysteine level were not examined among the other laboratory parameters related to vitamin B12.

CONCLUSION

The study data indicate that vitamin B12 and folic acid levels should be routinely evaluated in children diagnosed with breath holding spells. Further prospective studies with larger numbers of participants are now required.

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Turkish Journal of Pediatric Disease
Türkiye Çocuk Hastalıkları Dergisi

Evaluation of Patients Treated with Omalizumab (Anti-IgE) During the Pandemic Period

Pandemi Döneminde Omalizumab Tedavisi Alan Hastaların Değerlendirilmesi

Zuhal KARALI[1], Sukru CEKIC[1], Oner OZDEMIR[2], Yakup CANITEZ[1], Nihat SAPAN[1]

[1] Department of Pediatric Allergy, Uludag University Faculty of Medicine, Bursa, Turkey
[2] Department of Pediatric Allergy and Immunology, Sakarya University Faculty of Medicine, Sakarya, Turkey

ABSTRACT

Objective: There are few studies investigating the impact of the COVID-19 pandemic on patients using omalizumab. In this study, it was aimed to investigate the effects of the COVID-19 pandemic on our patients who have been treating with omalizumab.

Material and Methods: From two centers, a total of 20 patients participated in the study. A questionnaire, consisting of 45 questions prepared by our department, and a visual analogue scale (0: minimum, 10: maximum) were applied face-to-face to the patients.

Results: It was observed that six patients (30%) did not continue their omalizumab treatment during the pandemic period. While 90% (n=18) of the patients were wearing masks, 85% (n=17) stated that they paid attention to social distance. In our study, the frequency of COVID-19 infection in patients using omalizumab was 10% (n=2). With the pandemic, while our patients' working-study habits were affected negatively (n=10, 50%), their appetite increased (n=8, 40%), and it was noted that there have been changes in their sleep patterns (n=8, 40%).

Conclusion: The COVID-19 pandemic has significantly affected our patients' treatments and follow-ups. Our results support the argument that the use of omalizumab does not increase the risk of SARS-CoV-2 infection.

Key Words: Asthma, COVID-19, Urticaria, Omalizumab

ÖZ

Amaç: Omalizumab kullanan hastalarda COVİD-19 pandemisinin etkisini araştıran az sayıda çalışma bulunmaktadır. Bu çalışmada, omalizumab tedavisi alan hastalarımızda COVİD-19 pandemisinin etkilerinin araştırılması amaçlandı.

Gereç ve Yöntemler: Çalışmaya iki merkezden toplam 20 hasta katıldı. Hastalara tarafımızca hazırlanan 45 sorudan oluşan anket ve görsel analog skala (0: minimum, 10: maksimum) yüz yüze uygulandı.

Bulgular: Altı hastanın (%30) pandemi döneminde omalizumab tedavisine devam etmediği görüldü. Hastaların %90'ı (n=18) maske takıyorken, %85'i (n=17) sosyal mesafeye dikkat ettiğini belirtti. Çalışmamızda omalizumab kullanan hastalarda COVİD-19 enfeksiyon sıklığı %10 (n=2)'di. Pandemi ile hastalarımızın ders çalışma alışkanlıkları olumsuz etkilenirken (n=10, %50), iştahlarının arttığı (n=8, %40) ve uyku düzeninde değişiklikler (n=8, %40) olduğu tespit edildi.

Sonuç: COVİD-19 pandemisi hastalarımızın tedavi ve takiplerini önemli ölçüde etkilemiştir. Sonuçlarımız, omalizumab kullanımının COVİD-19 enfeksiyonu riskini artırmadığı görüşünü desteklemektedir.

Anahtar Sözcükler: Astım, COVİD-19, Ürtiker, Omalizumab

0000-0002-4568-0121 : KARALI Z
0000-0002-9574-1842 : CEKIC S
0000-0002-5338-9561 : OZDEMIR O
0000-0001-8929-679X : CANITEZ Y
0000-0002-7601-8392 : SAPAN N

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. Our study was approved by Ethics Committee of Uludağ University Faculty of Medicine as a number of 2021-2/24.

Contribution of the Authors / Yazarların katkısı*: *KARALI Z: 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 the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***CEKIC 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 logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***OZDEMIR O:*** Reviewing the article before submission scientifically besides spelling and grammar. ***CANITEZ Y:*** Reviewing the article before submission scientifically besides spelling and grammar. ***SAPAN N:*** Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study.

How to cite / *Atıf yazım şekli* : Karalı Z, Cekic S, Ozdemir O, Canitez Y and Sapan N. Evaluation of Patients Treated with Omalizumab (Anti-IgE) During the Pandemic Period . Turkish J Pediatr Dis 2023;17:118-125.

Correspondence Address / Yazışma Adresi:
Nihat SAPAN
Department of Pediatric Allergy,
Uludag University Faculty of Medicine, Bursa, Turkey
E-posta: nihatsapan@yahoo.com.tr

Received / Geliş tarihi : 13.05.2022
Accepted / Kabul tarihi : 06.09.2022
Online published : 06.10.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.1116584

INTRODUCTION

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared by World Health Organization on March 11, 2020. Although countries have developed rapid and effective strategies to prevent the virus, it spread worldwide (1,2). Studies have shown that children are much less affected by COVID-19 than adults, and their clinical symptoms are often milder (3).

Omalizumab is a recombinant human IgG1 anti-IgE monoclonal antibody and is widely used for the treatment of severe asthma and chronic urticaria (4,5).

During the COVID-19 pandemic, there has been confusion about the management of patients treated with monoclonal antibodies, e.g. omalizumab. It has been stated that especially for these patients if they are infected with SARS-CoV-2, an Allergy/Immunology Specialist should be consulted and it should be discussed whether omalizumab and other biological agents are safe for the continuation of their treatment (6-9).

Even though monoclonal antibodies are generally considered safe in adults; the data, which is from clinical studies, on long-term use of the drug is limited (10). It is recommended to continue using omalizumab during the COVID-19 pandemic, in spite of the fact that there are not enough studies on this subject (11). In our study, we aimed to evaluate the attitudes of our patients treated with Omalizumab during the COVID-19 pandemic and to determine whether the use of anti-IgE poses a risk for SARS-CoV-2 infection.

MATERIALS and METHODS

Twenty patients with Omalizumab treatment, followed by Pediatric Allergy Departments of Uludağ University Medical Faculty Hospital and Sakarya University Medical Faculty Training and Research Hospital, participated in the study. The questionnaire consisting of 45 questions prepared by our department, which was applied face to face, questioned the lifestyle changes of the patients during the pandemic period, their anxiety levels about the risk of transmission, the protection methods they applied to prevent transmission, and the clinical course of the disease of the patients if they infected with COVID-19.

In addition to that to measure our patients' concerns about SARS-CoV-2 infection, a test consisting of 8 questions scored with a visual analogue scale (0: minimum, 10: maximum) was applied. Visual analogue scale scoring is a scale method used to digitize some values that cannot be measured quantitatively. In the VAS scoring system, scoring is done between 0-10. The increase in the numbers in the answers given to the questions indicates an increase in the anxiety-worry rate. Number zero indicates no concern, whereas number ten indicates very severe anxiety. Our study was approved by Ethics Committee of Uludağ University Faculty of Medicine as a number of 2021-2/24.

Statistics

Statistical analyses were performed using the SPSS 23 (IBM corp.) statistical package. Categorical data were expressed as frequencies and percentages, continuous data as mean ± standard deviation (SD) or median (minimum and maximum). Kolmogorov-Smirnov test and histogram were used to test the normality of the data distribution. Categorical variables were compared using Pearson's chi-square test and Fisher's exact test.

RESULTS

The mean age of the patients was 16 (8-21) years, and the female/male ratio was 9/11. The diagnosis of the patients was chronic urticaria (n=13, 65%) and asthma (n=7, 35%). Atopic dermatitis was seen in 5 (25%) patients, allergic rhinitis in 4 (20%) and allergic keratoconjunctivitis in 1 (5%) patients, in order of accompanying comorbid diseases. Other treatments received by the patients are shown in Table I. Antihistamine and montelukast treatment were used in three patients. Two patients were receiving immunotherapy treatment in addition to omalizumab treatment. There was an increase in patient complaints of five patients (25%) during the pandemic period. While three patients using omalizumab, one with asthma and two with urticaria, had symptoms; two patients with asthma and urticaria had an increase in their complaints who discontinued omalizumab.

Omalizumab was administered 150 mg/month in 4 (30.7%) and 300 mg/month in 9 (69.3%) patients with chronic urticarial. The mean duration of patients receiving omalizumab treatment was 15.6 (2-48) months. Treatment of 3 patients with chronic urticaria was increased from 150 mg/month to 300 mg/month due to the persistence of symptoms. The dose was increased to 600 mg/month in 2 asthmatic patients because of failure of asthma control with 300 mg/month of omalizumab treatment. All but one of the patients using omalizumab therapy (n=19, 95%) reported that they benefited from the treatment. The treatment doses in the last controls of 20 patients treated with

Table II: Other treatments used by patients.

Drugs	n (%)
Inhaled steroid	5 (25)
Montelukast	3 (15)
Long-acting Beta2 Agonist	0
Immunotherapy	2 (10)
Nasal steroid	0
Antihistamine	3 (15)

Table II: According to diagnoses; lifestyle changes, compliance with methods of protection against COVID-19 infection.

	Asthma n (%)	Urticaria n (%)	p
Have you had a diagnosis with COVID-19?	0	2	0.270
Have you been hospitalized due to a COVID-19 infection?	0	0	-
Changes in treatment during the COVID-19 pandemic No Those whose treatment was interrupted New drugs added to their treatment Changing the medication regimen	 4 (57.1) 2 (28.6) 0 (0) 1 (14.3)	 7 (53.8) 4 (30.8) 1 (7.7) 1 (7.7)	0.860
Has there been an increase in complaints about your illness during the COVID-19 pandemic? Yes No	 2 (28.6) 5 (71.4)	 3 (23.1) 10 (76.9)	0.780
The use of mask outside, Yes No	 7 (100) 0 (0)	 11 (86.4) 2 (15.4)	0.270
Regular attendance at school, Yes No	 4 (57.1) 3 (42.9)	 8 (61.5) 5 (38.5)	0.840
Do you think your school success was affected during the COVID-19 pandemic? Yes No	 6 (85.7) 1 (14.3)	 9 (81.8) 2 (18.2)	0.820
Keeping a distance of at least 1.8 meters from people, No Yes Sometime	 0 (0) 6 (85.7) 1 (14.3)	 0 (0) 11 (84.6) 2 (15.4)	0.940
Keeping a distance of at least 1.8 meters from family members within the home, Yes No	 2 (28.6) 5 (71.4)	 2 (15.4) 11 (84.6)	0.480
Have you lived in the same house as the person diagnosed with Covid-19? Yes No	 1 (25) 3 (75)	 1 (10) 9 (90)	0.490
The use of mask in the home, No Yes	 7 (100) 0 (0)	 13 (100) 0 (0)	-
Have you had contact with a person who has been diagnosed with Covid-19? Yes No	 1 (14.3) 6 (85.7)	 2 (15.4) 11 (84.6)	0.940
Have you ever stopped going to the hospital for fear of contracting a SARS-CoV-2 infection despite your symptoms? Yes No	 2 (28.6) 5 (71.4)	 3 (23.1) 10 (76.9)	0.780
Have you used an herbal medicine during the COVID-19 pandemic period? Yes No	 0 (0) 7 (100)	 2 (15.4) 11 (84.6)	0.270
Do you believe that the COVID-19 pandemic will be over ? Yes No	 2 (28.6) 5 (71.4	 6 46.2 7 53.8	0.440
Have you ever been unable to receive omalizumab treatment due to the pandemic Yes No	 2 (28.6) 5 (71.4)	 4 (30.8) 9 (69.2)	0.910
Have you stopped taking omalizumab yourself due to the pandemic? Yes No	 2 (28.6) 5 (71.4)	 2 (15.4) 11 (84.6)	0.480
Do you think that omalizumab treatment can have a negative effect on SARS-CoV-2 infection? Yes No	 1 (14.3) 6 (85.7)	 0 (0) 11 (100)	0.160

	Asthma n (%)	Urticaria n (%)	p
Would you get the Covid-19 vaccine?			
Yes	5 (71.4)	10 (76.9)	0.780
No	2 (28.6)	3 (23.1)	
Did you have a hard time finding the medications you use constantly during the pandemic?			
No	7 (100)	13 (100)	-
Has there been any change in sleep patterns during the pandemic period?			
No	4 (51.7)	8 (61.5)	0.890
Prolongation of sleep time	1 (14.3)	1 (7.7)	
Shortening of sleep time	2 (26.8)	4 (30.8)	
Has your appetite changed due to the Covid -19 pandemic?			
No	4 (57.1)	8 (61.5)	0.840
Increased appetite	3 (42.9)	5 (38.5)	
Decreased appetite	0 (0)	0 (0)	
Has there been a change in your body weight?			
No	4 (57.1)	7 (53.8)	0.880
Yes	3 (42.9)	6 (46.2)	
Change in the economic situation?			
No	4 (51.7)	9 (69.2)	0.270
Positively affected	0 (0)	2 (15.4)	
Negatively affected	3 (42.9)	2 (15.4)	
Have you been affected by the pandemic in your relationship with your parents?			
No	5 (71.4)	10 (83.3)	0.530
Negatively affected	2 (28.6)	2 (16.7)	
Have you had a change in your study/work habits during the COVID-19 pandemic?			
No	2 (28.6)	5 (41.7)	0.820
Positively affected	1 (14.3)	1 (8.3)	
Negatively affected	4 (57.1)	6 (50)	

Table III: Evaluation of anxiety levels about SARS-CoV-2 infection by VAS (visual analogue score).

	Mean± Std	Min.-max.
How afraid are you of the COVID-19 infection in general?	5.15±2.207	0-10
Do you believe that COVID-19 will infect you more easily?	3.75±3.092	0-10
How afraid are you of going out during the pandemic period?	4.15±2.739	0-10
Are you worried about the spread of COVID-19 from market products coming from outside the home?	3.40±3.033	0-10
Have your concerns about your health increased during the pandemic period?	4.50±3.170	0-10
Are you afraid to go to the hospital during the pandemic period?	5.85±3.55	0-10
How sad is it for you not to go out during the pandemic period?	6.00±3.583	0-10
How much do you think the COVID-19 pandemic has affected your treatment?	3.90±3.905	0-10

omalizumab were 150 mg/month in 5 patients, 300 mg/month in 13 patients, and 600 mg/month in 2 patients.

For six patients (30%), omalizumab treatment was interrupted during the COVID-19 pandemic. Four of them had self-terminated the treatment. Four patients stated that they stopped treatment because they were worried to go to the hospital during the pandemic. On the other hand, the treatment of two patients diagnosed with chronic urticaria was stopped by us because symptom control was provided.

In our study, the incidence of SARS-CoV-2 infection was 10% (n=2). During the pandemic period, one patient infected with SARS-CoV-2 never took a break from his treatment, while the other took a break for 2 months by himself and then continued regularly. Patients infected with SARS-CoV-2 were monitored at home and no symptoms requiring hospitalization were observed. The first patient who used omalizumab for the diagnosis of asthma became infected with SARS-COV 2 at the 10th month of treatment. The patient stated having mild fatigue and fever during the COVID-19 infection, but asthma attacks increased and symptom control worsened following the Post-COVID-19 period. The other patient who was treated with omalizumab with the diagnosis of chronic urticaria became infected with SARS-COV-2 at the 4th month of treatment. Mild nasal discharge and fatigue were observed as symptoms, but

Tablo IV: Evaluation of anxiety levels about SARS-CoV-2 infection by VAS (visual analogue score) according to the diagnoses.

	Asthma (Mean± Std)	Urticaria (Mean± Std)	p
How afraid are you of the SARS-CoV-2 infection in general?	5.71±3.147	4.85±1.573	0.410
Do you believe that SARS-CoV-2 will infect you more easily?	4.14±3.532	3.54±2.961	0.680
How afraid are you of going out during the pandemic period?	4.29±3.773	4.08±2.178	0.870
Are you worried about the spread of SARS-CoV-2 from market products coming from outside the home?	2.71±2.360	3.77±3.370	0.470
Have your concerns about your health increased during the COVID-19 pandemic period?	4.14±3.716	4.69±2.983	0.720
Are you afraid to go to the hospital during the COVID-19 pandemic period?	4.71±3.251	6.46±3.688	0.300
How much do you think the COVID-19 pandemic has affected your treatment?	3.43 ± 3.457	4.15±4.240	0.700
How sad is it for you not to go out during the COVID-19 pandemic period?	6.00±3.606	6.00±3.719	1.000

Table V: Evaluation of anxiety levels related to SARS-CoV-2 infection by VAS (visual analogue scale) in patients with and without a change in sleep pattern.

	Sleep pattern changes (Mean± Std)	No change in sleep pattern (Mean± Std)	p
How afraid are you of the COVID-19 infection in general?	4.63±2.973	5.50±1.567	0.510
Do you believe that COVID-19 will infect you more easily?	3.63±2.973	3.83±2.887	0.410
How afraid are you of going out during the pandemic period?	4.63±3.292	3.83±2.406	0.720
Are you worried about the spread of COVID-19 from market products coming from outside the home?	3.75±3.284	3.17±2.980	0.860
Have your concerns about your health increased during the pandemic period?	6.00±3.505	3.17±2.167	0.170
Are you afraid to go to the hospital during the pandemic period?	6.00±4.375	5.75±3.108	0.110
How sad is it for you not to go out during the pandemic period?	6.00±4.243	6.00±3.275	0.330
How much do you think the COVID-19 pandemic has affected your treatment?	5.00±4.064	3.17±4.064	0.380

no urticaria attack was observed during and after the infection. Covid symptoms of both patients lasted for about 5 days.

While 90% (n=18) of the patients were wearing masks, 85% (n=17) stated that they paid attention to social distance. The proportion of patients who followed the social distance rule with the mask was 85%.

For the "Do you get the COVID-19 vaccine?" question, 15 people (75%) answered yes. Among the questions asked about the sleep duration, change in appetite, and the effect of the pandemic on family relations of our patients, It was observed that among them, the ones most commonly negatively affected were study-working habits (n=10, 50%), appetite (n=8, 40%), and sleep duration (n=8, 40%). Four (20%) patients stated that their relationships with their parents were negatively affected by the pandemic. Only 5 patients (25%) stated that their economic situation was adversely affected.

According to the diagnosis, there was no significant difference between diagnoses, lifestyle changes, and compliance with methods of protection against SARS-CoV-2 infection (Table II).

Patients reported that their study/working habits were affected negatively, their appetite increased and sleep duration was shortened. The evaluation of patients' concerns about SARS-CoV-2 infection with VAS (visual analogue scale) is shown in Table III. The question "How sad is it not to go out during the pandemic period?" which was asked to the patients who had the highest score on the VAS. The situation they were least concerned about was that 'COVID-19' would be easy to infect them. There was no significant difference in the VAS scores of the patients according to the diagnoses (Table IV). No statistically significant difference was found between VAS anxiety scores in all patient groups based on whether or not they had sleep disorders (Table V).

DISCUSSION

In our study, the effects of the pandemic period on our patients who were treated with omalizumab for asthma and chronic urticaria were investigated. Recommendations are presented

for the management of allergic diseases, which are an important health problem worldwide during the COVID-19 pandemic.

Considering the balance between pros and cons, for patients receiving asthma treatment, if there is no opportunity for individualized treatment and the patient cannot be involved in the medical decision-making process, it has been recommended that the patient's disease-controller medication should not be "stepped down". In the follow-up of chronic urticaria, postponing the follow-ups, initiating antihistamine twice a day, and postponing laboratory tests in most of the patients were recommended as suggestions (12). It has been stated that more frequent follow-up or face-to-face visits should be considered, including initiation of omalizumab protocol in resistant urticaria; on the other hand, face-to-face visits of patients with well-controlled urticaria may be delayed (13,14).

After omalizumab treatment, the decrease in IL-33 levels and the increase in the production of proinflammatory cytokines (including IL-6, IL-1β, TNF-α, MCP-1, and prostaglandin D2) will affect the SARS-CoV-2 infection, where pro-inflammatory cytokines are already increased. (15,16). The American Academy of Allergy, Asthma, and Immunology (AAAAI) stated that biologic therapies can be continued in patients with proven efficacy unless there is any report showing the harmful potential of anti-IgE therapy during the pandemic period (17). In other guidelines that have been published so far, discontinuation of omalizumab treatment has not been recommended (18,19).

Because patients with severe asthma are at higher risk of severe SARS-CoV-2 infection, optimal control of chronic disease is extremely important (20). At this point, the continuation of the control status of the patients whose diseases were controlled with omalizumab is critical importance. Although the advantage of omalizumab treatment provides effective disease control, it also has the disadvantage of frequent hospital admissions requirements for injection and thus increasing the risk of viral exposure (21). To overcome this problem during the pandemic period, the option of self-administration at home has been brought to the agenda.

In another study an online questionnaire was applied to 41 patients who switched to at-home treatment with omalizumab in the hospital during the pandemic period. Ninety-three percent (93%) of the patients preferred self-injection at home. Concerns about the home environment were reported less frequently; 18% of patients fear of wrong injection (n = 7/40), 13% feared forgetting a dose (n = 5/38) and 15% feared developing an adverse reaction to omalizumab (n = 6/ 39) reported respectively (22). In a study evaluating patients with asthma who received omalizumab treatment in the hospital, only 44.7% of the patients reported that they preferred to switch to self-injection at home (23).

Our study as being the first in Turkey to evaluate patients using omalizumab during the pandemic period, omalizumab treatment was applied in the hospital during the pandemic period, as it was in the pre-pandemic period, since the at home-use preparation of omalizumab has not yet been approved for use on our patients. In our country, at home-omalizumab treatment is not applied yet. For six patients (30%), omalizumab treatment was interrupted during the pandemic period. Four of them had self-terminated treatment. There was no hospitalization under omalizumab therapy.

In the joint recommendation of European Allergy Societies (German Society of Allergy and Clinical Immunology, Austrian Society of Allergy and Immunology, European Academy of Allergy and Clinical Immunology, Luxembourg Society of Allergy and Clinical Immunology, Austrian Pneumology Society), suggested that children who have mild SARS-CoV-2 infection and treated with biologic agents, their treatment can be continued. However, the treatment should be postponed until recovery in adults or children who develop severe COVID-19 symptoms (24). Among the patients in our study, omalizumab treatments were not administered during the disease in patients with SARS-CoV-2 infection as a precaution.

In a study, it was determined that the COVID-19 pandemic caused anxiety in adolescents (25). As Ding et al. conducted in a study, in the adolescent group, anxiety scores were found to be high (26). Likewise, in our study, an increase in anxiety rates against COVID-19 infection and a negative impact on study habits were found in our patients, most of who were in the adolescent age group, in line with studies that have been done before.

Anxiety developing due to any reason, including the pandemic period, and sleep disturbance as a result of depression are expected situations (27). In a randomly selected adult survey conducted in Spain during the pandemic period, 39.7% of the participants stated that they had lower quality sleep, most often with difficulty falling asleep (28). In a study on lifestyle changes in asthmatic patients of the pandemic, changes in sleep patterns were found in 38.7% of asthmatic patients and 42.9% of controls. In addition, it has been determined that asthmatic patients with changes in sleep patterns have a higher fear of contagion against SARS-CoV-2 infection (29). In our study, changes in sleep patterns were detected in 40% of our patients. In addition, there was no statistically significant difference in the evaluation of anxiety levels related to SARS-CoV-2 infection by VAS (visual analogue scale) between our patients with and without a change in their sleep pattern. In general, we thought that the patients did not have much worry and anxiety due to the below-average scores of the answers given to the VAS scoring.

In a survey study on the disruptions in the education of university students in Romania; lack of communication with teachers, lack of opportunity to carry out practical applications, and high probability of passing online exams (e.g. probability of cheating); it was stated that their desire and motivation to study decreased (30). In a study, which conducted in India, the

survey questioned about the quality of the instructor, course design, student expectations, satisfaction, and performance in an online platform of 544 university students and it showed that among the factors that are studied, the most important factor affecting student satisfaction in online courses was found to be the quality of the instructor. When all factors were evaluated, they concluded that both teachers and students have equal responsibility for better performance in lessons (31). Similarly, it was determined that 50% of our patients had a worse effect on their study habits, and it was thought that this could be the factor of the first encounter with online education, low motivation due to pandemic anxiety and the trainer. Questioning the patients about the underlying reason for the decline in their study habits was not done in this study.

In conclusion, our patients using omalizumab had a mild clinical course of SARS-CoV-2 infection. Although no adverse effect was observed in 2 patients who received omalizumab treatment during COVID-19 infection, this is insufficient to generalize. The widespread use of home treatment will facilitate the treatment of patients in difficult conditions such as the COVID-19 pandemic. In our patients participating in the study; lifestyle changes, disruption in sleep patterns, changes in eating habits and study habits, and an increase in anxiety levels due to the risk of infection have been detected. Anxiety that develops as a result of deterioration in the quality of life and lifestyle changes, especially in adolescent patients, should be further investigated during physician visits.

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Evaluation of Baby Sleep Position Practices and Sleep Environment

Bebek Uyku Pozisyonu Uygulamalarının ve Uyku Ortamının Değerlendirilmesi

Tulin CATAKLI[1], Saliha SENEL[2]

[1]Department of Child Health and Diseases, Lokman Hekim University, Ankara, Türkiye
[2]Department of Pediatrics, Ankara Yildirim Beyazit University, Ankara, Türkiye

ABSTRACT

Objective: The aim of this current study was to determine mothers' infant sleep position practices and their awareness of a safe sleeping environment.

Material and Methods: This descriptive survey was conducted with 418 mothers who had infants aged 0-6 months and who agreed to participate in pediatric outpatient polyclinics of two hospitals. Data were collected between January-December 2020 via-structured questionnaires by face-to-face interview.

Results: Of the 418 mothers; 28% placed their babies in the supine sleeping position, 59.6% used a pillow when they put their babies in bed and 76.8% used a soft mattress. 42.3% of mothers covered their babies' faces during sleep; primary school graduate mothers were more intended on covering their babies' faces than high school and university graduates ($p<0.001$). 4.1% of mothers smoked during pregnancy, 9.8% during the lactation period and 15.3% were exposed to household smoke. All of the mothers shared a room with their babies without sharing a bed. There was also a positive correlation between the number of prenatal visits of mothers and their preference to put their babies to sleep in the supine position ($p=0.010$).

Conclusion: Most of the mothers placed their babies in a side sleeping position. Mothers' avoiding sharing beds and smoking cigarettes and prone positioning their children at a very low frequency were pleasing measures. Mothers who had more prenatal visits were found to place their babies more in the supine sleep position. Increasing the awareness of healthcare providers and other secondary caregivers about a safe sleeping environment and baby sleep position during pre and postnatal visits would make right practices become widespread.

Key Words: Infant, Mothers, Sleep, Sudden infant death syndrome

ÖZ

Amaç: Bu çalışmanın amacı, annelerin bebek uyku pozisyonu uygulamalarını ve güvenli uyku ortamı farkındalıklarını belirlemektir.

Gereç ve Yöntemler: Tanımlayıcı tipte olan bu araştırma, iki hastanenin çocuk polikliniklerine çalışmaya katılmayı kabul eden 0-6 aylık bebeği olan 418 anne ile yapıldı. Veriler, Ocak-Aralık 2020 tarihleri arasında yapılandırılmış anket yoluyla yüz yüze görüşme yoluyla toplanmıştır.

0000-0001-6670-1078 : CATAKLI T
0000-0001-7203-5884 : SENEL S

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 protocol was approved by Bozok University Faculty of Medicine Ethics Committee (dated 11.12.2019, ID: 2019-12-294).

Contribution of the Authors / Yazarların katkısı*: *CATAKLI T: 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. ***SENEL 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.

How to cite / *Atıf yazım şekli* : Catakli T and Senel S. Evaluation of Baby Sleep Position Practices and Sleep Environment. Turkish J Pediatr Dis 2023;17:126-132.

Additional information / *Ek bilgi*: We thank Dr. Osman Ozturk for providing the data from Yozgat University, Department of Pediatrics.

Correspondence Address / Yazışma Adresi:
Tulin CATAKLI
Department of Child Health and Diseases,
Lokman Hekim University, Ankara,Türkiye
E-posta: tcatakli@gmail.com

Received / Geliş tarihi : 04.11.2022
Accepted / Kabul tarihi : 26.12.2022
Online published : 24.01.2023
Elektronik yayın tarihi
DOI: 10.12956/tchd.1199280

Bulgular: 418 annenin %28'i bebeklerini sırtüstü pozisyonda yatırırken, %59.6'sı yastık ve %76.8'i yumuşak yatak kullanmış, %42.3'ü uykuda iken bebeklerinin yüzünü örtmüşlerdir. İlkokul mezunu anneler, lise ve üniversite mezunlarına göre daha fazla bebeklerinin yüzünü örtmeye eğilimli idiler (p<0.001). Annelerin %4.1'i gebelikte, %9.8'i emzirme döneminde sigara içmişler ve %15.3'ü ev içi sigara dumanına maruz kalmıştı. Annelerin tamamı yatak paylaşımı olmaksızın bebekleriyle aynı odayı paylaşıyordu. Annelerin doğum öncesi ziyaret sayısı ile bebeklerini sırt üstü yatırma tercihleri arasında pozitif yönde ilişki bulundu (p=0.010).

Sonuç: Annelerin çoğu bebeklerini yan yatış pozisyonuna yerleştirmişlerdir. Annelerin yatak paylaşımından, sigara içmekten kaçınmaları ve çocuklarını çok düşük sıklıkta yüzüstü pozisyonda uyutmaları sevindirici önlemlerdi. Doğum öncesi ziyaretleri daha fazla olan annelerin bebeklerini daha çok sırt üstü yatış pozisyonuna yerleştirdiği saptandı. Doğum öncesi ve sonrası ziyaretlerde sağlık hizmeti sunucuları ve diğer ikincil bakıcıların güvenli uyku ortamı ve bebek uyku pozisyonu konusunda bilinçlendirilmesi doğru uygulamaların yaygınlaşmasını sağlayacaktır.

Anahtar Sözcükler: Bebek, Anneler, Uyku, Ani bebek ölümü sendromu

INTRODUCTION

Baby caring practices of mothers are important determinants of infant mortality and morbidity (1). Making the baby sleep in a safe environment and sleeping position is one of the most important practices that will reduce the risk of sudden infant death syndrome (SIDS). Sudden Infant Death Syndrome (SIDS) is defined as the sudden unexpected death of an infant of <1 year, occurring during sleep, that remains unexplained after a whole investigation (2). The exact etiology of SIDS is not clear. Studies suggest that SIDS is associated with suboptimal physiologic responses to hypoxemia and hypercarbia and a combination of several intrinsic and extrinsic factors. The most important preventable SIDS risk factor is a supine sleeping position. Acknowledging prone sleeping as a means of preventing SIDS has resulted in advocacy that significantly decreased SIDS deaths. The incidence of SIDS declined by more than 50 percent in the United States after physicians began to promote "On the back to sleep" (3,4). The American Academy of Pediatrics (AAP) recommends a safe sleeping environment to reduce the risk of SIDS. Recommendations for a safe sleeping environment include supine positioning, the use of a firm sleeping surface, room-sharing without bed-sharing, and the avoidance of soft bedding and overheating. Additional recommendations to reduce SIDS include the avoidance of exposure to smoke, alcohol, and illicit drugs; breastfeeding; routine immunization; and the use of a pacifier. Despite campaigns recommending the avoidance of prone sleeping, mothers in different countries place their babies in unsafe sleeping positions (5,6). There is no national data on the frequency of SIDS, also known as "crib death" in our country. The Data on SIDS were generally derived from the studies exploring the causes and frequency of infant deaths, which were carried out on provincial scales. Turkey Statistical Institute data, crude birth rate was 15.3 per thousand and the infant mortality rate was 9.3 per thousand. It has been reported that 1.2% to 2.5% of these deaths are associated with SIDS (7). Although research in Turkey are province specific, they indicate, in approximately 1.250.000 live births 750-1200 infants die because of SIDS, which is considered a preventable death cause. There has been no national campaign on the safe sleeping position of babies in our country. The aim of this current study was to determine mothers' infant sleep position practices and their awareness of a safe sleeping environment.

MATERIALS and METHOD

This descriptive survey was conducted in pediatric outpatient clinics of two hospitals, one of which was a private hospital located in Ankara, the capital city of Turkey and the other was a public university hospital located in the central district of Yozgat. The research was conducted between January and June 2020 with 418 mothers of children aged 0-6 months-old who were admitted to outpatient clinics either as well-child or sick visits and who agreed to participate in the study were included. Parents of children with physical and developmental disabilities and neurological disorders were excluded from the study. Only mothers were included in the study.

The investigators collected data using a semi structured questionnaire (Supplement 1). The questionnaire was prepared by the researchers based on information in the literature (8-10). There were questions on the form related to the mothers characteristics (mother's age and educational level, monthly family budget) and descriptive characteristics of infants(gender, gestational weeks, birth weight, infant age, breastfeeding status, pacifier use), sleep position and potentially risky behaviors of mothers (sleeping mattresses, covering their babies' faces, not using pacifiers, smoking during pregnancy, smoking during pregnancy and/or lactation smoking during lactation, bed-sharing, not monitoring the temperature, etc.) and counseling about infant sleeping position and heard of sudden infant death syndrome. Mothers were informed about the purpose of the research and written informed consent to participate in this study was obtained. One of the authors (TC) read the questions to the mothers and wrote their answers on the questionnaire, which took approximately 10-12 min to complete. After obtaining these data, researchers instructed the mothers about safe sleeping environments and SIDS prevention measures. The study protocol was approved by Bozok University Faculty of Medicine Ethics Committee (dated 11.12.2019, ID: 2019-12-294).

Statistical analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences) for Windows 17 version 20 (Chicago, USA). Categorical variables were compared using the chi-square test. The level of statistical significance was set at p <0.050.

RESULTS

Of the 418 mothers; 45.2% (n=189) were between 31-37 years of age. 41.6% (n=174) had graduated from high school. The demographic characteristics of the mothers are shown in Table I. Of the 418 infants; 46.7% (n=195) were female, 49.5% (n=207) were aged between 1-3 months, 88.3% had a birth weight of >2500 g and 68.9% (n=288) were breastfed (Table II).

Of the 418 mothers; 28% (n=117) placed their babies in the supine sleeping position, 72% (n=301) in a non-supine position. Of the infants in non-supine positions; 59.4% (179/301) were right or left-sided, 5.6 % (n=17) were prone, and 34.8% (n=105) were in either two or three positions.

Examining the relation between the maternal educational level and the sleeping position revealed that high school and university graduate mothers placed their children more frequently in supine position than primary school graduates (p=0.001) (Table III).

Table I: Demographic characteristics of mothers

Characteristics	Number (n)	Percent (n/418)
Mother's age		
Age < 20	24	5.7
Age 20-30	154	36.8
Age 31-37	189	45.2
Age > 37	51	12.2
Parity		
1	115	27.5
≥2	303	72.5
Mothers' education level		
Primary school	102	24.4
High school	174	41.6
University	142	34.0
Monthly household income		
Less than expenses	44	10.5
Equal to expenses	286	68.4
Higher than expenses	88	21.1
Profession		
Housewife	254	60.8
Having a job	164	39.2
Family type		
Nuclear	374	89.5
Extended	44	10.5
Type of public prenatal care service		
Public	239	57.2
Private	179	42.8
Method of delivery		
Vaginal	143	34.2
Cesarean	275	65.8

Table II: Descriptive characteristics of infants

	Number (n)	Percent (n/418)
Gender		
Female	195	46.7
Male	223	53.3
Gestational weeks		
≤37 week	63	15.1
>37	355	84.9
Birth weight		
≤2500 g	49	11.7
>2500 g	369	88.3
Infant age (month)		
<1	99	23.7
1 to 3	207	49.5
4 to 6	112	26.8
Feeding		
Currently breastfeed	288	68.9
Never breastfed	11	2.6
Breast milk+formula	119	28.5

Of the mothers; 4.1% (n=17) smoked cigarette during gestation, and 9.8% (n=41) smoked cigarette during lactation. 15.3% (64/418) were exposed to household smoke. All mothers shared their rooms with their babies. None of them shared the same bed.

59.6% (249/418) of mothers used a pillow for their babies. Using infant soft bedding was reported by 76.8% (n=321) of mothers (Table III). There was no significant relationship between the maternal educational level and the use of a pillow and soft bedding (p = 0.772).

42.3% (177/418) of mothers covered their babies' faces during sleep. 'Not to be disturbed by light' was the most frequent 51.9%, (92/177) reason for covering faces. 'Not to have cold in the face' 23.2%, (41/177), 'fast recovery of neonatal jaundice' (15.8%, 28/177), and 'to avoid the evil eye' 9.0 %, (16/177) were the other reasons, respectively. Primary school graduate mothers were more intent on covering their babies' faces than high school and university graduates (p<0.001). 54.8% (229/418) of mothers used pacifiers to help their babies sleep easily. 74.6% (319/418) of mothers monitored the 'baby's breathing' during.

When the relationship between the number of prenatal visits the mothers had and their preference for the sleeping positions of their babies is examined, it was found that 22.2 % (26/117) of mothers who put their babies to sleep in supine position had 1-5 prenatal visits and 77.8% (91/117) of them had ≥ 6 prenatal visits. There was also a significant relation between the supine position and the number of prenatal visits (p=0.010).

There were no significant relations between the sleeping position and the type of hospital where the delivery was made,

Table III: Infant sleeping practices of mothers

Characteristics	Position the Baby Sleep			p
	Supine (n/117)	Non Supine(Prone/Lateral) (n/301)	Total n (n/418)	
Maternal age				
<20 year	12 (10.3)	2 (4)	24 (5.7)	0.073
20-30 year	38 (32.5)	116 (38.5)	154 (36.8)	
31-37 year	50 (42.7)	139 (46.2)	189 (45.2)	
>37 year	17 (14.5)	34 (11.3)	51 (12.2)	
Level of education				
Primary	16 (13.7)	86 (28.6)	102 (24.4)	0.001
High school	64 (54.7)	110 (36.5)	174 (41.6)	
University	37 (31.6)	105 (34.9)	142 (34.0)	
Type of prenatal care service				
Public	75 (64.1)	164 (54.5)	239 (57.2)	0.074
Private	42 (35.9)	137 (45.5)	179 (42.8)	
Getting knowledge about sleep position				
Health care professional	68 (58.1)	145 (48.2)	213 (51.0)	0.068
Other(grandmother, self-experience)	49 (41.9)	156 (51.8)	205 (51.0)	
Infant's sleep surface				
Soft	102 (87.2)	219 (72.8)	321 (76.8)	0.223
Don't pay attention	15 (12.8)	82 (27.23)	97 (32.2)	
Pillow use				
Yes	71 (60.7)	178 (59.1)	249 (59.6)	0.772
No	46 (39.3)	123 (40.9)	169 (40.4)	
Using pacifiers				
Yes	70 (59.8)	159 (52.8)	229 (54.8)	0.196
No	47 (40.2)	142 (47.2)	189 (45.2)	
Covering infant's face				
Yes	44 (37.6)	133 (44.2)	177 (42.3)	0.222
No	73 (66.4)	168 (55.8)	241 (57.7)	
Smoking during pregnancy				
Yes	1 (0.9)	16 (5.3)	17 (4.1)	0.038
No	116 (99.1)	285 (94.7)	401 (95.9)	
Smoking during lactation				
Yes	12 (10.2)	29 (9.6)	41 (9.8)	0.031
No	105(89.7)	272 (90.3)	377 (90.1)	
Smoking in house				
Yes	15 (12.8)	49 (16.2)	64 (15.3)	0.378
No	102 (87.2)	252 (83.7)	354 (84.7)	
Number of prenatal visits				
1–5	26 (22.2)	106 (35.2)	132 (31.6)	0.010
≥ 6	91 (77.8)	195 (64.8)	286 (68.4)	

number of births, gestational age, birth weight, breastfeeding, family type and monthly income (p> 0.050).

52.4% (n=219) of mothers had heard about SIDS but there was no history of SIDS in the family or among the relatives of any mother. There was no significant relation between the mothers' knowledge of SIDS and the sleeping position (p=0.419).

58.1% of mothers who placed their babies in a supine position, and 48% of those who placed them in non-supine positions had received prior knowledge about sleeping positions from healthcare professionals. There was no significant relation between the choice of sleep position and the source of information (p>0.050).

DISCUSSION

The American Academy of Pediatrics recommends that infants should be put to sleep in a supine position to reduce the risk of SIDS (2). In this study, only 28% of mothers placed their infants to sleep in the supine position, which is recommended as a safe sleeping position. Most of the mothers (59.4%) placed their babies in right or left side sleeping positions. Mothers justified their avoidance of supine positioning as to avoid choking in case of vomiting, make breastfeeding easier, and avoid occipital flattening. Different studies also reported choking in case of vomiting as the common concern of parents who do not prefer supine positioning (8,10-14). Despite these concerns

of the parents, it was reported that the supine position did not increase the risk of suffocation and aspiration even in infants with gastroesophageal reflux of the protective airway, and there was no increase in the incidence of aspiration after switching to supine sleep recommendations (15). Another concern of the mothers was that supine sleeping position would cause occipital flattening. Flat head syndrome is also called positional plagiocephaly; one out of every five babies who were put to sleep in supine position were reported to have occipital flattening and that this difference was remedied approximately in the 18th month (16). This concern of the mothers was thought to be compatible with the findings in the literature.

The prone sleeping positions are strong risk factors for SIDS (6). In our study, 5.6% of the mothers declared that they preferred a prone sleeping position together with the other positions during daytime. They believed that this position would have decreased infantile colic. Mothers' frequency to prefer a prone sleeping position is lower than the results of similar studies conducted in our country (8,11,13,17). Research reported that more educated mothers prefer supine sleeping position for their babies, which was recommended as the correct sleeping positioning (9,18). In this study it was detected that high school graduate mothers prefer supine sleeping positions more than primary and secondary school graduate mothers. However, it was not different from university graduate mothers. This was explained by the small number of university graduate mothers.

AAP primarily recommends room sharing without bed sharing for a safe sleep (6). In this study all mothers were sleeping with their babies in the same room without bed-sharing. Özbörü Aşkan et al. (11) reported in their study that 86.4% of parents sleep in the same room with their babies without sharing the same bed. In our country it is a traditional practice that mothers have their babies sleep in a crib beside their bed in their bedrooms. This provides them with easier breastfeeding and better safety control. These practices of the mothers were thought to be compatible with the recommendations on successful breastfeeding and safe sleep.

Pillow use and use of soft bedding were reported to be the other risk factors for SIDS (6). In this study 59.6% of mothers used a soft pillow and 76.8% a soft bedding. There was no relation between the use of pillows or soft bedding and the level of maternal education. Research revealed that parents usually use soft pillows and soft beds as they think these would make their babies sleep in a warmer and comfortable setting (8,10,11,20-23).

Covering the face during sleep is considered to be a factor that increases the risk of SIDS (6). In this study, 42.3% of mothers covered their babies› faces while they were sleeping. Reasons for covering their babies' faces were declared as "avoiding disturbance by light", "protecting his/her face from cold", "recovering from jaundice soon" and "avoiding evil eye" by the mothers. One of the traditional practices in our country is to cover the face of the newborn baby with yellow cheesecloth, with the thought that jaundice will pass more quickly (22). This attitude may increase the risk of SIDS as well as delay in the detection and treatment of neonatal jaundice. In studies conducted in our country, it has been reported that parents cover their babies' faces with similar concerns (8,23,24). It has been reported that traditional practice preferences decrease as maternal education level increases (20). In the current study, primary school graduate mothers were significantly more intent on covering their babies' faces than high school and university graduates.

It has been reported that breastfeeding has a protective effect against SIDS in addition to the several benefits in terms of mother and infant health (6). During our study, 73.2% of infants aged 0-3 months were exclusively breastfed, and this rate was higher than the 2018 Turkish Statistical Institute data (25). Breastfeeding practices of mothers are pleasing in terms of reducing infant morbidity and mortality.

AAP suggests offering pacifiers to infants at the onset of sleep to reduce the risk of SIDS but recommends avoiding pacifier use until breastfeeding is well established (6). More than half of the mothers in this study used a pacifier to calm their babies and help them sleep. The reasons for mothers to use pacifiers are similar to the results of other studies (9,11,13). It is good that the traditional practice of mothers using pacifiers are among the SIDS preventing measures.

Maternal smoking is one of the most important risk factors for SIDS. Maternal smoking during pregnancy increases the risk of SIDS with an estimated 22% of SIDS directly attributable to smoking (6, 26). In this study 4.1% of the mothers smoked cigarettes during pregnancy, 9.8% smoking during lactation. The smoking frequency of mothers during pregnancy was found to be lower than the results of similar studies in our country (8,10, 27).

One of the risk factors for SIDS is smoking in the house in which the infant lives (6). In our study, the proportion of smoking in the house in which the infant lived was found to be 15.3%. Mothers stated that smoking was not allowed in the baby's room, but on the balcony or at the window opening to the outside of the house. In our study, the rate of smoking at home was found to be lower than the results of similar studies conducted in our country (8, 24).

Prenatal visits allow mothers to inform about healthy infant care practices. It has been reported that the risk of SIDS is lower in babies whose mothers receive regular prenatal care (28). To reduce maternal and infant mortality in Turkey, mothers and their babies are observed at least four times during pregnancy, six times during the puerperium, three times after delivery in the hospital and three times at their home (29). In this study mothers who had more prenatal visits were found to place their babies more in the supine sleep position. Differing from the findings of our study, Cesar et al reported that the number

of prenatal visits did not have an effect on the mothers' infant sleeping position practices (9).

Mothers' decisions about sleeping positions and the environment may be influenced by guidance provided by infants' grandmothers. In this study, approximately half of the mothers declared that they determined the sleeping positions of their babies upon the recommendations of grandmothers of their babies (particularly maternal grandmothers). Similarly, Aitken et al reported that grandparents who look after their grandchildren younger than six months-old prefer supine position less as they think this position would increase the risk of choking (30).

More than half of the mothers stated that they received advice from the midwife/nurse or pediatrician of the hospital where they gave birth. Despite this, it was observed that most of the mothers in our study preferred to sleep their babies in the side sleeping position. In some studies conducted, it has been reported that healthcare professionals recommend the side sleeping position as the 'correct' baby sleeping position (10,31-33).

In this study half of the mothers had heard about "crib death" (SIDS) but there was no history of SIDS in the family or among the relatives of any mother. The practice of sleeping positions was similar between mothers with and without crib death information. In our study, nearly two-thirds of the mothers stated that they monitor their babies' breathing at regular intervals during sleep. Although they generally prefer a side sleeping position for their babies, this attitude of the mothers can be related to the traditional behavior to protect babies from "cradle death".

The relatively low sample size may be considered as a limitation of our study and the results do not reflect the whole country. Nevertheless, the results provide valuable data about infant sleeping practices among young mothers in two Anatolian cities despite these limitations.

CONCLUSION

Mothers mostly placed their babies in a "side sleeping position. Risky sleeping attitudes such as covering the babies' faces, using pillows and soft bedding were detected at high rates but fortunately, they avoided sharing beds and smoking cigarettes and putting their babies in a prone position at a very low frequency was pleasing.

Mothers who had more prenatal visits were found to place their babies more in the supine sleep position. Increasing the awareness of healthcare providers and other secondary caregivers about safe sleeping environments and baby sleep position during pre and postnatal visits would make right practices becoming widespread.

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Supplement 1: Evaluation of Baby Sleep Position Practices and Sleep Environment

Questionnaire (*Survey answered by only mother*)			
Demographic characteristics of mothers			
Mother's age			
Parity			
Mothers' education level	Primary school	High school	University
Monthly household income	Less than expenses	Equal to expenses	Higher than expenses
Profession	Housewife	Having a job	
Family type	Nuclear	Extended	
Type of public prenatal care service	Public	Private	
Method of delivery	Vaginal	Caesaria	
Descriptive characteristics of infants			
Gender	Female	Male	
Gestational weeks			
Birth weight			
Infant age (month)			
Breastfeeding	Formula	Breastmilk+formula	
Infant sleeping practices of mothers			
Getting knowledge about sleep position	Health care professional	Other	
Infant's sleep surface	Soft	Don't pay attention	
Pillow use	Yes	No	
Using pacifiers	Yes	No	
Covering infant's face	Yes	No	
Smoking during pregnancy	Yes	No	
Smoking during lactation	Yes	No	
Smoking in house	Yes	No	
Number of prenatal visits	1–5	≥ 6	

Demographic and Clinical Characteristics of Children with Gender Dysphoria Symptoms: A Turkish Sample

Cinsiyet Hoşnutsuzluğu Belirtileri Gösteren Çocuklarda Demografik ve Klinik Özellikler: Bir Türkiye Örneklemi

Hatice GUNES[1,2], M. Levent KAYAALP[1,3]

[1]Istanbul University, Cerrahpasa Faculty of Medicine, Department of Child and Adolescent Psychiatry, Istanbul, Turkey
[2]Istanbul Gelisim University, Department of Psychology, Istanbul, Turkey
[3]Private Practice, Istanbul, Turkey

ABSTRACT

Objective: In this study, we aim to describe the demographic and clinical characteristics and psychological functioning of children with gender dysphoria (GD) symptoms aged between 3-12 years.

Material and Methods: The study group included 20 children (17 males, 3 females; mean age 6.63±2.43 years) with GD symptoms. A sociodemographic data form was used to collect data with regards to demographic and clinical characteristics, and pre- peri-and postnatal features. The Child Behavior Checklist (CBCL) is used to assess behavioral and emotional problems in the child.

Results: The boy/girl ratio in the study group was 5.66. The mean age at onset of gender-nonconforming behaviors was 2.85±1.17 years and the mean age of admission to our clinic was 5.82±2.27 years. 20% of the mothers reported a preference for an opposite-sex child prior to conception; 20 % of the mothers reported prenatal stress, 20% of the mothers had prenatal and 25% had postnatal depressive symptoms. There was a risk of miscarriage in 10% of children and 25% were born prematurely. 55% of our study sample exceeded the clinical threshold for internalizing problems and 40% exceeded the clinical threshold for externalizing problems in CBCL ratings.

Conclusion: There were more prepubertal boys than girls referred for GD symptoms and the age at referral was younger compared to western countries. In addition, findings of this study indicate that children with GD have poorer psychological functioning possibly due to social intolerance for cross-gender behaviors and/or interests alongside the GD per se.

Key Words: Children, Gender Identity, Gender Dysphoria, Prepubertal

ÖZ

Amaç: Bu araştırmada cinsiyet hoşnutsuzluğu (CH) belirtileri gösteren 3-12 yaş aralığındaki çocuklarda demografik ve klinik özelliklerin tanımlanması amaçlanmıştır.

Gereç ve Yöntemler: Araştırmaya CH belirtileri gösteren 20 çocuk dahil edilmiştir (17 erkek, 3 kız; ortalama yaş 6.63±2.43 yıl). Araştırmada demografik ve klinik veriler ile pre-peri- ve postnatal özelliklerin kaydedilmesi amacıyla sosyodemografik veri formu; davranışsal ve duygusal sorunların değerlendirilmesi amacıyla ise Çocukluk Çağı Davranış Değerlendirme Ölçeği (ÇÇDDÖ) kullanılmıştır.

0000-0003-4840-1770 : GUNES H
0000-0002-3018-7182 : KAYAALP ML

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 protocol has been approved by Medical Ethics Committee of Istanbul University, Cerrahpasa Faculty of Medicine and Bakirkoy Training and Research Hospital for Psychiatric and Neurological Disorders (12.07.2016/566).

Contribution of the Authors / Yazarların katkısı*: *GUNES H: 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. ***KAYAALP ML:*** 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.

How to cite / *Atıf yazım şekli* : Gunes H and Kayaalp ML. Demographic and Clinical Characteristics of Children with Gender Dysphoria Symptoms: A Turkish Sample. Turkish J Pediatr Dis 2023;17:133-138.

Correspondence Address / Yazışma Adresi:

Hatice GUNES
Istanbul Gelisim University,
Department of Psychology, Istanbul, Turkey
E-posta: dr_haticegunes@yahoo.com

Received / Geliş tarihi : 09.07.2022
Accepted / Kabul tarihi : 23.09.2022
Online published : 06.10.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.1142786

Bulgular: Araştırmamız örnekleminde erkek/ kız oranı 5.66'dır. CH belirtilerinin ortaya çıkma yaşı ortalama 2.85±1.17 yıldır. Ortalama başvuru yaşı ise 5.82±2.27 yıl bulunmuştur. Annelerin %20'si gebelik öncesinde karşı cinsiyetten bir çocuk tercihi olduğunu belirtmiş; %20 'si prenatal dönemde stres, %20'si prenatal, %25'i ise postnatal dönemde depresif belirtiler bildirmiştir. Katılımcıların %10'unda düşük riski öyküsü mevcuttur ve %25'i prematüredir. Katılımcıların %55'nin ÇÇDDÖ içe yönelim sorun davranış puanları; %40'nın ise dışa yönelim sorun davranış puanları klinik eşiğin üzerinde yer almıştır.

Sonuç: Ergenlik öncesi dönemde, kız çocuklarına kıyasla daha fazla erkek çocuğu CH belirtileri ile kliniğimize yönlendirilmiştir. Ülkemizde CH belirtileri ile ilk başvuru yaşı batı ülkelerinde göre daha düşük bulunmuştur. CH olan çocuklarda ruhsal işlevsellik düşük bulunmuştur. CH olan çocuklarda yaşanan ruhsal sorunların CH'nun kendisinin yanı sıra karşı cinsiyet ilgileri ve davranışlarına karşı toplumsal tutumların da etkili olduğu düşünülmüştür.

Anahtar Sözcükler: Çocuk, Cinsiyet Hoşnutsuzluğu, Cinsiyet Kimliği

INTRODUCTION

The number of gender variant children and adolescents has augmented since the 2000s all over the World (1). Gender variant is a broad term referring to the individuals whose experience of gender is on a continuum of possibilities beyond the binary understanding of gender (2). Gender nonconforming is a related term used to describe individuals whose gender identity, role, or expression differs from the cultural norms prescribed for their birth-assigned sex. Gender dysphoria refers to the distress that is caused by an incongruence between an individual's gender identity and that individual's sex assigned at birth. Some but not all gender nonconforming people experience gender dysphoria (3).

Gender dysphoria was formerly referred to as 'gender identity disorder (GID)' and placed in the chapter 'Sexual and Gender Identity Disorders' in the DSM-IV with distinct criteria for children and adolescents (4). The diagnostic label has changed to 'Gender Dysphoria (GD)' in the DSM-V with significant changes mainly to avoid stigmatizing effect of the diagnosis. Furthermore, the DSM-V defines gender dysphoria in children as a marked incongruence between one's experienced/ expressed gender and assigned gender distinguishing from DSM IV which rather emphasizes cross-gender identification (4–6). A strong desire to be of the other gender or an insistence that one is the other gender or some alternative gender different from one's assigned gender is a prerequisite criterion for a DSM V diagnosis. Other behavioral features include a strong preference for cross-dressing or simulating the opposite sex attire, for wearing clothing of the opposite sex, for cross-gender roles in make-believe play or fantasy play, and the toys, games, or activities stereotypically used or engaged in by the other gender, for the playmates of the other gender, and a strong rejection of typical toys, games, and activities of the assigned gender, a strong dislike of one's sexual anatomy, and a strong desire for the physical sex characteristics that match one's experienced gender (5).

There is no epidemiologic study assessing the prevalence of GD or former label GID in children with rigorous methodology (7). An indirect data with respect to cross-gender behavior/ identification in children comes from the standardization studies of the Child Behavior Checklist (CBCL), a valid measure of problem behavior in children. In the original version, there were two items pertaining to gender nonconforming behavior: Item 5 ("Behaves like the opposite sex") and Item 110 ("Wishes to be the opposite sex") rated on a 0–2-point scale (1/somewhat or sometimes true; 2-/very true or often true). For nonreferred boys aged between 4-11 years, 3.8% of parents endorsed Item 5 as somewhat or sometimes true and 1.0% as very true or often true. In nonreferred girls, comparable percentages were 8.3% and 2.3% respectively. For Item 110, 1% of the nonreferred boys received 1 point and 0% received 2 points. 2.5% of the nonreferred girls received 1 point and 1% received 2 points for the same item (7). Zucker (7) reported that in the 1991 CBCL standardization sample 1% of parents of 4- to 11-year-old non-referred boys and girls endorsed the item pertained to cross-gender identity. In the 1999 standardization sample of the CBCL, for children aged 6–12 years, less than 1% of parents of non-referred boys and 1.2% of non-referred girls rated this item as either 'somewhat or sometimes true' or 'very true or often true' (7). In a Dutch twin sample, the prevalence of cross-gender behavior as evaluated by a maternal report of behaving like or wishing to be the other sex was 3.2% and 5.2% for 7-year-old boys and girls respectively and decreased to 2.4% and 3.3% for 10-year-old boys and girls (8).

There is scarce evidence on clinical and demographic characteristics of gender nonconforming prepubertal children, yet the majority of the existing research is conducted in western countries (9,10). In Turkey, there is few research on GD in children and adolescents; of those only two have study samples that include prepubertal children; however, the mean age of the participants in these studies is considerably higher (11–13). Therefore, in this study, we aim to describe the demographic and clinical characteristics and psychological functioning of Turkish children aged between 3-12 years presenting with GD symptoms.

MATERIAL and METHODS

The study was conducted between May 2009 and February 2010. The study group included 20 patients (17 males, 3 females) aged between 3-12 who were admitted to Istanbul University, Cerrahpasa Faculty of Medicine, Child and Adolescent Psychiatry Department outpatient clinic with complaints of gender nonconformity. 10 patients (7 males, 3 females) met DSM IV TR criteria for GID (4). When the data

recorded for the study was reviewed after the publication of DSM V, all the patients who met DSM IV TR criteria for GID also met DSM V diagnostic criteria for GD (5). The assessment was based on clinical interview with the parents and direct examination of the child. School teachers were consulted when necessary. The children who did not meet DSM IV TR criteria for GID displayed significant cross-gender behavior and interests that required clinical attention.

A sociodemographic data form was created by the authors to collect data. The data form comprised of questions with regards to age, gender, age at onset of GD symptoms, age at referral for GD symptoms, mother's and father's age at birth, maternal and paternal education, parent's marital status, monthly family income, mother's preference for an opposite sex child prior to conception, mother's prenatal stress, maternal prenatal depressive symptoms, risk of miscarriage, prematurity, and mother's postnatal depressive symptoms. The data form was completed by the researchers via directing question to the parents during the clinical interviews.

The Child Behavior Checklist (CBCL/4–18 years)

In this study, the Child Behavior Checklist (CBCL/4–18) is used to assess behavioral and emotional problems in children presenting with GD symptoms. The CBCL is a valid and reliable screening tool for behavioral and emotional problems and competencies in children and adolescents based on parent reports (14). The adaptation and standardization studies on Turkish children and adolescents were done. The questionnaire consists of 113 items and 9 scales. Parents or parental surrogates are asked to rate each item on a three-point Likert scale. An internalizing problem score is obtained from withdrawn, somatic complaints, and anxious/depressed scales. The sum of delinquent behavior and aggressive behavior scales scores forms externalizing problem score. The remaining four scales pertain to social, thought, attention, and sexual problems. A total score is acquired by summing the scores of all scales. Raw scores are converted to gender and age-standardized T-scores (15,16). A T-score of 67 was accepted as the cut-off point for each syndrome scale and a T-score of 60 for broadband and total problems scales (14).

The study protocol has been approved by Medical Ethics Committee of Istanbul University, Cerrahpasa Faculty of Medicine and Bakirkoy Training and Research Hospital for Psychiatric and Neurological Disorders (12.07.2016/566). The procedures followed in this study were in accordance with the ethical standards of the medical ethics committee and with the Helsinki Declaration of 1964, as revised in 2000 (17). An informed consent was obtained from the parents before participation in the study. All participants were younger than 12 years old; therefore, informed consent of the children was dismissed.

Statistics

In this study, the distribution of variables was classified by computer analysis. The descriptive statistics were calculated by using SPSS version 24 (Statistical Package for the Social Sciences for Windows) program. Demographic and clinical data are reported as mean ± standard deviation, number, and percentage.

RESULTS

20 children (17 males, 3 females) aged between 3-12 years were included in this study. The mean age of the study sample was 6.63±2.43 years (males, 6.91±2.44; females, 5.05±2.04). The boy/girl ratio was 5.66. The mean age at onset of gender nonconforming behaviors was 2.85±1.17 years and the mean age of admission to our clinic was 5.82±2.27 years. There were approximately 3 years between the onset of symptoms and the first admission. All the participants displayed significant cross-gender behavior, cross-gender interests, and preference for friends from the opposite sex. The demographic and family characteristics of the participants are shown in Table I.

The presence of mother's preference for an opposite sex child before conception, mother's prenatal stress, maternal prenatal

Table I: Sociodemographic characteristics of the children with gender dysphoria symptoms.

	Children with GD* symptoms (n=20) n (%); mean±SS
Mothers' age at birth	29.75±5.26
Fathers' age at birth	31.80±5.75
Mothers' educational level	
Primary and secondary school	10 (50)
High school, university, or higher academic degree	10 (50)
Fathers' educational level	
Primary and secondary school	12 (60)
High school, university, or higher academic degree	8 (40)
Parents' marital status	
Married	18 (90)
Divorced	2 (10)
Level of monthly income	
Low	4 (20)
Middle	10 (50)
High	6 (30)

**gender dysphoria*

Table II: Prenatal, perinatal, and postnatal features.

	Children with GD* symptoms (n=20) n (%)
Mother's preference for an opposite sex child	4 (20)
Mother's prenatal stress	4 (20)
Mother's prenatal depressive symptoms	4 (20)
Risk of miscarriage	2 (10)
Prematurity	5 (25)
Mother's postnatal depressive symptoms	5 (25)

**gender dysphoria*

Table III: CBCL scale scores of children with gender dysphoria symptoms and number of children with clinically significant problems.

	CBCL-T scores mean±SS	Number of children with T scores in the clinical range n(%)
Withdrawn	57.80±9.17	4 (20)
Somatic complaints	54.80±7.84	3 (15)
Anxiety/depression	61.30±8.43	6 (30)
Social problems	58.30±8.63	4 (20)
Thought problems	60.30±7.28	5 (25)
Attention problems	58.60±6.12	3 (15)
Delinquent problems	57.70±6.67	3 (15)
Aggressive behaviors	57.75±8.41	4 (20)
Sexual problems	67.05±9.99	12 (60)
Internalizing problems	58.70±12.21	11 (55)
Externalizing problems	56.25±9.77	8 (40)
Total	60.50±11.18	12 (60)

depressive symptoms, risk of miscarriage, prematurity, and mother's postnatal depressive symptoms are shown in Table II. Table III shows CBCL withdrawn, somatic complaints, anxiety/depression, social problems, thought problems, attention problems, delinquent problems, aggressive behaviors, sexual problems, internalizing, externalizing, and Total T scores.

DISCUSSION

In this study, we aimed to present demographic, family, and clinical characteristics of Turkish children aged between 3-12 years admitted with symptoms of GD. 50% of the participants met the diagnostic criteria for DSM IV/GID /DSM V/GD. Despite being subthreshold for a DSM diagnosis, the remaining participants were included in the study since they displayed significant stress caused by gender nonconforming behaviors. GD is a dimensional phenomenon that may exist to a greater or lesser degree, and it can manifest itself in various ways. Children with strong gender dysphoric feelings may be very sensitive to their environment and verbalize these feelings only at certain times and under certain circumstances, whereas other children may express their dysphoria more openly (18). Cultural differences across countries might influence behavioral expressions of different gender identities (9). In Turkish culture, gender roles are highly prescriptive and cross-gender behaviors are generally stigmatized. Therefore, one may assume that Turkish children might abstain from expressing their gender dysphoric feelings. Furthermore, follow-up studies show that GD may persist into adulthood not only in children who receive a DSM diagnosis but also in subthreshold cases although persistence rates are considerably higher in threshold children (19).

The boy/girl ratio in referrals to our clinic was 5.66. In a cross-natural cross-cultural comparative analysis by Cohen Kettenis et al. (20), the reported sex ratio in referrals to specialized gender identity clinics was 5.75:1 in Canada and 2.93:1 in the Netherlands. In London, the boy/girl ratio in referrals to a specialized gender identity development service was 3.8:1 (21). However, there has been a shift in the proportion of referral rates for those of the female sex at birth compared with the male (2). After the 2000s the boy/girl ratio in the referrals decreased to 3.41:1 (2008–2011) in Canada, to 1.68:1 in the Netherlands, and to 1.27:1 in London (22-24). The sex ratio in our study is more in line with the reported sex ratio in Canada before the 2000s. The sex ratios for referred children always being in favor of natal boys was considered to be a direct effect of a difference in increased acceptance of masculinity in girls compared to femininity in boys (24). Cohen-Kettenis et al.'s (20) study verifies a decreased tolerance for cross-gender behavior in boys. In their study, boys were referred at a younger age, were less likely to meet DSM criteria compared to natal females, and had lower ratings on the two CBCL gender items. In line with this, all the girls in the current study met DSM IV GID criteria and had more prominent cross-gender features. In Turkey, feminine behaviors in boys are less accepted than masculine behaviors in girls, and therefore the threshold for clinical referral is probably higher for girls than for boys.

The mean age of admission to our clinic was 5.82±2.27 and gender nonconforming behaviors were started approximately 3 years prior to the first admission. In the abovementioned cross-cultural cross-clinic study, the mean age at assessment was 7.2 in the Canadian sample and 8.1 in the Dutch sample. The Canadian sample was about a year younger than the Dutch sample. Additionally, the Canadian sample had a substantially higher percentage of referrals between the ages of 3–4, 4–5, and 5–6 years than did the Dutch sample, and these differences were particularly pronounced for the age intervals of 3–4 and 4–5 years. Between the age intervals of 6–7 and 11–12 years, the Dutch sample had a higher percentage of referrals. According to the authors, sociocultural factors probably best account for the cross-national difference in the age at referral. The Dutch parents were assumed to be less concerned about cross-gender behavior in their children than were parents in the Canadian sample (20). Our study sample is approximately one year younger than the Canadian sample which is presumably associated with stronger anxiety around cross-gender behaviors and interests in Turkish families compared to western families.

Psychological, social, and biological determinants of cross-gender behavior are yet to be elucidated. Structural equation modeling showed that 70% of the variance in the liability of cross-gender behavior could be explained by genetic factors (8) Biological theories suggested that transgender individuals may have brain structure and brain functioning more congruent with their experienced gender. Other studies focused on exposure to prenatal steroids considered to have a role in the brain's sexual differentiation (25–27). Psychosocial factors hypothesized to contribute to the development of cross-gender identification include a maternal wish for a child of the opposite

gender, paternal absence, parental psychological functioning, maternal depression, parent's lack of limit setting with respect to cross-gender behaviors, physical appearance, and anxiety in the child. However, the literature fails to provide consistent evidence to prove associations between any of these psychosocial factors and cross-gender identification (26,28). In our sample 20% of the mothers reported a preference for an opposite sex child prior to conception; 20 % had prenatal stress, 20% had depressive symptoms during the prenatal period, and 25% of the mothers had postnatal depressive symptoms. There was a risk of miscarriage in 10% of our study sample and 25% of children were born prematurely. Since there is no control group in the study, we cannot compare the rates of pre- peri and postnatal factors between children admitted with problems with regard to their gender identity and children with other psychiatric problems or healthy counterparts. On the other hand, recent research suggests that neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are common in children and adolescents with GD (13,29–31). Maternal prenatal stress, maternal pre and postnatal depression, risk of miscarriage, and prematurity are risk factors associated with ASD and/or ADHD (32–35). Therefore we suggest that pre, peri, and postnatal factors merit researchers' attention as possible etiological factors shared by GD and neurodevelopmental disorders.

Studies show that the psychological functioning of children referred for GD symptoms is poor. Psychiatric problems such as anxiety, depression, suicidal behaviors, self-harm, eating disorders, ASD, and disruptive disorders are more prevalent in children and adolescents with GD. Literature suggests that in youth experiencing GD, internalizing problems (such as depression, social withdrawal, and anxiety) are more frequent than externalizing problems (such as aggression) (10,13,26,30,36,37). Along with similar lines, 55% of our study sample exceeded the clinical threshold for internalizing problems and 40% exceeded the clinical threshold for externalizing problems in CBCL ratings. The younger age of our study sample might account for high rates of externalizing problems. Our study doesn't have a control group to compare the psychological functioning of children with GD symptoms versus healthy controls. However, in a large national mental health survey of Turkish children aged between 4-18, mean scores in CBCL withdrawn, somatic complaints, anxiety/depression, social problems, thought problems, attention problems, delinquent problems, aggressive behaviors scales, and mean internalizing, externalizing, and Total T scores were 2.7, 1.0, 4.8, 1.8, 0.5, 3.4, 1.2, 5.5, 8.4, 6.9, and 24.0 respectively (38). In Erol and Simsek's study, 16.7% of children and adolescents were in the borderline range and 11.3% were in the clinical range (38). Our results suggest that Turkish children with GD symptoms have poorer psychological functioning compared to the general population. Previous research emphasizes poor peer relations, peer bullying, family rejection, discrimination, and prejudice in society as predictors of increased rates of psychological problems in children and adolescents with GD symptoms (26,37,39,40). In Turkey, social intolerance for cross-gender behaviors might be greater compared to western societies where these studies on the psychological well-being of children and adolescents with GD are conducted (10). Therefore, one might expect increased rates of psychological problems in Turkish children with GD compared to those in western countries.

Our results show that there are more prepubertal boys than girls referred for GD symptoms and the age at referral is younger compared to western countries. In addition, findings of this study indicate that similar to their western peers and Turkish adolescents, Turkish children with GD have poorer psychological functioning (10,12). Although the lack of a control group and small sample size in this study restrain us from drawing any conclusion, our results suggest that future research may focus on prenatal and obstetric problems and maternal prenatal stress as possible biological determinants of GD. As mentioned, the lack of a control group and small sample size are significant limitations of this study; however, considering that GD is a rare disorder, and the literature is scarce on information with regard to children and adolescents referred for GD symptoms outside western cultures, we believe that our study might provide background data for further research on children with GD from a different culture, and biological and psychological determinants of gender variant behaviors in children.

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Vaccine Hesitancy and Refusal: A Case Study of Amasya

Aşı Tereddüdü ve Reddi: Bir Amasya Örneği

Zehra INCEDAL SONKAYA[1], Ahmet OZTURK[2]

[1]Sabuncuoğlu Şerefeddin Health Services Vocational School, Amasya University, Amasya, Turkey
[2]Department of Public Health, Erciyes University, Faculty of Medicine, Kayseri, Turkey

ABSTRACT

Objective: This study conducted with parents who have vaccination hesitation or refused to be vaccinated in Amasya is aimed to determine the factors that affected their decision.

Material and Methods: In this study, the characteristics of families who refused to vaccinate their children in Amasya in 2019–2020 were questioned and compared with a group of families who had their children vaccinated.

Results: In the study group, thinking that there are harmful substances in the vaccine, thinking that the vaccine will harm the child, and not giving confidence because all childhood vaccines come from abroad were stated as the three most expressed reasons for not vaccination. The rate of prenatal screening tests, sugar loading and tetanus vaccine was found to be significantly higher in the study group who refused vaccination compared with the control group. Having negative experiences related to vaccination (OR = 6.57) and not taking measures for communicable diseases (OR = 32.64) were positively associated with not having the vaccine.

Conclusion: This study is one of the limited number of studies evaluating parents' sociodemographic characteristics and attitudes toward vaccination. Due to the provision and financing of vaccines, families have concerns related to confidence in vaccines. The fact that vaccination is necessary not only for individuals but also for social immunity should be explained to all individuals in society considering modern scientific knowledge.

Key Words: Childhood, Immunization, Vaccine Hesitancy, Vaccine Refusal

ÖZ

Amaç: Amasya'da aşı tereddüdü yaşayan veya aşı yaptırmayı reddeden ebeveynler ile yapılan bu çalışmada onların kararını etkiyen faktörleri belirlemek amaçlanmıştır.

Gereç ve Yöntemler: Bu araştırma, 2019-2020 yılı içinde Amasya ilinde çocuklarına aşı yaptırmayı reddeden ailelerin özellikleri sorgulanarak, aşı yaptıran bir grup aile ile karşılaştırılmıştır.

Bulgular: Çalışma grubunda aşının içinde çocuğa zararlı maddelerin olduğunu düşünme, aşının çocuğa zarar vereceğini düşünme ve bütün çocukluk çağı aşılarının dış ülkelerden geldiği için güven vermemesi aşı yaptırmama nedenleri ile ilgili en çok ifade edilen üç neden olarak belirtilmiştir. Aşı yaptırmayı reddeden çalışma grubunda doğum öncesi tarama testleri, şeker yükleme ve tetanos aşısı yaptırmayanların oranı kontrol grubuna göre anlamlı derecede yüksek olarak saptanmıştır. Aşıyla ilgili olumsuz deneyimlere sahip olma (OR= 6.57) ve bulaşıcı hastalıklara yönelik tedbir almama (OR= 32.64) aşıyı yaptırmamayla pozitif yönde ilişkili bulunmuştur.

0000-0002-5446-9707 : INCEDAL SONKAYA Z
0000-0003-1353-4397 : OZTURK A

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 ethical approval was received from the Erciyes University Ethical Committee (dated 12.02.2020 and numbered 2020/95) and research permission was received from Amasya Provincial Health Directorate (dated 19.02.2020 2020 and numbered 68724985–772.02).

Contribution of the Authors / Yazarların katkısı*: *INCEDAL SONKAYA Z: 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. ***OZTURK 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 logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / *Atıf yazım şekli* : Incedal Sonkaya Z and Ozturk A. Vaccine Hesitancy and Refusal: A Case Study of Amasya. Turkish J Pediatr Dis 2023;17:139-146.

Correspondence Address / Yazışma Adresi:
Zehra INCEDAL SONKAYA
Sabuncuoğlu Şerefeddin Health Services Vocational School,
Amasya University, Amasya, Turkey
E-posta: zehra.incedal@amasya.edu.tr

Received / Geliş tarihi : 12.09.2022
Accepted / Kabul tarihi : 28.10.2022
Online published : 09.11.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.1174169

Sonuç: Bu çalışma ebeveynlerin sosyodemografik özellikler ile aşıya tutumlarını değerlendiren sınırlı sayıdaki çalışmalardan biridir. Aşıların temini ve finansmanından dolayı ailelerde aşılara karşı güven endişesi mevcuttur. Aşılamanın sadece bireysel değil toplumsal bağışıklık için gerekli olduğu gerçeği toplumdaki tüm bireylere çağdaş bilimsel bilgiler ışığında anlatılmalıdır.

Anahtar Sözcükler: Çocukluk Çağı, Bağışıklama, Aşı Reddi, Aşı Tereddüdü

INTRODUCTION

Vaccination is known as the most effective method for preventing infectious diseases and it has also been reported that vaccination contributes to major global reductions in morbidity and mortality of diseases and even eradicated some diseases. For example, smallpox is completely and poliomyelitis is almost eradicated by vaccination campaigns. Vaccination provides both individual and herd immunity, so as the number of vaccinated individuals in society increases, the probability of contact of unvaccinated people with the disease decreases, and accordingly, the prevalence of the disease in that community gradually decreases (1). However, herd immunity can only be acquired when most of the population is immune to that infectious disease by vaccination. However, the growing number of individuals who hesitate or refuse vaccinations is a threat to herd immunity.

Vaccine hesitancy is defined by the World Health Organization Strategic Advisory Group of Experts on immunization as "to delay in acceptance or refusal of vaccines despite the availability of vaccine services" (2). According to the Strategic Advisory Group of Experts on Immunization, this situation is not just about trust in vaccines. It is linked with different factors such as socio-cultural characteristics of families, religious beliefs, etc. (3, 4).

Although vaccine refusal movements have been present for many decades, it has accelerated with the 1998 Lancet paper that implied a link between MMR vaccine and autism. Although this paper was then withdrawn and this claim has been refuted, it naturally gave a golden opportunity for anti-vaccine activists who seek a foundation for their thesis. The discourses of these groups have reduced the vaccination rates of some vaccines. In 2015, the measles immunization rate declined to 85% in Italy and 88% in entire Europe (5). According to 2017 WHO data, the rate of immunization with diphtheria, tetanus and pertussis vaccines has declined to 92% in Europe and 91% in the United States. The measles vaccination rate for the first dose has decreased to 92% that was above 95% in 2012 and the rate for two doses decreased to 54% (6).

Such declines in vaccination rates have voiced concerns regarding the increase in the prevalence of such diseases. For example, a report of European Centre for Disease Prevention and Control (ECDC) published in 2017 indicated that the number of measles cases has increased almost thrice compared to the previous year and 87% of the people diagnosed were not vaccinated (7). In France, more than 22,000 cases of measles were reported between January 2008 and May 2012 and it was stated that this outbreak was largely caused by unvaccinated individuals. Furthermore, WHO reported that most of the 29,150 measles cases in Europe in 2013 were unvaccinated people. Moreover, the large measles epidemic that started in May 2013 in the Netherlands was linked to Orthodox Protestants who refused vaccination on religious grounds (8). Due to the above-mentioned events, WHO identified vaccine hesitancy as one of the ten biggest health threats in 2019 (9).

However, in Turkey, because of a lawsuit filed in 2015, the court decided to obtain parental consent for the vaccine and the number of vaccine refusal cases increased dramatically as this decision became popular in the newspapers and social media. The number of families who refuse to vaccinate their child (ren), which was 183 in 2011, has exceeded twenty-three thousand as of 2018 (10).

In fact, many countries have mandatory childhood vaccination policies and even some countries ban unvaccinated children from attending schools. However, vaccination is not mandatory in Turkey and there is no legal sanction for parents who refuse to vaccinate their child (ren). However, recently, parental refusal of childhood vaccines has been considered to child neglect and there are serious debates on this issue. In 7 of 9 cases of vaccine refusal in the USA, the court considered the case as neglect (11). However, parental refusal to childhood vaccines is not legally considered child neglect in Turkey. On the other hand, because vaccination is not just about individual immunization but also has an impact on herd immunity, the relevant article of the constitution stating "Fundamental rights and freedoms also includes the duties and responsibilities of the individual toward society, his family, and other individuals" clearly states the necessity of vaccination (12).

People who refuse vaccination put forward many reasons such as vaccines are toxic due to the chemicals they contain, they can have various side effects, companies producing vaccines may be malicious due to large financial returns, natural immunity or natural methods are more effective in protecting against diseases (13). Furthermore, in addition to perceptions about the safety, efficacy and importance of vaccines, religious beliefs across society are used by anti-vaccine activists. For example, a survey conducted by WHO and UNICEF in 154 countries showed the fact that vaccines do not have a halal certification was identified as a reason for vaccine refusal (14). The reasons for vaccine refusal or hesitancy may vary from country to country and region to region. To decrease the rates of vaccine refusal, countries need solid and reliable data sources. In this

regard, a literature survey revealed that only a limited number of studies have been conducted in Turkey on parents who have vaccine hesitancy or refused vaccination. Therefore, this study aims to identify the factors affecting parents' vaccine refusal decisions and to develop solutions.

MATERIAL and METHODS

This case control study examines the characteristics of parents who refuse childhood vaccinations in Amasya province and compares them with a parents group who accept childhood vaccinations.

A total of 37 families residing in Amasya province in 2019–2020 and refusing childhood vaccinations included in the national immunization schedule of the Ministry of Health for their child (ren) according to the data of the Provincial Health Directorate were determined as the study group. All families were included in the study without sampling. To compare the characteristics of parents, family health centers were consulted and 76 families (about twice the sample size) residing in Amasya province and vaccinated their child (ren) were included in the study as the control group. The ages of the children in both groups are in the range of 0–4 years.

These 76 parents that consisting the control group were randomly chosen by drawing lots from Family Health Centers records. Seven families in the study group refused to participate in the study and 3 families could not be contacted. Also, 6 children were not vaccinated according to doctor advice due to immunodeficiency. Thus, the survey was conducted with 21 families (13 mothers and 8 fathers were surveyed) who refused to vaccinate their child (ren). Regarding the control group, a family with missing data was excluded from the study and survey was conducted with 75 families (57 mothers and 18 fathers were surveyed).

Data Collection Instruments

The data for this study were collected by data collection instruments developed by the authors. The survey consists of questions regarding the sociodemographic characteristics of parents (age, education level and employment), whether they implemented preventive measures in addition to vaccines to prevent infectious disease, ss where they obtained their current knowledge about vaccines, whether they had sufficient information on vaccines and receive medical care during pregnancy. This survey was applied to both parent groups. However, some additional questions were asked to the sample group, such as reasons for refusing to vaccinate their child (ren) and conditions in which they may agree to vaccinate. On the other hand, some different questions were also asked the control group, such as whether they knew the reasons for parents who refuse childhood vaccinations and the possible methods to persuade them to vaccinations.

Before beginning the research, the parents were informed about the study and the survey was then applied. The participants were responded to surveys by telephone interview.

The ethical approval was received from the Erciyes University Ethical Committee (dated 12.02.2020 and numbered 2020/95) and research permission was received from Amasya Provincial Health Directorate (dated 19.02.2020 2020 and numbered 68724985–772.02).

Analysis of Data

The data obtained in this study were analyzed using the SPSS 21 statistical software package and Stata 14.1 software. While continuous variables are presented as mean and standard deviation values, categorical variables are shown as frequency and percentages. To compare mother and father age between both groups, the Mann–Whitney U test was applied. Chi-square and Firth's logistic regression analysis was performed to determine which answers of the participants were related to vaccination status. Parents who agreed and refused to vaccinate their child (ren) were determined as dependent variables and receiving screening tests, having a glucose tolerance test, and getting tetanus vaccination during pregnancy and negative vaccination experience, implementing precautionary actions against infectious diseases, and opinion about COVID-19 vaccination was accepted as independent variables. Only survey items determined as significant by Chi-square analysis were included in the analysis. Firth's logistic regression analysis is a statistical method for two or more variables used to determine variables related to rare events and with small sample sizes (15). Results of Firth's logistic regression analysis were presented by odds ratios (OR) and 95% confidence intervals for the odds ratio. A significance level of $p < .05$ was used in all statistical analyses.

RESULTS

Sociodemographic characteristics of both families who agreed or refused to vaccinate their children and the comparisons between groups are presented in Table I. As shown in Table I, the age of the fathers who refused childhood vaccinations was significantly higher than those who agreed to vaccinate their children. No significant differences were found in other variables. While 23.8% of the families in the study group stated that they got some of their children vaccinated, 4.8% declared that they refused childhood vaccinations for all their children. A total of 98.7% of the parents in the control group stated that their children received all childhood vaccinations.

Table I: Socio-demographic characteristics of the study and control groups

Socio-demographics Variables	Study Group n=21 (%)	Control Group n=75 (%)	p
Age of Mothers	29.81±5.60	28.52±5.41	0.322
Age of Fathers	31.76±4.40	29.28±5.26	0.020
Education Level of Mothers			
Primary	3 (14.3)	14 (18.6)	.894
Secondary	11 (52.4)	38 (50.7)	
College and above	7 (33.3)	23 (30.7)	
Education Level of Fathers			
Primary	2 (9.6)	9 (12.0)	.826
Secondary	9 (42.9)	34 (45.3)	
College and above	10 (47.6)	32 (42.7)	
Employment of Mothers			
Employed	3 (14.3)	20(26.7)	.240
Unemployed	18 (85.7)	55 (73.3)	
Employment of Fathers			
Employed	20 (95.2)	72 (96.0)	.877
Unemployed	1 (4.8)	3 (4.0)	
Total	21 (100.0)	75 (100.0)	

Table II: Refusal reasons of study group families for childhood vaccinations

Variables	Study Group n=21 (%)
Vaccinations contain substances that can be harmful to their children's health (mercury, aluminum, etc.)	18 (85.7)
Vaccinations may harm this child	17 (81.0)
Lack of trust in vaccinations since they exported from abroad	15 (71.4)
Vaccinations may contain religiously prohibited substances (pork products, etc.)	10 (47.6)
Concerns about vaccinations may cause autism	9 (42.9)
Getting affected by anti-vaccine comments made by well-known specialists and persons through TV and media	9 (42.9)
Observation of side effects on this child after a previous dose	6 (28.6)

Multiple items were selected.

Frequencies and percentages regarding the refusal reasons for families for childhood vaccinations are given in Table II. The three most frequently reported reasons for refusing childhood vaccinations were believing that vaccinations contain substances that can be harmful to children's health, vaccinations can harm their children, and lack of trust in vaccinations since they are exported from abroad.

Frequencies and percentages regarding possible situations/conditions in which parents can be persuaded to get their children vaccinated are given in Table III.

The analysis results regarding the behavior and attitudes of both groups toward receiving medical care during pregnancy are presented in Table IV.

Table III: Situations/conditions in which parents can be persuaded to get their children vaccinated

Variables	Study Group n (%)
If vaccines are domestic and national production	17 (81.0)
If an unvaccinated child gets sick or dies	3 (14.3)
If the president, health minister, or political party leaders declare that it is safe to get vaccinated	3 (14.3)
If well-known doctors or specialist on TV or media declare that it is safe to get vaccinated	2 (9.5)
If my spouse or family elders force me	2 (9.5)

Table IV: Certain behaviors and attitudes of study and control groups during pregnancy

Variables	Study Group n=21 (%)	Control Group n=75 (%)	p
Were you examined by a doctor/health personnel during pregnancy?			
Yes	21 (100.0)	74 (98.7)	1.000
No	0 (0.0)	1 (1.3)	
Did you receive a tetanus vaccine during pregnancy?			
Yes	11 (52.4)	61 (81.3)	0.015
No	10 (47.6)	14 (18.7)	
Did you get double and quad screening tests during pregnancy?			
Yes	10 (47.6)	63 (84.0)	0.002
No	11 (52.4)	12 (16.0)	
Did you have a glucose tolerance test during pregnancy?			
Yes	9 (42.9)	59 (78.7)	0.004
No	12 (57.1)	16 (21.3)	
Did you have a newborn blood spot (heel prick) test after birth?			
Yes	21 (100.0)	75 (100.0)	-
No	0 (0.0)	0 (0.0)	
Did you have a newborn hearing screening after birth?			
Yes	21 (100.0)	72 (96.0)	1.000
No	0 (0.0)	3 (4.0)	
Did you give vitamin D & iron supplements to your baby?			
Yes	19 (90.5)	62 (82.7)	0.511
No	2 (9.5)	13 (17.3)	
Total	21 (100.0)	75 (100.0)	

Table V: Certain behaviors and attitudes of study and control groups towards vaccines

Variables	Study Group n=21 (%)	Control Group n=75 (%)	p
Do you think that you have sufficient vaccine knowledge?			
Sufficient	16 (76.2)	36 (48.0)	0.054
Insufficient	4 (19.8)	22 (29.3)	
Not sure	1 (4.8)	17 (22.7)	
Where did you get your knowledge on vaccines?			
Internet/social media	12 (57.1)	33 (44.0)	0.237
Health personnel	5 (23.8)	33 (44.0)	
TV, newspaper, etc.	3 (14.3)	4 (5.3)	
From family, relatives, neighbors, or friends	1 (4.8)	5 (6.7)	
Has anyone in your family or any of your relatives ever had a negative immunization experience?			
Yes	6 (28.6)	4 (5.3)	0.007
No	15 (71.4)	71 (94.7)	
Do you implement precautionary actions against infectious diseases in addition to vaccines?			
Yes	11 (52.4)	0 (0.0)	0.0001
No	10 (47.6)	75 (100.0)	
Do you get seasonal flu vaccines?			
Yes	3 (14.3)	15 (20.0)	0.755
No	18 (85.7)	60 (80.0)	
Will you/your child get rabies vaccine if you/ your child is bitten by a rabid animal?			
Yes	13 (61.9)	73 (97.3)	0.0001
No	8 (38.1)	2 (2.7)	
Do you consider getting a Covid-19 vaccine?			
Yes	4 (19.0)	35 (46.7)	0.003
No	8 (38.1)	7 (9.3)	
Not sure	9 (42.9)	33 (44.0)	
Total	21 (100.0)	75 (100.0)	

The analysis results regarding behaviors and attitudes of both groups toward vaccines are shown in Table V.

As shown in Table VI, negative immunization experiences (OR= 6.57) and not implementing precautionary actions against infectious diseases (OR= 32.64) are positively correlated with vaccine refusal. In other words, individuals who have had a negative immunization experience and tried avoiding infectious diseases using methods other than vaccination are significantly more likely to not get vaccinated than those vaccinated individuals.

Table VI: Results of Firth's logistic regression analysis

Variables	OR	95% CI OR	p
Will you get rabies vaccine if you or your child is bitten by a rabid animal?			
No (Reference)			
Yes	0.13	0.01, 1.47	0.100
Do you consider getting a Covid-19 vaccine?			
No (Reference)			
Not sure	0.89	0.14, 5.60	0.898
Yes	0.95	0.13, 7.20	0.963
Did you receive a tetanus vaccine during pregnancy?			
No (Reference)			
Yes	0.53	0.11, 2.66	0.440
Did you get double and quad screening tests during pregnancy?			
No (Reference)			
Yes	0.56	0.11, 2.69	0.465
Did you have a glucose tolerance test during pregnancy?			
No (Reference)			
Yes	0.35	0.07, 1.77	0.203
Has anyone in your family or any of your relatives ever had a negative immunization experience?			
No (Reference)			
Yes	6.57	1.22, 35.48	0.029
Do you implement precautionary actions against infectious diseases in addition to vaccines?			
Yes (Reference)			
No	32.64	5.21, 204.48	0.001

DISCUSSION

There has been an increase in global vaccine refusal and hesitation recently. However, only a few studies conducted so far on groups refusing childhood vaccinations in Turkey. In this study, no significant correlation was found between the children in the group that refused vaccination and the control group regarding the age of mothers, education level and employment status of parents. However, a significant relationship was obtained between groups for the age of fathers. The mean age of fathers who refused to vaccinate their child (ren) was significantly higher than those in the control group. Regarding this finding, different results have been reported in the literature. For example, the results of a study conducted in Croatia showed that the probability of vaccine hesitancy increases significantly at relatively younger ages (16). Another study suggests that the young population has relatively insufficient knowledge about vaccine-preventable diseases and pandemics caused by infectious diseases (17). However, Topçu et al.(18) conducted a study with families who refused vaccination and found that no significant difference existed between parental age and vaccine refusal (18).

Recently, many concerns were raised by parents about immunization practices due for many reasons. However, only a few of these are concerns are based on scientific evidence and such concerns/claims have never been clinically proven. Nevertheless, people continue making such claims about vaccines. The most frequently stated concern about vaccines is related to vaccine ingredients. Similarly, according to the results of this paper, the most frequently stated reason by parents for vaccine refusal is that they believe that vaccines contain harmful ingredients and have some potentially dangerous side effects such as autism and infertility. Also, similar reasons were reported in other studies on vaccine refusal and hesitation (19–23). In a qualitative study by Bond and Nolan conducted with 45 families, they found that parents have concerns regarding the short- and long-term side effects of vaccinations and that vaccinations may cause genetic changes (24). A study investigated the reflection of the autism/vaccine hypothesis that exists in media and it was reported that although unscientifically based, contradictory information on the internet feeds concerns about the vaccine and therefore, reduces vaccine acceptance. The low health literacy rate in society and the fact that individuals do not know how to reach the right information can be considered risks that increase vaccine refusal. Also, although the hypothesized link between the measles vaccine and autism has not been clinically proven, some parents' concerns about the MMR vaccine causes such problems to continue to affect vaccination rates significantly (25, 26). Those who refuse vaccinations believe that the likelihood of contracting diseases that can be prevented by vaccination is lower than the side effects and risks associated with the vaccine (23).

According to our findings, the fact that there is no domestic production of vaccines in Turkey and that all childhood vaccines come from abroad is determined as an important reason for vaccine refusal among families. However, the fact that the vaccines come from abroad strengthens the claims that the vaccines contain religiously prohibited substances, thus families' confidence in vaccines decreases. According to a literature survey, the rate of those who consider foreign production of vaccines as a problem was determined 18% and 9% by Hough-Telford et al. (27) and Massimi et al. (28), respectively. Furthermore, İlter conducted a study with families who refuse vaccinations and he found that about 70% of families believe that vaccines are recommended to protect the commercial interests of pharma companies (29). To strengthen the public confidence in vaccines and reduce vaccine refusal rates, starting domestic production of vaccines could be very effective. Likewise, families' comments in our study that they get their child (ren) vaccinated if vaccines are domestic production can be considered evidence for this claim.

Moreover, we examined parents' behavior regarding receiving medical care during pregnancy. In the group who refused childhood vaccinations, the ratio of mothers who did not make screening tests, a glucose tolerance test and tetanus vaccine during pregnancy was found to be significantly higher than those in the control group ($p<0.005$). Statements made to prevent vaccine refusal are more effective on parents when the person making the statement is perceived as trustworthy (30). Having information about families, dealing with their problems and being perceived as reliable people are critical factors for Family Health Center personnel, who provide services at the first stage, in reducing vaccine refusal rates. However, providing adequate and proper medical care during pregnancy, establishing accurate, reliable and effective communication between health personnel and families are factors that positively affect not only maternal health but also infant-child health.

Our study revealed that the most frequently used information sources by the parents in both groups were the internet and social media. These were followed by health personnel. Today, the internet is central to the rapid spread and popularity of concerns about vaccines. The fact that families can access and question any kind of information easily emerges as an increasing threat. In a study, 52.0% of the participants stated that they consider the information available on the internet is reliable (31). Furthermore, in a study by Callender conducted in the USA in 2016, it was found that 32% of the information on vaccines contained anti-vaccine statements (32). Consistent with this finding, according to the results of a study examining newspaper reports about the anti-vaccine movement in Turkey, the number of newspaper reports in 2018 was found to be significantly higher than in previous years (33). Research has shown that people come together and affect each other easily with technological advances. Increasing confidence in healthcare workers who provide care at the first stage and receive information about vaccines, which is one of the important issues in child health, from these workers are critical in addressing vaccine hesitancy.

Our findings also showed that implementing precautionary actions against infectious diseases in addition to vaccines is significantly higher in the study group who refused childhood vaccinations than those in the control group. Parents, who do not trust in vaccines to protect from infectious diseases, stated that they implement several practices such as eating naturally, following hygiene rules and taking herbal supplements to strengthen their immunity. A literature survey revealed that there are many reports highlighting similar results. Topçu et al. (18) determined that the use of complementary and alternative medicine is significantly higher in the group who refuse vaccines than those in the control group. Furthermore, in a qualitative study by Benin et al. (34), they found that parents who refuse vaccines rely on natural treatments and herbs. Moreover, a study conducted with a population in Croatia pointed out that religiosity and the use of alternative medicine increase the likelihood of vaccine refusal (16). Among parents who hesitate to vaccinate their children, some have serious concerns regarding the relative efficacy of vaccine immunity vs. natural immunity acquired through the natural infection,

some parents prefer their children to acquire natural immunity (35,37). Misinterpreting natural immunity has also emerged as an important reason for increased vaccine refusal by parents that hesitates to vaccine their children. The chickenpox that the parents had during their childhood is an important factor in the emergence of this misconception. However, families are not aware of the serious complications that may arise because of this disease. According to a study conducted in Australia, the rate of support for vaccination is lower in individuals who practice alternative medicine (38). A qualitative study was conducted with 29 families in South Australia who refused some or all vaccinations and it was found that complementary medicine treatments are recognized as reliable methods more natural, chemical-free, with no side effects and exclude big pharma companies' concerns for earning money (20).

CONCLUSION and RECOMMENDATIONS

Although many studies have examined vaccine refusal and hesitancy behaviors in different segments of society, only a limited number of studies have been conducted with individuals who refuse vaccination. From this perspective, it can be argued that more comprehensive, long-term, and more detailed studies are needed on vaccine refusal to determine and implement policies that will increase the confidence of society.

Another factor related to vaccine refusal and hesitancy is about the safety of vaccines. Parents have concerns regarding the safety of vaccines because of their supply and financing methods. Accordingly, supporting domestic vaccine production and informing parents would are central to reducing vaccine refusal rates. The vaccine production has been carried out in Turkey since the Ottoman Empire period and the necessary infrastructure already exists, therefore making the necessary investments in vaccine production will contribute to increasing levels of trust in society.

TV, internet, and social media platforms are the most effective tools for reaching large audiences in today's constantly developing and evolving technology. However, information pollution about vaccines on these platforms, which the public often use to obtain information on divergent fields, also causes some concerns among parents. In this regard, healthcare personnel have important responsibilities. Increasing the health literacy rates in the public and driving them to use reliable sources to obtain information is critical.

All individuals in society should be informed using contemporary scientific knowledge that vaccination is necessary not only for individual immunity but also for herd immunity. In this regard, healthcare personnel working at the first level have a great responsibility. Parents should be informed about vaccines while they receive medical care during pregnancy. Furthermore, note that immunization is a social responsibility to ensure the protection of the most vulnerable groups in society also by acting together in immunization.

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Robotic Assisted Endoscopic Surgery Practices in Pediatric Surgery, Single Center Experience

Çocuk Cerrahisinde Robotik Yardımlı Endoskopik Cerrahi Uygulamaları, Tek Merkez Deneyimi

Gokhan Berktug BAHADIR, Mehmet Bahadır CALISKAN, Sevim Ecem UNLU BALLI, Huseyin Emre ATASEVER, Gulenay KORKMAZ, Ibrahim YILDIRIM, Ozlem EKICI, Mehmet Oguz CEVIK, Kadri Cemil ULUBULUT, Ervin MAMBET, Haluk OZTURK, İlhami SURER, Suzi DEMIRBAG

Department of Pediatric Surgery, Gulhane Training and Research Hospital, Ankara, Turkey

ABSTRACT

Objective: While robot-assisted laparoscopic surgery (RALS) is spreading rapidly all over the world, In pediatric surgery, this spread is slower than in adult surgery for many reasons. In this study, we discuss our initial experiences with pediatric robotic surgical cases.

Material and Methods: Robotic-assisted endoscopic surgery between November 2017 and April 2022 was retrospectively reviewed. The medical records of the patients were reviewed retrospectively for some demographical features, surgical details, and follow-up time.

Results: Of the 48 children, 27 were male and 21 were female. The youngest of the cases was 10 months old, while the oldest was 17 years old (mean 7.72±5.6, median 7). The shortest follow-up period after surgery was 5 months, while the longest follow-up was 60 months. A total of 63 surgical procedures were performed on 48 pediatric patients. 17 pyeloplasty (left 10, right 7), 9 Lich Gregoir operations (right 6, left 3), 4 ureteral reimplantation and tapering procedures due to left ureterovesical junction obstruction (UJO), 3 Hemi nephrectomy, one appendicovesicostomy, One right ureteral reimplantation, 11 Nissen fundoplication, 10 gastrostomy and one gastrojejunostomy, two ovarian sparing surgeries for ovarian cyst were performed. One urachal remnant excision, one adrenal mass excision, and one thoracic outlet mass excision were performed.

Conclusion: This is the first study that includes a wide range of pediatric robotic surgical procedures in our country. Robotic-assisted laparoscopic procedures in pediatric surgery can be safely performed for many surgical pathologies. We think at the beginning some simple surgical procedures and then turning to the more complex procedures after at least 15 cases will be more appropriate.

Key Words: Children, Robot-Assisted Surgery, Minimally Invasive Surgery

ÖZ

Amaç: Robot yardımlı laparoskopik cerrahi (RALS) tüm dünyada hızla yayılırken, pediatrik cerrahide bu yayılım birçok nedenden dolayı erişkin cerrahisine göre daha yavaştır. Bu çalışmada pediatrik robotik cerrahi olguları ile ilgili ilk deneyimlerimizi tartıştık.

0000-0003-4250-9350 : BAHADIR GB
0000-0003-1281-7416 : CALISKAN MB
0000-0002-0844-4728 : UNLU BALLI SE
0000-0002-3511-6797 : ATASEVER HE
0000-0001-7026-8334 : KORKMAZ G
0000-0003-2197-2995 : YILDIRIM I
0000-0002-9879-6953 : EKICI O
0000-0002-3415-7079 : CEVIK OM
0000-0002-6422-8114 : ULUBULUT KC
0000-0002-2433-2451 : MAMBET E
0000-0003-1473-0779 : OZTURK H
0000-0002-9896-0784 : SURER I
0000-0002-3845-1398 : DEMIRBAG S

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

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by the local ethics committee of the Gulhane Training and Research Hospital (11.05.2022/ 2022/59).

Contribution of the Authors / Yazarların katkısı*: *BAHADIR GB: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***CALISKAN MB:*** Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***UNLU BALLI SE:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Reviewing the article before submission scientifically besides spelling and grammar. ***ATASEVER HE:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Reviewing the article before submission scientifically besides spelling and grammar. ***KORKMAZ G:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***YILDIRIM I:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in the writing of the whole or important parts of the study. ***EKICI O:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***CEVIK OM:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***ULUBULUT KC:*** Taking responsibility in necessary literature review for the study. ***MAMBET E:*** Taking responsibility in necessary literature review for the study. ***OZTURK H:*** Taking responsibility in the writing of the whole or important parts of the study. ***SURER I:*** Reviewing the article before submission scientifically besides spelling and grammar. ***DEMIRBAG S:*** Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / *Atıf yazım şekli* : Bahadir GB, Caliskan MB, Unlu Ballı SE, Atasever HE, Korkmaz G, Yildirim I ,et al. Robotic Assisted Endoscopic Surgery Practices in Pediatric Surgery, Single Center Experience. Turkish J Pediatr Dis 2023;17:147-153.

Correspondence Address / Yazışma Adresi:

Gokhan Berktug BAHADIR
Department of Pediatric Surgery,
Gulhane Training and Research Hospital, Ankara, Turkey
E-posta: berktugg@gmail.com

Received / Geliş tarihi : 18.01.2023
Accepted / Kabul tarihi : 22.02.2023
Online published : 02.03.2023
Elektronik yayın tarihi
DOI: 10.12956/tchd.1233709

Gereç ve Yöntemler: Kasım 2017-Nisan 2022 tarihleri arasındaki robotik yardımlı endoskopik cerrahi vakaları retrospektif olarak incelendi. Hastaların tıbbi kayıtları, demografik özellikleri, cerrahi kayıtları ve takip süreleri retrospektif olarak incelendi.

Bulgular: 48 çocuğun 27'si erkek, 21'i kızdı. Olguların en küçüğü 10 aylık, en büyüğü ise 17 yaşındaydı (ortalama 7.72±5.6, medyan 7). Ameliyat sonrası en kısa takip süresi 5 ay iken en uzun takip süresi 60 aydı. 48 pediatrik hastaya toplam 63 cerrahi işlem uygulandı. 17 piyeloplasti (sol 10, sağ 7), 9 Lich Gregoir ameliyatı (sağ 6, sol 3), 4 sol üreterovezikal bileşke obstrüksiyonu (UJO) nedeniyle üreteral reimplantasyon ve tapering, 3 Hemi nefrektomi, bir apendikovezikostomi, bir sağ üreteral reimplantasyon,11 Nissen fundoplikasyonu, 10 gastrostomi ve bir gastrojejunostomi, over kisti olan iki hastaya over koruyucu cerrahi uygulandı. Bir urakus remnant eksizyonu, bir adrenal kitle eksizyonu ve bir torasik outlet kitle eksizyonu yapıldı.

Sonuç: Bu çalışma, ülkemizde pediatrik robotik cerrahi prosedürlerin geniş bir yelpazesini içeren ilk çalışmadır. Çocuk cerrahisinde robot yardımlı laparoskopik işlemler birçok cerrahi patolojide güvenle uygulanabilmektedir. Başlangıçta bazı basit cerrahi işlemlerin ardından en az 15 vakadan sonra daha karmaşık işlemlere geçilmesinin daha uygun olacağını düşünüyoruz.

Anahtar Sözcükler: Çocuklar, Robot Yardımlı Cerrahi, Minimal İnvaziv Cerrahi

INTRODUCTION

Today, although robotic-assisted laparoscopic surgery (RALS) applications have entered into routine clinical use in adults, it is still not possible to say the same for pediatric surgery (1). The first pediatric case (Nissen fundoplication) was reported only ten years after RALS in adults (2). The reasons for this delay in the widespread use of RALS in children depend on many factors. In our country, pediatric robotic surgery practices follow the developments in this field from behind in parallel with the world. Currently, there are only two centers actively using RALS in our country.

As a center, we started RALS applications for the first time in November 2017 and we continue in the appropriate patient group. Our study aims to discuss our experiences of the first 48 cases and to share the difficulties we encountered and the solutions we found for them.

MATERIALS and METHODS

The files of pediatric patients who underwent robotic-assisted endoscopic surgery between November 2017 and April 2022 were retrospectively reviewed. This study was approved by the local ethics committee of the Gulhane Training and Research Hospital (11.05.2022/ 2022/59). Sociodemographic data of the patients, gender, body weight, body mass index, diagnosis, accompanying diseases, findings during the surgery, surgery performed, duration of anesthesia, console duration, complications during and after surgery and hospital stay, intensive care requirements, blood and blood product needs were recorded.

In our center; It was performed by two pediatric surgeons experienced in RALS in the same center and with the same anesthesiologist. The da Vinci®, Si version (Intuitive Surgical, Inc., Sunnyvale, CA, USA was used for interventions. Two robotic work arms, 8 mm or 12 mm robotic 30° lenses for the three-dimensional camera, and a 5-10 mm trocar for an assistant's trocar were used for the procedures, depending on the surgical technique. Robotic arm placement positions recommended for standard entry sites were modified due to insufficient space for children. Especially in small children, a 3 cm or less distance between the trocars had to be left sometimes during the operation.

Definition of terms:

Operation time: It was defined as the time from skin incision (trocar placement) to skin closure. ,

Docking time: Connecting the robotic system to the patient and placing the trocar

Console time: Time from the end of the pre-console time to undocking the robot.

Anesthesia duration: It includes the total time the patient was taken to and removed from the operating table.

Surgical procedures:

In pyeloplasty; The child was placed in 45° flank position (lombotomy position). The robot was approached from the patient's back. The trans-Abdominal approach was preferred. 12 mm camera trocar over the umbilicus, surgical side (right or left lower quadrant) 8 mm from the lower quadrant, 8 mm from the surgical side (right or left upper quadrant) upper quadrant robotic working trocar, and between the camera and the upper robotic trocar A 10 mm assistant trocar was entered. Anderson Hynes technique was performed. A JJ catheter was placed in the children, and the bladder was filled with saline or methylene blue with 10% povidone-iodine to confirm the position of the catheter.

In hemi nephrectomy, the patient's position and trocar entry sites were the same as in pyeloplasty.

In vesicouretheral reflux surgery; the robot was placed in the Trendelenburg position at 20-30 degrees in the supine position, and the robot was approached from the foot side. A 12 mm camera trocar close to the umbilicus was inserted between the umbilicus and the xiphoid, an 8 mm robotic working trocar under the umbilicus from both rectus laterals, and a 10 mm assistant trocar from the left upper abdomen was inserted. Lich-Gregoir operation was performed. A catheter is placed in the bladder to fill and empty the bladder during the surgery.

In ureterovesical junction obstruction (UJO), the position of the patient and the trocar entry sites, and the position of the robot were the same as in ureteral reimplantation surgery. The ureter was separated from the entrance to the bladder and applied as reimplantation, tapering was added.

In the adrenal mass excision, the robot was approached from the patient's back in the lateral decubitus position. A 12 mm camera trocar at the level of the umbilicus, 8 mm robotic working trocars from the left lower quadrant and left upper quadrant, and a 10 mm assistant trocar 3 cm above the umbilicus were inserted.

The patient with a right thoracic outlet mass was placed in the left decubitus position. A 12 mm camera trocar was inserted at the junction of the mid-axillary line 6th intercostal space, anterior and posterior axillary lines 5, two 8 mm robotic working trocars at the junction of the intercostal space, and a 10 mm assistant trocar was inserted between the posterior trocar and the camera trocar.

In the Nissen fundoplication, the patient was placed in the supine position at 10-30 degrees reverse Trendelenburg position, and the robot was approached from the cranial side of the patient. A 12 mm camera trocar at the umbilicus level, 8 mm robotic working trocars from both lateral rectus, a 10 mm assistant trocar from the right lower quadrant, and a 5 mm liver retractor (Nathanson, Strong ArmTM, Nathanson liver retractor system, USA) under the xiphoid were inserted.

RESULTS

Of the 48 children whose families' consent was obtained, 27 were male and 21 were female. The youngest of the cases was 10 months old, while the oldest was 17 years old (mean 7.72±5.6, median 7). The children's body weights were between 8-102kg (mean 29.3±22.1kg). Body mass indexes ranged from 8-43kg/m^2 (mean 18.6±6.4 kg/m^2). The diagnoses of the children are indicated in Table. The shortest follow-up period after surgery was 5 months, while the longest follow-up was 60 months (mean 37.9±16.7 months).

Initially in older children, simpler surgical techniques were used (due to ovarian masses at 15 and 17 years old), and later on to younger children and more complex surgeries with progression to different points of the learning curve for RALS.

A total of 63 surgical procedures were performed on 48 pediatric patients. 17 pyeloplasty (left 10, right 7), 9 Lich Gregoir operation (right 6, left 3), ureteral reimplantation and tapering procedure due to left UJO (n=4), Hemi nephrectomy (n=3), appendicovesicostomy (n=1), One right ureteral reimplantation, Nissen fundoplication (n=11), gastrostomy (n=10) and one gastrojejunostomy, two ovarian sparing surgeries for ovarian cyst were performed. One urachal remnant excision, one adrenal mass excision, and one thoracic outlet mass excision were performed.

Pyeloplasty

In patients who underwent robotic-assisted laparoscopic pyeloplasty; A total of 17 patients were operated on (left 10, right 7), 10 months -17 years old (median 6 years old). Anesthesia duration ranged from 3.5 to 7.5 hours (median 4.5 hours); operative time was between 3-6.5 hours (median 4 hours). The hospital stay ranged from 3 days to 22 days (median 5 days). Since the JJ catheter did not work effectively in two patients, one developed urinoma on the 5th and the other 7th postoperative day. A nephrostomy catheter was placed with interventional radiology. And these patients were discharged on the 19th and 22nd postoperative days.

Ureteral reimplantation

A total of eleven ureteral reimplantation surgeries were performed in eight children (1-14 years; median 3 years, 2 boys and 5 girls) due to vesicourethral reflux, four of which were right, one left, and three were bilateral. Appendicoveiscostomy was added to one patient due to a neurogenic bladder. Anesthesia duration ranged from 4.5 hours to 6.5 hours (median 5 hours), and operative times ranged from 4 hours to 5.5 hours (median 4.5 hours). In the postoperative controls of the patients with the shortest follow-up period of 2 years and the longest 4 years, two patients had recurrence (bilateral right grade 5 left grade 3), and subureteric injection was performed and reflux was corrected.

A total of 5 pediatric patients aged between 1 and 8 years (median 5 years), all male due to UJO, were operated on. In one of these patients, due to an accompanying urachal cyst, the robotic intervention was performed in the same session. Anesthesia duration was between 5.5-7 hours (median 6 hours) and operation times varied between 5-6 hours (median 5 hours). The hospital stay was between 4 and 19 days (median 5). Urinoma developed in one patient because the DJ catheter fell into the distal ureter.

Hemi nephrectomy

Left Hemi nephrectomy was performed on a total of three patients, one girl and two boys, aged two years 2 and one 5 years old. They were discharged 3,4,6 days after surgery without any complications.

Fundoplication

Of the patients who underwent robotic-assisted laparoscopic Nissen fundoplication, 10 had severe neurological sequelae and one had milder neurological sequelae. In addition, these patients had also severe extremity contractures and posture disorders. Two of the 11 patients who underwent Nissen fundoplication were female and 9 were male. An additional gastrostomy was performed in 10 patients, and an additional gastrojejunostomy was performed in one patient. Two children

Table: Demographical Features, Surgical Details, and Follow-Up Time of the Patients.

Patient	Age (Y)	Gender	Weight (Kg)	Height (M)	Bmi	Operation	Operation Time (H)	Anesteshia Time (H)	Hospitalization (Day)	Complication	Intensive Care	Follow Up (M)
1	16	M	31.0	1.50	13.78	Fundoplication+ Gastrostomy	5.00	6.00	16	None	No	56 Months
2	7	M	30.0	1.20	20.83	Fundoplication+ Gastrostomy+ Hiatal Hernia Repair	4.00	4.50	8	None	No	56 Months
3	16	M	32.0			Fundoplication+ Gastrostomy+ Hiatal Hernia Repair	6.50	8.00	2	None	Yes	51 Months
4	2	M	8.0	0.80	12.50	Fundoplication+ Gastrostomy+ Hiatal Hernia Repair	2.50	3.50	3	None	Yes	49 Months
5	10	M	45.0	1.50	20.00	Fundoplication+ Hiatal Hernia Repair	3.00	4.00	8	None	No	48 Months
6	16	M	17.0	1.50	7.56	Fundoplication+ Gastrostomy	3.50	4.00	2	None	Yes	42 Months
7	4	M	12.0	1.00	12.00	Fundoplication+ Gastrostomy	2.50	3.00	5	None	No	39 Months
8	9	M	15.0	1.30	8.88	Fundoplication+ Gastrostomy+ Hiatal Hernia Repair	2.50	3.00	6	None	No	35 Months
9	2	M	11.0			Fundoplication+ Gastrostomy	3.50	4.00	6	None	No	35 Months
10	5	M	34.0	1.20	23.61	Left Uretheral Reimplantation + Tapering	6.00	7.00	5	None	No	56 Months
11	8	M	25.0	1.25	16.00	Right Uretheral Reimplantation+ Appendicovesicostomy	5.50	6.50	6	None	No	38 Months
12	5	M	20.0	1.10	16.53	Left Hemi Nephrectomy	5.00	6.00	6	None	No	50 Months
13	11	M	40.0	1.56	16.44	Left Pyeloplasty	4.00	5.00	22	Urinoma (Post-Op 6th Days)	No	48 Months
14	1	M	12.0	0.53	42.72	Left Pyeloplasty	3.00	4.00	4	None	No	43 Months
15	16	M	79.0	1.82	23.85	Left Pyeloplasty	3.15	3.45	7	None	No	42 Months
16	6	M	23.0	1.10	19.01	Left Pyeloplasty	6.50	7.50	6	None	No	40 Months
17	4	M	17.0	1.05	15.42	Left Pyeloplasty	4.00	5.00	5	None	No	36 Months
18	3	M	16.0	0.98	16.66	Left Pyeloplasty	4.00	5.00	6	None	No	22 Months
19	6	M	26.0	1.20	18.06	Right Pyeloplasty	3.50	5.00	3	None	No	13 Months
20	17	M	62.0	1.80	19.14	Left Pyeloplasty	3.00	4.00	5	None	No	11 Months
21	2	M	14.0	0.86	18.93	Right Hemi Nephrectomy	4.50	5.50	3	None	No	58 Months
22	11	M	30.0	1.41	15.09	Right Thoracal Mass Excision	3.00	4.50	7	Intraoperative Hypertension	No	44 Months
23	3	M	14.0	0.90	17.28	Bilateral Uretheral Reimplantation (Vur)	4.00	5.00	4	Re-Reflux + / Urethral Stricture(Cystostomy)	No	22 Months

Patient	Age (Y)	Gender	Weight (Kg)	Height (M)	Bmi	Operation	Operation Time (H)	Anesteshia Time (H)	Hospitalization (Day)	Complication	Intensive Care	Follow Up (M)
24	1	M	12.0	0.81	18.29	Right Uretheral Reimplantation (Vur)+ Urachal Remnant Exision	4.50	5.50	19	J-J Catheter Slides Into Bladder / Urinoma	No	50 Months
25	6	M	21.0	1.15	15.88	Left Uretheral Reimplantation+ Tapering+ (Uvo)	6.00	7.00	7	None	No	21 Months
26	5	M	15.0			Left Uretheral Reimplantation+ Tapering+ (Uvo)	5.00	6.00	5	None	No	14 Months
27	2	M	12.0	0.83	17.42	Left Uretheral Reimplantation+ Tapering+ (Uvo)	4.50	5.50	4	None	No	13 Months
28	11	F	33.0	1.50	14.67	Fundoplication+ Gastrostomy Take Down+ Gastrostomy	6.00	7.00	19	None	No	61 Months
29	6	F	18.0	1.10	14.88	Fundoplication+ Gastrostomy	3.50	4.00	6	None	No	42 Months
30	2	F	16.0	1.00	16.00	Right Hemi Nephrectomy	3.00	4.00	4	None	No	47 Months
31	17	F	42.0	1.64	15.62	Ovary Cyst	2.00	2.50	4	None	No	68 Months
32	15	F	62.0	1.57	25.15	Ovary Cyst	2.00	2.50	2	None	No	62 Months
33	7	F	33.0	1.45	15.70	Right Pyeloplasty	3.50	4.50	7	None	No	51 Months
34	2	F	12.5	0.78	20.55	Left Pyeloplasty	4.50	5.00	6	None	No	45 Months
35	11/12	F	9.0	0.73	16.89	Right Pyeloplasty	3.50	4.50	9	J-J Catheter Obstruction / Nephrostomy	No	40 Months
36	18	F	95.0	1.75	31.02	Left Pyeloplasty	5.00	6.00	4	None	No	23 Months
37	15	F	102.0	1.60	39.84	Left Pyeloplasty	4.00	5.00	3	None	No	22 Months
38	14	F	48.0	1.60	18.75	Right Pyeloplasty	5.50	7.00	4	None	No	19 Months
39	5/6	F	9.0	70.00	0.00	Right Pyeloplasty	3.00	4.50	4	None	No	7 Months
40	7	F	25.0	1.20	17.36	Left Pyeloplasty	2.00	2.50	4	None	No	1 Months
41	9	F	33.0	1.45	15.70	Right Pyeloplasty	5.50	6.50	5	None	No	59 Months
42	16	F	71.0	1.75	23.18	Left Surrenal Mass Excision	2.00	2.50	5	None	No	37 Months
43	1	F	11.5	0.76	19.91	Left Uretheral Reimplantation (Vur)	3.50	5.00	5	None	No	55 Months
44	14	F	34.0	1.35	18.66	Right Uretheral Reimplantation (Vur)	4.50	5.00	7	None	No	53 Months
45	12	F	37.0	1.52	16.01	Right Uretheral Reimplantation (Vur)	4.00	4.50	2	None	No	52 Months
46	1	F	10.0	0.82	14.87	Right Uretheral Reimplantation (Vur)	4.50	5.00	3	None	No	40 Months
47	3	F	18.0			Bilateral Uretheral Reimplantation (Vur)	4.50	5.50	6	None	No	35 Months
48	5	F	16.0	90.00	0.00	Bilateral Uretheral Reimplantation (Vur)	5.50	6.50	5	None	No	7 Months

had gastrostomy previously, the gastrostomy was taken down initially robotically, and gastrostomy was performed again after fundoplication. The age at surgery was between 25 months and 17 years (median 10 years), body weight was between 8-44 kg (median 19 kg), and body mass index was between 7.7 and 36.4 (median 18.3). The duration of anesthesia was between 2.5 hours and 8 hours (mean 4 hours), while the duration of surgery was between 2 and 6.5 hours (mean 4 hours).

While the first Nissen fundoplication was 240 minutes (45-300 minutes) (the longest time belonged to the patient who had fundoplication, gastrojejunostomy, and gastrostomy), it was observed that this time decreased to 45 minutes (fundoplication without gastrostomy).

Three pediatric patients with severe neurological problems who underwent fundoplication were transferred to the intensive care unit due to respiratory distress after surgery. They needed intensive care for up to two months. Independent of the interventions, three children died due to their primary pathology (two children died 3 and 4 years after the operation). Another child died 6 months after the operation due to the development of esophageal cancer.

Other procedures

A 16-year-old female patient was discharged 5 days after surgery for a left adrenal mass. The duration of anesthesia was 2.5 hours and the operation time was 2 hours.

A ten-year-old patient with a right thoracic outlet mass. Anesthesia time was 4.5 hours and surgery time was 3 hours. Histopathological examination was compatible with paraganglioneuroma. He was discharged on the 4th day of hospitalization after surgery.

Ovarian-sparing surgery was performed in two female cases as initial robotic cases due to ovarian cysts.

In terms of hospital stay, the shortest was two days and the longest was 22 days (mean 6.2 days, median 5 days). After the operation, five children needed blood and blood products transfusion; Four of them were given erythrocyte suspension, two of them were given FFP and one patient was given albumin.

There was no need for conversion to open or endoscopic surgery in any of the cases.

DISCUSSION

This is the first study in our country that includes the use of RALS in the field of pediatric surgery. Unfortunately, there is not much data available on RALS nationally on this subject. On the other hand, more than 400 international studies have been conducted on RALS in pediatric surgery since the first case report in 2001. An important part of these publications belongs to pediatric urology.

The learning curve of RALS is much shorter than endoscopic surgery, however in conventional endoscopic surgery, It takes a long time to acquire the sufficient skill. Moreover, studies have shown that RALS has a shorter learning curve (1, 3-6). At the same time, important limitations of RALS include the lack of tactile feedback, but this deficiency can be overcome over time by the brain's evaluation of visual data (7).

In our first cases, while the console time was 4.3 hours on average in the first 5 pyeloplasty cases, it decreased to 2.5 hours in the last 5 cases. However, there was no statistically significant decrease in surgeries performed with ureteral-reimplantation(mean 4.5 hours).

Some lesions which are difficult to reach due to locations such as thoracic outlets can cause a dangerous challenge to surgeons and could be accomplished more easily by RALS than by conventional thoracoscopic approach. In one of our cases, a paraganglioma of approximately 4x3 cm in diameter located at the thoracic outlet could be removed in a very short time (operation time; 2,5 hours).

Robotic pyeloplasty; is becoming the preferred procedure of choice in the pediatric age group. According to a study, robotic pyeloplasty has become reported as the most frequently performed intervention in childhood for UPJ obstructions in the USA (8). In most of the existing robot series for pyeloplasty, the hospital stay has decreased to <24 hours (9-11). Although our postoperative hospital stay in robotic pyeloplasty seems longer than in other studies, Its stays continue to decrease. Robotic fundoplication has significant advantages when considering laparoscopic or open surgery, especially in patients with severe anatomical problems. Although the positioning of the patient with severe neurological impairment in robotic fundoplication causes some challenges to the surgeon, this problem could be overcomed by experienced robotic surgery team.

In the beginning one of the factors that causes prolonged operation time is docking procedures, it can be shortened with getting more experience. While in our series the mean docking time for the first 15 cases was 33 minutes, it decreased to 13 minutes for the last 15 cases. This data was also supported by other studies about docking time (1-3). While Gutt et al. (12) was reported an average docking time of 23 minutes Salö et al.(1) had been showing a lower docking time of 5-10 minutes in fundoplication. According to our data, the longest docking time belong to the patients with severe anatomical problems which underwent Nissen fundoplication (mean 39 minutes), and unfortunately, this time was not reduced significantly despite getting more experience. The mean undocking time including skin closure of the patient from the operating table was 30 minutes (15-38 minutes).

One of the other problems faced by surgeons who have just started or are willing start RALS is an adaptation to the console and operation room setup, which is different from endoscopic or

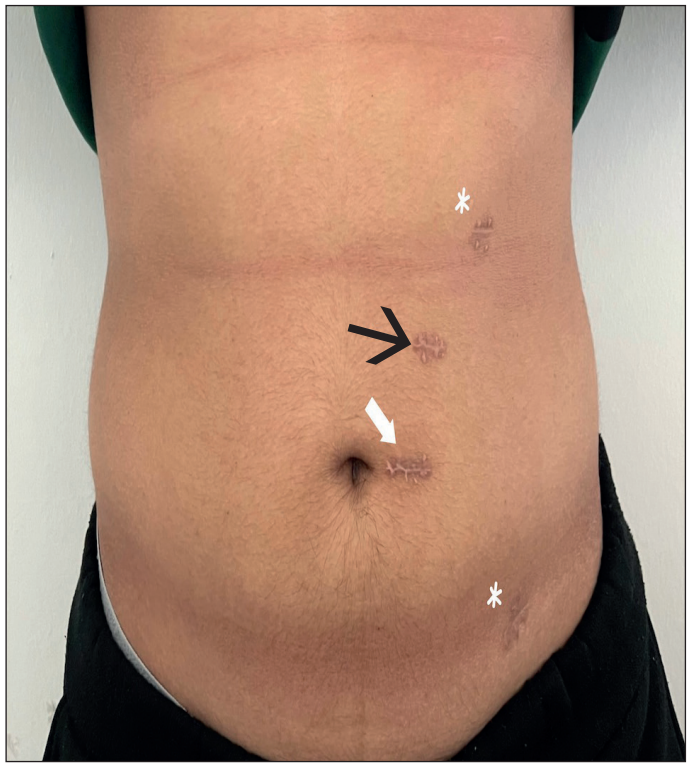

Figure: Hypertrophic scar-like port-side wound healing is shown. Postoperative 3th month. *Robotic ports, → assistant port, ⇨ Camera port

open surgery. In this period, the help of doctors and technicians experienced in robotic surgery will help them overcome the initial problems. Since we had the advantage of working with a group of very experienced technicians (approximately 1500 cases in total) when we started, we did not encounter any problems.

Cost-effectiveness issue is still a limitation problem of routine use of robotic surgical devices. According to one study, it had been reported that between 3 and 5 robotic cases, per week, should be required to overcome the cost-effectiveness problem (13). We solved this problem by sharing the robot with other surgical specialties.

Currently, many pediatric surgery centers actively practice robotic surgery in the world. When the literature is searched, the rates of conversion to open surgery have been reported within a wide range (0-50%) depending on the surgical procedures. (1). While this rate was initially 36% in pyeloplasty and 40% in hemi nephrectomies, it has been reported to decrease in that rate rapidly with the increase in cases (1). The most important reasons for conversion to open surgery are; the high body mass index of the patient, severe anatomical problems, and technical reasons that have been reported (1). No technical problems were encountered in our series. There has been no conversion to open or laparoscopic surgery in our series.

It is known that the main advantage of minimally invasive surgery is better cosmetic results. However, in some of our cases, we found hypertrophic scar-like port-side wound healing problems which was has been not reported in pediatric cases and we are still investigating the cause of that (Figure).

This is an initial experience report from a third level pediatric surgeon center. The growing robotic pediatric surgical experience will result in better scientific data.

As a result; Robotic-assisted laparoscopic procedures in pediatric surgery can be safely applied to many surgical pathologies. We think that it would be more appropriate for centers to start robotic surgical procedures, that is, to prefer simple surgical procedures at the beginning and then turn to more complex procedures.

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Autologous Free Reverse Inlay Vein Graft in The Treatment of Cripple Hypospadias; An Experimental Rabbit Model

Kriple Hipospadias Tedavisinde Otolog Serbest Ters Inlay Ven Greftini; Deneysel Bir Tavşan Modeli

Mehmet Bahadır CALISKAN[1], Ilhami SURER[1], Omer GUNHAN[2]

[1]Department of Pediatric Surgery, University of Health Sciences, Gülhane Training And Research Hospital Ankara, Türkiye
[2]Department of Patology, TOBB University, Ankara, Türkiye

ABSTRACT

Objective: The aim of this study is using the autologous reverse inlay jugular vein graft as a substitute for defective urethral plate and the incorporation of the graft to the urethral plate. Cripple hypospadias are the patients who have a history of previous multiple unsuccessful hypospadias surgery and still having anatomical and functional complications. Insufficient local or support tissue for the repair of defective urethral plate is always a problem.

Material and Methods: In the study fourteen male 8-10 months old which is weighting four kg, New Zealand type rabbit are divided into two equal groups. Juguler vein graft (1st group) and buccal mucosal graft (2nd group) harvested and transferred to defective area in the urethral plate as a free flap.

Results: In the histopatologic examination, epithelization, fibrosis and inflammation degrees were evaluated between the groups and in-groups. In the histopatological examination of the 1st group, uroepithelization is complete or nearly complete, fibrotic activity is (+) and the inflammation was found minimal. In the second group after 21st day, the uroepithelization on the graft is nearly thirty percent, fibrotic activity is (++) and the inflammation is also found minimal.

Conclusion: From the results of the study, in the treatment of defective urethra in cripple hypospadias cases, reverse free juguler vein graft can be used as an alternative for buccal mucosa graft as a substitution material which has been used for a long time.

Key Words: Graft enhancement, Hypospadias, Urethra

ÖZ

Amaç: Çalışmanın amacı hipospadias sakatlı olgularda defektif üretranın yerine juguler venin serbest reverse greft olarak getirilmesi ve bu dokunun üretral plak ile olan uyumunun incelenmesidir. Hipospadias sakatlı olgular, daha önce hipospadias nedeni ile tamir edilmeye çalışılmış, fonksiyonel ve anatomik komplikasyonları devam eden hipospadias grubu olarak tanımlanabilir. Bu hastalarda defektif üretral plak onarımında tübülarize edilecek lokal yada destek dokusunun bulunmayışı hemen daima sorun oluşturmaktadır.

Gereç ve Yöntemler: Çalışmada on dört adet genç erişkin, ortalama ağırlığı dört kilo olan, 8-10 aylık, erkek New Zealand cinsi tavşan; yedi tavşandan oluşan iki gruba bölündü. Birinci gruptan juguler ven grefti, ikinci gruptan bukkal mukoza grefti alındı ve alınan greftler üretral plakta oluşturulan defekte serbest flep olarak aktarıldı.

Bulgular: Histopatolojik incelemede grup içi ve gruplar arası epitelizasyon, fibrozis ve inflamasyon değerlendirildi. Juguler ven grefti kullanılan grubun (Grup 1) histopatolojik incelemesinde üroepitelizasyonunun tam veya tama yakın olduğu,

0000-0002-9896-0784 : CALISKAN BM
0000-0002-3712-1469 : SURER I
0000-0003-1281-7416 : GUNHAN O

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

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. This experimental study was approved as a research project of Gülhane Military Medical Faculty Research Scientific Committee, numbered AR 2005-63, and was approved by the Ethics Committee of the Experimental Research Center ARGE-9029-9-06/ Ethics Committee

Contribution of the Authors / Yazarların katkısı*: *CALISKAN BM: 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. ***SURER I***: 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 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. ***GUNHAN O:*** Planning methodology to reach the Conclusions, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study.

How to cite / *Atıf yazım şekli* : Caliskan MB, Surer I and Gunhan O. Autologous Free Reverse Inlay Vein Graft in The Treatment of Cripple Hypospadias; An Experimental Rabbit Model. Turkish J Pediatr Dis 2023;17:154-159.

Correspondence Address / Yazışma Adresi:
Mehmet Bahadır CALISKAN
Department of Pediatric Surgery, University of Health Sciences,
Gülhane Training and Research Hospital Ankara, Türkiye
E-posta: bahadircaliskan@hotmail.com

Received / Geliş tarihi : 18.01.2023
Accepted / Kabul tarihi : 23.02.2023
Online published : 02.03.2023
Elektronik yayın tarihi
DOI: 10.12956/tchd.1237471

fibrotik aktivitenin (+) ve inflamasyonun minimal olduğu izlendi. Bukkal mukoza grefti uygulanan grupta (Grup 2) ise üroepitelizasyonun yirmi birinci gün sonunda greft üzerinde yüzde otuz civarında olduğu, fibrotik aktivitenin (++) ve inflamasyonun minimal olduğu izlendi.

Sonuç: Çalışmamızın sonucunda hipospadias sakatlı olgularda defektif üretranın onarımında reverse serbest juguler ven greftinin uzun zamandır kullanılagelen bukkal mukozaya alternatif olarak kullanılabileceği sonucuna varılmıştır.

Anahtar Sözcükler: Greft alımı, Hipospadiyas, Uretra

INTRODUCTION

Hypospadias is the most common congenital anomaly of penis and is seen in approximately 19.4 per 1000 male live-births (1). It is an anomaly associated with abnormal localization of the external urethral meatus in the ventral of penis, abundant cape-like skin on the dorsum of the preputium, absence of the frenulum, and often accompanied by chordee in the penis (2). Many different surgical repair methods have been defined according to different clinical types of hypospadias (3). In the last two decades, hypospadias surgery has been successfully applied at an early age with the use of magnification loops, better suture materials, glandular hemostasis, artificial erection test and testosterone stimulation (4). Cripple hypospadias can be defined as the hypospadias group, which has been tried to be repaired before, and whose functional and anatomical complications continue (5). The absence of local or support tissue to be tubularized is almost always a problem in repair of defective urethral plate in these patients. Today, buccal mucosa is most commonly used for this purpose, but difficulties in obtaining it and reducing postoperative patient comfort are important shortcomings (6). For this purpose, it is aimed to use the easy-to-obtain vein graft in distal penile dorsal urethral plate grafting.

The use of tubularized vein grafts has been tried in recent years due to complications in skin grafting such as hair growth, diverticulum, fistula and stone formation, which are generally used in urethroplasty (7). Vein grafts are preferred because they can be grafted with a simpler technique, are easily accessible and have a diameter of approximately as much as the urethra. External jugular, internal jugular or saphenous veins can be used for grafting, but internal jugular vein is preferred both as having no valves and sufficient diameter (8).

MATERIAL and METHODS

This experimental study was approved as a research project of Gülhane Military Medical Faculty Research Scientific Committee, numbered AR 2005-63, and was approved by the Ethics Committee of the Experimental Research Center ARGE-9029-9-06/ Ethics Committee

Fourteen male New Zealand rabbits, 8-10 months old, average weight four kilograms; divided into two equal groups of seven rabbits. Jugular vein graft was taken from the first group and buccal mucosa graft from the second group. All rabbits were sedated with preanesthetic intramuscular Alfazyne 3-5 mg/kg (Xylazine HCL, 20 mg/ml, 30 ml vial, Ege Vet Livestock) and Alfamine 20-40 mg/kg (Ketamine HCL, 100 mg/kg) ml, 10 ml vial, Ege Vet Animal husbandry) were placed in the supine position.

After the skin preparation, the internal jugular vein was freed by crossing the layers with a vertical neck incision, and a 1-centimeter graft was first incised in the middle and then excised from both ends by ligating from the lower and upper ends (Figure 1). The graft was left in 0.9% saline solution, while excess surrounding tissue was removed. Under sterile conditions, the urethra was catheterized with an 8 Fr feeding catheter and a suspension suture with 5/0 prolene was placed on the glans of the penis. The hypospadiac urethra was incised ventrally from the tip to the base of the penile body, sagittally, and the dorsal urethral plate was exposed. Then, with using a 2.5X magnification loop, a region of about 1 cm of the urethral plate was excised through the midline. The reverse jugular vein graft was anastomosed to the defective area one by one with eight 7/0 polyglactone sutures (Figure 2). After the anastomosis was completed, the ventral urethra was tubularized over the catheter with a 6/0 polyglactone by continuous locking technique. The catheter was fixed with 5/0 prolene suture and the operation was completed.

In the buccal mucosal graft group, sufficient oral cavity space was provided with the help of the injector placed between the teeth and a suspension suture with 6/0 polyglactone was placed on the four corners of the buccal mucosal graft. After the incision with a scalpel, the buccinator muscle was dissected with the help of sharp scissors (Figure 3). The prepared graft was left in 0.9% saline solution and excess subcutaneous tissue and glands were removed. A suspension suture with 5/0 prolene was placed on the glans of the penis and catheterized with 8 Fr feeding tube. The urethra was prepared ventrally in the same way and the urethral plate was exposed. Then, an area of approximately 1 cm from the midline of the urethral plate was excised, and the buccal tissue graft was anastomosed one by one with eight 7/0 polyglactone sutures to the defective area created with the help of magnification loop (Figure 4). After the anastomosis was completed, the ventral urethra was tubularized over the catheter with a 6/0 polyglactone suture by continuous locking technique. The catheter was fixed with 5/0 prolene suture and the operation was terminated.

The rabbits were controlled daily for urinating, the catheters placement and infection. Postoperatively for five days,

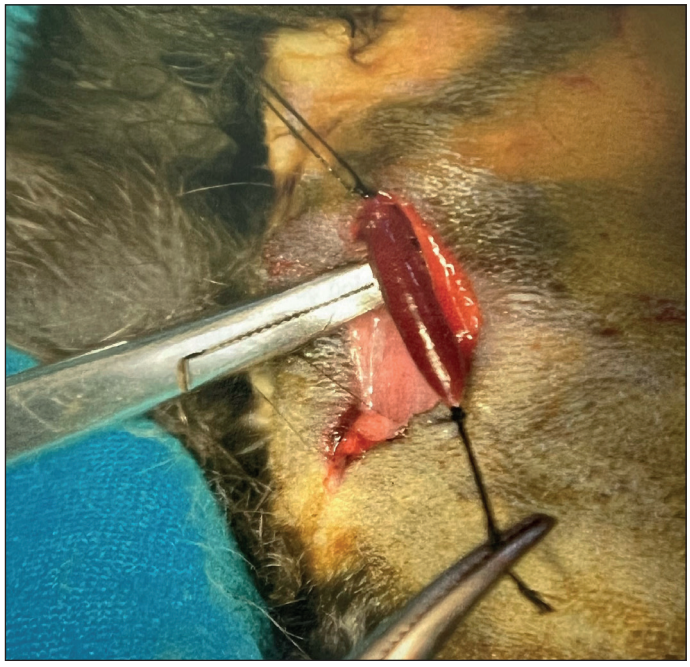

Figure 1: After the skin preparation, the internal jugular vein.

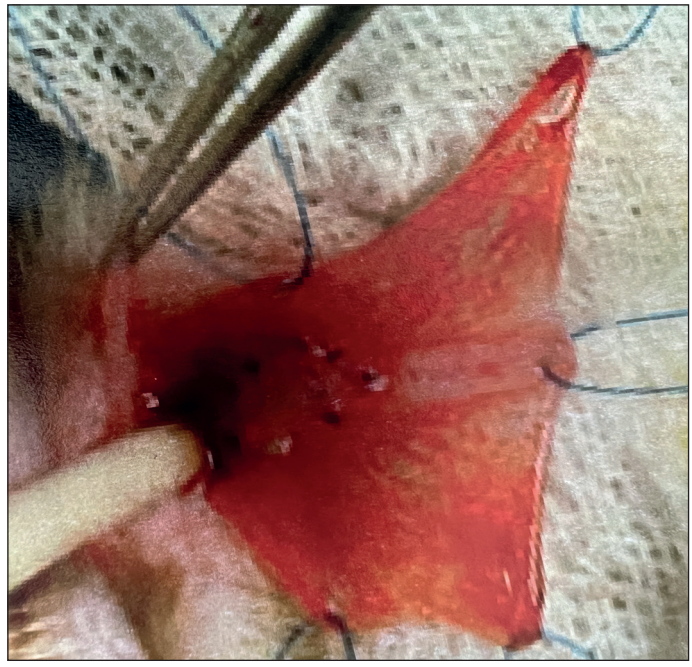

Figure 2: The reverse jugular vein graft was anastomosed to the defective area.

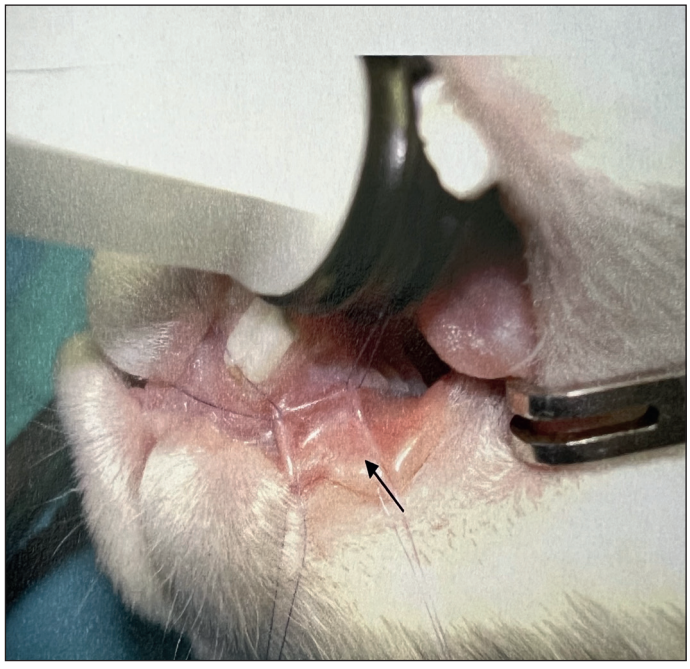

Figure 3: After the incision with a scalpel, the buccinator muscle was dissected with the help of sharp scissors.

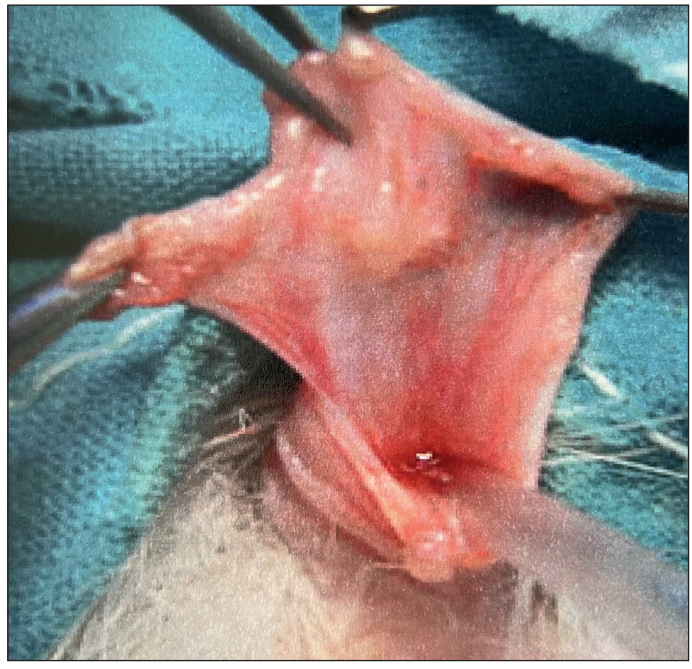

Figure 4: Area of approximately 1 cm from the midline of the urethral plate was excised, and the buccal tissue graft was anastomosed.

prophylactic antibiotic therapy was administered with 0.1 cc/kg intramuscular Terramycin (oxytetracycline, 100 ml vial, 30 mg/ml, Pfizer) once a day.

Twenty-one days after graft anastomosis, rabbits underwent partial penectomy. The penis was tied with 2/0 silk from the proximal of the graft anastomosis line and the distal penis was excised with the help of a scalpel along with the grafted area. Bleeding control was achieved with bipolar cautery. The tissue was fixed on hard plastic by stretching it from its four corners with the help of an insulin injector needles and left in formalin solution.

Tissue samples were investigated comparatively for histopathological changes. Tissue samples fixed in ten percent buffered formalin solution were then sampled in longitudinal sections, showing the urethral mucosa. After standard tissue follow-up, paraffin blocks were prepared and 4 micron thick sections were obtained from each block and stained with Hematoxylin and Eosin. The distance between the basal layer

of the epithelium and the tunica albuginea was measured visually with the help of a millimeter scale ruler on the carriage of the microscope and measured from the thickest point. Results are recorded in millimeters. Evaluation of the data was done in SPSS - 22 package program and Mann-Whitney U test was used. Values with $p<0.050$ were considered statistically significant.

RESULTS

All rabbits were followed up in a cage life for three weeks. When the cage bottoms were examined, no obstruction findings were found during voiding. Three weeks later, in the macroscopic examination performed during penectomy, it was observed that there was no polyp in the urethra and stenosis in the anastomosis line in both groups. It was observed that the vein grafts did not differ from the normal urethra in macroscopic view, and their location was determined only with the help of sutures. It was observed that the buccal mucosa was slightly lighter in color and was noticeable from the surrounding tissue. In the histopathological examination, differences in epithelialization, fibrosis and inflammation between and within groups were evaluated. In the histopathological examination of the jugular vein graft group (Group 1), it was observed that uroepithelialization was complete or nearly complete, fibrotic activity (+) and inflammation were minimal (Table I) (Figure 5).

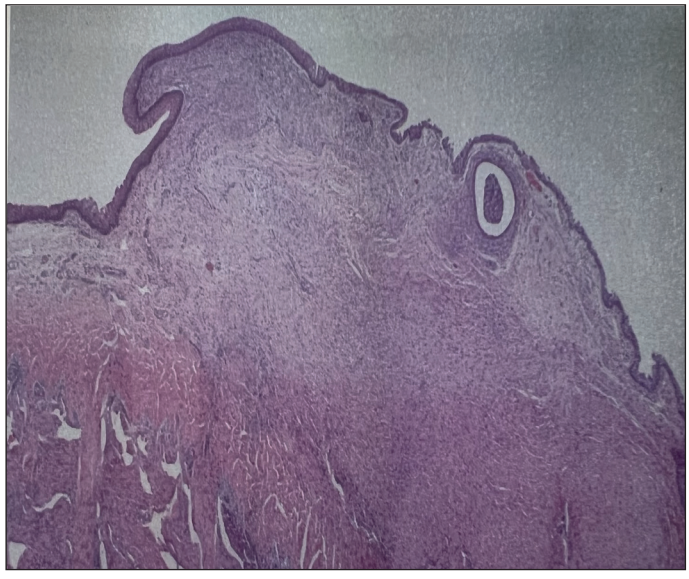

Figure 5: Uroepithelialization was complete or nearly complete.

Table I: Experimental Group 1 (Jugular vein graft).

Rabbit No:	Inflammation	Fibrosis	Fibrosis mm width	Uroepithelialization
1	-	++	1.20	%100
2	-	++	1.00	%80
3	-	++	1.40	%80
4	minimal	+	1.00	%100
5	-	+	0.60	%80
6	-	+	1.10	%100
7	-	+	0.80	%100
Mean			1.01	%91.4

Table II: Experimental group 2 (Buccal mucosal graft)

Rabbit No:	Inflammation	Fibrosis	Fibrosis mm width	Uroepithelialization
1	Minimal	++	1.50	%20
2	Minimal	+	1.10	%20
3	Medium	+++ (nodular)	1.60	%60
4	Minimal	++ (nodular)	1.40	%50
5	-	+	1.00	%30
6	Minimal	++	1.20	%30
7	Minimal	++	1.20	%20
Average			1.28	%32.8

In the buccal mucosa graft group (Group 2), it was observed that uroepithelialization was around 30% on the graft at the end of the twenty-first day, fibrotic activity was nodular (++) and inflammation was minimal (Table II).

There was no statistically significant difference between the two groups in terms of fibrotic activity ($p=0.061$), but a significant difference was found in terms of uroepithelialization ($p=0.001$)

DISCUSSION

For many surgeons dealing with hypospadias surgery, the first option is usually one-session repair methods using urethral plates or skin flaps with natural blood supply (9). Various grafts such as buccal mucosa, bladder mucosa and genital skin are used for urethral defect repair in cases of cripple hypospadias whose penile skin and urethral plate are not suitable for use due to previous unsuccessful operations. Skin grafts are not preferred as the first choice due to complications such as infection, hair growth, fistula and stone formation, development of diverticula and stenosis (10). The most important problem encountered when the bladder mucosa is used as a replacement material in urethral defect repair is the hypertrophy and stickiness of the mucosa in the part of the newly formed urethra exposed to air at the tip of the penis as seen in bladder exstrophy (11). Prolapsed bladder mucosa at the newly formed meatus level often requires revision. In addition, due to the tendency of the bladder mucosa graft to shrink, larger tissue should be removed by open surgery compared to the defect. Fistula, meatal stenosis, urethral stenosis and graft loss are also common problems in cases where buccal mucosal grafts are used (12,13). When the buccal mucosal graft used for urethroplasty as a ventral flap, it contracts due to insufficient

blood supply and the soft support tissue of the ventral flap (14). As a result of this, in the neourethra, fistula, stenosis, and the development of megalourethra due to the stenosis is inevitable (15). If the dorsal urethroplasty is performed as the buccal mucosal graft forms the dorsal half of the urethra, the viability of the graft will increase and related complications will be reduced because of a solid ground with sufficient blood support such as the tunica albuginea dorsally (16). In this case, the ventral surface of the urethra will be closed with local flaps.

The staged buccal mucosal grafting method, in which the urethral plate is excised in cases where the urethral plate is excessively scarred, as described by Bracka (17), was the basis for the above mentioned method. In this method, the unhealthy urethral plate, which has been damaged to such an extent that it cannot be used in urethral repair with dense scar tissue, is excised and removed, and the buccal mucosal graft is anastomosed to the corpus cavernosum, from the proximal urethrostomy to the tip of the glans, and tubularization is performed in the second session six months later (18). In cases where the urethral plate or midline ventral skin is extensively scarred after hypospadias surgery, a free tissue graft can be provided for urethroplasty by using a vein graft, which is easily accessible, has minimal complications that may occur during graft retrieval, and minimizes patient comfort. Veins are easily accessible tissues.

For the last hundred years, vein grafting has been experimentally tested in animal studies. Saphenous vein was used by many researchers which resulted in fistula and graft rejection (19). The first successful study with a vein graft was in 1982 by Frang et al. (20) made by the use of autologous everted vein graft for urethral defect in dogs and then lately by Xu et al in rabbits in 2017 (21). Both the jugular vein graft and the buccal mucosal graft are superior to other grafts in urethral reconstruction because they are wet and thin. It was observed that the removal of the jugular vein graft in rabbits did not cause any complications and deterioration of comfort. Access to the jugular vein was very easy between the muscles and the vein was easily dissected from the surrounding tissue. Both the tight adhesion of the buccinator muscle and the difficulty in reaching the oral mucosa while obtaining the buccal mucosal graft seems to be the disadvantage of this technique. While there was no difficulty in the anastomosis stage of both tissues, in the light of the data we obtained as a result of our study, it was decided that the free jugular vein graft in the repair of defective urethral plate is more advantageous than the buccal mucosa graft because it is easy to obtain and can be easily prepared from the surrounding tissue.

Macrophages and lymphocytes in the lamina propria of the buccal mucosa play a role in fibrosis, especially in the nodular form in our study. Although there was no statistically significant difference between them (p=0061), significantly more fibrosis was observed in buccal mucosa grafts than in jugular vein free grafts. Many authors have pointed out that after buccal mucosal grafting, a second operation is required for small fistula and meatal revision (22). In our study, in order to protect the endothelial surface of the jugular free vein graft, the graft was anastomosed reversely to the defective urethral plate. Thus, the jugular vein graft was better supplied with the endothelial tissue by passive diffusion from the adjacent tunica albuginea. Hubner et al. (23), who studied the reverse use of the jugular vein and the longer survival of the graft, also reached the same conclusion. Inflammation was minimal in both graft tissues. The most important difference we obtained in our study is the degree of uroepithelialization on both grafts, which was evaluated at twenty-one postoperative day. In the histopathological examination of the jugular vein graft, uroepithelialization was observed as complete or almost complete in all grafts, while it was observed as a patchy and small amount in the buccal mucosa. It has been determined that the uroepithelium covers on the graft surface starting from the edges and epithelialization is completed on the twenty-first day. In a different experimental study performed by Kahveci et al. (24) on 44 rabbits, have shown that, similar findings as in our study on the postoperative 3, 6, 9, 15 and 22 days, the transitional epithelium began to progress from the corners on the 6th day, turned into stratified on the 15th day, and the transitional epithelium appearance seen on the 22nd day.

Recently two adult man studies who have chronic tobacco exposed oral mucosa have been reported in the literature, urethroplasty using an everted saphenous vein graft (SVG). Substitution urethroplasty using an SVG was performed using a dorsolateral onlay technique in 20 male patients reported by Akhtar et al. The result of the report, an autologous SVG is a viable option in long-segment urethral strictures, with minimum morbidity (25). Swatantra Nagendra Rao et al reported that, thirty male patients were taken up for urethroplasty, to compare the initial outcomes of everted SVG and buccal mucosal graft as dorsolateral onlay urethroplasty. They found that outcomes of everted saphenous vein graft urethroplasty are comparable to oral mucosa graft urethroplasty (26).

CONCLUSION and SUGGESTIONS

In hypospadias surgery, the urethral plate has been the most preferred tissue for urethral reconstruction in recent years, due to its good vascularity, rich nerve support, and extensive muscle and connective layer. However, almost complete uroepithelialization of the free jugular vein graft in cases with defective urethral plate due to excessive scary tissue increases the chance of success in the next step of tubularization and also thought that reverse free vein graft could be an effective replacement material for the reconstruction of the defective urethral plate in cases of cripple hypospadias as a result of studies.

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Investigation of the Effect of Cranial Vault Surgery On Parenchymal Perfusion Before and After Surgery in Craniosynostosis Patients

Kraniyosinostoz Hastalarinda Kubbe Cerrahisinin, Cerrahi Öncesi ve Sonrası Parankimal Perfüzyon Üzerine Etkisinin İncelenmesi

Suleyman Taha ASLAN, Harun DEMIRCI

Department of Neurosurgery, Ankara Yildirim Beyazit University, Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objective: In our study, it is aimed to examine the effect of surgery on brain perfusion with ASL sequence perfusion MRI taken before surgery and 12 weeks after surgery in cases of non-syndromic craniosynostosis treated in our clinic.

Material and Methods: The study was conducted between 28.12.2021-16.09.2022 with 10 patients who were evaluated preoperatively and treated surgically at the Neurosurgery Clinic of Ankara City Hospital. Perfusion MRI was performed preoperatively and 12 weeks postoperatively. The preoperative and postoperative images obtained were evaluated comparatively at the workstation.

Results: After the exclusion of patients who did not appropriate the study criteria, the results of 9 patients were examined. MRI scans were taken preoperatively and 87 days as average postoperatively. After surgery, there is perfusion enhancement in 7 patients and a perfusion impairment in 2 patients. Regarding the average perfusion rates, the results were found to be statistically significant in four of the seven patients in whom an increase was detected ($p \leq 0.050$), while the results were found to be statistically significant in one of the patients in whom a decrease was observed ($p \leq 0.050$).

Conclusion: Surgical treatment is effective on brain perfusion in patients with non-syndromic craniosynostosis. Perfusion alteration may be different according to surgical technique, patient age at the time of surgery, and type of craniosynostosis. In addition to cosmetic improvement, surgical treatment can also be effective in changing neurological functions. ASL sequence perfusion MRI, which doesn't require contrast and is non-invasive, is a successful method of demonstrating the quantitative effectiveness of surgery in patients with craniosynostosis.

Key Words: Cerebral Blood Flow, Craniosynostosis, Magnetic Resonance, Nonsyndromic, Perfusion Imaging

ÖZ

Amaç: Çalışmamızda kliniğimizde tedavi edilen non-sendromik kraniyosinostoz olgularında cerrahi öncesi ve cerrahiden 12 hafta sonra çekilen ASL sekans perfüzyon MRG ile cerrahinin beyin perfüzyonu üzerindeki etkisinin incelenmesi amaçlanmaktadır.

Gereç ve Yöntemler: Çalışma 28.12.2021-16.09.2022 tarihleri arasında Ankara Şehir Hastanesi Beyin ve Sinir Cerrahi kliniğinde cerrahi tedavileri, preoperatif ve postoperatif tetkikleri gerçekleştirilen 10 hasta ile yapıldı. Hastalara preoperatif

0000-0002-8981-8794 : ASLAN ST
0000-0003-2213-5953 : DEMIRCI H

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 Ankara City Hospital, No. 2 Clinical Research Ethics Committee (E-21-1157/19.01.2021)

Contribution of the Authors / Yazarların katkısı*: *ASLAN ST: 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. ***DEMIRCI H:*** 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 the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / *Atıf yazım şekli* : Aslan ST and Demirci HInvestigation of the Effect of Cranial Vault Surgery On Parenchymal Perfusion Before and After Surgery in Craniosynostosis Patients. Turkish J Pediatr Dis 2023;17:160-165.

Correspondence Address / Yazışma Adresi:
Suleyman Taha ASLAN
Department of Neurosurgery, Ankara Yildirim Beyazit University,
Faculty of Medicine, Ankara, Turkey
E-posta: tahaslann@gmail.com

Received / Geliş tarihi : 18.02.2023
Accepted / Kabul tarihi : 21.03.2023
Online published : 22.03.2023
Elektronik yayın tarihi
DOI: 10.12956/tchd.1252646

ve postoperatif 12. haftada Perfüzyon MRG çekimleri yapıldı. Preoperatif ve postoperatif elde edilen görüntüler çalışma istasyonunda karşılaştırmalı değerlendirildi.

Bulgular: Çalışma kriterlerini karşılamayan hastaların çalışma dışında bırakılmasını takiben 9 hastanın sonuçları incelendi. Beş hastaya açık cerrahi rekonstrüksiyon dört hastaya endoskopik cerrahi uygulandı. Preoperatif ve postoperatif ortalama 87 gün sonra MRG çekimleri yapıldı. Cerrahi sonrası 7 hastada perfüzyon artışı ve 2 hastada perfüzyonda azalma oldu. Ortalama perfüzyon hızlarına bakıldığında artış saptanan yedi hastanın dördünde sonuçlar istatistiksel olarak anlamlıyken ($p \leq 0.050$) azalma görülen hastaların birinde sonuçlar istatistiksel olarak anlamlı bulundu ($p \leq 0.050$).

Sonuç: Non-sendromik kraniyosinostoz hastalarında cerrahi tedavi beyin perfüzyonu üzerinde etkilidir. Perfüzyon değişikliği cerrahi teknik, cerrahi sırasında hasta yaşı ve kraniyosinostoz çeşidine göre farklı olabilir. Cerrahi tedavi kozmetik düzelmenin yanında nörolojik fonksiyonların değişikliğinde de etkili olabilir. Kontrast gerektirmeyen ve non-invaziv olan ASL sekans perfüzyon MRG kraniyosinostoz hastalarında cerrahinin kantitatif etkinliğini göstermede başarılı bir yöntemdir.

Anahtar Sözcükler: Kraniyosinostoz, Manyetik Rezonans, Non-sendromik, Perfüzyon Görüntüleme, Serebral Kan Akımı

INTRODUCTION

Craniosynostosis, known as premature closure of the cranial sutures, is the second most prevalent craniofacial developmental disorder. According to the literature, it occurs 1 in every 2000-2500 live birth (1). There are many etiological factors. This suggests that there are multiple parameters for its occurrence (2). The vast majority of cases are sporadic cases with no accompanying medical problems or an identified mutation and genetic factor (3). Craniosynostosis can be classified in many different ways as simple or complex according to the type of occurrence, primary or secondary according to the reason of occurrence, and syndromic or non-syndromic according to its relationship with the syndromes.

It is thought that the morphological changes that occur in the cranium with craniosynostosis may cause functional impairments as well as cosmetic effects (4,5). The recent studies about intracranial pressure and cerebral perfusion changes in the cases of craniosynostosis supports that there may be functional disorders besides head deformities. However, the relationship between brain parenchymal perfusion change following intracranial pressure change and cortical dysfunctions continues to be discussed (6–8).

When we review the recent medical literature, it's shown that the disorders in neurocognitive functions such as speech, cognition, and behavior in cases of craniosynostosis are more frequent than normal population (9,10). It's thought that the intracranial pressure increment, the change of cerebral circulation dynamics, and the structural disorders of tissues embryologically interacted with sutures are effective in neurocognitive dysfunctions; but if we understand what the actual reason is, whether pressure or structural disorganization, will guide us developing existing surgical techniques (1,11–13).

In our study, we try to show the change in cerebral parenchymal perfusion with Arterial Spin Labeling (ASL) perfusion Magnetic Resonance Imaging (MRI) among the cases of non-syndromic craniosynostosis who had operated between December 2021 and July 2022 in our clinic and aged 0-18 months and ASL perfusion MRI images taken preoperatively and 12 weeks postoperatively. And we plan to determine surgical effectivity with the quantitative data.

MATERIALS and METHODS

We informed the patients, who were admitted pediatric neurosurgery outpatient clinic of Ankara Bilkent City Hospital between December 2021 and July 2022 and diagnosed with craniosynostosis, about surgical treatment techniques and all possible complications. The patients, who accepted the surgery, signed the written consent. Ten 0-18 months aged patients were selected then ASL perfusion MR images were taken with 1.5T Ge Signa Explorer MRI machine preoperatively and 12 weeks after surgery.

Compared to other imaging modalities, most MRI sequences need more time to acquire sufficient data to form an image. Motion artifacts are well-known problems of MRI for a long time. For young children, motion prevention with sedation is a successful technique during MRI according to the literature (14). In our study, all patients were sedated for imaging with the standard dose of sedation ketamine 1mg/kg IV and midazolam 0.1mg/kg IV. Sedation is a challenging factor for brain imaging. Two main mechanisms affect cerebral perfusion imaging. The first one is elevating intracranial pressure, and the second is hypotension after the cardiovascular effect. Theoretically, ketamine increases intracranial pressure and cerebral perfusion pressure, and midazolam depresses the cardiac and respiratory systems. According to the literature, the combination of these drugs in adequate doses ensures physiology and makes sedation safer and more effective (15).

Ten patients were included in the study, seven of them were diagnosed with sagittal synostosis, two of them were diagnosed with coronal synostosis, and one of them was diagnosed with metopic synostosis. A total of 20 MRI sessions were performed on each patient before and after surgery. Obtained images processed with GE Advantage Workstation Ready View software. We removed one patient from the study

due to inappropriate imaging techniques and technical issues with the workstation. We applied open cranial vault surgery for 5 patients and endoscopic surgery for 4 patients.

ASL Perfusion MRI

ASL perfusion MRI is an imaging technique that can show parenchymal blood supply quantitatively with the use of water molecules in the blood, which penetrates the brain parenchyma freely, marked with radiofrequency inversion pulses. The main advantages, compared with other imaging techniques that show blood perfusion, are showing regional blood perfusion rate and being a non-invasive imaging method. The main disadvantage of ASL perfusion MRI is low Signal to Noise Ratio (SNR). However, with comparing adults, higher cerebral blood flow and faster flow rate at carotid arteries and higher cerebral water content of pediatric patients are parameters for better SNR physiologically. Because of that ASL imaging is effective and featured for the pediatric population (16,17).

There is no standard for processing ASL perfusion MRI images in literature. In this study, we used brain segmentation that was used frequently previous some other studies and described by Limperopoulos et al.(18) At first, with a plane that passes from Anterior Commissure (AC) and Posterior Commissure (PC) each hemisphere is divided into two segments craniocaudally. After that with 3 coronal planes, each hemisphere is divided into 8 segments named Dorsolateral Prefrontal (DLPF), Premotor (PM), Sensorimotor (SM), Parieto-occipital (PO), Orbitofrontal (OF), Subgenual (SG), Midtemporal (MT), Inferior occipital (IO) (18). OF and IO segments weren't used, because of the measurement artifact due to anatomical neighborhoods (Figure 1).

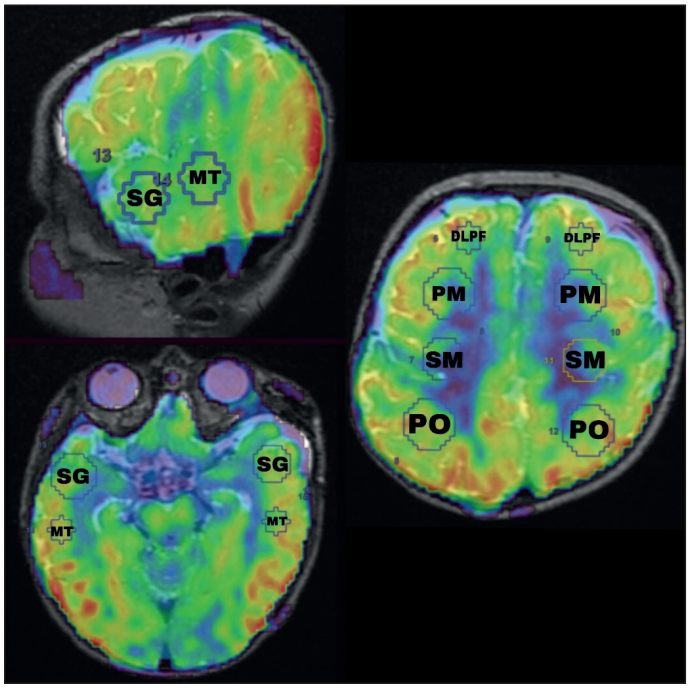

Figure 1: Brain segmentation described by Limperopoulos et al (18).

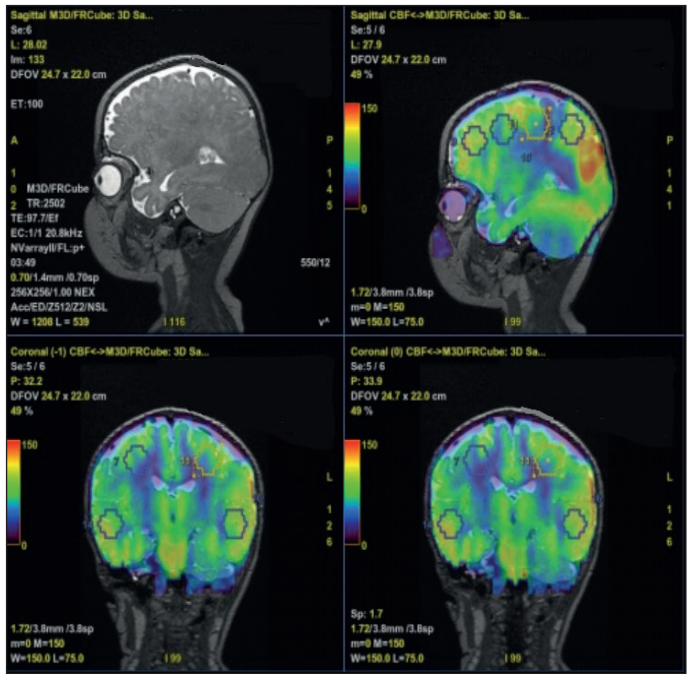

Figure 2: ROI placement at workstation

During the measurement of processed images, we used 3-Dimensional (3D) Region Of İnterest (ROI). We chose the biggest ROI volume for each imaging session after brain segmentation. In this study, the biggest ROI was 3.28 cm^3 and the smallest ROI was 3.96 cm^3. Cerebral Blood Flow (CBF) rate unit was "ml/100gr/min". We placed the ROI's subcortical levels, due to measurement artifacts that extremely high CBF caused by cortical vessels and extremely low CBF caused by ventricles and cisterns. All ROIs were controlled in axial, coronal, and sagittal planes and then confirmed as the proper position for segmentation.

The study was approved by Ankara City Hospital, No. 2 Clinical Research Ethics Committee (E-21-1157/19.01.2021)

Statistics

In this study, the patient's age at MRI session and the time between surgery and postoperative MRI session for each patient were analyzed statistically within the "day" unit. After excluding the patient, for the remaining 9 patients, a total of 12 segments were placed in each hemisphere symmetrically (Figure 2). Then with the measurement of 3D ROIs, for each segment we obtained minimum, maximum, and average CBF values after that we compare preoperative and postoperative results with Wilcoxon Analysis.

RESULTS

The 9 patients included in the study operated at the mean age of 160 days (SD: ± 135). Postoperative imaging was done

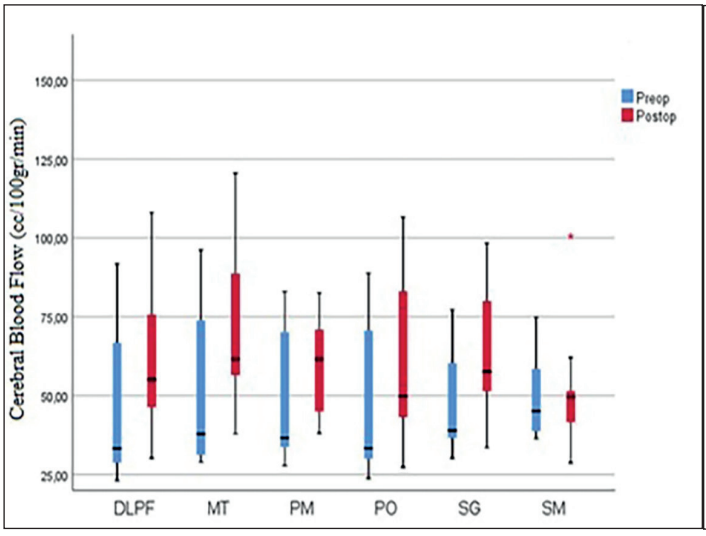

Figure 3: Average perfusion rate of right hemisphere.

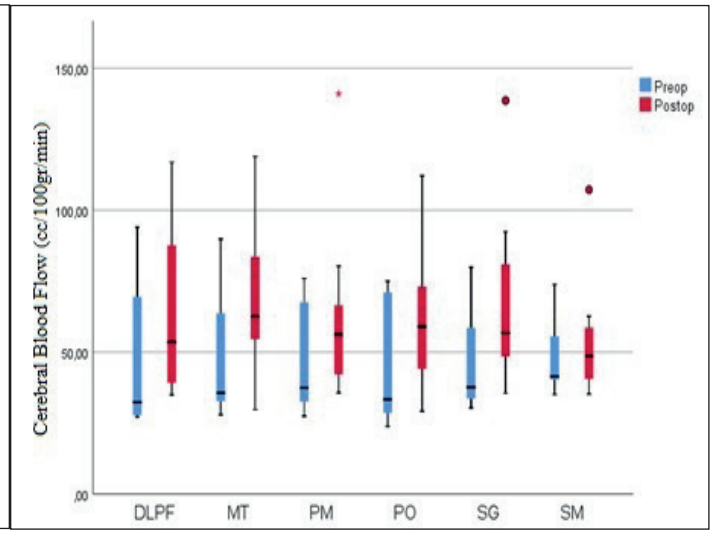

Figure 4: Average perfusion rate of left hemisphere.

mean 87 days (SD: ± 6) after surgery. Average ROI volumes were 3.78 cm^3 (SD: ±0.211) at preoperative measurement and 3.72 cm^3 (SD: ±0.176) at postoperative measurement.

In this study, there were seven sagittal synostoses, one unilateral coronal synostosis, and one metopic synostosis. About unilateral coronal synostosis; there were increased CBF on both hemispheres, but statistically insignificant (p>0.050). According to measurements of metopic synostosis, both hemispheres had increased cerebral perfusion and all changes were statistically significant except the change of left hemisphere minimum CBF (p≤0.050). About sagittal synostosis; 5 patients had increased CBF in all measurements, one patient had decreased CBF in all measurements; one patient had increased maximum CBF, decreased minimum and average CBF on both hemispheres. Two of the patients, whose results were all increased, data were found statistically significant and the patient's data, whose all CBF results decreased, was found statistically significant (p≤0.050).

With the comparison of all segment minimum, maximum, and average CBF values we found that cerebral perfusion rates of all segments raised after surgery, except the left SM minimum value. According to statistics; right DLPF maximum, right SG minimum and average, left SG average, right MT maximum, and left MT maximum CBF changes were found statistically significant (p≤0.050). Other than that, found statistically insignificant (p>0.050). Postoperative results showed that minimum perfusion rate enhanced 26.40%, maximum perfusion rate enhanced 36.94%, average perfusion rate enhanced 28.32% at right hemisphere and minimum perfusion rate enhanced 42.76%, maximum perfusion rate enhanced 26.73%, average perfusion rate enhanced 34.98% at left hemisphere (Figure 3,4).

DISCUSSION

Craniosynostosis affects cranial development with premature suture fusion and disarranges cerebral parenchyma with the change of intracranial volume (19,20). Regardless of shape and volume change, there is also neuronal disorganization. Theoretically, with surgical reconstruction, the aim is to make room for cerebral growth and restore the physiological position of the brain parenchyma. But the neurodevelopmental effects are not limited to sutures and their surroundings according to recent MRI studies (4).

In recent studies, this is told that there are two main mechanisms described in neurodevelopmental disorders of craniosynostosis patients. One of them is intracranial pressure rise and hypovascularity, the other one is cerebral extraordinary development (19). The goal of treatment was primarily craniofacial cosmetic appearance previously but, with recent studies, neurological improvement is also as important as cosmetic results. Because of that, new researchers try to find the relationship between neurodevelopment, intracranial pressure and surgical timing, and surgical technique (8,9,21,22). So, we could choose the optimal technique and optimal timing for the treatment of craniosynostosis.

According to the age of the patients on the operation day, 7 of them were younger than 180 days, and 2 of them were older than 180 days. And aside from that, with postoperative results, the most improved cerebral perfusion was found in the second youngest patient and the two oldest patients (older than 180 days) were the only patients whose cerebral perfusion decreased. The surgical treatment is recommended for non-syndromic craniosynostosis as soon as possible due to prevent deformity complicated with time and reduce the probability of neurological disorders. By the delay of surgery, experts worry about decreasing cosmetic and functional cosmetic results in recent literature (4,9). Our data shows us the operated patients'

results differ, between the age younger and older than 180 days, which supports the literature about surgical timing. When we tried to connect postoperative perfusion results and surgical technique, we couldn't establish a significant relationship between them.

By reviewing the literature, a few studies could be found about the neurocognitive effects of craniosynostosis. For example, in a review conducted by Speltz et al. (23) examining 17 studies that contain the cases followed between 1972 and 2003, there were decays of 35-40 % of patients in advanced neurological functions such as language, cognition, and behavioral development, although patients IQ was mostly within the normal range. According to the estimation made with the results of this study, independent from the suture type, craniosynostosis cases have 3-5 times higher risk of developing neurological disorder than normal population (4). Becker et al. (9) composed a study with 214 cases of craniosynostosis and found there was 23 % speech disorder that require speech therapy, there were 45 % psychological disorders. Then Becker et al. (9) tried to compare their results with recent studies about neurological disorders found in normal population. The results were found as speech disorders were 23 % in cases of craniosynostosis and 5.5 % in normal population, problems with school success were found as 16 % in cases of craniosynostosis and 5 % in normal population, behavioral disorders were found as 35 % in cases of craniosynostosis and 16% in normal population. As a result, Becker et al. (9) found similar results with Speltz et al. (23) and proved the previous estimation. Besides, the results of operated and unoperated patients couldn't be compared, due to the very low number of unoperated patients, according to Becker et al.(9). In addition to this, they commented that surgery stops the p rogression of neurological problems, but can't correct the effects of primary brain deformation caused by disruption of the structural organization of the brain (9). There is also increasing evidence of disorders in neuropsychological functions such as planning, spelling, reading, language development, and attention in studies conducted with older children diagnosed with craniosynostosis. In summary, the evidence shows us that craniosynostosis may be related to mental retardation and loss of neurological function, regardless of age (24). However, the number of studies that compare cognitive functions and anatomical changes, which use neuropsychological data and imaging modalities, are insufficient.

In this study, we realized that with surgical reconstruction, because of decreased intracranial pressure, postoperative cerebral blood flow increased. As stated in the literature, with increased CBF we try to reassure the homeostasis of brain parenchyma affected premature suture fusion and we plan to enable the recovery of neurological functions, theoretically (6,9). At the same time, we revealed the effectivity of applied surgical technique with perfusion measurement, quantitively.

Considering the functions of the brain regions, complex neurological functions such as memory, impulse control, and planning are managed by the dorsolateral frontal region (25,26). When we paraphrase the data of this study with literature, it may suggest that surgical treatment of craniosynostosis paves the way for the development of advanced neurological functions such as memory, impulse control, attention, and planning. Regarding social attention deficits and visual motor problems of pediatric autism spectrum disorders and schizophrenia cases, in the literature authors thought that may be related to functional and structural anomalies of the premotor and prefrontal regions (4). In light of the literature, it may be thought that parenchymal deformation of the brain in craniosynostosis cases gives rise to neuropsychological pathologies. The postoperative changes of CBF in premotor and prefrontal regions show us surgical treatment may be protective against developing neuropsychological pathologies of craniosynostosis cases.

According to Becker et al. (9), in craniosynostosis cases, speech disorders and problems with school success are more frequent than normal population. Becker and other researchers thought that the problems with school success were the result of visual and reading disturbances (9,27). In consideration of Broadmann's areas; on the occasion of increasing CBF of parietooccipital (PO), subgenual (SG), and midtemporal (MT) segments with surgery; theoretically, it is thought that the frequency of speech and school success disorders in craniosynostosis cases decrease with treatment.

In this study, with increasing the number of patients and varying the types of craniosynostosis included, the surgical numeric results guide us to create new treatment techniques or find new treatment algorithms or build new ideas. Besides, the statistical significance will be steadier with an increasing number of studied patients.

CONCLUSION

In the end, until the last two decades, craniosynostosis was only known as the deformed head shape and used to be operated on for appearance. Nowadays, with scientific advancements, the effects of craniosynostosis on neurological development have also gained importance. The literature and this study show that craniosynostosis should be treated at the most appropriate time and with the most appropriate technique to maintain or develop complex neurological functions in addition to their external appearance for patients.

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Turkish Journal of Pediatric Disease
Türkiye Çocuk Hastalıkları Dergisi

Use of Valacyclovir Prophylaxis in Herpes Virus-Associated Recurrent Erythema Multiforme Cases

Herpes Virüs İlişkili Tekrarlayan Eritema Multiforme Olgularımızda Valasiklovir Profilaksisi Kullanımı

Selma ALIM AYDIN[1], Azize Pınar METBULUT[1], Emine DIBEK MISIRLIOGLU[2], Ayse METIN[2]

[1]Department of Pediatric Allergy and Immunology, Ankara City Hospital, Ankara, Turkey
[2]Department of Pediatric Allergy and Immunology, University of Health Sciences, Ankara City Hospital, Ankara, Turkey

ABSTRACT

Erythema multiforme (EM) is an immune-mediated condition characterized by symmetric erythematous rash with typical target lesions. Drugs, infections, immunologic conditions and food additives are among etiologic causes; but Herpes simplex virus infection is the most commonly seen reason.

We report three cases of recurrent EM associated with herpes labialis infection. They all presented with typical target lesions appearing nearly one week after the herpes labialis lesion had begun. Each patient had similar EM episodes with different frequencies. All three patients were initially treated orally with valacyclovir, then prophylactic valacyclovir with a daily dose of 500 mg for six month period.

Autoreactive T cells triggered by Herpes virus infection, are suggested to play an important role in Herpes-associated EM (HAEM) pathogenesis. The first line management of recurrent HAEM is antiviral treatments and they are generally safe and well tolerated in pediatric and general populations. Early administration of oral acyclovir or valacyclovir are recommended to reduce the severity and duration of the EM rash. Prophylactic antiviral treatment using for 6 months may be effective in controlling recurrent epizodes of HAEM. HSV infection and HAEM may recur; but prophylactic treatment may reduce the frequency and severity of epizodes.

Key Words: Children, Erythema Multiforme, Herpes Simplex Virüs

ÖZ

Eritema multiforme (EM) tipik hedef lezyonlarıyla simetrik eritematöz döküntü ile karakterize, immün aracılı bir durumdur. İlaçlar, enfeksiyonlar, immünolojik durumlar ve gıda katkı maddeleri etiyolojik nedenler arasındadır, ancak Herpes simplex virus enfeksiyonu en yaygın olanıdır.

Herpes labialis enfeksiyonu ilişkili üç rekürren EM olgusu sunuyoruz. Hepsi herpes labialis döküntüsünden yaklaşık bir hafta sonra ortaya çıkan tipik hedef lezyonlarla başvurdu. Her hastanın farklı sıklıkta tekrarlayan benzer atakları vardı. Her üç hastaya da önce oral valasiklovir tedavisi, ardından günlük 500 mg dozda 6 ay profilaktik valasiklovir tedavisi uygulandı.

Herpes virüs enfeksiyonu ile tetiklenen otoreaktif T hücrelerinin, Herpes ilişkili EM (HAEM) patogenezinde önemli bir rol oynadığı ileri sürülmüştür. Tekrarlayan HAEM'in birinci basamak tedavisinde, antiviral tedaviler genellikle güvenlidir ve pediyatrik ve genel popülasyonlarda iyi tolere edilir. EM döküntüsünün şiddetini ve süresini azaltmak için oral asiklovir ya da valasiklovir tedavisinin erken uygulanması önerilir. Altı ay süreyle verilen profilaktik oral asiklovir veya valasiklovir, tekrarlayan HAEM ataklarını kontrol etmede etkili olabilir. HSV enfeksiyonu ve HAEM tekrarlayabilir ancak profilaktik tedavi bu epizotların sıklığını ve şiddetini azaltabilir.

Anahtar Kelimeler: Çocuk, Eritema Multiforme, Herpes Simplex Virüs

0000-0002-0102-0711 : ALIM AYDIN S
0000-0001-8823-5960 : MERBULUT AP
0000-0002-3241-2005 : DIBEK MISIRLIOGLU E
0000-0002-0731-5799 : METIN A

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

Financial Disclosure / *Finansal Destek*: The authors declared that this case has received no financial support.

***Confirmation / Onay*:** The written consent was received from the patient who was presented in this study.

How to cite / *Atıf Yazım Şekli* : Alım Aydin S, Metbulut AZ, Dibek Misirlioğlu E, Metin A. Use of Valacyclovir Prophylaxis in Herpes Virus-Associated Recurrent Erythema Multiforme Cases. Turkish J Pediatr Dis 2023;17:166-170.

Correspondence Address / Yazışma Adresi :

Selma ALIM AYDIN
Department of Pediatric Allergy and Immunology,
Ankara City Hospital, Ankara, Turkey
E-posta: selmaalimaydin@gmail.com

Received / Geliş tarihi : 23.11.2021
Accepted / Kabul Tarihi : 26.04.2022
Online published : 04.07.2022
Elektronik yayın tarihi
DOI:10.12956/tchd.1015205

INTRODUCTION

Erythema multiforme (EM) is an immune-mediated condition characterized by symmetric erythematous rash with target lesions, often accompanied by erosions or bullae involving the oral and other mucus membranes (1,2). Drugs, infections, immunologic conditions and food additives are among the etiologic causes (Table I). But Herpes simplex virus (HSV) type1 and to a lesser proportion HSV type 2 infection has been identified in up to 70% of the EM cases. Periodic reactivations of HSV induce frequent reactivations of EM which is named herpes associated EM (HAEM). The annual incidence of EM is estimated to be less than 1%, which is highest in males and in the 2nd decade of life. Children comprise of 20% of all the cases (2).

Erythema multiforme minor refers without or with only mild mucosal involvement and systemic symptoms. EM major is the term used to describe EM with severe mucosal involvement and may be associated with systemic symptoms, such as fever and arthralgias. Although it was previously thought that EM was on the same pathologic spectrum with Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN); now it was accepted that these are separate entities (3,4).

In this report, we aimed to emphasize that among other predisposing factors, HSV also may cause recurring EM and recurrences can be prevented with prophylactic antiviral treatment.

Table I: Predisposing factors of erythema multiforme.

Infectious agents
Herpes simplex virus type 1/2
Epstein-Barr virus
Cytomegalovirus
Hepatitis C virus
Influenza virus
Mycoplasma pneumoniae
Vulvovaginal candidiasis
Drugs
Erythromycin
Nitrofurantoin
Penicillins
Sulfonamides
Tetracyclines
Antiepileptics
Barbiturates
Nonsteroidal
anti-inflammatory drugs
Phenothiazines
Statins
Sulfonamides
Tumor necrosis factor-α inhibitors
Other conditions
Vaccines
Inflammatory bowel disease
Malignancy (leukemia, lymphoma)
Menstruation
Food additives/chemicals

CASE REPORTS

We report three cases of recurrent HAEM. All three patients presented with typical target lesions appearing nearly one week after the herpes labialis rash had begun. Symmetric eruptions were presented especially on the extremities, more intensely on their hands and feet including palms and soles.

First patient was 17 years old female patient. She had recurrent attacks every 2-3 months in the last 9 years.

Second patient was 12 years old male patient. He had EM lesions more frequently on his face and hands (Figure 1 and Figure 2). He had about five similar attacks per year in the last six years.

Third patient was 12 years old male patient. He had mucosal involvement including the eye and mouth preventing him from feeding (Figure 3). He had two similar episodes that had recurred in an interval of 1.5 months.

These episodes were not related to drugs and other triggering factors. In either patients there was no considerable feature in the patient and family history of the patients. Herpes infections were supported with typical lip rash and detection of positive serology for HSV type1. There was no history for other viral, bacterial and fungal infections, acute or chronic drug usage and the other diseases, thus the diagnosis was confirmed as HAEM. Due to the recurrences of HSV infection we evaluated the patients with immunological screening tests (complete blood count, differential serum Immunglobulins (Ig), Ig G subclasses, lymphocyte subpopulations, Nitroblue tetrazolium test, CH50, complement C3, C4, lymphocyte blastic transformation) to investigate congenital immunodeficiency disease or primary immunodeficiencies that may be the cause of susceptiblity to

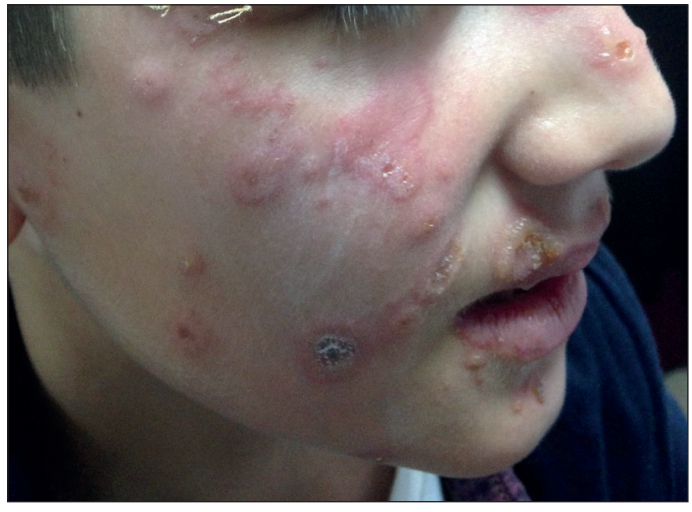

Figure 1: Fasial lesions of the second case.

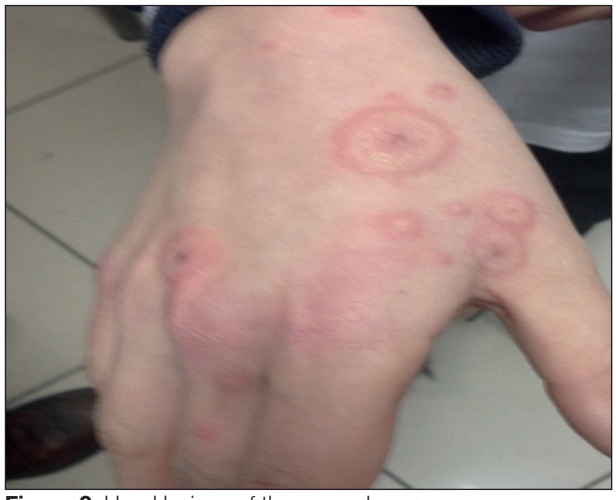

Figure 2: Hand lesions of the second case.

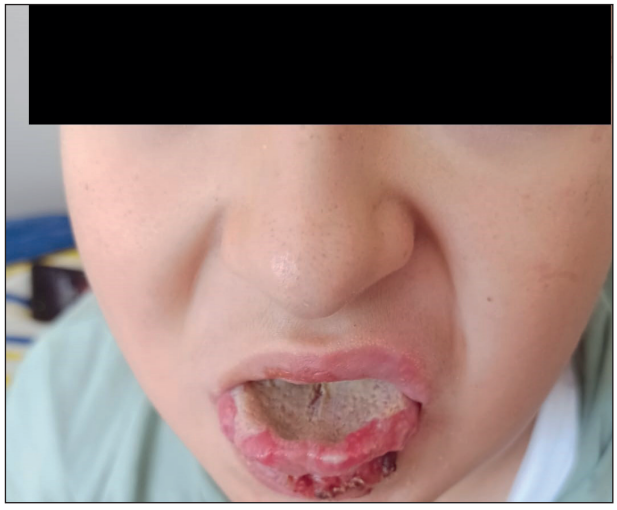

Figure 3: Oral mucosal lesions of the third case.

viral infections. Our third patient had low Ig G, 744 mg/dl (normal range for age 835-2094 mg/dl) and Ig A 57 mg/dl (range 67-433) and his other tests were within normal limits. There was no abnormality in the screening tests of the other two patients.

All patients were initially treated orally with a prolonged course of the antiviral drug valacyclovir. Dosage was 500 mg twice per day for four weeks. Orally methylprednisolone was given in dose of 40 mg/day for five days and reduced and stopped in the following 5 days in third patient with mucosal involvement. We used topical corticosteroids for mouth and skin lesions. Skin lesions healed with skin hyperpigmentation in about 4 weeks in our patients.

Prophylactic valacyclovir treatment with a daily dose of 500 mg were begun to all patients. In all of our patients valacyclovir prophylaxis discontinued after 6 months of drug usege. During this period renal functions were monitored with intermittent blood tests. No oral or skin lesions developed during prophylactic treatment. After prophylaxis treatment; in the first patient mild rashes recurred only on the hands 2-3 times per a year, in the six year follow-up period. There was no recurrence in the one year follow-up of the second patient. Only one recurrence was observed two months after the ending of prophylactic treatment in the one year follow-up of our third case. He had only mild rashes on the hands and feet without developing mucosal lesions.

DISCUSSION

A target lesion is a round skin lesion with three concentric colour zones: A darker centre with a blister or necrosis, a ring around this that is paler pink and raised due to edema and a brightered region outer ring. Target lesions typically occur in EM. They can arise on any body site and mucous membranes. An iris lesion represent an early target lesion and has two parts; a central dark or blackish zone and a red outer zone. Target lesions appear within the first 3 days of an episode of erythema multiforme and once one lesion has appeared, it stays in the same location for 7 days or more until the skin heals. Atypical target lesions show just two zones. In EM, these lesions are raised papular in SJS and TEN, they are flat as erythematous or purpuric macules. Targetoid lesions can be caused by several skin conditions such as melanocystic naevus, urticaria, fixed drug eruptions, subacute cutaneous lupus erythematosus, immunobulluous disorders like pemphigoid and some forms of vasculitis which include Kawasaki disease and acute haemorrhagic edema of ancy. As targetoid lesions are descriptive rather than diagnostic, a careful medical history and full skin examination are necessary to make the correct diagnosis (3,5). Considering the time course of development, drug history, total number and type of skin lesions and if necessary a skin biopsy can help to distinguish these disorders.

Erythema multiforme is a rare condition which is characterized by target lesions. Eruptions appear within 72 hours and remain for an average of 7 days in a typical episode. Lesions generally resolve without sequelae in approximately two weeks, but in darker pigmented individuals , pigmentary alterations at the site of lesions can be long-standing. Mucous membran involvement is usually presented as erythematous macules on the lip and buccal mucosa, followed by epithelial necrosis, bullae and ulcerations (4).

Among the various etiologic factors of EM, infection with HSV is the most commonly seen. Periodic reactivations of HSV, induce recurrences of erythema multiforme which is named HAEM (6). Eruptions of HAEM often develop 10-14 days after a HSV infection. Recurrences are seen in approximately 20-25% of HAEM cases and patients may experience 2-24 episodes a year, an average of 6 attacks annually, with each episode may last nearly 2 weeks (2). Most patients experience a single self-limited episode of EM (4). HSV DNA has been detected in 60% of patients clinically diagnosed with recurrent HAEM and in 50% of patients with recurrent idiopathic EM using polymerase chain reaction (PCR) of skin biopsy specimens.

(7). Detection of interferon-gama (IFN-γ) in HAEM lesions can also be used as evidence of viral antigens (6). Detecting specific IgM and IgG antibodies to identify HSV-1 and HSV-2 may confirm a suspected history of HSV infection, although it is not necessary for diagnosis (8). We did not consider biopsy because our patients had clinical signs of herpes labialis before typical rashes and had serologically detected HSV-1 positivity.

The presence of the human leukocyte antigens A33, B62, B35, DQW3 and DR53 is associated with an increased risk of HAEM, particularly in the recurrent form (4).

When compared to general population, male predominance rate was higher in pediatric population and had lesser attacks per year. Hospitalization was more common in children. The severity of skin lesions was similar between the children and the general population. But there is a higher incidence of mucosal involvement in children (6,9). Consistent with the literature, two of our cases were male and one of them had mucosal involvement (6).

New data have been presented showing that autoreactive T cells triggered by virus infection play an important role in HAEM pathogenesis. Disease begins with viral DNA fragmentation and the transport of DNA fragments by mononuclear cells (Langerhans cells) to distant skin areas. The HSV genes in DNA fragments (specifically DNA polymerase) deposited on the skin, are expressed by langerhans cells to HSV spesific CD4 Th1 cells . IFN-γ is produced by these Th1 cells and initiates an inflammatory cascade involving the increased sequestration of leukocytes, monocytes, natural killer cells and autoreactive T cells in the skin lesions (10).

Immune system must be evaluated in all HAEM cases. Monogenic defects of innate immunity components have been described in children which affect antiviral responses. TLR3, IRF3, TBK1, TRIF, TRAF3 and UNC93B1 deficiency (associated HSV encephalitis), TLR3, IRF7, IRF9 deficiency (associated severe infuenza) are some of the mutations previously identified (11,12). Bucciol and colleagues detected a pathogenic variant at TLR3 in a patient with HAEM. This mutation is thought to affect the antiviral response by reducing the production of type 1 interferon (5,11). One patient was diagnosed with Ig G1 subclass deficiency in another study (13). We also detected borderline hypogamaglobulinemia in the third patient. He had mucosal involvement in both EM recurrences.

Management of EM depends on the underlying etiology and the disease severity. If HSV is the etiologic cause, expert opinion recommends early administration of oral acyclovir treatment to reduce the severity and duration of the EM eruption (5). However, there is no evidence that antiviral therapy improves the time to lesion resolution (1,6).

The first line management of recurrent EM are antiviral treatments and they are generally safe and well tolerated in pediatric and general populations (6,13). It has been recommended that based on pathophysiologic reasoning that therapy may be continuous or intermittent. But only continuous therapy has been studied (3,14). A single placebo-controlled trial of 20 patients was reported that there was a significant reduction in recurrences with 400 mg of acyclovir treatment which was administered twice daily over a six-month period (15).

In cases that were unresponsive to acyclovir therapy, treatment with valacyclovir and famciclovir which have better bioavailability, reported to cause remission in both children and adults. Acyclovir (400 mg twice per day), valacyclovir (500 mg twice per day), or famciclovir (250 mg twice per day) are options that can be used. But there are limited studies to determine the recommended duration of treatment (3,5). We applied low dose valacyclovir prophylaxis of 500 mg daily to our patients continuously.

Mucosal EM may be very painful. Treatment options are topical corticosteroid gel and oral antiseptic or anesthetic solutions. Topical emollients, systemic antihistamines, and nonsteroidal antiinflammatory drugs can be used symptomatically. Severe cases of mucocutaneous EM may cause decreased oral intake, which may lead to hospitalization (1,4). Ocular involvement should be evaluated by an ophthalmologist immediately because visual sequelae may be permanent.

Prednisone was found to be effective in the treatment of recurrent EM, but no controlled studies have supported this treatment (3,6). In cases unresponsive to antiviral therapy, immunosuppressive treatments (dapson, azathioprine, mycophenolate mofetil), antimalarials, corticosteroids and IVIG therapy can be applied. There is little evidence to support these treatments (1,5). A small study indicated thalidomide as a treatment for reducing the duration of EM episodes, but further research is necessary (15). Heinze and colleagues' series of 26 patients, remission rate with immunosuppresive treatment was found lower in children compared to the general population (6).

In conclusion, use of antiviral drugs in HAEM treatment was seen to be effective if it was started in the first few days when semptoms had begun. Prophylactic oral acyclovir or valacyclovir that are given for 6 months, may be effective in controlling recurrent episodes of HAEM. Despite treatment HSV infection, HAEM may recur; but treatment may reduce the frequency and severity of episodes as we also seen in our patients.

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Turkish Journal of Pediatric Disease
Türkiye Çocuk Hastalıkları Dergisi

Abdominal Giant Mass in An Adolescent Girl: Uterine Leiomyoma

Adölesan Bir Kızda Abdominal Dev Kitle: Uterus Leiomyomu

Vildan Selin CAYHAN[1], Can Ihsan OZTORUN[2], Ayse Selcen OGUZ ERDOGAN[3], Dogus GUNEY[2], Mujdem Nur AZILI[2], Emrah SENEL[2]

[1] Department of Pediatric Surgery, Ankara City Hospital, Ankara, Turkey
[2] Department of Pediatric Surgery, Ankara Yildirim Beyazit University, School of Medicine, Ankara, Turkey
[3] Department of Pathology, Ankara City Hospital, Ankara, Turkey

ABSTRACT

Uterine leiomyoma is very common in women, but it is extremely rare in adolescence. Herein, we present the case report of uterine leiomyoma in a 14-year-old girl. She was admitted to the hospital with complaints of abdominal distension and a palpable mass. Transabdominal ultrasound and magnetic resonance imaging revealed a mass with a diameter of 16 cm. Laparotomy and myomectomy were performed. The postoperative period was uneventful. The pathology report was uterine leiomyoma. In the follow-up, there was no pathological sign. Uterine leiomyomas should be considered in the differential diagnosis of abdominal pain and pelvic mass in adolescent girls.

Key Words: Adolescent, Myomectomy, Uterine leiomyoma

ÖZ

Uterus leiomyomu kadınlarda çok sık görülür, ancak ergenlik döneminde oldukça nadir görülür. Bu olgu sunumunda, 14 yaşında bir kız çocuğundaki uterus leiomyom olgusunu sunuyoruz. Karında şişkinlik ve ele gelen kitle şikayeti ile hastaneye başvurdu. Transabdominal ultrason ve manyetik rezonans görüntülemede 16 cm çapında kitle saptandı. Laparatomi ve myomektomi yapıldı. Postoperatif dönem sorun olmadı. Patoloji raporu uterus leiomyomuydu. Takipte patolojik bulguya rastlanmadı. Adolesan kızlarda karın ağrısı ve pelvik kitle ayırıcı tanısında uterus leiomyomu düşünülmelidir

Anahtar Kelimeler: Adolesan, Myomektomi, Uterus leiomyomu

INTRODUCTION

Uterine leiomyomas are benign gynecological tumors originating from smooth muscle cells of the uterine wall. Although they are very common among women of reproductive age, are found in an estimated 20% to 30% of women under 50 years of age, are infrequently seen in children and adolescents, with few reported cases in the literatüre (1-3). In this case report, we presented a uterine leiomyoma in an adolescent girl with an abdominal giant mass.

CASE REPORT

A 14-year-old girl was admitted to the hospital with complaints of abdominal distension for the last six months. In her history, complaints increased over time, swelling became apparent during the menstruation period and she had no menorrhagia or pain. On physical examination, a mass, approximately 17 cm, starting from the umbilicus into the pubis was palpated. On the abdominal ultrasonography, a mass of 12x10x16 cm size which could not be separated from the uterus was seen

0000-0002-9769-1754 : CAYHAN VS
0000-0002-5408-2772 : OZTORUN CA
0000-0001-8350-8704 : OGUZ ERDOGAN AS
0000-0001-7168-2123 : GUNEY D
0000-0002-5137-7209 : AZILI MN
0000-0002-0383-4559 : SENEL E

Conflict of Interest /*Çıkar Çatışması:* *On behalf of all authors, the corresponding author states that there is no conflict of interest.*
Financial Disclosure / *Finansal Destek*: The authors declared that this case has received no financial support.
***Confirmation* / *Onay*:** The written consent was received from the patient who was presented in this study.
How to cite / *Atıf Yazım Şekli* : Cayhan VS, Oztorun CI, Oguz Erdogan AS, Guney D, Azılı MN, Senel E. Abdominal Giant Mass in An Adolescent Girl: Uterine Leiomyoma. Turkish J Pediatr Dis 2023;17:171-173.

Correspondence Address / Yazışma Adresi :
Can Ihsan OZTORUN
Department of Pediatric Surgery, Ankara City Hospital, Ankara, Turkey
E-posta: vselinsahin@gmail.com

Received / Geliş tarihi : 16.05.2022
Accepted / Kabul Tarihi : 16.08.2022
Online published : 14.09.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.1117144

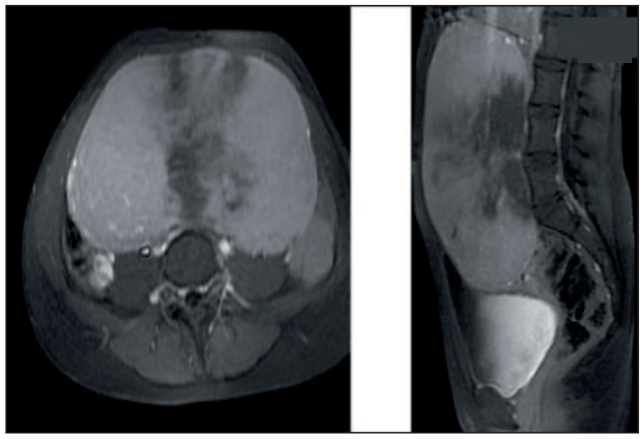

Figure 1: The MRI view of the mass.

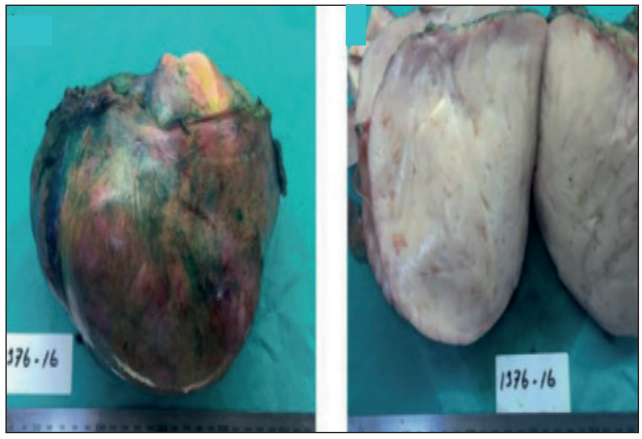

Figure 2: Macroscopic view of the mass

in the midline. In magnetic resonance imaging (MRI), a mass that extends from the level of the umbilicus to the pelvis, with heterogeneous enhancement in T1 and T2 weighted sequences and 17x18 cm in size, was detected (Figure 1). The ovaries could not be detected in the MRI. The patient's complete blood count, blood biochemistry, serum βhCG, and AFP levels were in the normal range. Only, the serum CA125 level was high (CA125=450(0-35)). Laparotomy was performed by midline incision under general anesthesia. In the exploration, a mass was observed in the pelvis with15x20x20 cm size. The mass was invasive to the tube and uterus and pushed the right and left ovaries. Myomectomy was performed, mass excised by dissections, and preserved the ovaries, tubes, uterus, and bladder. The patient was followed up post-operatively. Oral feeding was started on the first day. She was discharged on the postoperative third day.

In the macroscopic examination, the mass was observed as 1808 g weighted, 20.5x15.5x11 cm in size, and with a smooth surface (Figure 2). In the pathological examination, the specimen was diagnosed as leiomyoma of the uterine which origins with tumor cells with strong staining of actin, desmin, and nuclear estrogen receptors. In the follow-up, ultrasonography was performed and there were no pathological signs in the ovaries and uterus.

DISCUSSION

Leiomyomas are seen as rare in adolescents. Patients are usually admitted with the complaint of abdominal pain, back pain, palpation of an abdominal mass, increased abdominal volume, and abnormal menstrual bleeding (4). In adolescents, the leiomyoma size ranges from 7 to 30 cm (5). The etiology of uterine leiomyoma in adolescents is also unknown. There are some suggestions such as; leiomyomas might originate from intrinsic anomalies in the myometrium; congenitally elevated levels of sex steroids; and an endometrial injury acquired during menstruation (6). The biological behavior of these tumors in this age group is unknown, but the surgical treatment results are good with a low recurrence rate (4).

Although there are various treatment options such as medical treatment, uterine artery embolization, abdominal myomectomy, and hysterectomy in adult leiomyomas (7). The treatment of uterine leiomyoma in adolescents is myomectomy preserved fertility, also hysteroscopic myomectomy, and abdominal hysterectomy were reported (8). In our case, we performed a myomectomy. Recurrence after myomectomy is very rare, but patients should be followed up along with the adolescent (9). We followed up on our patient for two years by physical examination and ultrasonography. We did not find any pathological signs.

In conclusion, uterine leiomyomas should be considered in the differential diagnosis of abdominal pain and pelvic mass in adolescent girls. Although optimal treatment of uterine leiomyoma is still not defined, myomectomy is preferable, considering fertility in the future.

Informed consent: Informed consent was obtained from the patient and parents for publication of this case report.

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